ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

CONSENSUS STATEMENT

ISHLT consensus statement: Perioperative management of patients with pulmonary hypertension and right heart failure undergoing surgery

Dana P. McGlothlin, MD,[a] John Granton, MD,[b] Walter Klepetko, MD,[c] Maurice Beghetti, MD,[d] Erika B. Rosenzweig, MD,[e] Paul A. Corris, MD,[f] Evelyn Horn, MD,[g] Manreet K. Kanwar, MD,[h] Karen McRae, MD,[b] Antonio Roman, MD,[i] Ryan Tedford, MD,[j] Roberto Badagliacca, MD,[k] Sonja Bartolome, MD,[l] Raymond Benza, MD,[m] Marco Caccamo, DO,[n] Rebecca Cogswell, MD,[o] Celine Dewachter, MD,[p] Laura Donahoe, MD,[b] Elie Fadel, MD, PhD,[q] Harrison W. Farber, MD,[r] Jeffrey Feinstein, MD,[s] Veronica Franco, MD,[m] Robert Frantz, MD,[t] Michael Gatzoulis, MD,[u] Choon Hwa (Anne) Goh, MD,[a] Marco Guazzi, MD,[v] Georg Hansmann, MD,[w] Stuart Hastings, MD,[x] Paul M. Heerdt, MD, PhD,[y] Anna Hemnes, MD,[z] Antoine Herpain, MD,[p] Chih-Hsin Hsu, MD,[aa] Kim Kerr, MD,[bb] Nicholas A. Kolaitis, MD,[cc] Jasleen Kukreja, MD,[cc] Michael Madani, MD,[bb] Stuart McCluskey, MD,[b] Michael McCulloch, MD,[dd] Bernhard Moser, MD,[c] Manchula Navaratnam, MD,[s] Göran Rådegran, MD,[ee] Cara Reimer, MD,[b] Laurent Savale, MD,[ff] Oksana A. Shlobin, MD,[gg] Jana Svetlichnaya, MD,[a] Keith Swetz, MD,[hh] Jessica Tashjian, MD,[a] Thenappan Thenappan, MD,[o] Carmine Dario Vizza, MD,[k] Shawn West, MD,[ii] Warren Zuckerman, MD,[jj] Andreas Zuckermann, MD,[c] and Teresa De Marco, MD[cc]

From the [a]Kaiser Permanente San Francisco, San Francisco, California; [b]University of Toronto, Toronto, Ontario, Canada; [c]Medical University of Vienna, Vienna, Austria; [d]Children's University of Geneva, University of Geneva, Geneva, Switzerland; [e]Columbia University Medical Center, New York Presbyterian Hospital, New York, New York; [f]Newcastle University, Newcastle upon Tyne, UK; [g]Weill Cornell Graduate School of Medical Sciences, Cornell University, New York, New York; [h]Allegheny Health Network, Pittsburgh, Pennsylvania; [i]Hospital Universitari Vall d'Hebron, Barcelona, Spain.; [j]Medical University of South Carolina, Charleston, South Carolina; [k]Sapienza University of Rome, Rome, Italy; [l]University of Texas Southwestern Medical Center, Dallas, Texas; [m]Ohio State University, Columbus, Ohio; [n]West Virginia University, Morgantown, West Virginia; [o]University of Minnesota Medical School, Minneapolis, Minnesota; [p]Hôpital Erasme, Brussels, Belgium; [q]Hôpital Marie Lannelongue and Université Paris-Sud, Paris, France; [r]Tufts Medical Center, Boston, Massachusetts; [s]Stanford University Medical Center, Lucile Packard Children's Hospital, Palo Alto, California; [t]Mayo Clinic, Rochester, Minnesota; [u]Royal Brompton and Harefield NHS Trust, and the National Heart and Lung Institute, Imperial College London, London, UK; [v]San Paolo Hospital, University of Milano, Milano, Italy; [w]Hannover Medical School, Hannover, Germany; [x]Alfred Hospital and Monash University, Melbourne, Victoria, Australia; [y]Yale New Haven Hospital and Yale School of Medicine, New Haven, Connecticut; [z]Vanderbilt University Medical Center, Nashville, Tennessee; [aa]National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [bb]University of California San Diego, San Diego, California; [cc]University of California San Francisco, San

1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2022.06.013

Francisco, California; [dd]University of Virginia Children's Hospital, Charottsville, VA; [ee]Lund University, and Skåne University Hospital, Lund, Sweden; [ff]Université Paris−Saclay; INSERM UMR_S 999; Assistance Publique Hôpitaux de Paris Hôpital Bicêtre, Hôpital Marie Lannelongue, Le Plessis Robinson, France; [gg]Inova Fairfax Hospital, Falls Church, Virginia; [hh]University of Alabama at Birmingham School of Medicine, Birmingham, Alabama; [ii]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania; and the [jj]Columbia University Medical Center, Morgan Stanley Children's Hospital of New York, New York, New York.

KEYWORDS:
pulmonary hypertension;
pulmonary arterial hypertension;
surgery;
anesthesia;
congenital heart disease;
pediatric pulmonary hypertension

Pulmonary hypertension (PH) is a risk factor for morbidity and mortality in patients undergoing surgery and anesthesia. This document represents the first international consensus statement for the perioperative management of patients with pulmonary hypertension and right heart failure. It includes recommendations for managing patients with PH being considered for surgery, including preoperative risk assessment, planning, intra- and postoperative monitoring and management strategies that can improve outcomes in this vulnerable population. This is a comprehensive document that includes common perioperative patient populations and surgical procedures with unique considerations.
J Heart Lung Transplant 2022;41:1135−1194

Pulmonary hypertension (PH) is a risk factor for morbidity and mortality in patients undergoing surgery and anesthesia. Successful management of the perioperative patient with PH is complex. It requires a thorough understanding of the pathophysiology of PH and right ventricular (RV) failure, as well as building a safety net preoperatively to mitigate the risks of surgery and improve outcomes. This approach includes ensuring accurate diagnostic classification of PH based upon the World Health Organization (WHO) clinical and hemodynamic classification of PH[1] (Figure 1), assessment of the patient's functional status and disease severity, evaluation of the risks vs benefits of anesthesia and surgery, development of a perioperative plan with a multidisciplinary team, preoperative hemodynamic optimization, and vigilant postoperative monitoring for the early recognition and treatment of any postoperative complications (Figure 2). Additionally, determination of the best location for surgery to occur (particularly for non-cardiac surgery) is important given data that suggests patients with WHO Group 1 pulmonary arterial hypertension (PAH) benefit from having surgery in a center with experienced PH providers[2]−an approach that has been advocated in recent guidelines.[3]

In the absence of robust literature to form clinical practice guidelines, this statement represents the consensus of international experts in the field on the perioperative evaluation and management for patients with a spectrum of PH etiologies undergoing various types of surgeries and procedures, including non-cardiac and cardiac surgeries, cardiothoracic and abdominal organ transplantation, surgery for acute and chronic pulmonary embolism, and procedures in children and adult congenital heart disease patients with PH. It is meant to serve as a guide for physicians, surgeons, anesthesiologists, and other providers who manage these patients.

Reprint requests: Dana McGlothlin, MD, Kaiser Permanente San Francisco, 2238 Geary Blvd, 8th floor Cardiology Dept, San Francisco, CA 94115.

E-mail address: dana.p.mcglothlin@kp.org

Preoperative evaluation and management of patients with PH

Risk assessment

A fundamental risk for patients with PH during and after surgery and anesthesia is the inability of a dysfunctional RV to accommodate to rapid changes in ventricular preload, afterload and contractility to provide adequate left ventricular preload and meet systemic oxygen demands. Volume shifts, anesthetic agents, mechanical ventilation, and changes in sympathetic tone can precipitate worsening PH, RV ischemia, or RV dysfunction[4-6] and lead to a cascade of hypotension, arrhythmias, metabolic acidosis, multiorgan failure, and death. These events often occur within the first 48 to 72 hours after surgery.

Risks vary with different surgeries, etiologies of PH, comorbidities, and the spectrum of clinical status among patients with PH. Risk assessment therefore demands a comprehensive approach to the preoperative evaluation of patients in order to prevent excessive peri-procedural morbidity and mortality. We strongly recommend a systematic preoperative risk assessment be performed and that an individualized perioperative plan be developed by a multidisciplinary team for *all* patients with WHO Groups 1 (PAH) and 4 (chronic thromboembolic pulmonary hypertension [CTEPH]) PH as well as other etiologies of PH when the PH is significant and RV dysfunction present. Even minor procedures requiring conscious sedation should be approached cautiously in patients with severe PAH and efforts to mitigate risk enacted.

Preoperative risk assessment should start with well-established general cardiac/non-cardiac perioperative risk assessment algorithms, and consider several factors that are

Clinical Classification (aka WHO Group)	
Group 1	Pulmonary arterial hypertension (PAH)
Group 2	PH due to Left Heart Disease
Group 3	PH due to Lung Diseases and/or Hypoxemia
Group 4	PH due to Pulmonary Artery Obstructions
Group 5	PH with unclear and/or multifactorial mechanisms

Hemodynamic Definitions		
Definitions	Characteristics	Clinical Groups
Pre-capillary PH	mPAP>20 PCWP≤15 PVR≥3	1, 3, 4, 5
Post-capillary PH (IpcPH)	mPAP>20 PCWP>15 PVR<3	2, 5
Combined pre- and post-capillary PH (CpcPH)	mPAP>20 PCWP>15 PVR ≥ 3	2, 5

Figure 1 Hemodynamic and clinical classifications of PH. Abbreviations: mPAP, mean pulmonary artery pressure ; PCWP, pulmonary capillary wedge pressure ; PVR, pulmonary vascular resistance.

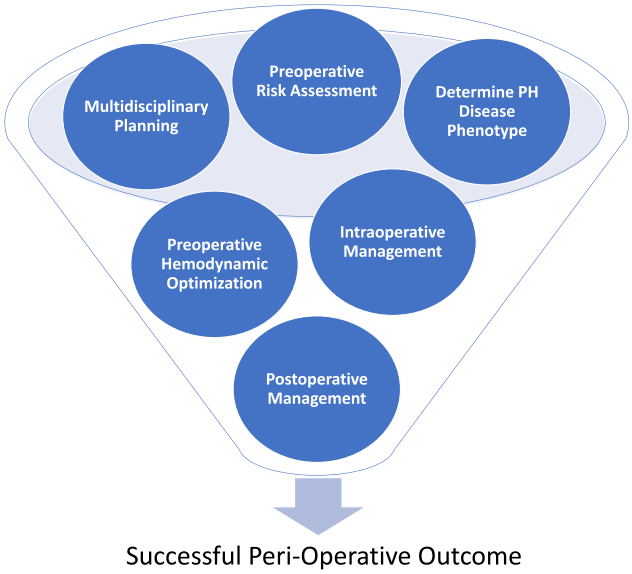

Figure 2 Recipe for successful perioperative outcome.

Table 1 Surgery Specific Risks

Lowest Risk Procedures
Procedures with local anesthesia for minor procedures
Dermatologic surgeries
Low Risk Surgeries
Dermatologic surgeries
Endoscopic procedures
Cataract surgery
Breast surgery
Intermediate Risk Surgeries
Carotid endarterectomy
Head and neck surgery
Gynecologic surgery
GI/abdominal surgery
Orthopedic surgery
Prostate surgery
High Risk Surgeries
Emergent major surgery
Cardiovascular surgery
Liver transplantation
Any operation with anticipated large fluid shifts and/or blood loss

germane to patients with PH, including the type and urgency of surgery, patient's functional status, etiology and severity of PH, RV function, and patient comorbidities. Unless the surgery is urgently needed, patients with previously undiagnosed PH should have an expedited evaluation to establish the pathologic etiology of PH (i.e., WHO clinical classification), assess disease severity, and guide treatment for PH following evidence-based PH guidelines.[7]

Emergency procedures,[8,9] American society of anesthesiologists class ≥ 2,[10] intermediate or high risk surgery,[8,9,11] longer duration of surgery and anesthesia (>3 hours),[9,11] coronary artery disease,[8,10] chronic renal insufficiency,[10] history of pulmonary embolism,[11] NYHA Functional Class ≥ 2,[11] RV dysfunction,[11] and hemodynamic derangement[8,10] are established risk factors for perioperative morbidity/mortality in patients with PH undergoing general surgery. Intermediate to high-risk procedures in patients with PH are those that involve general anesthesia and/or the potential for rapid blood loss (e.g., organ transplantation, vascular surgery), significant perioperative systemic inflammatory response (e.g., cardiopulmonary bypass), venous air embolism, carbon dioxide (CO2) (e.g., laparoscopic surgery), fat or cement emboli (e.g., orthopedic surgery), and reduction in the pulmonary vasculature (e.g., lung resection). Table 1.

The preoperative evaluation (Figure 3) should include a detailed history, including elicitation of PH related symptoms of exertional dyspnea, chest discomfort, and/or presyncope/syncope to determine functional status. A thorough physical examination with particular attention to signs of RV failure (RVF) is required. Preoperative testing in patients with PH should be done within 2 weeks of elective surgery and include natriuretic peptide level (correlates with severity of disease in PAH and heart failure) along with basic chemistry (especially renal function),

- **History:**
- Determine Functional Classification
  - Exertional SOB, CP, syncope to determine FC
- **Physical Exam:**
- Look for signs of RHF
  - Elevated JVP, RV gallop, TR mumur, ascites, edema, cool periphery, reduced capillary refill
- **Tests:**
- BNP, basic chemistry, CBC, coagulation panel
- CXR, ECG
- 6 min walk test/CPET
- Echo within 2 weeks
- RHC in selected patients

WHO Functional Classification

Class	Description
I	No limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
II	Slight limitation of physical activity; no discomfort at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
III	Marked limitation of physical activity; no discomfort at rest; less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
IV	Unable to carry out any physical activity without symptoms; signs of right-heart failure; dyspnea and/or fatigue may be present at rest; discomfort is increased by any physical activity

Figure 3 Preoperative assessment checklist.

coagulation panel, chest X-ray, ECG, 6 minute walk test, and an echocardiogram with detailed attention to the right ventricle. Measures of RV size and function, including tricuspid annular plane systolic excursion (TAPSE) and RV S', degree of interventricular septal flattening from RV volume and pressure overload, and an estimate of the pulmonary artery systolic pressure (PASP) by echocardiography are helpful to identify patients with more severe PH and RV dysfunction who may be at greater risk. An estimate of physiological reserve can also inform risk. Patients with PAH and a 6-minute walk distance <399 m at the last preoperative assessment are at higher risk of major postoperative complications.[12] Preoperative right heart catheterization (RHC) should be considered in patients with clinical evidence of severe PH and RV dysfunction and/or planned high risk operation. Table 2.

The prognostic scoring systems for PAH from the European Respiratory and European Cardiology Society and the United States Registry to Evaluate Early And Long-term PAH Disease Management, may also be helpful to generally assess disease severity in patients with WHO Group 1 PAH,[13-15] however their perioperative utility has not been assessed nor have they been validated in patients with *non*-WHO Group 1 PH.

In high perioperative risk situations, surgery should be performed at a center with the expertise (PH specialists, CV anesthesiologists, intensivists) and resources (inhaled nitric oxide, extracorporeal membrane oxygenation [ECMO]) to effectively manage the patient postoperatively should complications arise. This may entail transfer to a tertiary care center, and if this is not feasible then urgent consultation with a PH expert center for management recommendations can be helpful. If time permits, medical and hemodynamic optimization should be attempted prior to surgery in patients with evidence of decompensated disease.

Very low risk procedures that involve minimal sedation and analgesia, such as cataract and dental surgeries, do not generally require a full reassessment of PH disease severity. However, for patients with advanced PH, recommendations

Table 2 PH Specific Risk Assessment Tools

	Low risk	High risk
Clinical symptoms/signs		
RHF	None	Present
Functional class	I/II	III/IV
Exercise capacity		
6 mwd	> 400 meters	< 165 meters
CPET	Peak VO2 > 15 ml/min/kg^{-1} VE/VCO2 slope < 36.0	Peak VO2 < 11 ml/min/kg^{-1} VE/VCO2 slope > 45.0
Imaging		
(echo, MRI)	Normal RV size & function Normal RA size	Markedly dilated RV, RV dysfunction Severe RAE, pericardial effusion
Hemodynamics	RAP < 8, CI > 2.5, SvO2 > 65%, RVSP/SBP < 0.33	RAP > 14, CI < 2.0, SvO2 < 60%, mPAP > 35 mm Hg, RVSP/SBP > 0.66
Biomarkers (ng/liter)	BNP < 50, NT-pro BNP < 300	BNP > 300, NT-pro BNP > 400
PAH risk score	Low risk	High risk

BNP, brain type natriuretic peptide; CI, cardiac index; mPAP, mean pulmonary artery pressure; RA, right atrium; RAE, right atrial enlargement; RAP, right atrial pressure; RV, right ventricle; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; SvO2, systemic venous O2 saturation; VE/VCO2, minute ventilation/carbon dioxide production; VO2, maximal oxygen consumption; .

to avoid nitrous oxide (reports suggest it can increase PVR) and epinephrine (may be proarrhythmic) along with minimizing oral sedation usually suffice.

Endoscopic procedures require sedation, which can cause hemodynamic and respiratory compromise if not approached with caution. Upper endoscopy is generally well tolerated and can often performed at the local facility. Recommendations for this procedure typically include administration of minimal sedation and close hemodynamic and respiratory monitoring. In urgent, higher risk cases (e.g., active GI bleeding in a patient with uncontrolled PH and RV/respiratory failure or Eisenmenger Syndrome), an anesthesiologist should be involved. Colonoscopy involves deeper sedation and therefore greater risk of cardiorespiratory compromise. Thus, in very high-risk PH patients, especially those with baseline severe PH/RV and respiratory failure, performing the procedure at a tertiary care center with anesthesia and PH expertise is most prudent. In some cases, the risks of the procedure may outweigh its potential benefits.

Absolute contraindications for surgery in patients with PH cannot be provided since the balance of relative risks vs benefits always needs to be considered, and ultimately the decision to proceed will be informed by the urgency of the procedure, prognosis of PH relative to the condition being addressed surgically (e.g., cancer), capability of altering risk by optimizing their PH and RV function, and patient preferences.

Table 3 lists key perioperative questions to answer preoperatively.

Multidisciplinary planning for the PH patient undergoing surgery

Carefully planned non-emergency surgery has better outcomes in patients with PH.[4-6] In order to achieve the best outcomes, the management team must be organized, proficient with knowledge and skills, and effective in communication. The PH specialist, anesthesiologist, and surgeon are at the core of the multidisciplinary group to develop an individualized perioperative plan and ensure clear communication of the plan with the respective team members (Figure 4).

Table 3 Key Perioperative Questions to Answer

- Do the benefits of the surgery outweigh the patient specific and surgery associated risks of the procedure?
- Is the patient medically optimized or are additional procedures and treatment needed?
- What is the urgency of surgery (e.g., is there time for optimization of PH/RV function)?
- Should the procedure be moved from its usual location to a tertiary location (e.g., available CV anesthesia, PH expertise, PAH meds, ECMO capabilities)?
- What is the intra- and postoperative monitoring plan?
- How should anesthesia staffing be allocated (CV vs general anesthesiology)?
- Is the patient a candidate for ECMO?
- What is the optimal postoperative disposition (e.g., postoperative recovery in ICU for 48 hours or more)?
- What is the plan for managing chronic PAH therapies?

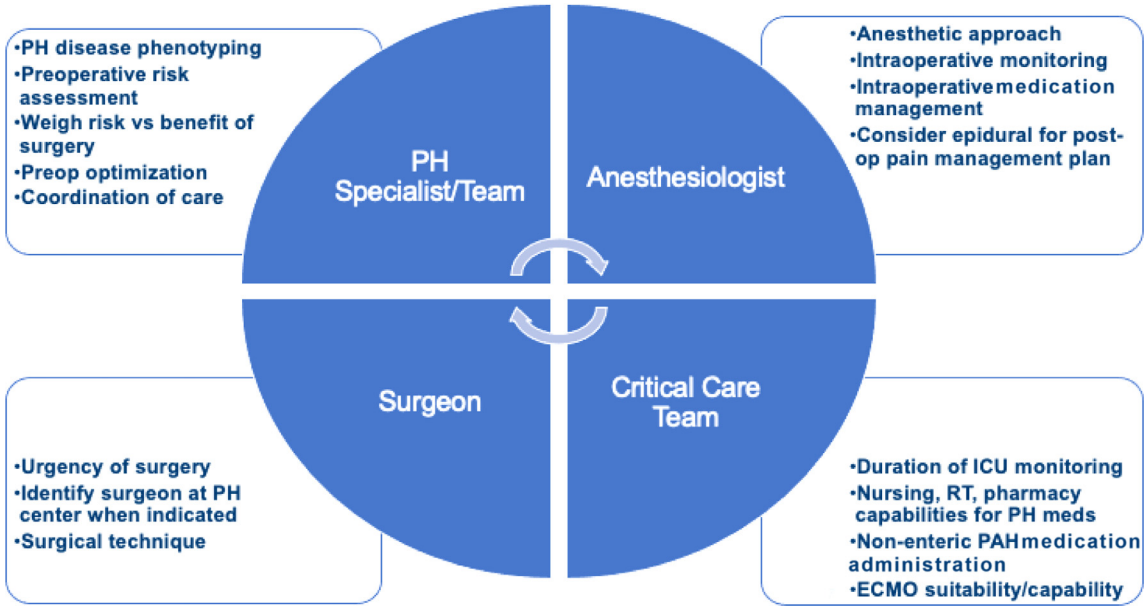

Figure 4 Preoperative multidisciplinary communications and planning: the core team.

Multidisciplinary team

PH specialist. The role of the PH specialist is to perform a thorough preoperative evaluation for disease phenotyping and risk assessment, help weigh the risks vs benefits of surgery, provide timely and effective communication with the surgeon and anesthesiologist to determine the urgency and best location for surgery, discuss intraoperative monitoring and medical management considerations with the anesthesiologist, consider potential need and patient candidacy for ECMO and communicate with the appropriate teams, optimize the patient's clinical and hemodynamic status preoperatively, and participate in the postoperative care and management based on institutional practices.

Importantly, preoperative plans for the perioperative administration of chronic PAH specific therapies for patients with PAH and CTEPH should be discussed with the anesthesiologist and intensive care unit (ICU) team, including the logistics of continuing chronic infused and inhaled prostacyclin analogues as well as options for non-enteral PAH drug administration while NPO.

Anesthesiologist. The anesthesiologist assesses patient and surgical/anesthesia risk, taking into account the severity of PH and RV dysfunction. The anesthesiologist, along with input from the PH specialist and surgeon determine appropriate intraoperative anesthesia plans including who should be present (institutions may have gradations of general, cardiac or intensivist anesthesiologists), preferred anesthetic modality, monitoring, fluid administration, ventilation strategy, additive pulmonary vasodilators (e.g., iNO and/or chronic infused prostacyclin analogues) and preferred inopressor use tailored to the patient's PH phenotype and hemodynamics. The anesthesiologist in concert with the surgical team should give a in-person sign over to the intensivist and/or PH specialist immediately after surgery to report intraoperative events that could affect the postoperative course.

Surgeon. The surgeon determines the need and urgency for surgery. Along with the anesthesiologist and PH specialist, the surgeon assesses the balance of anticipated benefits vs associated risks of surgery and determines the best location for surgery (this may be at a tertiary care center with CV anesthesia and PH expertise availability requiring a change in surgeon). The surgeon decides the surgical approach, along with input from the anesthesiologist in some cases (e.g., laparoscopic, robotic, minimally invasive or open procedures), and coordinates with the PH specialist on the timing of surgery in elective cases.

Intensivist. The risk of death from acute decompensated RV failure (ADRVF) in patients with PAH is highest within 48 to 72 hours of the procedure.[9,12] If the preoperative evaluation revealed intermediate to high PH-related morbidity/mortality risk, or if the surgery is emergent or prolonged, planned postoperative recovery in the ICU for 24 to 72 hours is advised. The role of the intensivist is to be vigilant for signs of worsened PH and/or decompensated RV, rapidly treat precipitating factors[5,16] and activate the multidisciplinary team if cardiogenic shock occurs. Close communication with the PH specialist is essential, particularly before changing or stopping PAH medications, and provide input into decision to use pharmacological or mechanical rescue strategies. The intensivist should be familiar with PAH therapies if managing WHO Group 1 PH patients. The half-life of agents varies, but typically is minutes to hours for prostanoids. A potential for rebound pulmonary vasoconstriction and PH crisis can occur after abrupt discontinuation, thus underscoring the importance of avoiding any interruption.[5-7]

Pharmacists. Pharmacists play a vital role in the care of the PH population (particularly for patients with PAH) during the postoperative period.[17] The PH pharmacy specialist may serve as a liaison to communicate the plan of care, concerns and recommendations among specialists. Further, they alert the PH specialist if the patient is unable to take oral PAH medications and alternatives need to be identified. The complexity of parenteral prostanoids leads to particularly high risk with medication errors, including accidental flushing of the dedicated line, incorrect dosing (calculation, compounding, or ordering errors), and pump-related errors, all of which can be fatal.[18] Medication reconciliation, reviewing and checking dosages, drug infusion preparation, are important roles. Hospital pharmacists also play a key role in monitoring adverse event reports and assure adherence to institutional compliance protocols.

Nurses. A PH nurse specialist plays a key role in navigating a PAH patient through the evaluation and perioperative phases. They should be invested in the education of the patient and family regarding risks and goals of treatment. They are integral to preoperative optimization of therapy −in particular optimization of fluid status. They are in a key position to advocate for the patient and work with the various teams to ensure continuity of care and realization of the treatment plan.

Only bedside nurses with training and proficiency in managing inhaled and infused pulmonary vasodilator therapies should care for patients with PAH in the postoperative setting. They play a vital role in the safe administration and adjustment of these therapies to PAH patients, and this is a key reason why WHO Group 1 and 4 PH patients should have surgery performed at a PH expert center.

Preoperative hemodynamic optimization

All attempts to lower PVR and improve RV function should be done prior to surgery (Figure 5). Patients with uncontrolled or decompensated cardiovascular disease have increased perioperative morbidity and mortality. Dyspnea at rest, syncope, severe RVF (low CO and central venous pressure [CVP] > 15 mm Hg), metabolic acidosis and marked hypoxemia signal advanced, unstable PH disease, and in such cases the surgery should be cancelled or

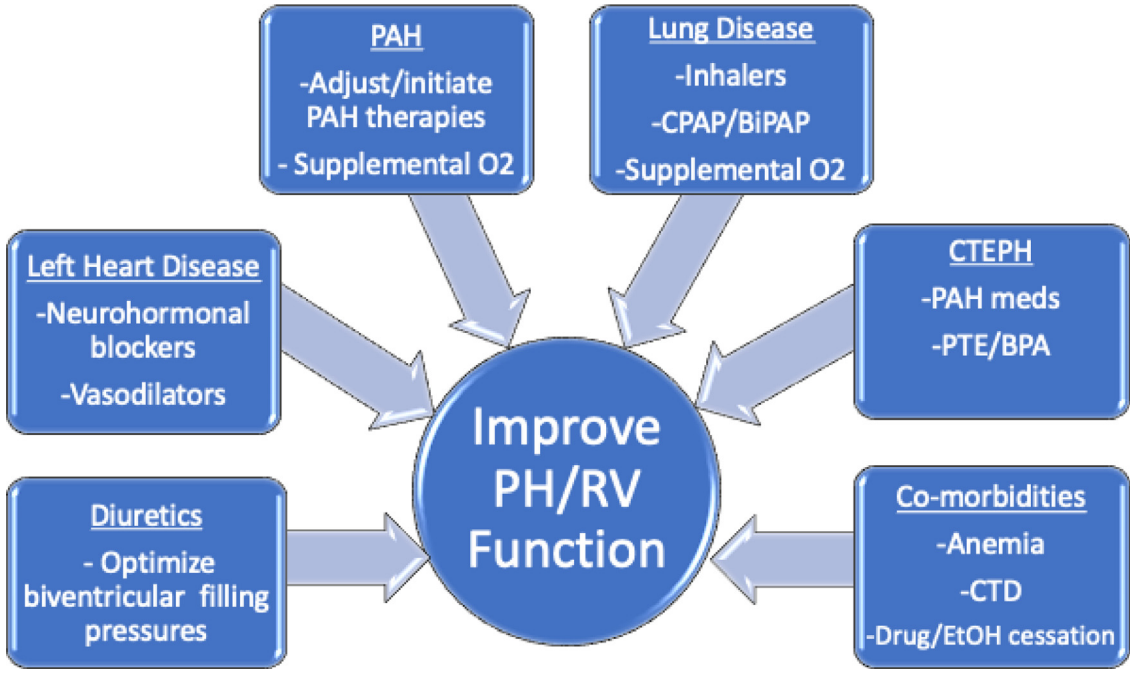

Figure 5 Preoperative optimization.

postponed until improvement and stabilization can be achieved, if possible.[4-6,16]

Preoperative optimization, whether guided clinically or by invasive assessment, mainly involves optimizing RV loading conditions with diuretic adjustment to improve or normalize ventricular filling pressures, maximizing evidence-based medical therapy for PH/PAH and heart failure, and identify conditions that may cause acute deterioration. Examples include the initiation or augmentation of PAH specific therapies for patients with WHO Group I PAH; administration of oxygen, bronchodilators, antibiotics, and steroids for patients with chronic obstructive pulmonary disease; use of BIPAP for patients with obstructive sleep apnea (OSA); and systemic vasodilators and other appropriate HF therapies for patients with WHO Group 2 PH. Additionally, pulmonary balloon angioplasty has been successfully performed preoperatively for CTEPH prior to non-cardiac surgery to reduce perioperative risk.[19]

In moderate to high-risk cases (e.g., high risk patient and/or operation), consideration should be given to preoperative invasive hemodynamic assessment of disease severity in order to guide optimization and decision making regarding intraoperative monitoring and postoperative location. Depending on the urgency of surgery, the assessment can be done several weeks in advance of surgery so that PAH therapies in appropriate patients can be initiated or escalated. For example, patients with idiopathic or associated PAH may benefit from preoperative RHC followed by the initiation of intravenous prostanoid therapy if poor prognostic findings are demonstrated (e.g., high right atrial pressure [RAP], low cardiac index [CI], severely elevated pulmonary vascular resistance [PVR], reduced central venous saturation). Patients with severe post-capillary PH may be optimized with appropriate diuresis, systemic vasodilators, and perhaps inodilators. In some cases a RHC may be done within days of surgery with anticipation of retaining the pulmonary artery catheter (PAC) depending on the hemodynamics and perioperative monitoring plan.

Although few randomized studies have been performed to determine optimal management practices, principles of management are commonly based on experience and consensus. Table 4 outlines reasonable hemodynamic goals that can be used to guide management throughout the perioperative period. These values may not be achievable in all cases, especially depending on underlying PH type/etiology, but are meant to serve as a target.

Table 4 Optimal Perioperative Hemodynamic Goals

- MAP > 60-65 mm Hg
- SBP > 90 mm Hg
- SpO2 > 92%
- RAP 5-10 mm Hg
- Mean PAP < 35 mm Hg[a]
- PVR/SVR ratio < 0.5[a]
- PCWP < 18 (for WHO Group 2 PH)
- CI ≥ 2.2 liter/min/m2[b]

CI, cardiac index; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SpO2, systemic pulse arterial oxygen saturation; RAP, right atrial pressure; SVR, systemic vascular resistance.

This table summarizes optimal perioperative hemodynamic conditions.

[a]Not all of these hemodynamics are achievable in patients with pulmonary hypertension; however, they represent goals for the medical management of patients during the perioperative period.

[b]Thermodilution or direct Fick CO methodologies.

Emergency surgery

Emergency surgery is associated with worse perioperative outcomes. In non-cardiac surgery in patients with PH, emergency surgery is an independent risk factor for perioperative mortality (mortality 15%-50%), which is significantly higher than reported for non-emergent surgeries in PH cohorts.[8,9,12]

There is little time to complete a preoperative risk assessment and optimize the patient before emergency surgery. Figure 6 provides a schematic for preoperative assessment in emergent and elective surgery. Emergency surgery typically cannot be postponed even in the face of a high surgical risk. In these instances, intraoperative and postoperative monitoring and management become the major focus. Emergency echocardiography should be arranged, and the information shared among the PH specialist, anesthesiologist, surgeon, and intensivist. Plans for the anesthetic approach and management of PH specific medications should be quickly established and communicated. If the patient is at very high perioperative mortality based on advanced PH disease and intermediate to high-risk surgery, urgent transfer to a PH center with ECMO capabilities should be discussed, depending on patient stability for transfer and candidacy for ECMO support. Patient selection for ECMO support in this situation depends heavily on the patient's age, likelihood of recovery, and transplant candidacy.

Key Points

1. A systematic preoperative risk assessment should be performed and an individualized perioperative plan developed by a multidisciplinary team for *all* patients with WHO Groups 1 (PAH) and 4 (CTEPH) PH as well as other etiologies of PH when the PH is significant and RV dysfunction present. Even minor procedures requiring conscious sedation should be approached cautiously in patients with severe PAH and efforts to mitigate risk enacted.
2. Patients with WHO Group 1 PAH should have surgery performed at a PH expert center
3. Preoperative risk assessment should start with well-established general cardiac/non-cardiac perioperative risk assessment algorithms, and also consider the type and urgency of surgery, etiology and severity of PH, RV function, patient's functional status, and comorbidities.
4. In moderate to high-risk cases (e.g., high risk patient and/or operation), consideration should be given to preoperative invasive hemodynamic assessment of disease severity in order to guide optimization and decision making regarding intraoperative monitoring and postoperative recovery location.
5. If time permits, medical and hemodynamic optimization should be attempted prior to surgery in patients with evidence of decompensated PH/RVF
6. Unless surgery is urgently needed, patients with previously undiagnosed PH should have an expedited evaluation to establish the pathologic etiology of PH (i.e., WHO clinical classification), assess disease severity, and guide treatment for PH according to evidence-based PH guidelines

Intraoperative considerations in patients with PH

The overarching goals in PH patients receiving anesthesia are to support RV function by maintaining adequate preload in addition to preventing increases in RV afterload or reduced contractility that may precipitate acute RVF. The general principles and fundamentals of intraoperative management have been reviewed in detail.[20] One of the most important fundamental goals is to avoid systemic arterial hypotension that can promote RV ischemia in the setting of a pressure and volume overloaded RV with altered right coronary artery perfusion. Periods of transient hypotension are common and may be due to the direct cardiovascular of anesthetic drugs, impact of withdrawing sympathetic tone, effects of mechanical ventilation, intraoperative fluid shifts, and / or manipulation of the heart and great vessels. Therefore, these events must be anticipated and effectively managed.

Regardless of anesthetic technique and agents, appropriate use of supplemental oxygen (a potent pulmonary vasodilator) should be used to avoid hypoxemia, and intravenous lines and syringes must be meticulously deaired to prevent even small amounts of air embolism that could be detrimental to the hypertensive pulmonary circulation or pass through a patent foramen ovale into the systemic circulation. Additionally, warming blankets, heat and moisture exchangers in the breathing circuit, and warmed IV fluids can help prevent hypothermia, which can inhibit physiologic hypoxic pulmonary vasoconstriction (HPV) and ventilation-perfusion (V/Q) mismatching.

Additionally, if significant postoperative pain is anticipated, consideration should be given to insertion of an epidural catheter for postoperative analgesia administration to mitigate the deleterious effects of systemic opioid use (hypoventilation, hypoxemia, hypercarbia).

Anesthesia and anesthetic management

The decision about the anesthetic method (e.g., general, regional, neuraxial) is determined by a combination of the planned surgery, severity of pulmonary vascular disease/RVF and other comorbidities, as well as patient preference. For instance, choosing an anesthetic technique that optimizes airway patency and gas exchange is essential in patients with co-morbid respiratory conditions such as chronic hypoxia from intrinsic lung disease, obesity, or OSA. We highly recommend avoiding general anesthesia (GA) in patients with significant PAH when adequate alternative anesthetic methods exist due to the hemodynamic risks related to mechanical ventilation and anesthetic agents. However, this must be balanced with the potential risk of hypoxemia and/or hypercarbia or oxygen supply/demand issues related to conscious sedation or insufficient pain control.

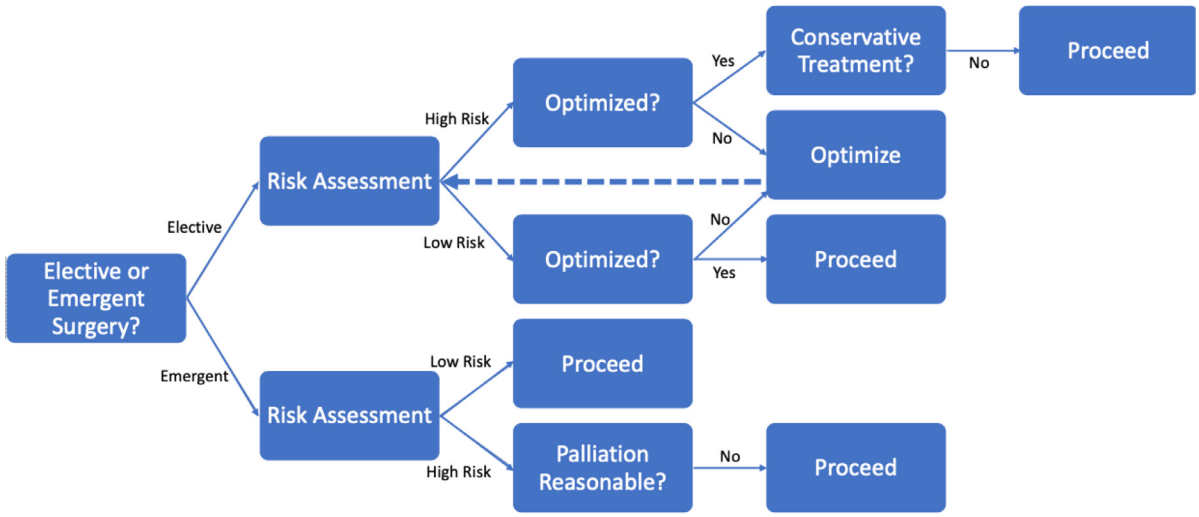

Figure 6 Schematic for preoperative assessment.

General anesthesia

The period of induction is high risk for hemodynamic compromise and collapse. There are many different approaches to achieve a stable induction, and the safest path is for the anesthesiologist to use medications and techniques they are comfortable with. Vasopressors should be readily available, and it may be wise to start infusion at the time of induction to prevent systemic hypotension rather than chase it.

The effects of common general anesthetic agents on the systemic and pulmonary vasculature as well as inotropy have been reviewed.[21-23] Most agents cause some degree of systemic hypotension and variable effects on the pulmonary arterial system and inotropy. For example, propofol has been shown to cause both vasoconstriction[24] and vasodilation of pulmonary arteries.[25] It also has myocardial depressant effects and predictably decreases systemic vascular resistance (SVR),[26] mean arterial pressure and venous return to the right heart.[27] This makes propofol a less than ideal isolated agent to use in the setting of PH, especially without concomitant vasopressor/inotrope support. The use of ketamine has been controversial, as early studies demonstrated increases in PAP, PVR[28,29] and myocardial oxygen consumption. Subsequent studies in patients with PH have shown negligible increases in pulmonary indices and maintenance of SVR superior to other drugs.[30-34] Etomidate causes minimal systemic hemodynamic changes[35] and has been shown to relax the pulmonary arteries,[25] making it an ideal agent for this patient population. Therefore, etomidate is generally considered a preferred agent for induction whereas the use of propofol is discouraged in most patients with significant PH and RV dysfunction.

Volatile (inhaled) anesthetics have little direct effect on the pulmonary arteries at clinically relevant concentrations[36] but can adversely affect RV contractility.[37,38] Nitrous oxide (N_2O) in patients with PH continues to be discouraged due to older data demonstrating an increase in PVR, pulmonary artery pressure (PAP) and decreased CI with N_2O administration in secondary PH.[39]

Modern neuromuscular blockers and opioids are mostly hemodynamically neutral agents in this group of patients,[40,41] although mild systemic hypotension can occur. Opioids have been shown to vasodilate pulmonary arteries in animal studies.[42] In the awake patient, they can cause respiratory depression, resulting in hypoxia and hypercarbia and potentially increasing PVR.

Regional anesthesia

The primary advantage of regional anesthesia in the PH population is the ability to avoid the negative effects of positive pressure ventilation on the right ventricle and the obligate use of systemic agents which affect hemodynamic parameters.

The concern with spinal anesthesia is the speed of onset and inability to control the extent of sympathetic blockade, which can result in precipitous vasodilation and hypotension. If neuraxial anesthesia is to be employed, either a slowly titrated epidural or spinal catheter or CSE (Combined Spinal opioid with Epidural local anesthetic) is recommended.

Some patients with PH are anticoagulated either for pulmonary (idiopathic PAH, CTEPH) or extra-pulmonary reasons (atrial fibrillation, systemic venous thrombosis, mechanical cardiac valves); these patients have greater risk of epidural hematoma with epidural anesthesia; therefore, oral anticoagulation should be held or reversed and the risks and benefits of bridging anticoagulation considered.[43,44]

Local anesthetic toxicity (LAST) is particularly devastating in this population, as symptoms include treatment-resistant myocardial depression, bradycardia, and hemodynamic collapse.[45]

Monitored anesthesia care (MAC)

MAC is increasingly becoming the preferred strategy in PH patients. It utilizes a combination of local anesthesia with conscious sedation (benzodiazepines and opioids) in a monitored setting.

Mechanical ventilation management

Transition from spontaneous respiration to mechanical ventilation is a critical event in the PH patient. Active airway management is required to avoid a prolonged period of hypoventilation and resultant hypoxia and hypercarbia, particularly in patients who are spontaneously hyperventilating in order to maintain alveolar oxygenation and respiratory compensation for any metabolic acidosis.

Mechanical ventilation mediates hemodynamic effects via changes in intrathoracic and transpulmonary pressures.[46] Positive airway pressure ventilation increases pleural pressure and decreases right and left ventricular preload.[47] Additionally, there is a U-shaped relationship between lung volume and PVR, which is minimal at the functional residual capacity and increases at high or low lung volumes.[48] PVR increases at high lung volumes due to compression of intraalveolar vessels. Large tidal volumes and high positive end-expiratory pressure (PEEP $\geq$ 10-15 mm Hg) may result in compression of the intraalveolar capillaries in well ventilated areas causing a marked increase in PVR and also an increase in dead space by diverting blood flow to less well-ventilated areas of the lung. PVR may also increase at low lung volumes or with the development of atelectasis, due to increased large vessel resistance through HPV and hypercarbia. Unfortunately, the optimum ventilation strategy requires ongoing recalibration in the OR and postoperatively, to find one that both avoids atelectasis and minimizes alveolar pressure.

There have been no prospective studies on the influence of different intraoperative mechanical ventilation strategies in patients with PH. However, it is generally recommended that tidal volume and PEEP be adjusted to maintain the plateau pressure below 27 to 30 cm H_2O and driving pressure below 14 cm H_2O with typical tidal volumes of 6 ml/kg to 8 ml/kg of predicted body weight and PEEP at 5 to 10 cm H_2O.[48,49] The optimal PEEP is associated with the best PaO_2/FiO_2 ratio, lung compliance[50] – while avoiding high transpulmonary alveolar pressures. Traditional lung protective ventilation strategies can result in hypercarbia with respiratory acidosis and subsequent increase in PVR. Respiratory rate should be adjusted to achieve mild hypocarbia (target PCO_2 30-35 mm Hg) with moderate hyperventilation under continuous blood gas analysis and without allowing the pH value to fall below 7.4.[51-53] During emergence, the patient needs close monitoring for hypoventilation and alveolar de-recruitment, with a low threshold for deferring extubation. Table 5 provides perioperative ventilator management recommendations for PH patients.[48,49,51-54]

Table 5 Ventilatory Management Principles

Adequate oxygenation (Goal O2 sat > 92%)
Moderate hyperventilation (goal PaCO2 30-35 mm Hg)
Avoidance of acidosis (goal pH > 7.4)
Plateau pressure <27 cm H2O via low tidal volume (6-8 ml/kg predicated body weight) and low PEEP (<5-10 cm H2O)

Medical management

Maintenance of SVR is crucial for preserving RV and systemic perfusion, especially in patients with PAH/CTEPH. All general anesthetics, including neuraxial techniques, lower SVR and therefore vasopressors are almost universally required to maintain hemodynamic stability in PH patients. Norepinephrine is a preferred agent to maintain SVR and support RV contractility. If hemodynamic monitoring suggests significantly decreased CO, inotropes are likely required. Clear clinical data does not exist to provide evidence-based recommendations on vasopressor or inotrope choice.[55] Inodilators (i.e., milrinone or levosimendan) benefit cardiac output at the expense of decreased SVR, and it may be difficult to compensate for additional systemic vasodilation under GA. These agents are typically inappropriate for use in patients with PAH/CTEPH, especially intraoperatively when other agents that reduce SVR are being used. No clinical data exist to guide evidence-based recommendations on the use of specific *inhaled* agents in the intraoperative period. They are most useful for patients who are hemodynamically decompensated or in the face of acute intraoperative RV decompensation unresponsive to vasopressors or inotropes.

An important tenet of intraoperative management for patients with PAH is to maintain their PAH medication regimen throughout the perioperative period. Patients should take their oral and inhaled medications immediately prior to surgery, and medications should be re-dosed throughout the perioperative period whenever possible. Subcutaneous and intravenous prostanoid infusions should be maintained at baseline levels, ensuring sufficient drug volume to last the duration of surgery, and backup cartridges for the patient's home infusion pump should be immediately available. Depending on the institution, subcutaneous treprostinil infusions may be switched to IV administration unless the procedure is relatively short. Importantly, trained personnel who can manage the patient's infusion pump should be available in case of pump malfunction. The PH team (nurse and MD) should be available to trouble shoot and assist in managing pump issues. For patients on epoprostenol, personnel trained on the infusing pump and a back-up pump should be present for the duration of the surgery, or else switching to an infusion pump that is more familiar to the operative and postoperative team should be considered, since interruptions in infusion may be poorly tolerated owing to its very short elimination half-life.

Hemodynamic monitoring and use of TEE

The development of acute RVF is a clinical challenge that can become catastrophic intraoperatively without adequate monitoring for its early identification and management.

Hemodynamic monitoring

The use of continuous EKG and pulse oximetry are standard of care. End tidal CO_2 monitoring is also required for

Table 6 Monitoring Considerations Based on Anesthesia Type and Perioperative Risk

	GA + low risk fluid shifts + short surgery	GA + high risk fluid shifts + mild-mod PH	GA + high risk fluid shifts + mod-severe PH	Neuraxial anesthesia + low risk fluid shifts	Neuraxial anesthesia + high risk fluid shifts or advanced PH/RVF	MAC anesthesia	Local/regional anesthesia
Arterial Line	X	X	X	X	X		
CVC	?	X			?		
PAC			X				
TEE		?	X				
SpO2	X	X	X	X	X	X	X
BP cuff	X	X	X	X	X	X	X
EKG	X	X	X	X	X	X	X

patients under GA. Invasive monitoring (e.g., arterial line, CVC, PA line) is used depending on the anesthetic technique, baseline condition of the patient, the magnitude of the proposed procedure, and anticipated physiological perturbations (Table 6). This permits rapid assessment of the effects of pharmacologic interventions, fluid shifts, and other conditions on systemic blood pressure, RV function, pulmonary artery pressure, cardiac output and global oxygen delivery. Monitoring RV function hemodynamically can be challenging, and consideration should be given to the potential risks of invasive monitoring and balanced against the validity, reliability and usability of the information derived.

Arterial line. In patients with significant PH or right heart dysfunction undergoing GA or neuraxial anesthesia, an arterial line for continuous systemic arterial blood pressure monitoring is warranted. Arterial lines are not usually necessary for procedures using MAC or local anesthesia. Arterial access also permits serial blood sampling for assessment of arterial blood gases and for metabolic monitoring, particularly of acid-base status, and lactate. End-tidal CO_2 (ETCO2) analysis is useful as a trend, and can also be used as an indirect indicator of pulmonary blood flow and CO (e.g., a drop in ETCO2 may indicate worsening CO). However, it is not an accurate for reflection of $PaCO_2$ in patients with increased dead space ventilation. ABG sampling can therefore be beneficial for assuring adequate ventilation and central venous saturations for evaluating adequacy of global cardiac function / oxygen delivery.

Central venous catheter. Central venous catheter (CVC) access provides a secure route for administration of the vasopressors and inotropes that are frequently required. It also allows for venous blood sampling to assess oxygen saturation as an index of cardiac output adequacy and CVP monitoring. When an introducer catheter (Cordis®) is used for monitoring, a PAC can subsequently be added intraoperatively if needed. Although the CVP itself may not be a reliable measure of RV preload in PAH patients perioperatively, it can be useful as an indicator of the coupling between RV function and venous return. The sudden increase in CVP should trigger an urgent assessment of the cause, as it may signal impending RV decompensation. For most intermediate risk surgical cases, the combination of a CVC and arterial line can provide adequate intra- and post-operative monitoring capabilities.

Pulmonary artery catheter. Whereas a PAC are generally not indicated for low to intermediate risk procedures, it can be helpful in guiding intraoperative fluid administration, vasoactive therapies or assist in cases where significant blood loss or changes in RV afterload are anticipated and adequate systemic perfusion needs to be monitored. PA catheters are widely used in cardiac and solid organ transplant surgeries, however results of clinical trials studying its utility in the perioperative period during non-cardiac surgery have been conflicting. Still, Anesthesiology Society guidelines have recommended PAC use in selected patients undergoing procedures associated with significant hemodynamic changes or patients with preexisting risk factors for hemodynamic disturbances, such as advanced cardiopulmonary disease.[56]

Maintenance of euvolemia during the intraoperative period can be particularly challenging with significant intravascular volume fluxes, and the PAC affords the capacity to monitor CVP along with mixed venous saturation for real-time assessment of oxygen extraction and global cardiac performance and their trends. Variables may be directly monitored or intermittently calculated and derived. Specialized catheters that allow continuous cardiac output, mixed venous oximetry, and right sided-ejection fraction may not be available in all centers.[6] When utilized intraoperatively in patients with PH, PAC may be employed as an alternative to, or in conjunction with transesophageal echocardiography (TEE). Interpretation relies on consideration of combined metrics and their trends rather than in isolation at specific time points beyond the baseline.

Transesophageal echocardiography. Intraoperative TEE affords constant and reproducible assessment of right and left ventricular performance as well as estimation of pulmonary artery pressures. However, the well-defined parameters described for transthoracic echocardiographic assessment lack validation in TEE for the intraoperative setting[57]; and challenges include the complex geometry and anterior location of the RV with respect to the probe and

the need to incorporate additional RV specific views to provide a comprehensive assessment.

Assessment of RV geometry provides insight into the nature and chronicity of the underlying pathology, as well as assisting with planning of intraoperative therapeutic intervention, particularly the identification of the volume vs pressure loaded ventricle where different therapeutic strategies may be warranted. Echocardiography offers the advantage of near simultaneous assessment of ventricular function, ventricular interactions, and indirect measures estimates of stroke volume. A comprehensive assessment following insertion of the TEE is paramount to provide a baseline against which regular and repeated evaluations may be compared.

Key Points

1. GA should be avoided in patients with PAH when adequate alternative anesthetic options are available, due to the hemodynamic risks related to induction, intubation, mechanical ventilation and anesthetic agents. Local/regional or Monitored Anaesthetic Care is preferred, as long as adequate analgesia can be provided.
2. Etomidate has a more favorable profile for induction of anesthesia in patients with PH and should be considered first line, however the use of propofol in patients with PH and RV dysfunction is not recommended due to its known hazards.
3. Vasopressors should be readily available at the time of induction for GA, and consideration should be given to starting infusion at the time of induction to *prevent* systemic hypotension.
4. If neuraxial anesthesia is to be employed, either a slowly titrated epidural or spinal catheter or CSE is recommended.
5. Arterial line monitoring is recommended for all patients receiving general and neuraxial anesthesia.
6. A combination of arterial and central venous catheter monitoring is recommended for most intermediate risk surgeries.
7. Perioperative monitoring with a PA catheter is recommended for selected patients undergoing procedures associated with anticipated significant hemodynamic changes or patients with advanced PH/RV dysfunction undergoing intermediate-to-high risk procedures.
8. Supplemental oxygen should be used for all procedures at a level to ensure maintenance of adequate alveolar and systemic oxygenation and acid-base balance.
9. If significant postoperative pain is anticipated, consideration should be given to preparation for postoperative regional analgesia with a paravertebral block or insertion of an epidural catheter for postoperative analgesia administration to mitigate the deleterious effects of oral/IV opioid use.
10. Inhaled pulmonary vasodilators (nitric oxide, epoprostenol, iloprost) are of uncertain benefit for many PH patients. Caution should be applied to their use in patients with decompensated LV failure and PH.
11. During mechanical ventilation, tidal volume and PEEP should be adjusted to maintain the plateau pressure below 27 to 30 cm H2O and driving pressure below 14 cm H2O with typical tidal volumes of 6 ml/kg to 8 ml/kg of predicted body weight and PEEP at 5 to 10 cm H2O.

Gaps in Knowledge

Additional clinical studies are needed to determine the best anesthetic, inopressor, and inhaled pulmonary vasodilator therapies for use in patients with PH/RV dysfunction during the perioperative period.

Postoperative considerations in patients with PH

Most perioperative complications and death in patients with PH occur during the postoperative setting within the first 48 to 72 hours. Postoperative clinical deterioration is often due to fluid shifts, respiratory failure and pulmonary vasoconstriction, systemic hypotension, arrhythmias, bleeding, infection/sepsis, and thromboembolism that can precipitate ADRVF and subsequently multisystem organ failure and death. Frequent serial evaluations should be performed in order to promptly identify and treat these triggers.

Basic measures in the postoperative period to prevent RVF include optimal pain control and respiratory management, maintaining adequate systemic perfusion pressure to preserve coronary perfusion, early identification and treatment of postoperative complications (e.g., infection/sepsis, bleeding, arrhythmia, PE), avoiding excessive fluid administration that can overload the RV, and the selective use of pulmonary vasodilator therapies to minimize RV afterload when needed and appropriate for the type of PH (Figure 7).

Postoperative monitoring

The immediate postoperative monitoring modalities, such as an arterial line, CVP or PAC, are determined by preoperative planning and placed intraoperatively. Patients at intermediate to high perioperative risk warrant being monitored initially in the ICU for at least 24 to 48 hours or more with providers experienced in managing PH, however for low-risk surgeries in patients with stable disease several hours of monitoring in the post-anesthesia care unit may be sufficient. Patients on infused parenteral therapy should be monitored in a location staffed by providers and nurses experienced in the management of these complex medications, regardless of surgical risk.

Invasive hemodynamic monitoring in patients suffering from PH and/or RVF postoperatively ensures early detection of hemodynamic instability; important since any delay in the management of RVF can worsen its outcome,[58] and the rapid assessment of treatment effects. PAC monitoring has been criticized for its risk of complications and the absence of demonstrable improvement on outcomes.[59] The lack of a demonstrable benefit of PAC in the ICU setting is explained by experts who emphasize that outside of the cath lab and OR, unless reliable data is being obtained from the PAC (i.e., proper transducer leveling and zeroing regularly ensured) and other clinical parameters are being followed, medication titration can lead to worse outcomes if the data is erroneous. Indeed, PAC usage in experienced hands to monitor complex patients is still

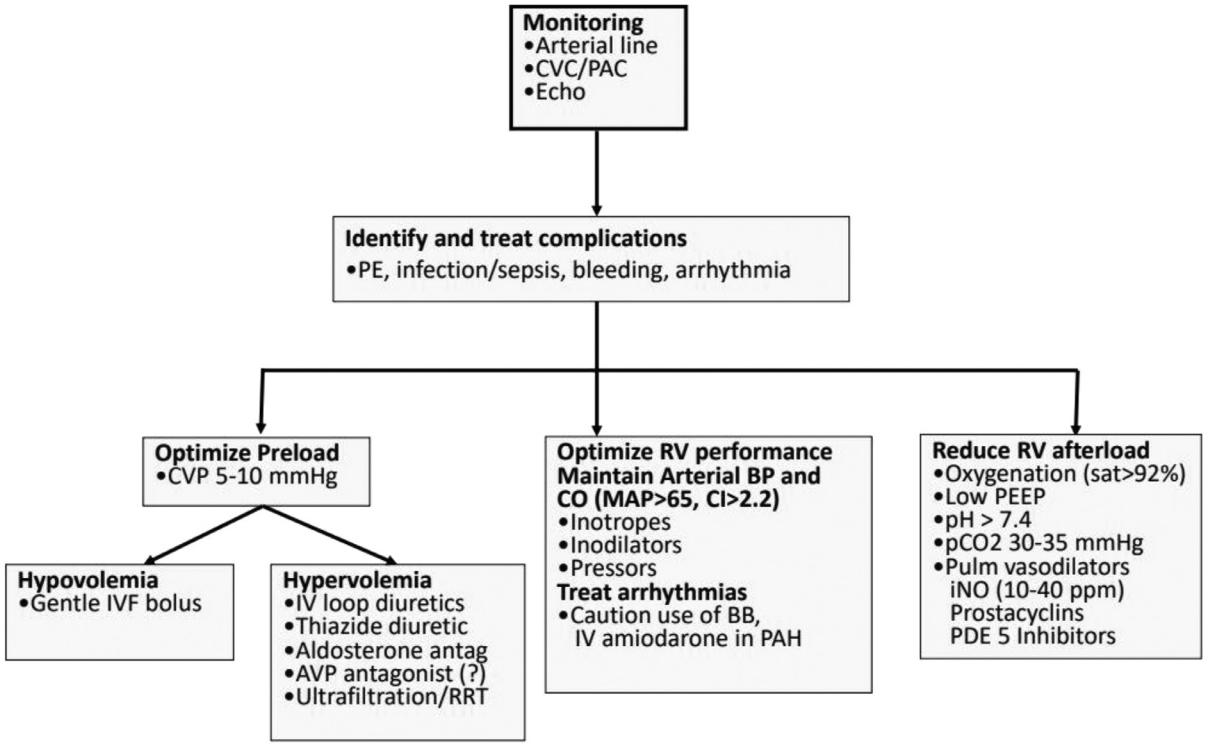

Figure 7 Peri-Operative Management Algorithm. Abbreviations: CVC, central venous catheter; PAC, pulmonary artery catheter; PE, pulmonary embolism; CVP, central venous pressure; IVF, intravenous fluid; AVP, arginine vasopressin; RRT, renal replacement therapy; RV, right ventricular; BP, blood pressure; CO, cardiac output; MAP, mean arterial blood pressure; CI, cardiac index; BB, beta blockers; PEEP, positive end-expiratory pressure; iNO, inhaled nitric oxide; PDE 5 Inhibitors, phosphodiesterase type 5 inhibitors.

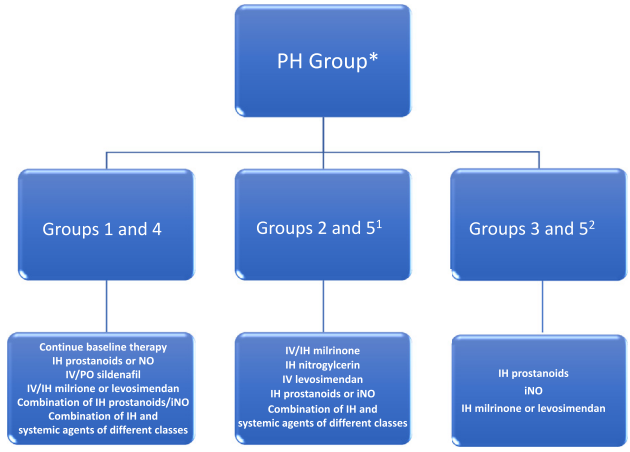

Figure 8 Summary of potential roles of vasodilator therapies for postoperative Ph based on Ph group * Note that off-label pulmonary vasodilator therapies mentioned have not been systematically studied for safety and efficacy beyond Group 1 PAH and should be used with caution, including monitoring for worsening hypoxemia, pulmonary edema, and systemic hypotension 1 If behaves like Group 2 PH 2 If behaves like Group 3 PH.

advocated by experts in the field, especially in the context of PH and decompensated RVF.[60] A potential alternative to continuous PA line monitoring is to obtain reliable RHC data when needed, make therapeutic adjustments, follow clinical parameters, and repeat RHC again if necessary, but this is not feasible or necessary in most situations. The duration of postoperative invasive monitoring should be adapted to each patient, considering the risks associated with an unnecessary prolongation of invasive monitoring (mainly infection and reduction of the early mobilization) balanced against the risk of hemodynamic instability with premature withdrawal during a sensitive period.

Critical care echocardiography is also a useful tool for postoperative monitoring of biventricular function, ventricular interactions, estimated RV systolic pressure and CVP, velocity time integral in the outflow tracts as a surrogate for stroke volume, and to exclude intracardiac shunting or pericardial effusion when suspected.

PAC and critical care echocardiography are considered adjunctive monitoring modalities, and their respective advantages are compared in Table 7.

Table 7 Pulmonary Artery Catheter and Critical Care Echocardiography Postoperative Monitoring Comparisons

Pulmonary artery catheter	Critical care echocardiography
Global hemodynamic monitoring	
Continuous CO monitoring without calibration.	Insights into RVF mechanisms, including ventricular interdependence and tricuspid regurgitation severity.
Continuous feedback on CO adequacy with the SVO_2 monitoring (including lactate and V-A PCO_2 gradient measurements to assess microcirculation).	Early detection of RV dilation and dysfunction (before a pathognomonic RAP elevation); screening for postoperative tamponade exclusion.
Fluid management	
Live monitoring of a volume expansion safety by tracking any abrupt rise in RAP.	Detection of a potential CO transient increase induced by fluid responsiveness maneuvers (ex: PLR or EEOT).
Left heart disease	
Detection and monitoring of pre- and post-capillary components to PH, with PCWP and PVR (or DPG) indices.	Insights into LVF mechanisms, including contractility reduction, valvular disease or dynamic obstruction.
Specific insights	
Continuous estimation of the driving pressure for RV myocardium perfusion.	Live guidance for the invasive mechanical ventilation settings (cardiopulmonary interactions).
Practical considerations	
Basic hemodynamic monitoring (CO, SVO_2, RAP) is continuously available and also interpretable without particular expertise (even for ICU nurses).	Versatile and completely non-invasive tool (but requiring a dedicated training and some level of expertise).

CO, cardiac output; *DPG, diastolic pulmonary pressure gradient;* EEOT, *end-expiratory occlusion test; ICU, intensive care unit; LVF, left ventricular failure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension;* PLR, passive leg raising; *PVR, pulmonary vascular resistance;* RAP, right atrial pressure; RV, right ventricle; RVF, right ventricular failure; SVO2, mixed venous oxygen saturation; V-A PCO2, veno-arterial gradient in CO2 partial pressure.

General postoperative medical management

Pain control

In the postoperative setting, adequate analgesia is important to prevent sympathetic activation and increased oxygen demand and PVR. Treatment of postoperative pain typically involves opioids. However higher doses can lead to decreased respiratory drive in response to hypercarbia and episodes of hypoxemia related to hypoventilation. In order to avoid exacerbating PH, non-opioid pain control methods such as regional blocks or epidural anesthesia, injection of local anesthetics, acetaminophen or ketorolac can reduce the need for opioid analgesics.

Respiratory management

Respiratory failure is a common complication of surgery in patients with PH and one of the most frequent contributing causes of morbidity and mortality.[11] Approximately 3 quarters of respiratory complications occur within the first 24 hours postoperatively.[8,61] In addition, patients with PH are at increased risk for prolonged mechanical ventilation. As discussed previously, HPV and respiratory acidosis must be avoided. Supplemental oxygen, an effective pulmonary vasodilator, should be used to maintain oxygen saturation greater than 92% to reduce PVR and increase cardiac output.[54] All attempts to avoid intubation in the ICU for respiratory failure among patients with WHO Group 1 PAH should be made, including the liberal use of high-flow nasal cannula oxygen, non-invasive positive pressure ventilation, inhaled pulmonary vasodilators to improve V/Q matching, early mobilization to reduce atelectasis, and in select dire cases, potentially veno-arterial ECMO (if the patient is a transplant candidate or if treatment to recovery is anticipated).

Volume management

Postoperative fluid shifts can lead to significant changes in intravascular volume. In assessing cardiac function, it is important to consider RV preload. The hypertrophied right ventricle in PH may have impaired diastolic function and therefore be more susceptible to a reduction in preload and tachycardia than a normal RV. On the other hand, in a volume and pressure overloaded RV, additional preload may further impair RV stroke volume via Starling forces increased RV wall tension, and left ventricle (LV) filling and CO can decrease due to ventricular interdependence. Indeed, optimization of volume status after surgery is a key issue to monitor and address postoperatively.

The optimal CVP range to maintain adequate but not excessive preload las not been determined, at least partially because the CVP does not necessarily correlate with preload. However, for most spontaneously breathing patients, a CVP goal between 5 and 12 mm Hg is reasonable. In a hypotensive PH patient with evidence of reduced tissue

perfusion, the effectiveness of small fluid bolus (es) of intravenous fluid can be considered as long as there is a positive response. Conversely, if the CVP is > 15 mm Hg or there is no increase in MAP with leg raising maneuver or a small fluid bolus, support of the systemic BP and RV with inopressor (s), consideration of inhaled pulmonary vasodilator therapies where appropriate (based on clinical PH phenotype), and consideration of diuretics may be more effective. Gentle diuresis should be considered in patients with a CVP higher than 15 mm Hg (especially with evidence of systemic venous congestion), in order to minimize the effect of LV preload via ventricular interdependence.

Anticoagulation

Anticoagulants should be held or reversed (if possible) prior to surgery. All patients should receive guideline based DVT prophylaxis in the perioperative period. Patients with WHO Group 1 PAH on oral anticoagulants do not require heparin bridging in the perioperative period. Anticoagulants for CTEPH (WHO Group 4 PH) and other chronic conditions (e.g., atrial fibrillation, mechanical heart valves, left ventricular assist device [LVAD]) should be resumed with/without heparin bridging when safe from a surgical standpoint.

Management of acute decompensated RV failure

Inotropes and vasopressors

Many postoperative factors can lead to ADRVF and require stabilization and support with the use of vasopressors and/or inotropes.[62] Invasive hemodynamic monitoring, when its use is combined with proper technique and interpretation, can be quite helpful to guide choice of inotrope vs pressor and their combination in postoperative patients with PH and RV dysfunction.

Norepinephrine has an advantage over phenylephrine as it both increases cardiac output and increases afterload to help with RV perfusion.[63] In vitro evidence suggests that vasopressin may have some selectivity in increasing SVR without increasing PVR.[64,65] For patients with PH and RVF, we recommend first line treatment of hypotension with norepinephrine or vasopressin.[48,66]

Dobutamine is generally recommended as the inotrope of choice in the setting of PAH and right heart failure although there are no randomized clinical trials to provide guidance in the perioperative setting.[20] Epinephrine is typically reserved for patients with severe RV dysfunction and refractory hypotension.[48] Inotrope-induced arrhythmias are poorly tolerated in these patients, and chemical cardioversion with amiodarone or electrical cardioversion may be required. Inodilators (i.e., milrinone or levosimendan) benefit cardiac output at the expense of decreased SVR, and they often require the addition of a pressor to maintain systemic pressure, especially in the postoperative state in patients receiving sedation and pain medication. They should be used with caution in patients with WHO Group 1 PAH. Tables 8 and 9 describe characteristics of the various inotropes and pressors used to treat patients with PH and RVF.

Pulmonary vasodilators

Postoperatively there may be a need to initiate a pulmonary vasodilator for worsening PH and RV dysfunction. In this setting, short-acting vasodilators are usually the easiest to titrate. Selective pulmonary vasodilator therapies and their potential role in postoperative care of PH patients are summarized in Table 10.

Table 8 Inotropic Drugs Used for Postoperative RV Failure in PH

Drug	Pharmacological properties	Beneficial hemodynamic effects	Side effects	Recommended doses	Clinical experience
Dobutamine	β1-adrenergic agonist	- increase in CO - decrease in PVR - improved V-A coupling	- decrease in SVR - tachycardia/ arrhythmia (dose dependent)	2-10 μg/kg/min	Large clinical experience in acute PH decompensation
Levosimendan*	calcium-sensitizing agent	- increase in CO - decrease in PVR - improved V-A coupling	- decrease in SVR - tachycardia/ arrhythmia (++)	0.05-0.2 μg/kg/min without bolus	- mainly studied in postcapillary PH after cardiac surgery or transplantation
Milrinone	selective PDE-3 inhibitor	- increase in CO - decrease in PVR - improved V-A coupling	- decrease in SVR - tachycardia/arrhythmia (+++)	0.25-0.75 μg/kg/min infusion	- limited data, use with caution in PAH
Dopamine	α- and β- agonist effects at higher doses	- increase in CO - increase in SVR	- tachycardia/ arrhythmia	2-10 μg/kg/min	Increase in renal blood flow Few clinical data in PH

CO, cardiac output; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; V-A, ventriculo-arterial.

*Not approved for use in North America, UK, or Australia.

Table 9 Vasopressor Drugs Used for Postoperative RV Failure in PH

Drug	Pharmacological properties	Beneficial hemodynamic effects	Side effects	Recommended doses	Clinical experience
Norepinephrine	β1 and α-adrenergic agonist	- increase in SVR - increase in CO	- tachycardia/ arrhythmia increase in PVR at high dose	0.05-0.1 μg/kg/min	First line vasopressor agent with RV dysfunction
Vasopressin	AVP agonist	- increase in SVR - decrease in PVR/SVR ratio	- tachycardia/ arrhythmia	0.01-0.04 U/min	Preferred vasopressor over phenylephrine
Phenylephrine	α-adrenergic agonist	- increase in SVR and MAP	- increase in PVR, may reduce CO	0.5-6 μg/kg/min	Often reserved for sepsis/SIRS

CO, cardiac output; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; V-A, ventriculo-arterial; AVP, Arginine Vasopressin.

Table 10 Vasodilator Therapies with a Potential Role in Postoperative PH

Group	Medication	Route	Dose
Nitric oxide	Nitric oxide	IH	5-20 ppm
Prostacyclin	Epoprostenol	IH	10 mcg/ml
		IV	1-10 ng/kg/min
Prostacyclin Analog	Iloprost, Treprostinil	IH/IV	9-25 μg by ultrasonic neb
		SQ/IV/IH	1-20 ng/kg/min
PDE-5 inhibitor	Sildenafil	PO	20-80 mg every 8 hours[a]
		IV	2.5/10 mg every 8 hours
PDE-3 inhibitor	Milrinone	IV	50 μg/kgBW bolus, followed by 0.5-0.75 μg/kgBW/min
		IH	Continuous 1 mg/ml nebulizer
Vasodilator	Nitroglycerin	IV	2-10 μg/kgBW/min
		IH	20 mcg/kg
	Nitroprusside	IV	0.2-0.3 μg/kgBW/min

[a]Although higher doses are sometimes used clinically, sildenafil is approved for the 20 mg dose only.

Inhaled pulmonary vasodilators (iNO, epoprostenol, iloprost, milrinone, levosemendan), intravenous prostanoids (epoprostenol and treprostinil), and oral PDE 5 inhibitors (e.g., sildenafil) can be used in patients with severe PAH and acute decompensated right heart failure. Inhaled vasodilators are particularly attractive in the postoperative setting because they are shorter acting and have the advantage of preferential vasodilation of the pulmonary circulation leading to improved V/Q matching with minimal or no effect on systemic blood pressure. However many patients with Group I and 4 PAH may not respond to these agents acutely. Furthermore the role of these agents in Group 3 PH disease is uncertain but may be considered when there is little recourse. The use of these agents in Group II PH is also uncertain and should be balanced against effective strategies to optimize LV function and recognize the potential inherent risks of pulmonary vasodilators in this group of patients where their use may cause pulmonary edema in the setting of elevated left ventricular end-diastolic pressure.

Most commonly used agents include nitric oxide (iNO) and inhaled prostacyclin analogs (iloprost and epoprostenol). Inhaled NO (iNO) works rapidly through activation of cGMP and thus relaxes pulmonary vasculature, resulting in a rapid decrease in PVR and mean pulmonary artery pressure (mPAP) without systemic vasodilation.[67] Those changes, along with maintenance of coronary perfusion pressure, can improve RV performance. It is deactivated immediately after binding to hemoglobin in red blood cells and therefore has no systemic effects. It can be delivered via endotracheal tube, mask, and high-flow nasal cannula in the doses of 10 to 40 ppm. Higher doses increase risk of methemoglobinemia. Inhaled prostanoids are generally less expensive than iNO but can be more cumbersome to administer. Inhaled nitric oxide and epoprostenol are administered continuously whereas iloprost is dosed intermittently. Rebound PH following abrupt discontinuation of both agents has been described and can be mitigated by re-initiation of the medication with a slower down-titration.[68] Sildenafil has also been used to help facilitate weaning of iNO without rebound PH.[69,70] Given that sildenafil does have some systemic effects, caution should be exercised when using in patients on vasopressors.

The initiation or addition of PAH-specific therapies peri- and postoperatively intended for long-term use should be guided by a PH specialist. Vasodilator therapies started perioperatively should also slowly be transitioned to the baseline regimen or continued based on clinical practice guidelines for PH prior to discharge.

Combined systemic and pulmonary vasodilators

Combined systemic and pulmonary vasodilators including intravenous nitroprusside, nitroglycerin and nesiritide are reserved for patients with PH in acutely decompensated HF. All 3 medications can be quite effective at reducing PAP and PVR as well as increasing CO when the LV filling pressure is high.[55] These agents typically work by decreasing SVR and increasing venous capacitance, thus reducing hydrostatic and reactive vasoconstrictive component of PH. They typically cause a significant decrease in SVR and LV filling pressure, and thus should not be used in patients with systemic hypotension or pre-capillary PH. Methemoglobinemia and/or cyanide are potential toxicities associated with the (prolonged) use of IV nitroglycerin or nitroprusside, respectively.

Inhaled nitroglycerin can be administered through continuous nebulization due to its short half-life, however, it appears to be less effective than 100% oxygen, inhaled milrinone, and iloprost.[71,72]

Combination therapy

Combination therapy approaches with agents of different classes intuitively makes sense. There have been a number of small studies and case reports combining various agents that demonstrated additive benefits. Potentially effective combinations include an inhaled medication such as iNO, iloprost or epoprostenol, and an oral sildenafil or parenteral/oral prostanoid.[73,74] Another approach is to combine 2 inhaled pulmonary vasodilators that work on different pathways to enhance pulmonary specificity without systemic side effects.[75-77]

Vasodilator choice based on clinical PH phenotype

Groups 1 and 4 PH. 2014 ACC/AHA Guidelines recommend continuation of chronic pulmonary vascular targeted therapy (i.e., phosphodiesterase type 5 inhibitors [PDE5I], soluble guanylate cyclase stimulators, endothelin receptor antagonists [ERA], and prostanoids) in patients with PAH (unless contraindicated or not tolerated) in patients with PH who are undergoing surgery.[78] Unlike other oral medications, in patients unable to take medications by mouth, sildenafil can be given either intravenously or via NG/OG tube. Bosentan is the only ERA that can be crushed and given through a NG/OG tube but there is no IV formulation. Patients on oral prostanoids such as treprostinil or selexipag unable to take medications by mouth may need to be converted to intravenous/inhaled pulmonary vasodilator. Inhaled treprostinil should be switched to another inhaled agent in a patient who cannot self-administer the medication.

Group 2 PH. As PAH specific ERA and prostanoid therapies may worsen left heart failure and pulmonary venous hypertension, the initial treatment should be directed at optimizing heart failure management. This may include the use of IV systemic vasodilators (IV nitroglycerin, nitroprusside, nesiritide). Inhaled pulmonary vasodilators may be preferred, as they may have preferential vasodilation in well-ventilated lung zones and are less likely to have effects on systemic blood pressure. At present, there is insufficient data (limited to small case series) to support the use of inhaled prostanoids, inhaled nitroglycerin, inhaled/IV milrinone/levosimendan, as well as sildenafil, in the routine perioperative care of patients with group 2 PH. If "off label" pulmonary vasodilator therapy is utilized in Group 2 PH (e.g., PH is severe and/or RVF is predominant), they should be used with caution, and patients' volume status should be optimized. They should be monitored for development of pulmonary edema or systemic hypotension.

Group 3 PH. Systemically administered pulmonary vasodilators can worse hypoxemia via V/Q mismatching and are not recommended. Based on the small series, inhaled therapies appear to be safe. The recent INCREASE trial of inhaled treprostinil for PH related to ILD demonstrated that it is effective at increasing 6 minute walk distance, decreasing NT-pro BNP levels and improving time to clinical worsening compared to placebo.[79] Under current regulations, inhaled treprostinil via an iNEB device can only be started in the outpatient setting. A combination of inhaled prostanoids with IV milrinone, IV levosimendan or PO/IV sildenafil can be considered in the presence of significantly reduced CI, particularly with severe PH and RV dysfunction, with careful attention to systemic blood pressure and oxygen saturation.

Group 5 PH. PH in patients with Group 5 PH should be dictated by their underlying pathophysiology and volume status. For example, patients with sarcoidosis without left ventricular dysfunction and predominantly parenchymal lung disease would be approached as Group 3 PH patients. On the contrary, patients with end-stage renal disease and fluid overload should be treated as Group 2 PH patients. As noted previously, cautious consideration of off-label pulmonary vasodilator therapies should be reserved for patients with more severe PH and RV dysfunction, and when they are used, patients should be closely monitored for the development of pulmonary edema, hypoxemia, and/or hypotension.

Management of complications

The incidence of different postoperative complications among patients with PH is poorly known. Postoperative complications such as atrial tachyarrhythmias, infection/sepsis, bleeding, and thromboembolic events can precipitate hemodynamic instability and increase the risk of RVF and death and should be promptly identified and treated.

Arrhythmias

Atrial tachyarrhythmias (e.g., atrial fibrillation and flutter) are associated with RVF and death in patients with PH.[80] For this reason, restoration of sinus rhythm is recommended for patients with PH and postoperative atrial arrhythmias. Amiodarone is the safest pharmacotherapy to restore sinus rhythm (with or without electrical cardioversion) in most cases. In patients with PAH and RV dysfunction, beta-blockers should generally be avoided, as they are poorly tolerated in these patients due to their negative inotropic effect on the RV.[81] Likewise, the calcium channel blocker verapamil should be avoided because of its negative inotropic and vasodilatory effects than can precipitate systemic hypotension. Digoxin should be considered for rate control.[80]

Infection and sepsis

Infection and sepsis are poorly tolerated in patients with poor RV reserve. Systemic hypotension from sepsis may precipitate hemodynamic collapse by decreasing coronary perfusion and promoting RV ischemia, RV-PA uncoupling, and ventricular interdependence leading to inadequate LV preload and CO. Vigilant monitoring for symptoms and signs of postoperative infection and early treatment are recommended. The risk vs benefit of invasive lines and Foley catheters should be reassessed on a daily basis and removed as soon as they are not needed.

Bleeding and anemia

Bleeding and severe anemia may be poorly tolerated and lead to hemodynamic instability in patients with PH due to a reduction in preload and increased myocardial oxygen demand. Moreover, multiple transfusions can lead to RV volume overload and acute RVF. Dosing of an IV diuretic between transfusion units may help control intravascular volume and maintain goal CVP.

Mechanical circulatory support

Despite careful preoperative planning, intra- or postoperative decompensation can still occur, typically in patients with more advanced cardiopulmonary disease. In the postoperative period, when decompensated RV failure persists despite maximal medical interventions (e.g., circulatory failure not improving despite 2 or more inopressors and/or respiratory failure at/near maximal support) mechanical support may be needed. Indications for mechanical support in patients with PAH remain a subject of debate. Mechanical support as a bridge to lung or heart/lung transplantation is the indication most supported by the literature. Other indications require a careful discussion of the risks and benefits of mechanical support between the patient, their family and the medical team. Such relative indications include patients who have a reversible cause of decompensation with reasonable chance of recovery, as may be the case in postoperative acute on chronic RV failure. Because failure to wean from mechanical support is a significant risk, mechanical support is contraindicated in patients without a reasonable chance of recovery or without the option of transplantation.

Extra-corporeal membrane oxygenation (ECMO) is currently the preferred method of mechanical support for decompensated patients with PAH who have not responded to medical therapy. Because of the failure of the right ventricle, an arteriovenous configuration is preferred to a veno-venous (V-V) configuration in the majority of patients. The arteriovenous (V-A) configuration allows an immediate "unloading" of the right ventricle. In most situations, because of the emergent requirement for cannulation, a femoral-femoral approach is utilized. However, centers have reported cases involving utilization of an upper extremity configuration in PAH patients that allows mobility during the convalescent or transplant waiting period.[82] Finally, in patients with a large patent foramen ovale or an atrial septal defect, utilization of a bi-caval dual lumen catheter in the internal jugular vein with directed oxygenated return across the interatrial defect has been described. This configuration has been reported as a way of achieving systemic mechanical support while preserving the advantages of venous cannulation.[83] Preserving mobility is of particular concern when mechanical support is being used as a bridge to transplantation. The settings of and monitoring of PAH patients while on mechanical support is similar to patients who utilized ECMO for other indications. If the V-A femoral-femoral approach is used, careful monitoring of upper body vs lower body oxygenation should be performed. Assurance of adequate brain and cardiac oxygenation should be monitored with right radial artery partial pressure of oxygen and venous troponin measurements, respectively. ECMO flows of 2.5 to 4 liter/min are appropriate for PAH patients who have been accustomed to lower cardiac outputs. This flow rate is enough to allow unloading of the right ventricle, preservation of pulmonary blood flow and adequate systemic oxygen delivery while avoiding overload of the left heart that may have secondary dysfunction in patients with severe RV failure.[62,84] A retained PAC can confirm achievement of these goals.

Pulmonary artery-left atrium oxygenators, or lung-assist devices, are also available for mechanical support of PAH patients. These pumpless devices utilize the patient's right ventricle but decrease the afterload on the right ventricle by bypassing the pulmonary circulation. An advantage of this approach is that it is an upper configuration that, again, allows ambulation of the patient. One disadvantage is that the cannulation itself is a more involved surgical procedure with a median sternotomy or thoracotomy and is therefore less practical in a patient with cardiogenic shock.[62,85]

RV assist devices have been attempted in patients with RV failure due to PAH, with disappointing results published in case reports. Complications such as increased pulmonary pressures with the increased flow, hemorrhage and pulmonary edema have been reported. Although some of the complications may be mitigated by using lower flows with the device, ECMO or extra-corporeal lung support

remain the preferred mechanical devices in patient with PAH.[86,87]

In summary, mechanical support may be utilized in the PAH patient who develops decompensated, refractory RV failure in the postoperative setting but careful consideration of overall prognosis, likelihood of recovery and candidacy for transplantation should be undertaken antecedently.

Role of palliative care in patients with PH undergoing surgery

With increased risk of intraoperative and postoperative morbidity for patients with PH, a high degree of complex care coordination and uncertainty regarding outcomes, proactively addressing concerns can be difficult. In these situations, consultation with specialty palliative care (PC) for patients with PH undergoing surgery may be a useful adjunctive approach to aggressive, life-prolonging therapy. In addition to having basic discussions regarding prognosis, goals of treatment, suffering and resuscitation preference, PC consultation is particularly important prior to major surgical interventions in patients with PH where they can be expected to have a period of incapacity during recovery. While many patients place highest priority on cure, prolonged survival, improved function and quality of life, and independence; others may prioritize comfort, achieving specific life goals, and obtaining support for caregivers as equally or more important. PC can work to assist PH specialists and patients in determining the optimal patient-centered care plan based on the patient's goals and preferences.

Additionally, if patients with PH develop life-threatening postoperative complications and fail to respond to maximal therapy, PC can help with end of life discussions including transitioning goals of care to comfort measures or hospice care.

Key Points

1. Frequent postoperative evaluations should be performed in the patient with PH and/or RVF in order to promptly identify and treat any triggers of acute decompensation.
2. Patients at intermediate-to-high perioperative risk warrant being monitored initially in the ICU for 24 to 72 hours in most cases with providers experienced in managing PH. For low risk surgeries in patients with stable disease, several hours of monitoring in the post-anesthesia care unit may be sufficient.
3. Patients on infused parenteral therapy should be monitored in a location staffed by providers and nurses experienced in the management of these complex medications, regardless of surgical risk.
4. Duration of postoperative invasive hemodynamic monitoring must be individualized balancing the risk and benefits of an indwelling catheter.
5. Fluid management must be monitored and adjusted with the goal to maintain near baseline preoperative values. A CVP of 5 to 12 mm Hg is an acceptable target for most patients.
6. Norepinephrine or vasopressin are recommended as first line agents for the treatment of systemic hypotension in patients with PH and RVF.
7. Dobutamine is the first line inotrope for treating patients with PH and acutely decompensated RVF.
8. Patients who belong to group 1 and 4 PH should continue their chronic pulmonary vascular targeted therapy during the postoperative period.
9. In WHO Groups 2, 3, and 5 PH, *systemically* administered selective pulmonary vasodilator therapies may worsen left heart failure and/or worse hypoxemia and should be avoided.
10. V-A ECMO is the preferred mode for a patient with PAH who requires mechanical circulatory support as bridge to recovery or transplantation. Consideration of overall prognosis, likelihood of recovery and candidacy for transplantation should be undertaken antecedently.
11. Experts in palliative care should be involved to promote proactive, high quality goals of care conversations for high-risk PH patients in anticipation of surgery, and for discussions regarding transitioning goals of care to comfort measures or hospice care when appropriate.

(*continued on next page*)

Gaps in Knowledge

1. Studies comparing the effectiveness of various inopressors and vasodilators in the perioperative setting of PH patients undergoing surgery are needed.
2. Future studies should clarify the relative effectiveness of different inhaled pulmonary vasodilators in the perioperative setting.
3. More research is needed into the indications/contraindications and the optimal configuration of mechanical circulatory support in PAH patients to allow recovery while avoiding complications.

Non-cardiac surgery procedures in patients with PH

Perioperative mortality rates in published studies of patients with PH undergoing elective non-cardiac surgery range between 0% and 18%.[2,8-11,88-94] Study characteristics and outcomes of studies of PH undergoing NCS are compared in Table 11.[2,8-11,89-94] An international, prospective study collected data from 114 patients with PAH undergoing non-cardiac and non-obstetric surgery.[2] Major complications and perioperative mortality were observed in 6% and 3.5%, respectively, with the highest mortality (15%) occurring in patients requiring an emergency procedure. The following risk factors predicted major complications: (1) emergency surgery, (2) RAP > 7 mm Hg, (3) 6MWD ≤ 399 meters, and (4) perioperative vasopressor use.

In addition to the general perioperative recommendations outlined earlier, certain surgical procedures present additional challenges for PH patients. This section provides an overview of the perioperative implications for patients with PH undergoing specific non-cardiac surgery procedures.

Table 11 Studies of PH in Non-Cardiac Surgery

	Ramakrishna (2005) (n = 145)	Minai (2006) (n = 21)	Lai (2007) (n = 62)	Price (2010) (n = 28)	Memtshoudis (2010) (n = 3543)	Kaw (2011) (n = 96)	Meyer (2013) (n = 114)	Kim (2014) (n = 115)	Bennett (2014) (n = 33)	Smilowitz (2019) (n = 143,846)	Deljou (2020) (n = 196)
Mortality	7%	18%	9.7%	7%	2.4% all 5% PPH	1%	3.5%	0%	3.8%	4.4% all 8.3% PAH	3%
Morbidity	42%	14%	24%	29%	—	28%	6.1%	34.7%	—	8.3% MACE	27%
Major surgery	79%	86%	58%	57%	THA/TKA	100%	100%	THA	30%	100%	
GA	100%	79%	58%	50%	—	100%	82%	1%	68%	—	
PH due to LHD included	No	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No
Study type/ limitations	RS No control Echo	RS No control Severe PAH	RS Control Echo	RS No control RHC	RS NIS Dx codes Matched	RS Control RHC	PS No control RHC	RS Control Ortho Echo	RS No control ES	RS NIS Dx codes Matched	RS No control

Dx, diagnosis; ES, Eisenmenger syndrome; MACE, major adverse cardiac events; NIS, US based national inpatient study; PPH, primary pulmonary hypertension; PS, prospective study; RS, retrospective study; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Thoracic surgery

No rigorous clinical trials specifically address perioperative care across the spectrum of PH in non-cardiac thoracic surgery. Published case reports and invited commentary suggest the greatest experience has been with patients undergoing lung biopsy or transplantation, with anatomic resections (segmentectomy, lobectomy) less common.[32,95-98] It should be noted that lung biopsy for diagnostic evaluation in patients with PH is not recommended due to the associated risk.

A unique feature of many procedures in the chest is non-ventilation of lung in the operative field.[99] In single lung ventilation (SLV), the goal is to optimize exposure by rendering lung in the operative field still and atelectatic. Minimally invasive thoracic surgical techniques involving video assistance and robotics are especially dependent upon SLV. SLV induces physiological perturbations related to increased airway pressure, impaired ventilation/perfusion matching, and re-expansion/reperfusion that can alter mechanical coupling between the RV and pulmonary circulation.[20,100,101] Overdistention or de-recruitment of the ventilated lung will augment the increased RV afterload imposed by extensive HPV in the non-ventilated lung.[100] Multiple lines of evidence demonstrate that when hypoxic or ischemic lung is re-expanded with oxygen, a marked oxidative stress response is elicited that can affect distant organs and persist postoperatively,[62] and the potential sequelae include exacerbation of PH and arrhythmias.[102] Atrial tachyarrhythmias are relatively common following thoracic surgery and may be poorly tolerated. Pulmonary arterial pressure and PVR may not return to baseline, particularly if the procedure involved vascular ligation and anatomic lung resection.[103] Finally, patients with PH requiring SLV include the spectrum of etiology including ILD with restrictive lung mechanics, and in this context the relative risks of acute changes in RV afterload during SLV and postoperative lung injury and residual function should be considered. For these reasons, the risk of thoracic surgery with SLV is very high in patients with significant PH, particularly those with parenchymal lung disease or PAH, and therefore should generally be avoided.

Laparoscopic abdominal surgery

Laparoscopy can have deleterious effects on RV hemodynamics and potentially increased risk of complications in PH patients. Insufflation of the abdomen with CO_2 can cause diaphragmatic displacement and an increase in inspiratory airway pressures, altering RV preload and afterload. Increased positive end expiratory pressure, often required to counteract increased intrathoracic pressures while mechanically ventilating patients with pneumoperitoneum, can increase PVR. In addition, mesenteric and aortic circulations may be compressed, causing increased LV afterload, increased pulmonary capillary wedge pressure and systemic hypotension[104] The carbon dioxide insufflated in the abdomen, can lead to systemic hypercarbia, which, in turn, can

increase PVR and RV afterload. Data also suggests that the increase in PA pressures during laparoscopy may not reverse immediately or completely when the pneumoperitoneum is relieved.[105-107] Delayed hypercapnia, often seen postoperatively from the carbon dioxide absorbed from subcutaneous emphysema occurring during laparoscopic procedures may also adversely influence cardiac function.

Another consideration with laparoscopic surgery is the effect of positioning. Laparoscopic surgery is often performed in head-up or head-down position to allow intraabdominal organs to fall away from the surgical field. These positions can affect RV loading conditions and cardiovascular function. Head-up position (reverse Trendelenburg) leads to venous pooling, can reduce venous return to the heart and can result in hypotension, especially in hypovolemic patients.[12,108] Head-down position (Trendelenburg) increases venous return and cardiac filling pressures.[109] CVP, mPAP, and pulmonary capillary wedge pressure (PCWP) increase 2-to-3-fold, and mean systolic blood pressure by ~1/3, without changes in CO, heart rate, or SV. Although these filling pressures usually normalize upon repositioning the changes in venous return may be poorly tolerated by patients with PH. Thus, the benefits of laparoscopic surgery (i.e., less bleeding and pain) may be outweighed by its risks, and open laparotomy should be considered in patients with PAH and RV dysfunction. Some centers advocate for open laparotomy and avoidance of laparoscopy in all patients with PAH, and in other centers, laparoscopic surgery may be planned with early conversion to open laparotomy in the occurrence of any adverse intraoperative hemodynamic changes during laparoscopy.

Orthopedic surgery

Orthopedic surgery offers the option to consider procedures under regional anesthesia. However, it also offers specific challenges, such as high risk for intraoperative cement or fat embolizing to the already compromised pulmonary circulation,[110-112] in addition to postoperative risk of pulmonary thromboembolism, which increases the risk for patients with PH. In a large case matched, retrospective study, patients with PH undergoing THA experienced an approximately 4-fold increased risk adjusted mortality (2.4% vs 0.6%), and those undergoing TKA had a 4.5-fold increased adjusted risk of mortality (0.9% vs 0.2%) compared with patients without PH in the matched sample ($p <$ 0.001 for each comparison).[91]

The risk of fat embolism may be reduced with newer surgical approaches, such as early fracture stabilization in trauma, or alternative cementation techniques.[112] however we recommend that patients with moderate to severe PH and significant RV dysfunction not undergo elective total joint replacement, with few exceptions. Patients with PH who do undergo joint replacement surgery should receive the usual prophylactic drugs (low-molecular weight heparin, direct anticoagulants).[113]

Obstetric surgery

Pregnancy is a particularly vulnerable time for patients with PH. Generally, the pulmonary vasculature is maximally dilated and recruited in patients with PH, thus the increase in CO that normally occurs in pregnancy cannot be accommodated by these normal physiologic mechanisms and right heart failure, may be precipitated or exacerbated, if already present.

Pregnancy outcomes in patients with PAH have been poor for both the mother and the fetus.[114-119] and recent literature has suggested a potentially elevated mortality among patients with other PH etiologies.[120-122] In the era of PAH-directed therapy a multinational report of 20 pregnancies reported 4 deaths.[123] However, a more recent prospective cohort of 16 patients and 25 pregnancies where an individualized, risk-based approach with shared decision making and a multiprofessional team experienced in managing PAH and pregnancy was used, reported no maternal deaths during pregnancy and no maternal or fetal deaths in all of the 13 patients and 18 offspring.[124] However, 8 pregnancies ended in abortion, 2 patients required ECMO as bridge to lung transplantation, and 6 patients showed signs of clinical worsening within 9 to 22 months after successful delivery.

There is a general consensus that pregnancy should be avoided in patients with PAH, and likely PH more broadly.[125] However, for cultural or personal reasons, patients may desire to conceive or continue a pregnancy regardless of risk to themselves or the fetus. Recognizing that there is scant literature to guide recommendations about obstetric surgery in PAH patients and even less for patients with other etiologies of PH, the following summarizes consensus recommendations from experts in the field.[125] In addition to these recommendations, there is a strong recommendation for care to occur at a center expert in care of pregnant PH patients and for involvement of a multi-disciplinary team to plan delivery including high risk obstetrics, anesthesia with experience in PH and neonatology. A risk based approach to counseling and managing patients has been proposed. Ideally this should involve maximizing medical treatments inclusive of the involvement of an interprofessional team before a woman elects to become pregnant.

Caesarean section is typically recommended as the preferred mode of delivery in the context of PH and pregnancy.[125] In general, it is felt that vaginal delivery carries more relative risks including Valsalva maneuver, which decreases venous return and may compromise CO, vasovagal syncope, sympathetic nervous stimulation, acid-base changes that may worsen PH and autotransfusion of blood after delivery of fetus that can precipitate acute RVF. Elective Caesarean section potentially allows for avoiding most of these risks, and also facilitates ready availability of the multidisciplinary team to assist in the delivery. Regional anesthesia is generally recommended to avoid risks associated with GA, which is supported by data from Bedard et al showing higher mortality with GA in delivery of the

pregnant PH patient.[126] Recent publications support epidural, spinal and combine spinal-epidural anesthesia in pregnant PH patients, suggesting that the experience of the anesthesiologist should play a key role in selection of method.[127] In a recent prospective cohort, all 13 patients successfully delivered 17 offspring via Caesarean section without any perioperative deaths, however 1 patient required ECMO support within a few hours after delivery.[124]

There are several considerations with regard to anesthesia during the delivery. Continuous monitoring of ECG, pulse oximetry, CVP and intraarterial blood pressure is recommended universally.[125] The use of PAC during delivery is not considered mandatory and CVP monitoring with echocardiography is an alternative hemodynamic monitoring route that some centers prefer. Patients should be euvolemic to optimize RV function and IV fluids administered judiciously to avoid worsening RV function. Inotropes and vasopressors may be required to support RV function and should thus be available at the bedside. Finally, in patients with significant RV dysfunction, the multidisciplinary team may consider use of ECMO or ensuring it's availability as a reserve measure.

Therapy for PAH, in particular, should be optimized predelivery to the extent possible. As prostacyclins (epoprostenol, treprostinil, iloprost), calcium channel blockers (for those patients that have demonstrable acute vasodilatory response), and PDE5Is are the only medications generally considered safe in pregnancy, the choices are limited.[125] In patients with significant RV dysfunction, prostacyclin therapy is indicated. Some institutions have used inhaled prostacyclins more frequently, while others generally prefer parenteral prostacyclins. At the time of delivery, inhaled and/or parenteral prostacyclins should be available, if not already in use.

The post-partum period is a high risk period for PAH patients, with the majority of mortality in some reports occurring in the month following delivery.[117] Monitoring in the ICU for at least 48 hours post-partum to manage fluid shifts with efforts to ensure that the patient is kept in a net negative daily fluid balance to mitigate the adverse influence of the mobilization of the extravascular fluid into the intravascular space on RV function.[125] This is especially relevant for high-risk patients. Routine obstetric care, including prophylactic anticoagulation, is also recommended.

Gynecologic non-obstetric surgery (GNOS)

There is a paucity of data regarding operative and perioperative management of patients with PH undergoing GNOS with most literature limited to case reports[128-130] and small case series.[8-12,94] A contemporary international survey of outcomes in patients with PAH undergoing non-cardiac surgery showed an overall 3.5% mortality and 6.1% morbidity rate; this study included 16% (n = 18) gynecologic procedures which had lower mortality (0%) but comparable morbidity (5.5%) rates.[12]

Many gynecologic procedures are considered low (cone biopsy) to intermediate (hysterectomy) risk. Procedures with potential for large-volume blood loss (hysterectomy of large fibroid uterus) and extensive fluid shifts (laparotomy for ovarian cancer with malignant ascites) are high-risk procedures for patients with PH.

Lithotomy is the most commonly used position in GNOS and has the effect of redistributing blood volume from the legs centrally and increasing venous return. Vaginal hysterectomy often requires exaggerated "head-down" lithotomy which has been showed to increase PAP and PCWP and decrease CO in PH.[131] Laparoscopy is frequently used in GNOS due to faster recovery and lower incidence of postoperative ileus[132] but is not without problems in patients with PH as described in the section on abdominal surgery.

Existing data support the use of regional anesthesia over GA as with other types of general surgery.[133,134] Epidural anesthesia is generally preferred to spinal anesthesia because of more gradual onset and relatively less risk of systemic hypotension as discussed in the intraoperative management section. Recent studies have highlighted the benefits of combined low-dose spinal-epidural anesthesia (better sensory block with fewer blood pressure-lowering effects) in peripartum management of PAH[134,135] and can be used in GNOS. Central hemodynamic monitoring is indicated for patients with severe PH or those undergoing high-risk procedures.

Epidural analgesia offers superior analgesia and decreased risk of hypercarbia due to opioid-related respiratory depression for pain control. Transversus abdominus plane blocks offers short term pain relief and reduces IV opioid use post hysterectomy[136]; the successful use of a transversus abdominus plane block has been described in PH.

Sterilization

Due to poor maternal and fetal outcomes with pregnancy and the teratogenic effects of endothelin-receptor antagonists, all female patients of child-bearing age should be counseled on effective contraception (sterilization or 2 methods of birth control). Hysteroscopic sterilization has been shown to be well-tolerated in a case series of 4 patients with relatively advanced PAH[98] and a case series of 18 patients with high-risk cardiac disease including secondary PH[137] Intrauterine-devices are safe and effective though care should be taken to avoid vasovagal reactions to insertion; a benefit of levonorgestrel-releasing devices is decreased menstrual blood loss[138] and a lower risk of iron deficiency anemia, especially in patients on anticoagulation.

Head and neck surgery

Head and neck surgery often requires GA, however the risk of significant fluid shifts is usually minimal and these surgeries are considered low cardiovascular risk. Moreover, reports of patients with PH due to hypoxemic and/or hypercarbic respiratory failure related to ENT conditions such as nasal polyposis and enlarged tonsils have shown an improvement in PAP after surgery. In most cases, PH patients do well with surgery, however because it requires

GA, PH treating physicians should discuss the anesthetic management principles, including avoidance of systemic hypotension and hypoxemia/hypercarbia, with the anesthesiologist prior to the procedure as well as the postoperative plan. Patients with advanced PAH and RVF are at greater risk with GA, and in these patients, the relative risk vs benefit of surgery should be carefully considered and an advanced multidisciplinary perioperative plan developed prior to surgery.

Ophthalmologic surgery

Ophthalmologic surgeries are low risk, even for patients with severe PAH. Recommendations to the surgeon for procedures should include minimization of sedation and monitoring of blood pressure and oxygenation for patients with severe PH and respiratory failure. Cataract surgery is done with local anesthesia and is very low risk such that special precautions are typically unnecessary.

Dental procedures

Dental procedures often involve anesthetic injection with epinephrine to minimize gum bleeding, which often gets into the systemic circulation and can cause an increase in heart rate, blood pressure, and risk of tachyarrhythmia. Therefore, among patients with RVF and PH, avoidance or minimization of epinephrine use is prudent. Additionally, systemic analgesia/sedation may be used for more extensive procedures. In patients with PH and respiratory failure, it recommended to minimize or avoid sedation when possible, and to monitor vital signs closely when sedation is administered. Additionally, patients with indwelling catheters for infused prostacyclin therapies should receive antibiotic prophylaxis before dental procedures. These recommendations should be given by the PH treating physician to the dentist when "clearance" is requested.

Key Points

1. The risks of laparoscopic surgery often outweigh the benefits in patients with PAH and RV dysfunction. We recommend consideration of open laparotomy for these patients, although planned laparoscopy with early conversion to open procedure may be reasonable in select cases.
2. Thoracic surgeries are high risk for PH patients. Single lung ventilation (e.g., thoracic surgical techniques involving video assistance lung biopsy, lobectomy) should be avoided in patients with moderate-to-severe pre-capillary PH, especially with significant underlying lung disease.
3. Elective orthopedic surgeries, such as elective total joint replacement, should only be undertaken when a joint decision by patient and surgeon conclude that the potential benefits outweigh the increased risk of mortality.
4. It is strongly recommended that care and delivery for a pregnant patient with PH occur at an expert center, and for involvement of a multi-disciplinary team to plan delivery including PH specialist, high risk obstetrics, anesthesia with experience in PH, and neonatology.
5. Ophthalmologic, Dental, and Maxillofacial Surgeries are generally low risk but may necessitate specific recommendations for high risk PAH patients when GA, local epinephrine injection, or oral/IV sedation are being considered.

Cardiac surgery procedures in patients with PH and/or RV failure

PH due to left heart disease (PH-LHD), e.g., WHO Group 2 PH, is the most common cause of PH and is associated with negative impact on prognosis, both in regards to morbidity and mortality.[139] LHD may be related to either aortic and/or mitral valvular disease, but is most commonly due to HF with reduced ejection fraction or preserved ejection fraction (HFpEF), and an intermediate group characterized by mid-range EF (HFmrEF).[139,140] PH-LHD results from elevated left-sided filling pressures (specifically, elevated left atrial pressure) leading to increased pulmonary venous pressure and concomitant pulmonary vascular congestion,[139,140] defined as isolated post-capillary PH. Chronic passive congestion with associated neurohormonal, cytokine, endothelin and other mediators, as well as altered gene expression leads to active pulmonary arterial vasoconstriction, pulmonary arterial and venous remodeling. This may result in combined pre- and post-capillary PH characterized by increased PVR.

The presence of PH adds significant challenge to the pre-, intra-, and postoperative management of patients undergoing cardiac surgery and interventional procedures. Despite its consistent association with worse outcomes, targeting PH directly has either yielded disappointing results or remains unexplored. However, strategies to assess the severity of PH and RV dysfunction, optimize their hemodynamic status when needed preoperatively, and vigilantly monitor for and treat PH with ADRVF postoperative may improve postoperative management and outcomes in these patients. Future studies are needed to define preoperative diagnostic, risk stratification, and optimization strategies as well as postoperative management.

PH due to left heart valve disease

Multiple studies have shown that PH is a risk factor for increased perioperative mortality in patients undergoing cardiac surgery, including one large retrospective study of patients undergoing cardiopulmonary bypass that found PH to be the only baseline variable independently predictive of perioperative mortality with an odds ratio of 2:1.[141] Moreover, while the Society of Thoracic Surgeons does not include PH in their perioperative risk model, the presence of PH is a risk variable included in the European models (EuroSCORE I and II).[142,143] PH frequently complicates left-sided valvular heart disease (VHD) and is more frequent among symptomatic patients. The prevalence of PH-VHD based on RHC is described in Figure 9,[144] where mild PH is defined as mPAP > 35 mm Hg, moderate PH is

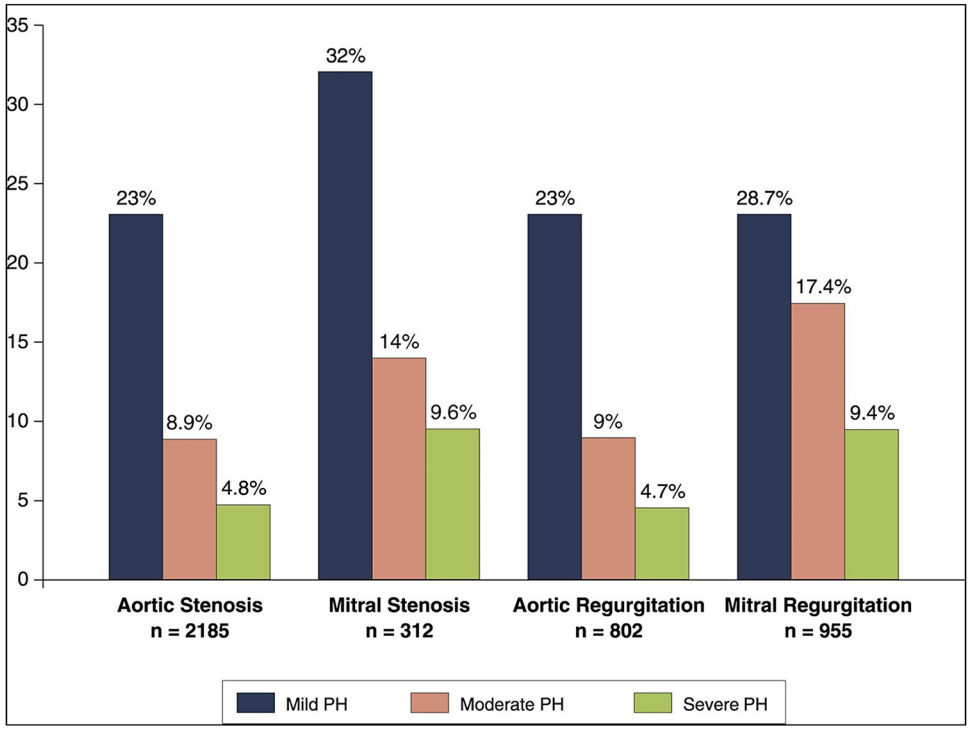

Figure 9 Prevalence and severity of PH due to left-sided valvular disease. Reprinted with permission from Magne J et al. JACC Cardiovasc Imaging. 2015 Jan;8(1):83−99

mPAP > 35 mm Hg, and severe PH is mPAP > 45 mm Hg. PH is associated with poorer outcomes among patients with VHD whether they are managed conservatively, undergo valve intervention, or if it persists following successful corrective procedures. Figure 10 outlines a suggested diagnostic approach and hemodynamic assessment pre- and post-valve intervention for patients with PH due to left-sided valvular disease.[145]

Preoperative assessment and management

When assessing the perioperative risk in patients with PH and heart disease with planned intervention, especially heart valve disease being considered for valve surgery, if a preoperative echocardiogram suggests severe PH (sPAP > 60 mm Hg) or moderate to severely elevated sPAP > 50 mm Hg with a disproportionately enlarged and dysfunctional RV, a full hemodynamic assessment by RHC is often clinically helpful to assess the severity of PH and RV dysfunction as an indicator of perioperative risk for RVF and mortality. However, pulmonary vascular hemodynamic assessment in a patient who is overtly fluid overloaded is less helpful to risk stratify, as the PA pressure and PVR are often high and can improve along with RV size/function with achievement of euvolemia via diuresis (or mechanical fluid removal), in addition to optimal guideline directed medical therapy for heart failure. A practical approach to patients with severe heart and/or heart valve disease and severe PH with RV dysfunction who are at elevated risk and marginal candidates for cardiovascular surgery are to consider optimizing the patient's fluid status to achieve euvolemia and then reassessing with RHC and/or echocardiography. In patients with persistently elevated filling pressures and PH on RHC, some centers will retain the PA line for hemodynamically guided optimization days prior to valve intervention before planned valve surgery.

Selective pulmonary vasodilators (including PDE5I) should generally not be used in patients with WHO Group 2 PH, nor should they (e.g., iNO) be used to assess pulmonary vasoreactivity due to the risk of increasing the PCWP/LV filling pressure. On the other hand, hemodynamic assessment of reversibility of PH and mitral valve operability with infusion of intravenous nitroprusside, a direct arterial vasodilator, may be useful in select cases of severe PH and elevated PCWP.[146] In the unlikely scenario that the patient has severe pre-capillary PH, a PDE5I and/or other guideline directed therapies should be considered preoperatively to improve the patient's condition.

Influence of PH with mitral and aortic valve interventions

Mitral stenosis. In patients with mitral stenosis that require surgery, 20% to 40% of patients will have moderate to severe PH (sPAP > 50-60 mm Hg by echo and/or mPAP > 35 mm Hg by RHC).[144,147] Presence of PH alone is not an absolute surgical contraindication, but the severity of PH and presence of significant RVF increase the risk. When PA pressures reach supra-systemic levels, mortality becomes exponential.[148] A recent retrospective study examined the association of PH severity with short (30 day) and long term (12-year) mortality after surgical intervention for

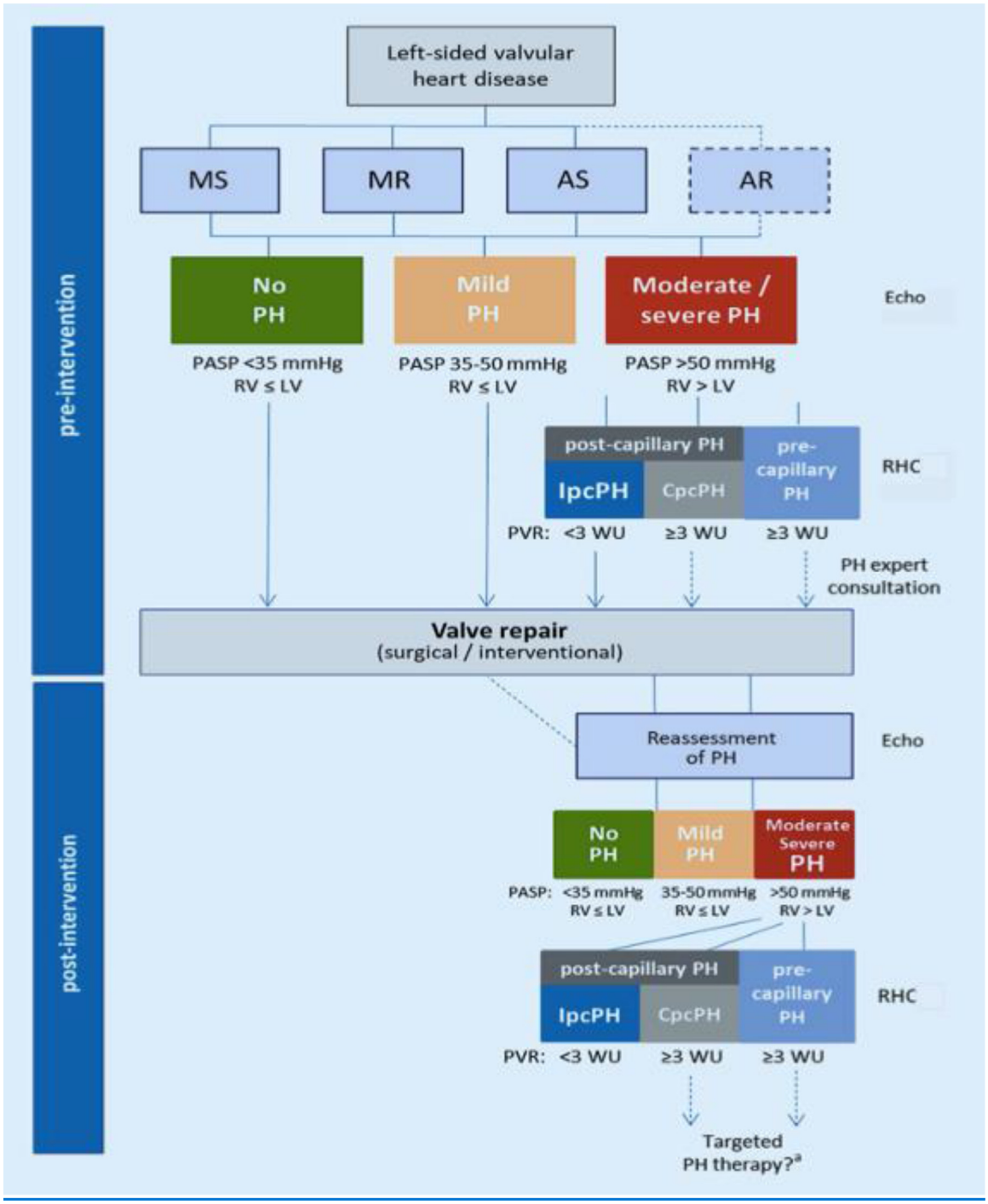

Figure 10 Diagnostic approach and hemodynamic assessment pre- and post-valve intervention for patients with PH due to left-sided valvular disease *Adapted from* Tichelbacker T, Dumitrescu D, Gerhardt F, et al. Pulmonary hypertension and valvular heart disease. Herz. 2019;44:491-501.[145] a: Targeted PH therapies are not approved to treat PH due to left heart disease including left-sided valvular heart disease. However, if pre-capillary PH or CpcPH are present after valve repair, pulmonary vascular disease may be present, representing a potential treatment target. Such patients should be evaluated is specialized centers, and clinical trials are needed.

mitral stenosis. Using data from both RHC and echo, patients were classified as none (n = 30, sPAP <35 mm Hg), mild (n = 64; sPAP 35-44 mm Hg), moderate (n = 94; sPAP 45-59 mm Hg) or severe PH (n = 128; sPAP ^{3} 60 mm Hg). The severe PH group were more likely to undergo mitral valve replacement (81%), have severe TR (31%), RVF (17%) and undergo concomitant tricuspid valve procedures (46%). At 30 days, operative mortality was 9% in the severe PH group and 1% in the mild group.[149] At 12 years, mortality of patients with moderate-severe PH was 49% compared with 21% in the none-mild group (risk adjusted HR 2.98; 95% CI, 1.55-5.75; $p = 0.001$). As one would expect, isolated post-capillary PH resolves quickly after mitral valve intervention; however, in patients with combined post- and pre-capillary PH (CpcPH), resolution of the pre-capillary component is variable and no clear-cut risk

factors for persistent PH after surgery have been identified.[150,151]

Mitral regurgitation. Mitral regurgitation (MR) is the most common cardiac valve disease. The association of PH with MR was initially described only in those with concomitant mitral stenosis, but future observations confirmed its association with isolated mitral regurgitation.[152] PH with a sPAP > 50 mm Hg is an adverse prognostic indicator, and even if asymptomatic, guidelines recommend intervention on primary mitral valve regurgitation.[153] The presence of ^{3} 3+ tricuspid regurgitation and elevated right atrial area index have been associated with increased mortality with surgery,[154] thus suggesting that preoperative hemodynamic optimization with improvement in these secondary issues may help outcomes with MV surgery for MR. It has been recommended that patients with primary mitral valve regurgitation and PH should be referred to centers experienced in repair.[155]

Transcatheter options for addressing mitral regurgitation in patients at increased risk with surgical intervention have shown promising results. The most widely used device is the MitraClip System (Abbott Vascular, Santa Clara, CA) which allows for mitral valve edge-to-edge repair.[156] Importantly, the COAPT study of functional MR excluded patients with severe PH (estimated PASP >70 mm Hg without hemodynamic reversibility in the catheterization laboratory) and those with moderate or severe RV dysfunction on echocardiogram. A recent retrospective cohort study analyzed 4,071 patients who underwent THV repair with the MitraClip system and found that the presence of PH was associated with increased mortality and readmission for heart failure.[157] The newer PASCAL transcatheter heart valve system is being studied in a pivotal trial against the MitraClip System for both degenerative and functional MR in the CLASP IID/IIF Trial without regard to the presence of PH or RVF.

Aortic stenosis. PH is highly prevalent in patients with severe aortic valve stenosis (AS) and is associated with increased mortality irrespective of surgery, functional status, or comorbidities.[158,159] The most frequent features of PH-AS are LV diastolic dysfunction w/increased LV end-diastolic pressure and concomitant MR. The degree of PH is mainly reflective of the diastolic filling pressure, LA size, and pulmonary artery compliance. There is a weak correlation to the extent of LV systolic function and PH does not correlate well to the severity of AS. Studies demonstrating that PH is independently associated with higher in-hospital mortality among patients undergoing aortic valve replacement (AVR) led the ESC to give a class IIa indication for AVR for patients with asymptomatic AS and an estimated sPAP > 60 mm Hg.[160,161] Not surprisingly, patients with more severe PH and/or CpcPH have worse survival.[159,162,163] The sPAP often improves immediately after surgical AVR (SAVR) or transcatheter AVR (TAVR), however in many patients the PH persists and is associated with higher 1-year mortality.[164,165] The sPAP can also decrease with balloon aortic valvuloplasty, but the improvement is not sustained over months.[162] Findings by the German Federal Bureau of Statistics on 107,057 patients undergoing isolated TAVR or SAVR between 2007 and 2014 revealed that the number of SAVR procedures declined by 20% in AS patients with PH.[166] In addition, patients with PH receiving SAVR treatment were at the highest operative risk and exhibited a prolonged time to post-surgery extubation. The actual in-hospital mortality was twice as high compared to PH patients receiving TAVR.[166] Overall, these findings have important implications in terms of choice of therapeutic approach and point in favor of TAVR as the elective technique for treating AS patients with severe PH, especially the elderly.

Aortic regurgitation. PH has been less studied in aortic valve regurgitation (AR), but appears to be relatively common in severe AR. A single-center retrospective study of 506 patients with severe AR demonstrated that severe PH (sPAP ≥ 60 mm Hg) was present in approximately 16% of patients and was associated with LV enlargement and dysfunction and higher grades of MR.[167] Severe PH was associated with a 3% operative mortality rate, and the sPAP dropped to near normal values in the vast majority of patients who underwent AVR. Moreover, the 1-and 5-year survival rates were much better for the patients with severe PH who underwent AVR compared to those who were managed conservatively.

Post-operative management of PH with left heart valve intervention

Systemic hypotension, rapid fluid shifts, acid-base and ventilatory fluctuations are all common conditions during cardiac surgery that can exacerbate PH and RVF, potentially leading to life threatening hemodynamic instability. Thus, many cardiac surgery centers use off-label inhaled vasodilators intraoperatively with iNO being the most commonly used agent for patients with severe PH and RV dysfunction despite the lack of randomized controlled trials (RCTs). Potential options for aerosolized vasodilators include the more selective pulmonary vasodilators iNO, iloprost, and epoprostenol, and less selective vasodilators milrinone, levosimendan, and nitroglycerin. As stated previously, isolated pulmonary vasodilators are particularly attractive to help "unload" the RV when needed, especially in situations where the systemic blood pressure runs low, as is often the case with cardiac surgery. A caveat to using inhaled pulmonary vasodilators in patients with left heart disease is the potential to raise LV filling pressure, worsen PAP and RV dysfunction especially when the upstream left atrial pressure is already high. However, cardiac surgery cases are typically performed with an invasive PAC continued postoperatively, thus permitting serial assessment of right vs left ventricular filling pressures, PAP, CO, and calculated PVR to guide decision making and monitoring of a response to a trial of inhaled pulmonary vasodilator therapy.

Studies of persistent PH after surgical or percutaneous left heart valve intervention have not demonstrated a benefit of targeted PH therapy to date. The largest, SIOVAC

study,[168] was a randomized, multi-center trial investigating the role of sildenafil (40 mg 3 times a day) in patients with persistent PH (defined as a mean PAP ^{3}30 mm Hg) at least 1 year after valvular intervention. More than 90% of patients had undergone mitral intervention, and 57% had a PVR >3 Wood units. Two hundred patients were included for analysis and the primary endpoint was the composite clinical score combining death, hospital admission for heart failure, change in functional class and patient global self-assessment at 6 months. Fewer patients in the sildenafil group improved their clinical score and a more worsened their score compared to placebo. Interestingly, patients had a short-term improvement in hemodynamics, a finding seen in other short-term studies. This improvement however did not translate to longer term improvement in outcomes and functional capacity. This data confirms the recommendation of the current guidelines against use of PAH therapies in patients with WHO group 2 PH.[169,170]

Key Points

1. Patients with severe PH and RVF associated with left heart valve disease being considered for valve intervention should be referred to expert centers.
2. Preoperative RHC should be considered for risk assessment and to guide medical optimization prior to left heart valve intervention when non-invasive imaging suggests severe PH and RV dysfunction.
3. Current data do not support the long-term use of selective pulmonary vasodilators after left heart valve intervention in patients with PH.

Gaps in Knowledge

1. Further studies need to clarify the role, if any, of selective pulmonary vasodilator therapies for treating PH before, during, or after left heart valve interventions.
2. Studies are needed to determine what threshold, if any, of PH and/or RV dysfunction severity should prohibit left heart valve surgery.
3. Whether aortic balloon valvuloplasty as a bridge to definitive therapy may be appropriate in patient with PH and/or severe RVF is unknown.

Tricuspid valve repair or replacement in the setting of PH

PH commonly occurs in patients undergoing tricuspid valve procedures and is associated with high early mortality and poor long-term outcomes after tricuspid valve repair and/or replacement.[171-176] Nearly half of the patients who undergo tricuspid valve repair during left heart procedure have residual PH, which has also been associated with increased long-term adverse events.[172] It is clear that both RV r dysfunction and PH have independent and additive prognostic impact in patients undergoing tricuspid valve procedures concomitant to mitral valve procedures.[177]

Perioperative considerations and management

Tricuspid valve repair or replacement is not recommended in patients with severe RV dysfunction or severe PH.[153,160] However, there is no clear consensus on the threshold criteria for the severity of RV dysfunction or PH that is prohibitive of tricuspid valve intervention. The sudden increase in the afterload to the right ventricle after tricuspid valve repair or replacement can lead to acute RVF and cardiogenic shock, especially in patients with coexisting PH and/or RV dysfunction. Figure 11 outlines a suggested approach to the diagnosis, hemodynamic assessment, and patient selection for surgical or interventional therapies in patients with tricuspid regurgitation.[145]

Perioperatively, patients undergoing tricuspid valve repair or replacement who have coexisting PH and/or RV function may respond favorably to iNO during the immediate postoperative period in order to reduce RV afterload. A CVP of less than 15 mm Hg should be targeted, in order to minimize ventricular interdependence and impaired LV preload. Inotropes and/or temporary mechanical support should be used as needed to support RV function. There is no data to guide the use of selective pulmonary vasodilator therapy during the perioperative period in patients undergoing tricuspid valve repair or replacement, however inhaled pulmonary vasodilators may be useful to decrease RV afterload improve LV filling in the perioperative period, at least until pressors are no longer needed.

Key Points

1. Patients requiring tricuspid valve repair/replacement should undergo a thorough evaluation to characterize RV function and pulmonary hemodynamics.
2. Tricuspid valve repair/replacement in the presence of PH and/or RV dysfunction should be referred to expert centers.
3. Routine preoperative use of pulmonary specific vasodilators in patients with PH-LHD who undergo tricuspid valve repair/replacement is not recommended.
4. Patients undergoing tricuspid valve repair/replacement in the presence of PH and/or RV dysfunction should be monitored closely in the postoperative period for RV failure and cardiogenic shock.

Gaps in Knowledge

1. No clear consensus exists on the threshold criteria for the severity of RV dysfunction and/or PH that is prohibitive of tricuspid valve repair or replacement.
2. The safety and efficacy of preoperative use of pulmonary specific vasodilators in patients with PH who undergo tricuspid valve repair/replacement is unclear.
3. The clinical benefit of early postoperative use of pulmonary specific vasodilators in patients undergoing tricuspid valve repair/replacement has not been studied systematically.

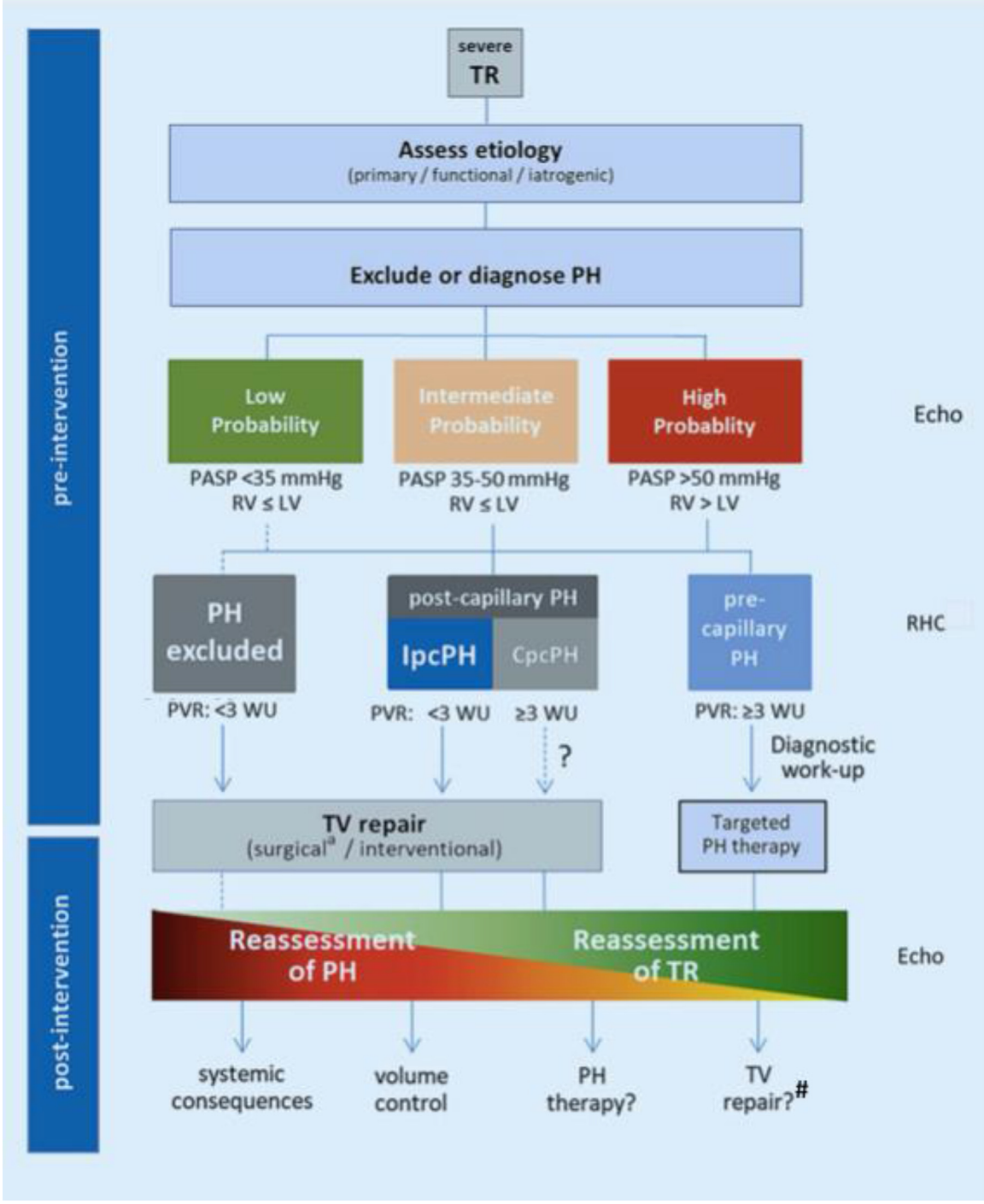

Figure 11 Suggested diagnostic approach, hemodynamic assessment, and patient selection for surgical or interventional therapies in patients with tricuspid regurgitation *Adapted from* Tichelbacker T, Dumitrescu D, Gerhardt F, et al. Pulmonary hypertension and valvular heart disease. Herz. 2019;44:491-501.[145] a: Isolated surgical repair of TR is considered a high-risk procedure # TV repair for secondary TR related to a pressure overloaded RV with Group 1 PAH is not recommended.

Cardiac surgery in the setting of advanced HF with preserved EF and PH

PH is common in patients with HFpEF (PH-HFpEF) and is associated with RVF and high mortality when present.[178] The severity of PH is greater in patients with advanced diastolic dysfunction. Advanced diastolic dysfunction can be seen patients with coronary artery disease or severe AS, and it is a common feature of idiopathic or acquired restrictive cardiomyopathies (RCM), including amyloidosis, hemochromatosis, sarcoidosis, connective tissue disease, and radiation myocardial fibrosis. Sometimes more than one mechanism for HFpEF can be present. For example, there is increasing recognition of wild type transthyretin

cardiac amyloid in patients undergoing TAVR.[179-181] Likewise, if significant radiation myocardial fibrosis is present, restrictive physiology will persist despite revascularization, pericardial striping and/or valve replacement. Echocardiographic and hemodynamic signs of underlying restrictive cardiomyopathy may be present preoperatively.[182] Thus, a thorough evaluation of the HFpEF phenotype and clinical status should be done preoperatively.

Data in patients with HFpEF undergoing CABG show a high risk of perioperative adverse outcomes and postoperative mortality.[183,184] In one study of 491 patients who underwent CABG, preoperative left atrial pressure elevation by echocardiogram predicted higher longer term mortality. In this same study, patients who had evidence of PH by echo (sPAP $\geq$ 36 mm Hg) or RV dysfunction (TAPSE $<$ 16 mm) had higher odds of 30 day perioperative adverse outcomes after CABG.[183]

For non-emergent surgery, it is recommended that heart failure is stabilized prior to surgery. This recommendation is based on poorer outcomes in patients who are classified as decompensated at the time of surgery.[185] In addition, high filling pressures are directly linked to clinical pulmonary edema and increased RV afterload,[186-190] therefore the risk for perioperative pulmonary edema and RVF should be reduced by preoperative optimization for elective cases. If cardiac surgery is emergent due to myocardial ischemia or unstable critical valve disease, waiting to improve volume status is not recommended.

Perioperative management

Hemodynamic considerations. For patients with RCM and low CO state, the stroke volume is often fixed, and a higher heart rate can improve CO. This can be achieved by decreasing/discontinuing inhibitors of the sinus node, increasing pacing rates in patients with permanently implanted pacemakers, or by administering an inotropic agent with chronotropic effect. These maneuvers may be especially helpful for patients with cardiorenal syndrome. Additionally, in addition to diuresis to reduce post-capillary PH as much as is renally tolerated by a relatively preload dependent restrictive LV, inotrope support for the RV may be needed if it becomes decompensated during the perioperative period.

Other management principles for patients with HFpEF-PH include good blood pressure and rhythm control. Vigilant monitoring and early management of atrial arrhythmias are particularly important for patients with RCM as they may acutely decompensate with loss of the atrial kick.

Pulmonary vasodilators. PAH specific therapies have not demonstrated a mortality benefit in patients with Group 2 PH and can raise pulmonary capillary wedge pressure acutely,[191] likely even more so in patients with advanced diastolic dysfunction. As discussed previously, different inhaled pulmonary vasodilators have been used with varying results in patients undergoing cardiac surgery, although patients with HFpEF including advanced diastolic dysfunction were not studied in particular.

Key Points

1. A thorough evaluation of HFpEF - PH phenotype and clinical status should be performed in the preoperative phase of cardiac surgery.
2. Diuretics should be adjusted to achieve euvolemia as much as possible prior to cardiac surgery in patients with advanced diastolic dysfunction.
3. The use of pre- and chronic postoperative oral pulmonary vasodilators is not recommended.

Gaps in Knowledge

1. Better classification of HFpEF phenotypes is needed to enhance perioperative risk prediction and to test perioperative management strategies.
2. Cardiothoracic surgery databases would benefit from the collection of preoperative invasive hemodynamic data, when available. This data would help inform risk prediction in HFpEF modeling.
3. Proper assessment of RV function in the setting of HFpEF-PH and associated risk remains suboptimal.

Management of PH and/or RV failure after LVAD implantation

RVF following LVAD implantation is a common yet highly morbid problem. The incidence of acute RVF ranges from 20% to 50% depending on the study definition,[192] and prediction of risk is imperfect,[193-196] Unexpected perioperative difficulties may precipitate RVF even when preoperative risk seemed acceptable.[195]

Hemodynamic optimization

In order to reduce the risks of acute RVF post-LVAD, especially in the presence of PH, preoperative optimization of left and right heart filling pressures and renal function is highly recommended. Factors contributing to RVF post-LVAD implantation and mitigating approaches are shown in Table 12.

Pulmonary vasodilators

Pulmonary vasodilators including iNO, inhaled prostanoids, PDE5-inhibitors, and ERAs have all been utilized in post-LVAD patients to help unload the right ventricle, although data are primarily based on case series.[197-200] Patients with RVF after LVAD implantation are often hypotensive in the perioperative setting and therefore inhaled vasodilators, when used, are continued until the patient is no longer requiring pressor support.

Table 12 Contributors and Approaches to RV Failure with LVAD Implantation

Factors contributing to RV failure	Possible mitigating strategies
Patient selection	Use of RV failure prediction tools
Volume overload, renal failure	Aggressive volume management: Diuretics, CVVHD in select cases
Tricuspid regurgitation	Proactive tricuspid repair at LVAD implant
Inadequate LV unloading	Pump speed and afterload optimization
PH due to elevated PVR	Nitric oxide, inhaled prostanoids, milrinone, sildenafil, endothelin receptor antagonists
RV contractile failure	Milrinone, other inotropes, RVADs, less invasive strategies

A large, retrospective study of the INTERMACS Registry suggested preimplant use of sildenafil actually resulted in higher rates of RVF as well as higher bleeding rates.[201] The use of PDE5 inhibitors (generally sildenafil, given shorter half-life than tadalafil, allowing easier dose titration) in post-LVAD patients with pulmonary vascular disease is common, although the evidence supporting their use is limited[202,203] and do not include RCTs. Interestingly, a recent large, retrospective observational study of the INTERMACS Registry that included 13,722 patients who received a LVAD showed that the post-LVAD use of PDE 5 inhibitors was associated with a lower rate of thrombotic events (ischemic stroke and pump thrombosis) and improved all-cause mortality, presumably due to the nitric oxide/cGMP anti-platelet/antithrombotic effects.[204] PDE 5 inhibitors were used in 36% of LVAD recipients and their use was more common among patients with a history of PH and/or RHF, however postop outcomes related to PH and RHF were not assessed in this study.

The rationale for post-LVAD pulmonary vasodilators rests on the concept that patients with elevated PVR after LVAD implant who have satisfactory left heart filling pressures have converted to a hemodynamic state that mimics that of WHO Group I PAH that should therefore be responsive to such therapy. However, significant elevation of PVR following LVAD implant is relatively uncommon,[205] and without careful measurement of PAWP it may not even be clear whether the PVR is elevated. Accordingly, it is critical to obtain the necessary measurements either at the bedside, or if doubt about accuracy, by return to the hemodynamic catheterization laboratory for formal measurements and hemodynamic optimization of LVAD parameters to fully understand the physiology.

In settings where the LV is adequately unloaded, and residual pre-capillary PH and RV dysfunction exist immediately post-LVAD, iNO/prostacyclins with transition to PDE5 inhibitor therapy may be a reasonable approach, especially for potential heart transplant candidates with prohibitive pulmonary hemodynamics and/or significant RHF due to residual pressure overload. Remodeling of the lung vasculature may result in improvement or normalization of the PVR, and the RV may improve in function, such that ongoing therapy may not be necessary.

ERA have also been utilized,[200] and initial results of the first randomized, multicenter, controlled trial of pulmonary vasodilators in the early post-LVAD population, the Clinical Study to Assess the Efficacy and Safety of Macitentan in Patients With PH After Left Ventricular Assist Device (SOPRANO) study, were recently presented and showed that macitentan significantly reduced PVR and was well tolerated.[206] Additional research including RCTs regarding acute and chronic use of pulmonary vasodilators is clearly important for advancing the field.

Right ventricular assist devices for perioperative right heart failure

If right heart failure (RHF) is allowed to persist to the point of multi-organ failure, mortality is high. Decisions regarding implantation of temporary RVAD systems or moving to extracorporeal membrane oxygenation (ECMO) should be made expeditiously either in the operating room at time of LVAD implant, or as soon as it becomes evident that non mechanical approaches are failing. Nonetheless need for implantation of an RVAD at time of the LVAD implant is associated with approximately 4-fold increase in mortality.[207] Options for mechanical support have recently been reviewed.[208] The Impella RP device (Abiomed, Danvers, CT) can be placed percutaneously through the femoral vein and provides up to 4 liter/min of flow; feasibility and acceptable safety with encouraging outcome was seen in the 18 patient LVAD cohort in the nonrandomized RECOVER RIGHT study.[209] The Protek Duo system (Cardiac Assist, Inc., Pittsburgh, PA) utilizes a cannula that can be placed percutaneously in the right internal jugular vein and is attached to an extracorporeal circulatory pump, allowing full patient mobilization and percutaneous removal.[210] An excellent review of contemporary ECMO strategies and management has recently been published.[211] When such systems are required in the bridge to transplant setting, patient priority for transplant becomes high, facilitating timely transplantation in critically ill patients.

In addition to acute RVF, there is an increasingly recognized phenomenon of late right heart failure >30 days after LVAD implantation, with incident rates of 8% to 11%.[212,213] The pathophysiology of late RVF remains poorly elucidated.

Key Points

1. Preoperative optimization of right and left heart filling pressures and renal function in patients undergoing LVAD implantation is recommended.
2. At this time, pre-LVAD use of sildenafil appears to be associated with higher rates of RVF and bleeding, and cannot be recommended.
3. The use of PDE5 inhibitors following LVAD is common, and appears to be associated with reduced thrombotic event rates and improved survival; however their use for PH should be re-evaluated 3 to 6 months post implantation.

Gaps in Knowledge

1. The safety and efficacy of pre-, intra- and postoperative pulmonary vasodilators need to be systematically evaluated.
2. Current risk stratification tools to predict RVF perform only modestly in external validation cohorts and require refinement.
3. Less invasive strategies and RV sparing techniques for LVAD implantation requires further study.

Transplant surgery in patients with PH and/or RV failure

Lung transplantation

WHO Group 1 PAH or Group 3 PH related to advanced lung disease (ALD) is associated with high early post-transplant mortality. In contrast, the long-term conditional survival for the first 3 months for PAH or PH due to ALD is one of the best or no different than transplant for other etiologies, respectively.[214-216] Consequently, the efforts to improve mortality concentrate on improving perioperative outcomes in this high-risk cohort.

Intraoperative management during transplantation

Anesthetic considerations. Induction is a critical time for patients with severe PH. Anesthetic agents, positive pressure ventilation, hypoxemia, hypercarbia are all factors that can lead to severe hypotension and RV collapse. The anesthesiologist should identify patients at risk of cardiopulmonary collapse ahead of time.[217,218] Despite etomidate's better hemodynamic profile, the overwhelming majority of centers worldwide use propofol as the drug of choice for induction.[52,219,220] Pulmonary vasodilators such as inhaled nitric oxide or inhaled prostacyclin, maximal inspired oxygen, and vasopressor infusion may mitigate elevation in pulmonary artery pressure (PAP) and reduce RV afterload resulting from the induction agents and conditions.[217,221] The surgical and perfusion teams should be present in the operating room at the time of induction in the event of emergent need for ECMO or full cardiopulmonary bypass (CPB) support. Emergency CPB support either via peripheral or central approach has been described or instituted successfully in some, but not all cases of cardiopulmonary collapse on induction. On occasion, preinduction awake peripheral femoral veno-arterial extracorporeal membrane oxygenation (VA ECMO) in local anesthesia is necessary in those with severe PH on high flow oxygen, hypercapnia, on inhaled NO, or inotropic support for the heart.[222,223]

Cardiopulmonary monitoring and management. While practice varies from center to center, intraoperative monitoring consists of radial artery cannulation, occasionally femoral arterial line, central venous access with or without PAC before or after induction depending on patients ability to tolerate supine positioning, and/or TEE.[218,221,220]. TEE has been remarkably helpful not only for intraoperative monitoring of the RV but also in assisting in making the decision to whether or not support the RV postoperatively with inotropy and/or ECMO/extracorporeal life support (ECLS).[224] Furthermore, TEE can help evaluate the patency and flows at the pulmonary arterial and venous anastomoses.

Intraoperative fluid management is of paramount importance in patients with PH and RVF undergoing lung transplantation to prevent graft edema upon reperfusion while maintaining optimal cardiac output both during surgery and after.

Surgical management. Lung transplantation for PAH patients these days requires the use of an extracorporeal circuit. The debate between full CPB vs ECMO has been largely settled. Several centers in Europe and North America and some in Asia now preferentially deploy VA ECMO over full CPB for intraoperative cardiopulmonary support during lung transplantation.[225-229] Though there are no RCTs, a recent meta-analysis comparing ECMO vs CPB during lung transplantation showed superior clinical outcomes for ECMO with no difference in operative and ischemic times observed.[230] While both CPB and VA ECMO offer hemodynamic stability, controlled reperfusion of the first allograft during implantation of the second and protective ventilation strategies, VA ECMO offers additional benefits such as, lower/no heparinization, bleeding risk, transfusion requirement, and closed system with minimal activation of platelets etc. CPB, however, remains a viable option for cases where excessive bleeding is anticipated and in cases of combined cardiac defects.

Primary graft dysfunction (PGD)

PGD contributes significantly to morbidity and mortality after lung transplantation. Especially patients with PH are known to develop PGD.[231,232] A number of donor, recipient, and procedural characteristics were identified to be associated with the occurrence of PGD in PH patients.[233] Most importantly, left ventricular diastolic dysfunction was recently reported to be an independent prognostic risk factor for PGD in patients with PH and may be associated with worse long term outcomes.[84,234]

Postoperative left ventricular dysfunction

The management of patients undergoing lung transplantation for PAH demands a focus on postoperative left ventricular cardiac function.[235-238] Patients with end stage PAH present with a chronically underfilled LV of reduced dimensions leading to reduced stroke volume. There is septal bowing to the left (echocardiographic 'banana shaped' LV). Lung transplantation ideally resets the PVR to physiologic conditions which results in improved LV filling and consequent increase in cardiac output. Not infrequently, the situation arises that the untrained LV cannot handle this sudden increase of volume load, which can lead to temporary LV failure and pulmonary edema[235-238] and lower 1-year survival.[84]

There is a clear chronological difference between the occurrence of classical PGD and left ventricular failure. PGD occurs within the first 24 hours after lung transplantation whereas temporary left ventricular failure occurs at a later time, usually during weaning from mechanical respiratory support when the reduction of positive pressure ventilation leads to an increase of cardiac inflow to the LV.

Several therapeutic strategies are important in the management of such patients postoperatively which help to overcome or avoid the deleterious complications of PGD and LV failure. Among them are optimization of fluid balance, inotropic support, providing hemodynamic stability and more importantly avoiding rapid LV loading at a time when the LV has yet to adapt to the new physiologic conditions.

Fluid management

The routine use of diuretics is central to reverse the effects of fluid retention in PH patients post-transplantation. Given the chronic congestive renal impairment, the sole use of diuretics may not be sufficient leading to liberal use of temporary hemofiltration in some patients.[237] Up to 45% of patients undergoing lung transplantation for PAH need temporary hemofiltration but without long term sequalae such a permanent hemodialysis or renal transplantation.[237] Careful attention has to be paid to maintain serum protein and hemoglobin concentrations over the whole time. Echocardiography is a valid tool to monitor cardiac performance in response to fluid administration in critically ill patients.[239,240] It is important to delay extubation or weaning from ECMO until the patient's fluid status has been normalized.

Post-operative ECMO prolongation

Measures to optimize the patient's fluid overload, such as forced diuresis or hemofiltration, pharmacologic inotropic support and delayed extubation alone are sometimes not sufficient to provide stable postoperative conditions.

A particular benefit of ECMO (over CPB) lies in the possibility to prolong it into the postoperative period to guarantee hemodynamic stability.[228,237,238] Prolonged VA ECMO reduces blood flow through the lungs, gives the heart and lungs the necessary time for slower adaptation to the new conditions.[228,237,238] and in this way provides optimally controlled reperfusion of the lung allografts.[241]

In addition, the prophylactic extension of ECMO postoperatively offers the possibility for lung protective mechanical ventilation such as low tidal volumes (TV) and plateau pressures thereby avoiding stretch injury associated with higher TV that would otherwise be required without ECMO to support ventilation.

Routine prophylactic postoperative use of VA ECMO[237,238,242] results in excellent outcome and is particularly recommended in patients with PAH.[22] Recently it has been suggested to make its use dependent on specific functional criteria: $p_aO_2/FiO_2 < 100$, $PAP_{mean}/SAP_{mean} > 2/3$, or a clear trend of worsening at the end of the operation.[242]

Right ventricular outflow tract (RVOT) obstruction

There is one specific exception from the typical hemodynamic pattern after lung transplantation in patients with PH. This is RVOT obstruction which can occur in cases with pronounced RV muscular hypertrophy. In this situation, unguided reduction of circulatory volume can exacerbate RVOT obstruction. The correct treatment in this situation consists of augmented volume status and consideration of beta-blockers (case reports:[243,244]). Repeated echocardiographic monitoring is mandatory to identify this condition.

Key Points

1. Double lung transplantation is now the procedure of choice for most patients with WHO Group 1 PAH.
2. VA ECMO and not CPB is recommended for intraoperative cardiopulmonary support during lung transplantation.
3. We recommend gradually weaning sedation, mechanical ventilation and/or ECLS to avoid rapid LV loading at a time when the LV has yet to adapt to the new physiologic conditions.
4. Prophylactic postoperative ECMO should be considered for patients with PAH and severe RV dysfunction.

Gaps in Knowledge

1. Determination of the optimal extracorporeal support configuration is needed.
2. Data regarding who would benefit from postoperative ECMO support are lacking.

Heart transplantation

PH and RV dysfunction in advanced heart failure

As discussed previously, PH is common among patients with left heart disease (LHD), including patients with advanced heart failure (AHF). Increased PVR, unresponsive to acute vasodilatation, may impose a contraindication to heart transplantation (HT), due to the risk of postoperative

acute RVF and early death following HT,[139,245] if not reversed by LVAD treatment. Additionally, long-standing advanced HF may itself result in remodeling of the right ventricle (RV), with concomitant RVF, worsening prognosis.[139] Such an impaired RV function may also impose a contraindication for treatment with LVAD prior to HT.

Pretransplant considerations in PH due to AHF

As previously summarized,[246] several studies have evaluated the impact of preoperative PH on outcome after HT.[247-256] Which hemodynamic parameter that best predicts outcome is, however, complicated by different cut-off values that have been used to characterize PH severity in among studies.[247-256] There are also diverging findings with regards to the influence of PH after HT, specifically when evaluating preoperative PH.[257]

Prior to HT, RHC is mandatory in candidate evaluation. Repeated RHC's should also be performed with intervals of 3 to 6 months, especially when HF is worsening. Relative contraindications for HT have previously been defined as: PVR > 4 to 5 WU, PVR index (PVRI) > 6 WU•m^{-2} and/or TPG > 15 mm Hg.[258] Acute vasoreactivity testing (AVT) is recommended during RHC in PH-AHF patients during transplant evaluation who exhibit a SPAP ≥ 50 mm Hg and either TPG ≥ 15 mm Hg or PVR > 3 WU. A SAP > 85 mm Hg should be maintained during AVT in order to be predictive. However, with current treatment options, such as LVAD, a patient previously considered ineligible for HT due to hemodynamic impairment, may today become eligible, due to offloading of the LV with normalization of PAWP and MPAP, as well as attenuation of the elevated PVR.[246]

PH 1 year after heart transplantation seems indeed to be a prognostic marker for long-term outcome.[257] Moreover, PH at repeated evaluations during the first year after HT have stronger impact than PH at a single measurement.[257] Thus, just as PH in LHD prior to HT is a negative prognostic marker of morbidity and mortality,[139] persistent PH after HT also impairs prognosis. Careful treatment of left heart failure (LHF) before as well as after HT is therefore of great importance to diminish the effect of sustained LA pressure to the evolution of PH.

Pre- and post-operative management of PH due to AHF

Management of PH in AHF remains challenging.[259-262] As CpcPH may be characterized by superimposed arterial vasoconstriction ± vascular arterial and venous remodelling above and beyond venous congestion, it has been suggested that pulmonary vasodilator therapy utilized for PAH, might be of value in PH due to LHD including LHF.

As discussed in the previous section on cardiac surgery in patients with PH, several randomized control trials have been performed with PAH therapy in patients with LHD, with the majority being negative or detrimental.[263-273] PAH therapy has therefore not received approval for PH due to LHD. However, it is occasionally and selectively used intermittently in the intensive care setting for predominately pre-capillary PH and RV dysfunction, along with careful hemodynamic monitoring and the use of IV diuretics, perioperatively in HT patients. The aim is then to decrease PVR and attenuate the load on the right ventricle. The general recommendation at present is to optimize treatment of the underlying LHD condition, including LHF.[259] The use of LVAD as a bridge to transplantation in patients with PH has been discussed previously.

Intra- and post-operative PH considerations and management

Many patients with PH-LHD prior to HT are treated with a LVAD to unload the LV and normalize pulmonary pressures before transplant listing due to increased mortality with transplantation in the setting of high PVR.[274-276] Nevertheless, there are patients who did not exhibit PH prior to HT and show a profound elevation of PVR at the time of HT. Moreover, a small but growing patient population with AHF and associated PH are not characterized by LV dilatation and hypokinesis, including restrictive-, hypertrophic-, and infiltrative cardiomyopathies, as well as some forms of congenital heart disease (e.g., Fontan circulation). Many of these patients may not be eligible for mechanical assist devices.[245]

There are also a number of factors that may increase PH during and right after HT. The release of vasoactive substances during bypass, volume overload and stress during awakening from anesthesia, can all be causes for intra- and postoperative PH.[277-279]

Even in those patients who do not have exclusionary PH pretransplantation, during and early after HT may develop RVF due to the fact that the donor heart is not adapted to elevated pulmonary pressures and may be impaired in its function by ischemia and reperfusion injury.[277,280] Hemodynamic and echocardiographic definition of isolated RVF and PH after HT has been previously been described.[281,282]

During HT, patients need to be continuously monitored for right heart dysfunction via RHC, TEE, and direct visualization of the graft. Right sided graft dysfunction can be either defined as PGD (due to ischemic and reperfusion injury) or secondary graft dysfunction (due to PH). In most cases, however, it is a mixture of both. In most HT recipients, low-grade right-sided dysfunction can be documented. In a consensus document, right-sided PGD (PGD-RV) was defined as RAP ≥15 mm Hg, PCWP <15 mm Hg, CI < 2.0 liter/min/m2 and/or TPG <15 mm Hg ± sys PAP <50 mm Hg and/or the need for mechanical support.[281]

Intraoperative management for PH-AHF patients follow principals discussed in earlier sections. Additionally, ventilator treatment of atelectasis needs to be performed before weaning from cardiopulmonary bypass, to prevent patients from high pressure ventilation, at a later stage. Moreover, pleural effusions need to be treated to allow ventilation that won't harm the right ventricle.

Optimal filling pressures are essential and a CVP of 12 to 14 mm Hg should be the upper limit in most cases. Echocardiographic monitoring of the tricuspid valve is important to detect sudden severe tricuspid valve insufficiency associated with RV dysfunction and /or volume overload. Sudden

volume overload can be counteracted via a reverse Trendelenburg position of the patient. if mean PAP pressure >25 mm Hg and/or SysPAP >45 mm Hg, associated with any degree of RV dysfunction immediate initiation of inhaled vasodilators is important. The surgeon also needs to closely monitor the RA and RV while weaning from CPB to avoid volume overload.

After weaning from CBP the use of protamine, to antagonize heparin, can lead to sudden increase of pulmonary pressures and acute RVF. Immediate therapy with steroids and histamine receptor antagonists can be used for treatment of this side effect. Protamine can rarely also lead to anaphylactic reactions that can cause cardiovascular collapse, requiring immediate treatment.

Therapeutic options for intra- and post-HT PH and RV dysfunction

Judicious use of perioperative vasoactive and inotropic agents has been proposed and found to be efficacious, as described previously for other patients with PH and RV dysfunction. Mechanical circulatory support (MCS) therapy is the final option to treat RVF due to PH and RVF after HT. Historically, this cohort of patients had severely decreased survival and most patients could not be weaned from MCS.[283] The use of ECMO showed significant improvement in weaning from support and survival.[283-285]

There are also data with other devices (centrifugal flow: Levitronix CentriMag, Tandem Heart; axial flow: RP Impella) for temporary RV support.[286-289] However, most of the data is based on RVF after LVAD implantation and there is still a lack of data in RVF after HT.[290,291]

Impella is an axial flow device that can be implanted percutaneously to support the failing RV. Several studies have examined the use of Impella Recover RD and the new Impella RP. The biggest series with the newer Impella RP device, consisted of 29 patients (7 of them transplant patients) pooled from the RECOVER RIGHT study and post marketing studies (PAS, CAP). Overall 30 day-survival was 72% and 62% at 6 months. Patients were supported for a median time of 3.1 days.[292]

Key Points

1. Vasodilator testing is recommended during RHC for patients with PH being considered for AHF therapies when the SPAP is ≥ 50 mm Hg and if the TPG ≥ 15 mm Hg or PVR > 3 WU. A systolic blood pressure ≥85 mm Hg should be maintained for the test to be predictive.
2. The use of pulmonary vasodilator therapies in patients with AHF being considered for transplant or LVAD therapies with prohibitive PH hemodynamics should be done with caution and in coordination with PH experts.
3. We recommend careful treatment of left heart failure before as well as after HT to diminish the effect of sustained LA pressure to the evolution of PH.

Gaps in Knowledge

1. How the new PH definition, proposed at the WSPH in Nice 2018,[259] will influence treatment decisions and eligibility criteria for HT remains to be solved.
2. Further studies are needed to better identify patients with PH and AHF who are at risk for post-transplant acute RVF and early mortality.
3. Data is needed to evaluate new therapeutic approaches in relation to the new PH definition to minimize the impact of right heart failure following HT.

Liver transplantation in patients with pulmonary hypertension

Liver transplantation: Preoperative considerations and management

Portopulmonary hypertension (POPH) is defined as the presence of PAH associated with portal hypertension.[293] It is a common form of PAH, accounting for 5% to 10% of all PAH.[294] In patients undergoing evaluation for liver transplantation, the estimated prevalence is 5%, with risk factors including female gender and autoimmune hepatitis.[295-297] Similar to other PAH subtypes, the newest WSPH hemodynamic criteria are as follows: mPAP > 20 mm Hg, PVR ≥ 3 WU, and PCWP < 15 mm Hg.[1,298] Although, as end-stage liver disease (ESLD) is often accompanied by other risk factors for elevated pressures and pulmonary venous congestion, the diagnosis is frequently one of exclusion.[299,300] In 33% of patients awaiting liver transplantation, elevations in mPAP are related to causes other than PVR.[301] Furthermore, a patient with a high CO or volume overload may have an elevated mPAP despite a normal pulmonary capillary bed.

Candidate assessment. As it relates to liver transplantation, the presence of severe and uncontrolled POPH is associated with increased risk of perioperative mortality (approaching 100% if mPAP > 50 mm Hg), prolonged mechanical ventilation, and longer length of stay.[302-305] All transplant candidates with portal hypertension should undergo screening for POPH.[306-308] Initial screening should be performed with TTE, with a low threshold for RHC.[301] The American Association for the Study of Liver Disease and the American Heart Association recommend RHC if estimated PASP > 45 mm Hg.[309,310] Based on the available data and clinical experience, our recommendation is to consider RHC in candidates for liver transplantation when the echo-Doppler estimated PA systolic pressure is ≥ 50 mm Hg or 40 mm Hg with secondary evidence of RV pressure overload on echo (RV enlargement/dysfunction, interventricular septal flattening, "notching" of the RVOT VTI).

Prior to transplantation, efforts should focus on reduction of mPAP to < 35 mm Hg because there is no increased risk of perioperative mortality below this threshold.[305,311]

In the United States and much of Europe, liver transplant allocation occurs through the Model For End-Stage Liver Disease (MELD) score.[312-314] Given the increased risk of morality with POPH, the United Network for Organ Sharing grants a standardized MELD exception in moderate POPH (baseline mPAP > 35 mm Hg), provided that PAH-specific therapy reduces mPAP to < 35 mm Hg and PVR < 400 dynes/second per cm^{-5}.[312,313,315,316] The International Liver Transplant Society also recommends consideration of MELD exceptions if unable to reduce the mPAP to < 35 mm Hg, provided that PVR and RV function normalize (e.g., mPAP 40 mm Hg with PVR < 3 WU and normal RV function).[317] Most centers consider mPAP > 50 mm Hg an absolute contraindication to transplantation due to an observed mortality rate of nearly 100%.[305,316] Unlike in hepatopulmonary syndrome, resolution of lung disease in POPH is not uniform after liver transplantation, and patients commonly require continued PAH-specific therapy.[318-321] For this reason, POPH in isolation is not considered an indication for transplantation.[309]

Pre-liver transplant management and vasodilator therapy. Despite being a form of PAH, randomized clinical trials of PAH-specific therapy historically excluded patients with POPH,[321] and treatment with PAH-specific therapies should be at the direction and monitored by a PH expert. Non-randomized studies do demonstrate efficacy of PAH-specific therapy in this population.[322-343] Parenteral and inhaled prostacyclin analogues improve functional capacity and hemodynamics.[323-329,344-346] It should be noted, however, that these agents require caution given the risk of thrombocytopenia and splenomegaly.[345-347] Phosphodiesterase-5 inhibitors (PDE-5I) are generally well tolerated, and small studies demonstrate improved functional capacity and hemodynamics.[322,330-334] Use of ERA are also effective.[335-343] Although, caution should also be taken given the increased risk of fluid retention and hepatotoxicity.[348-350] For this reason, the United States Food and Drug Administration recommends to avoid ERAs in moderate to severe liver dysfunction. Notably, early results from a multicenter placebo controlled trial using the nonselective ERA, macitentan, in portopulmonary hypertension are promising.[351] Evidence for the use and safety of newer agents such as the non-prostanoid IP receptor agonist, selexipag, and the soluable guanylate cyclase stimulator, riociguat, is more limited,[352] and it is recommended to reduce the administration of selexipag to once daily in patients with moderate liver impairment (Child-Pugh Class B) and avoid in patients with severe liver impairment (Child-Pugh Class C).

In patients with refractory ascites or variceal bleeding, transjugular intrahepatic portosystemic shunt (TIPS) improves survival without extending waiting times or increasing surgical complications.[353,354] Unfortunately, it has the unintended consequence of increasing RV loading and cardiac output.[355] As such, patients with POPH should undergo TIPS with extreme caution. Furthermore, it is contraindicated if mPAP ≥ 45 mm Hg.[356]

In addition to PAH-specific therapy, the principal component of management in POPH is to improve RV function, even normalize RV function for transplant eligible patients. Diuretics are necessary to mitigate risks of volume overload. Spironolactone is appealing given its effect on pulmonary vascular remodeling; however, caution should be used given the risk for hyperkalemia from renal dysfunction associated with end-stage liver disease (ESLD).[357]

Waiting list management. While wait-listed, routine screening should occur to ensure that patients do not develop worsening PH and RV dysfunction. The timing of repeat screening is center-dependent, with most centers repeating echocardiogram screening every 3 to 6 months for those with a prior diagnosis of POPH, and every twelve months in those without prior POPH.[301,358,359] Despite the high frequency of echocardiogram screening, there are no accepted guidelines for when to pursue a RHC on the waitlist. Some centers use estimated PASP, others use Doppler derived variables including estimates of PVR.[305,360-362] Ultimately, the goal is to ensure that patients have enough RV reserve to tolerate liver transplantation, so there is a low threshold to perform a repeat RHC if evidence of RV dysfunction is present.[358] Some centers even advocate for serial RHC every 3 months given the risks associated with undertreated POPH.

Preoperative assessment. Having fully assessed and optimized the POPH patient prior to liver transplantation does not obviate the need for a focused preoperative assessment by the attending anesthesiologist. The focus should be on the recent changes in medication or acute changes in exercise tolerance, shortness of breath or oxygen requirements. Finding no recent changes in health status, the primary objective in the intraoperative period is to avoid management that might exacerbate the PH and RVF.[49]

Intra-operative management. For liver transplantation, the intraoperative period is described by dramatic fluctuations in hemodynamics; preload, cardiac output (CO), and SVR. The optimized POPH patient is defined by a reduction in pulmonary pressures and improvement in RV function. For the intraoperative management of these patients, it must be understood that they their clinical stability is extremely tenuous, and can change quickly from stable hemodynamics to and profound decompensated cardiac failure, specifically right heart failure. The objectives in the operating room can be managed in many different, potentially additive ways, but essential is the maintenance of SVR, maintaining or lowering PVR and supporting cardiac contractility.

Arterial pressure monitoring is routinely monitored in liver transplant surgery. However, when the transplant candidate comes to the operating room with POPH the use of central arterial line (e.g., femoral) access should be considered. The requirement for significant vasopressors can result in an underestimation of central pressure when using peripherally placed arterial cannulas.[363]

While the use of the PAC in liver transplantation is waning, its use in patients with suspected or presumed POPH should be encourage as a real-time tool to assess

CO or cardiac function.[58,364] Preoperative subjective patient optimization based of functional capacity prior to surgery does not always correlate with hemodynamic monitoring and the placement of a PAC allows for a final assessment of patient status prior to committing to liver transplantation, that is, resection of the inferior vena cava (IVC). In addition, the PAC can be used to assess the therapeutic effectiveness of veno-venobypass, piggyback surgery with partial caval cross-clamping, and preoperative PAH therapies.[328] More importantly, continuous monitoring of RAPs and mPAP will help to identify those at risk of acute RVF.[58]

The use of TEE to diagnose and manage PH has been documented in case reports,[365] and TEE is an excellent monitor to access RV filling and function. The presence of grade III esophageal varices or recently banded varices may increase the risk of esophageal bleeding, but the use of TEE in liver transplantation is considered safe.[366] With the implementation of fractional area change to assess RV and LV size, the use of mid-esophageal views may minimize the need for gastric access.

Surgical management. While optimizing ventilation, fluid therapy, and inotropes can allow for successful transplantation in POPH, it is important to determine if these measures are sufficient to tolerate the complete cross-clamp of the IVC. If blood pressure cannot be maintained with a temporary IVC cross-clamp then an alternative surgical strategy should be considered. The options include placing a temporary portosytstem shunt, veno-veno bypass, ECMO, and the use of a partial cross clamp of the IVC with preservation of the posterior vena cava and maintenance to cardiac return. As with other transplant surgery in patients with PH and severe acute RVF, intraoperative ECMO should be considered during liver transplantation.

Cancelling surgery. The mortality associated with liver transplantation in patients with poorly managed, severe POPH approaches 100%, and cancelling surgery after line placement and full TEE evaluation should always be reserved as an appropriate option.[301,305,321,367] If the mean mPAP is > 35 mm Hg after adjusting for perioperative aggravating factors and there are signs of RV dysfunction, then pursuing liver transplantation may not be justified.[368]

Key Points

1. We recommend RHC for PH in ESLD patients when the screening echo-Doppler estimated RVSP is ≥ 40 mm Hg with secondary evidence of RV pressure overload on echo.
2. Treatment of POPH should focus PAH-specific therapy to achieve a mPAP < 35 mm Hg and PVR < 400 dynes/second per cm^{-5} to become transplant eligible.

Gaps in Knowledge

1. The role of pulmonary vasodilators in improving eligibility for liver transplant, outcome and long-term survival in patients with POPH needs to be systematically evaluated.
2. The benefits of temporary veno-venous bypass to control venous return to a marginalized RV during surgery needs to be evaluated.

Kidney transplantation in patients with pulmonary hypertension

Pre-operative considerations and management

The presence of PH in end-stage renal disease (ESRD) is important yet under recognized. The pathogenesis of this often mild to moderate PH is not well understood, but likely involves several cardiovascular changes associated with ESRD such as increased cardiac output as a result of volume overload, anemia, arteriovenous fistulas, and hemodialysis.[369,370] A reduced vascular compliance of the pulmonary venous system due to a disturbance in endogenous vasoactive metabolite may also be contributory.[371,372]

Epidemiology. A meta-analysis of 16 studies estimated that prevalence of PH by echocardiography in chronic kidney disease (CKD) is 23%.[373] Its presence was associated with increased mortality and cardiovascular events, with the highest risk in the group receiving dialysis. While notable, none of the included studies used RHC for diagnosis. The associated chronic volume overload, systemic vasoconstriction, diastolic dysfunction, and an increased CO from arteriovenous fistulas make a diagnosis of PH by echocardiography challenging because of the inability to differentiate pre- and post-capillary disease.[374] An elevated PASP may be driven by high CO or systemic vasoconstriction, so many patients may not actually have pulmonary vascular disease. The largest study with invasive hemodynamics in CKD comes from a retrospective cohort who underwent RHC for reasons other than CKD.[375] In the subset with CKD and PH, the predominant phenotype (76%) was post-capillary disease. Interestingly, prevalence of post-capillary PH rose with increasing stage of CKD, while prevalence of pre-capillary PH decreased; indicating that early stage CKD may be the consequence of pre-capillary PH, whereas co-morbidities associated with CKD may be the culprit in post-capillary PH.

Candidate assessment. In renal transplantation, most literature investigating the association of PH with post-transplant outcomes uses echocardiography. An estimated PASP ≥ 35 mm Hg is associated with increased risk of early graft dysfunction in deceased-donor recipients.[376] Others found an association between pretransplant PASP > 50 mm Hg

and decreased survival after transplantation.[377] Interestingly, there was no association in models adjusted for LV ejection fraction (LVEF), indicating that the results were likely driven by left heart disease. Another retrospective study enriched for a lower LVEF did not find any association between elevated PASP and survival.[378] To date, there is only one study, a retrospective cohort study, investigating the association of measured PA pressures with outcomes.[379] In this study, RHC was routinely performed at induction for transplant surgery, and patients were dichotomized by PASP $\geq$ 35 mm Hg. The presence of elevated PASP was associated with longer time on dialysis, diabetes, delayed graft function, and an attenuation of survival. While novel in characterizing the risk of measured PASP, the results are similar to the non-invasive association studies because it lacked the PCWP measurements necessary for differentiation between types of PH.

The association between PH and post-transplant graft function and survival may be valid, however, the predominant phenotype in ESRD is post-capillary PH, likely driven by the co-morbidities of CKD. As such, the survival outcome is probably driven by co-morbidities rather than true pulmonary vascular disease. Careful attention in the perioperative period should focus on management of co-morbid conditions, attaining euvolemia, and control of blood pressure. Alternatively, if there is a concern about the presence of PAH, a RHC should be performed at euvolemia and normotension to ensure the accuracy of the PCWP. If unable to achieve a normal PCWP, assessment of the pulmonary-to-systemic vascular resistance ratio can help alleviate concerns.

For patients with true pre-capillary PAH, the goal is to mitigate its risk in transplantation by reduction of mPAP and optimization of RV function. Patients should be treated with pulmonary vasodilators appropriate to their diagnosis in the setting of true PAH.[380] In addition, management of volume overload with diuretics and dialysis is beneficial to optimize cardiac function.[381] In patients with a high output state from arteriovenous fistulas, closure of the fistula can reduce CO and improve mPAP.[382]

Key Points

1. In ESRD patients being considered for kidney transplantation with non-invasive evidence of PH, RHC should be performed at euvolemia and normotension to assess the hemodynamic phenotype and guide management.
2. ESRD patients should be treated with pulmonary vasodilators appropriate to their diagnosis in the setting of true PAH. The goal of PAH specific therapies in these patients is to mitigate its risk with kidney transplantation by reduction of mPAP and optimization of RV function.
3. Management of volume overload with diuretics and dialysis is beneficial to optimize cardiac function before kidney transplantation.

Gaps in Knowledge

1. A better understanding of the true prevalence of PAH and therapeutic options are necessary in patients with ESRD.
2. Hemodynamic criteria for patients with ESRD and PH being considered for kidney transplantation should be established.

Surgery for acute and chronic pulmonary embolism

Pulmonary thromboendarterectomy

Pulmonary thromboendoarterectomy (PTE) or pulmonary endarterectomy (PEA) is the definitive treatment for suitable CTEPH patients, offering excellent long-term outcomes.[383,384] When performed successfully at an experienced center, PEA significantly improves PH, RV dysfunction, tricuspid regurgitation and perfusion of the ventilated lung. Although the procedure can be technically challenging and requires cardiopulmonary bypass with periods of profound hypothermic circulatory arrest, it allows complete resection of the thromboembolic material into the distal segmental and subsegmental branches in a bloodless field.[385-387]

This procedure can be done concomitantly with cardiac surgery such that patients with CTEPH suitable for treatment with PEA needing CABG, valve replacement, PFO/ASD closure, etc. should be considered for PEA at the same time. Additionally, PEA should be considered as first line therapy to alleviate PH in patients prepared for curative surgery for malignancies (e.g., early stages of renal or breast cancer, etc.).

Preoperative management

The key goal of preoperative management should focus on expedited surgery in operable patients. Although there is no 'upper limit' of PAP, or degree of RV dysfunction that excludes patients from an operation, severe RV dysfunction and PVR over 1500 dynes/sec/ cm-5 have been shown to correlate with postoperatively mortality.[75,384,388-390] Preoperatively optimization of RV function and fluid balance is helpful in patients with decompensated RVF. This can usually be achieved by low dose inotropic support (e.g., Dopamine at 1-3 mcg/kg/min) and intravenous diuretics for a few days prior to surgery. Although all patients do require baseline RHC, continuous monitoring using a PAC and ICU admission prior to surgery is rarely required. Due to the obstructive nature of this disease, pre- or intraoperative use of inhaled agents, such as iNO or inhaled prostacyclin, is not beneficial, unless the patient has a significant component of non-obstructive vasculopathy.[391-393]

Although the preoperative use of PH directed medical therapy can potentially decrease the surgical risks and

improve postoperative outcomes there is currently no data on the efficacy of these therapies preoperatively.[394-397] The potential benefit of medical therapy preoperatively may be offset by the delay in offering such patients timely surgery. Any theoretical benefit offered by medical therapy also needs to be balanced against the potential side-effects, financial burden and the unknown effect of such therapies on the pulmonary vasculature. Hence, "bridging therapy" with PH directed medication needs further evaluation through a randomized clinical trial. A randomized, controlled clinical trial of riociguat prior to PEA in operable patients was recently terminated due to slower than expected related in part due to the COVID-19 pandemic (ClinicalTrials.gov Identifier: NCT03273257. For patients undergoing PTE, bridging PH targeted therapies are typically discontinued at the time of surgery.

Intraoperative management

With deep hypothermia and circulatory arrest during PEA, a central-peripheral blood pressure gradient is common in the post bypass period resulting in the radial arterial line underestimating the systemic pressure.[398] Central blood pressure monitoring (usually the femoral artery) should be used in the immediate postoperative period until this gradient resolves and peripheral blood pressure approaches central measurements. Sinus bradycardia and junctional rhythms are quite common in the immediate postoperative period and for this reason, temporary epicardial atrial and ventricular pacing wires are often placed at the time of surgery. The cardiac conduction system remains functional and the vast majority of patients can maintain an adequate CO with an atrial pacing rate of 80 to 100 beats/min until normal sinus rhythm is restored, usually within 24 to 48 hours after surgery.[399]

If other cardiac procedures are required, such as closure of patent foramen ovale/atrial septal defect, coronary artery bypass grafting, mitral, or aortic valve surgery, these are usually performed during the systemic rewarming period. Although tricuspid valve regurgitation (TR) is invariable in these patients and is often moderate to severe, tricuspid valve repair is not necessary unless there is an anatomic abnormality with the valve leaflets, chords, or overall structure. TR secondary to annular dilation is typically left alone as RV remodeling occurs within a few days, with the return of tricuspid competence. However, in cases with severe annular dilation, with annular measurement of over 4 to 4.5cm, it may be advisable to proceed with tricuspid annuloplasty to prevent potential recurrence in the future.

Although extracorporeal circularity support (ECMO), has been used for postoperative management of patients with severe residual PH, severe reperfusion injury with pulmonary edema, and/or significant airway bleeding, its use in the preop setting is extremely rare. These patients typically present with an acute exacerbation of their RV dysfunction which may be related to an acute episode of embolic disease over the existing chronic component, or an acute exacerbation due to other causes. In most patients, urgent or emergency surgery is indicated, however if this is not possible, then peripheral extracorporeal support should be considered while the patient awaits surgery or transfer to an expert center.

Postoperative medical management

Following PEA, the acute changes in RV afterload and redistribution of pulmonary blood flow are the 2 unique physiologic changes that must be understood when optimizing care.[400] The hemodynamic improvement can be appreciated immediately with echocardiography upon separation from cardiopulmonary bypass and hemodynamics obtained by PAC also confirm a reduction in PAP, PVR and an improved cardiac output.[401-403] The in-hospital mortality ranges between 2.2% and 11%. Common PEA related complications include reperfusion edema, need for ECLS, severe airway hemorrhage, and residual PH.

ICU care is typically focused on providing adequate RV preload, inotropic support as needed to support cardiac output following prolonged cardiopulmonary bypass times and deep hypothermic circulatory arrest, and vasopressors to raise blood pressure to ensure adequate coronary artery perfusion in the presence of a low SVR. A high CI (> 3.0 liter/min/m2) is purposely avoided to limit the risk of reperfusion lung injury.[399] Patients are routinely diuresed in the early postoperative period as long as there is no adverse effect on CO. In the absence postoperative complications, patients are typically extubated and weaned off inotropic support within the first 24 hours.

Postoperative residual/ persistent PH is associated with an increased perioperative mortality and may be due to inadequate endarterectomy, small vessel arteriopathy, or reversible factors such as hypercarbia, hypoxemia and/or reperfusion edema. Modest residual PH is not uncommon following PEA surgery, but the majority of these patients experience significant functional and symptomatic improvement with no apparent adverse effect on medium-term survival.[404,405] Exceptions would include those who clearly did not experience any significant hemodynamic improvement following surgery and those with ongoing RVF. A single center study showed that patients with a residual PVR of > 500 dynes/sec/cm-5 experienced a mortality of 10.3% compared to a mortality of 0.9% in those with a postoperative PVR < 500 dynes/sec/cm-5.[385]

Treatment of persistent PH in the immediate perioperative period focuses on minimizing oxygen consumption, reversing hypoxemia and hypercarbia, optimizing RV preload and inotropic support. Systemic pulmonary artery vasodilators are typically avoided in the early postop operative period due to their potential to contribute to systemic hypotension and exacerbate ventilation-perfusion matching and hypoxemia.[399] Reduction in PVR and/or improvement in oxygenation can be accomplished in some patients with iNO or iloprost without an associated decrease in blood pressure.[75,406,407] Extracorporeal support may be required in severe cases as a bridge to transplant or support during recovery.

Hypoxemia is particularly profound in patients who experience reperfusion edema (RPE). This is a high permeability edema that occurs in areas that have been reperfused following PEA surgery.[408,409] This complication occurs in 10% to 30% of postop PEA patients, depending on the definition used and the study cohort.[403,410] It is an early postoperative complication that typically manifests in the first 48 hours after surgery.[383] Severity of preoperative PH and the presence of residual PH are associated with an increased risk of RPE.[411] Several studies have attempted to identify interventions that might reduce the incidence of RPE. The treatment of RPE remains primarily supportive with diuresis to reduce lung water and avoidance of high cardiac output. RPE is typically self-limited, but is a major cause of postoperative mortality.

In rare cases of severe postoperative complications related to massive hemoptysis, severe reperfusion injury and pulmonary edema, and/or residual PH and RVF, extracorporeal circulation can be used as an adjunct to other therapies. Institutional practices vary in the indications and type of ECMO employed (veno-venous or veno-arterial) with survival reported to be 30% to 57% in the post-PEA population.[412-414] Although survival was about the same in patients with pulmonary hemorrhage and severe reperfusion injury, the patient with severe residual PH/RVF postoperatively did not survive. In patients who only have pulmonary complications and can tolerate VV ECMO, there seems to be a survival benefit over VA ECMO.

Key Points

1. Central blood pressure monitoring should be used in the immediate postoperative period after pulmonary thromboendarterectomy until peripheral blood pressure approaches central measurements.
2. CI (<3.0 liter/min/m2) should be targeted to reduce the risk of reperfusion lung injury.
3. Routine diuresis in the early postoperative period is recommended in most patients following PEA surgery.
4. Persistent PH in the immediate perioperative period should prompt methods to reduce oxygen consumption (e.g., sedation), reversing hypoxemia and hypercarbia, and optimizing RV preload and inotropic support.
5. Reperfusion pulmonary edema should be managed by diuresis and restriction of CO.
6. ECMO may be required to reduce perfusion mediated lung injury and improve oxygenation.

Gaps in Knowledge

1. The role of "bridging therapy" with pulmonary vasodilators needs further evaluation through ongoing randomized clinical trials.
2. Role of pulmonary vasodilators in RPE needs to be systematically evaluated.

Surgical embolectomy for acute PE and RV failure

Indications and other preoperative consideration

Massive or high-risk acute pulmonary embolism (PE) can result in circulatory collapse due to the development of acute, severe RVF.[415] The goal of surgical embolectomy (SE) is to expeditiously relieve RV afterload and hence reverse acute RVF. Recently, though, there has been a resurgence of interest in SE as treatment for massive PE due to the lower mortality rates reported, which are often equivalent to the mortality rates of treating massive PE with thrombolysis. Interest in the use of extracorporeal life support (ECLS) either before or after SE has also been growing, as centers gain more experience with ECLS and extracorporeal cardiopulmonary resuscitation (eCPR).[416] In a meta-analysis, 18 studies of 621 patients found that 27.2% of SE were performed after preoperative initiation of ECLS. There is an increased use of ECMO to provide hemodynamic support in patients undergoing thrombolysis, which has allowed SE not to be used for highly unstable patients, hence lowering the burden of associated mortality.[417] The indications and contraindications of SE in acute PE are summarized in Table 13.

Preoperative management

Once the decision for surgical pulmonary embolectomy has been made, there should not be a significant delay in transferring the patient to the operating room (OR). A close collaboration between anesthesiologist and surgeon is of utmost importance. Although restoration of systemic pressure is necessary for end-organ perfusion, only small volumes (i.e., 500 ml) of fluid should be perfused to avoid deleterious compensatory overstretch responses that may further compromise RV function. In combination, inotropes and vasopressors such as vasopressin and epinephrine are good choices to restore systemic blood pressure, while adding dobutamine can restore CO and RV-PA coupling. Before anesthetic induction, the patient should be prepped and draped, CPB lines secured, including both groins in case of the need of ECMO. As anesthetic induction may induce systemic hypotension, the patient should be fully monitored. Positive intrathoracic pressure from intubation may worsen venous return; tidal volume not exceeding the 6−8 cc/kg lean body weight range may preserve the fragile preload-sensitive hemodynamics of RVF. After induction of anesthesia and intubation, an intraoperative TEE probe should be inserted to monitor the cardiac filling, rule out presence of thrombus in the right chambers or a patent foramen ovale (PFO), or a paradoxical embolus in transit. If the patient remains hemodynamically unstable despite the use of inotropic support escalation, or is post CPR, the patient should be expeditiously transferred to the OR, and preferably, a VA-ECMO support is inserted under local anesthesia through the femoral vessels prior to transfer to the OR.

Table 13 Indications for Surgical Embolectomy in Acute Pulmonary Embolism

Absolute indications
• Circulatory collapse
• Contraindication to thrombolysis
• Failure of thrombolysis
• Embolus in right atrium or ventricle
• Impending paradoxical embolism (embolus across PFO)
Relative indications
• Prolonged cardiopulmonary resuscitation (>30 minutes)
• Sub-massive pulmonary embolism
• Contraindications
• Acute on chronic pulmonary embolism
• Out of hospital cardiac arrest
• Extensive comorbidities

Intraoperative management

Following careful extraction of the pulmonary thromboemboli with a combination of gallbladder stone forceps or sponge holder and suction under direct vision, removal of more distal clots are preferentially achieved by a large suction tube, followed by atriotomy if needed to remove any suspected clots in the right heart chambers, and if present, a PFO is closed. A pulmonary artery catheter is inserted through the internal jugular vein allowing monitoring of PAP and cardiac output. Depending on the SGC and the SvO2 monitoring, the patient is progressively weaned from CPB. In patients with very severe RV dysfunction preventing safe CPB weaning, transient central or peripheral VA-ECMO support may be used.

Post-operative management

The postoperative course of these patients needs focus on the several issues: First, persistent RVF, which can be due to persistent PH (for example if it was a misdiagnosis of an acute PE in a patient with a CTEPH). In that case, removal of the fresh clots is insufficient to decrease the RV afterload. It can also be due to RV ischemia in massive acute PE requiring cardiopulmonary resuscitation with prolonged cardiac massage and high level of inotropic support. Second, other vital organ failure: brain, kidney or intestinal ischemia or necrosis due to prolonged preoperative low flow. Postoperatively, organ failure may contribute to further bleeding by disseminated intravascular coagulation or hemodynamic instability. Postoperative circulatory support is therefore often required. The use of ECLS devices postoperatively should be adapted to the postoperative complications. As previously mentioned, in RVF preventing CPB weaning, a VA-ECMO is preferably used through either central or peripheral cannulation sites, as a bridge to recovery (usually obtained after a few days). In patients developing respiratory failure (i.e., ARDS secondary to reperfusion edema or to pneumonia) usually in ICU after the first postoperative 6 hours, a VV-ECMO is indicated to improve ventilation conditions.

Postoperatively, anticoagulation is prolonged for at least a 6-month period. Inferior vena cava filter is indicated in patients with contraindication for effective anticoagulation or recurrent PE despite efficient anticoagulation. In conclusion, SE is a good option for patients with massive PE in the presence of hemodynamic instability or a clot in transit, with lower mortality rates in the modern era and often near-complete recovery of RV function postoperatively.

Key Points

1. Surgical embolectomy is a viable option for some patients with massive PE in the presence of hemodynamic instability or a clot in transit.
2. Once the decision for surgical pulmonary embolectomy has been made, there should not be a significant delay in transferring the patient to the operating room.

Surgery and anesthesia in children with PAH or patients with PH associated with congenital heart disease

Children with PAH or PH associated with CHD undergoing surgery, including cardiac catheterization, are at increased risk of major adverse perioperative events including perioperative cardiac arrest and death.[418-425] In the absence of evidence-based guidelines, multidisciplinary providers who manage these patients would benefit from expert consensus recommendations in order to minimize these risks. The specific management including anesthetic approaches and the use of mechanical support for pediatric patients undergoing cardiac and non-cardiac surgery and cardiac catheterization will be discussed as well as the perioperative management of children and adults in the presence of PH and CHD, pre and post transplantation and also specifically in the univentricular heart. These recommendations aim to improve the care of PH patients knowing that these procedures may decompensate a very fragile balance.

Numerous studies have documented the increased risk of morbidity and mortality that PH carries for both cardiac and non-cardiac surgeries and across age groups.[90,418,426] The incidence of major adverse perioperative events reported in pediatric PH patients undergoing non-cardiac surgery are also substantially higher than reported for the general pediatric population, including the incidence of perioperative cardiac arrest (0.014%-0.033%) and perioperative mortality (0.0036%-0.011%)[427,428] and higher than the risk of cardiac arrest for all children with heart disease undergoing cardiac catheterization (0.5%-0.96%)[429,430] The majority of published data on pediatric PH patients undergoing non-cardiac surgery including cardiac catheterization comes from retrospective, single center studies. The reported risk of perioperative cardiac arrest for these patients varies between 0% to 5.7% with a perioperative

mortality rate ranging from 0% to 1.4%.[418-423,425] A recent multicenter registry of 6339 procedures in 4,401 pediatric patients from 38 centers reported that 3.5% of patients with PH required rescue ECMO support within 1 day of cardiac catheterization.[431] However, this analysis did not exclude patients having interventional procedures and included a large number of post-capillary PH patients. While major and emergent procedures, whether cardiac or non-cardiac, carry higher mortality rates, minor and/or minimally invasive procedures are also not without significant risk. Furthermore, non-emergent procedures seem to be rising in frequency, as pediatric PH patients seem to be living longer. Careful assessment, preparation and coordination between disciplines before during and after surgery are essential to reduce these risks and optimize outcomes. At the most basic level, preparation and a healthy respect and understanding of the risks involved for the pediatric PH and CHD population is critical. In both children and adults, guidelines include recommendations that "elective" surgery in patients with PH should be performed at hospitals with expertise in PH, and in consultation with a multi-disciplinary group of PH experts.[5,432,433] When urgent/emergent surgery at a center without PH expertise is required, phone or telehealth should be considered, and if at all feasible, transfer to a PH center undertaken as soon as safely as possible.

Cardiac catheterization procedures in PAH-CHD and other forms of PH in children

As in adults, a comprehensive standardized diagnostic (initial) cardiac catheterization (including acute vasoreactivity testing in appropriate candidates) should be performed in nearly all pediatric patients prior to the initiation of PAH-targeted therapy.[433-435] Exceptions to this recommendation may apply to premature infants at high risk and/or very low body weight, children with systemic vasculopathies, or patients with an infection and/or hemodynamic instability.[436-438] The complexity of childhood PVD often requires an individualized approach. In general, cardiopulmonary hemodynamics and physiology differ substantially between patients whose PAH is either idiopathic or primarily due to CHD (e.g., PH-CHD with large left—to-right shunts such as ASD, VSD, PDA) or multivessel disease (e.g., TOF/pulmonary atresia/MAPCAs, peripheral pulmonary stenoses, complex pulmonary vein stenosis). The recommended technical approach for diagnostic hemodynamic assessment of PH in children without structural heart disease (e.g., IPAH/HPAH) in the existing guidelines differ slightly regarding whether or not a routine LHC should be done along with the RHC,[433,435] and is therefore left to individual expert opinion. In the absence of LHC, experts may still continuously monitor systemic blood pressure invasively via a femoral or radial arterial line. Similar to adults, acute vasoreactivity testing (AVT) is indicated in IPAH/HPAH and drug-induced PAH to determine eligibility for CCB therapy, and frequently in PAH-CHD to assess risk of shunt closure.[433,435]

Analgesia/Anesthesia during cardiac catheterization for children with PH

In general, diagnostic cardiac catheterization in a child with PH and near-systemic PAP or greater (mPAP > 75% of mSAP), is a diagnostic procedure with increased risk for pulmonary vascular crisis and biventricular failure. In these cases, emergency medication (atropine, epinephrine, calcium) should be drawn up in syringes on the sterile table and VA-ECMO support should be available in the hospital. These higher risk PAH patients can be monitored in an ICU or step down, intermediate care unit, after cardiac catheterization. In most instances, patients with PAH and RVF should be treated first in the ICU before considering diagnostic cardiac catheterization. The complication rate for cardiac catheterization with or without anesthesia is higher in PAH children[439,440] than in adults with PAH[441,442] (children: 5.9% morbidity: pulmonary hypertensive crisis, need for inotropic support and/or cardiac arrest; 0.55% mortality[439]; adults: 1.1% morbidity, 0.06% mortality[441,442]). Nevertheless, cardiac catheterization with AVT remains an essential part of the comprehensive PH work-up at diagnosis and follow up[436,443] and can be performed with a satisfactory risk-benefit ratio in specialized children's hospitals.[436,439,440]

In children with suspected or confirmed PH, ideally cardiac catheterization should be performed in spontaneously breathing patients (either awake or moderately sedated), if there is no contraindication.[436,438] Exceptions may rarely apply to patients with very small, obstructive and/or reactive airways (e.g., trisomy 21, asthma, OSA, prematurity, underlying parenchymal/interstitial lung disease or diaphragm/chest wall abnormalities), who may develop hypercapnia and do better with mechanical ventilation. A spontaneously breathing child with optimized upper airway positioning but hypercapnic respiratory acidosis on the first arterial blood gas analysis ($PaCO_2$ > 50 mm Hg, pH < 7.35) should be intubated before proceeding in most instances—secondary intubation is very rarely needed with optimal preparation. In cases where anesthesia with GA for catheterization is used, avoidance of acidosis, agitation while intubated and hypoxia are essential.

Key Points

1. Diagnostic catheterization in a child with near-systemic PAH or greater (mPAP > 75% of mSAP) should be performed with emergency medications (atropine, epinephrine, calcium) at the ready. Patients should be monitored in an ICU or intermediate care unit after the procedure.
2. In children with suspected or confirmed PH, cardiac catheterization should generally be performed in spontaneously breathing patients (either awake or moderately sedated), if there is no contraindication, and in the absence of hypercapnic respiratory acidosis on preprocedure blood gas analysis.
3. Cardiac catheterization in children with severe PH should be perfomed in expert centers with inhaled nitric oxide and V-A ECMO available.

Gaps in Knowledge

- Studies are needed to develop and validate non-invasive testing in order to hopefully replace cardiac catheterization in children.

Preoperative risk assessment and management

Successful and safe perioperative care of these patients requires thorough preoperative evaluation, risk stratification and preoperative hemodynamic optimization, as in adults. The preoperative assessment should include identification of risk factors which may place patients in the high-risk group (including hemodynamic, patient related, surgical and anesthetic risk factors), and gauge medical optimization and procedural preparedness. Three risk factors commonly identified as predictive of increased perioperative morbidity in children are supra-systemic PH, age < 1 year and complexity/increased duration of procedure/anesthesia. Numerous other factors that identify patients with PH at high risk of perioperative morbidity are outlined in Table 14.[444]

Wherever possible, adjustments should be made to the perioperative plan in order to mitigate risks. Non-urgent procedures should be performed at centers with intraoperative and postoperative expertise in managing pediatric PH.

Table 14 Summary of Patient, Procedural, and Anesthetic Factors to Identify Pediatric Patients with PH Who are at High Risk for Adverse Peri-Operative Events*

Hemodynamic factors
- Cardiac Index < 2.5 liter/min/m2
- mean PAP/mean SAP ratio or systolic PAP/ systolic SAP ratio >0.75
- Mean right atrial pressure > 10-15 mm Hg
- Indexed pulmonary vascular resistance > 15 WU/m2
- ECHO: Severe right ventricular enlargement, dysfunction, or failure
- ECHO: TAPSE < 10 mm (> 1 year old)
- ECHO: Systolic: Diastolic ratio > 1.4 (TR jet)
- ECHO: Pericardial effusion

Patient factors
- Treatment naïve or recent progression/exacerbation of disease
- Younger age, especially < 1 year of age
- History of syncope
- Clinical evidence of right ventricular failure
- Failure to thrive
- WHO functional class III or IV
- Elevated BNP, NT-pro BNP level
- Comorbidities: obesity, significant sleep disordered breathing, reactive airway disease, chronic aspiration, neuromuscular dysfunction, sickle cell disease, coronary anomalies, congenital / acquired cardiac disease, or other major organ dysfunction
- Chronic lung disease
- Abrupt withdrawal of PH−specific therapy
- Intercurrent illness (e.g., acute lung injury, infection/sepsis)

Surgical/procedural factors
- Emergent surgery
- Major surgery associated with major fluid shifts or bleeding (including delivery and the postpartum), significant systemic inflammatory response, extreme sympathetic tone, compromise of lung vessels, risk of embolization of surgical materials
- Increased risk secondary to age or potential cardiopulmonary compromise (Airway, abdominal, cardiac, or interventional cardiac catheterization surgery/procedures)
- Long procedural duration
- Systemic inflammatory response, reperfusion injury, excessive pain
- Potential for airway compression or compromise, airway bleeding/tracheal secretions

Anesthetic factors
- Use of general anesthesia
- ASA status ≥ III
- Unstable hemodynamic or respiratory intraoperative course: arrhythmias, intraoperative vasoactive agent use; oxygenation or ventilation difficulties
- Difficult airway
- Difficult postoperative pain management; Increased requirement for long-acting opioids
- Prolonged postoperative recovery +/- escalated cardiopulmonary support

ASA, American Society of Anesthesiologists; BNP, brain natriuretic peptide; CI, cardiac index; NT-pro BNP,N-terminal pro-BNP; PAP, pulmonary artery pressure; SAP, systemic arterial pressure, TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

Collaboration should occur between the anesthesiologist and patient's cardiologist to ensure PH has been optimized prior to surgery as well as the risk/benefit of the procedure.

When assessing patients for an upcoming surgery, remotely performed diagnostic testing may not accurately represent the current status at the time of surgery. In addition to the preoperative bloodwork specific to the given diagnosis and procedure, tests should include assessment of end-organ function (BUN/Creatinine, CBC with hemoglobin and platelet count, liver function and coagulation profile, natriuretic peptides, and if time permits, thyroid studies). If not performed within 6 months, or if the clinical status has changed, a chest x-ray, ECG and a TTE should be performed prior to the procedure to provide specific anatomic details, and an assessment of the degree of PH and ventricular health. For some patients with unclear hemodynamic phenotype, for example, mixed pre and post capillary PH, a cardiac catheterization in an experienced center may provide additional information to assist with perioperative planning. However, this comes with its own set of inherent risks and should be undertaken after a careful assessment of whether the information obtained would potentially help to minimize perioperative risk of acute decompensation and/or change the management of the PH or the planned procedure.

Preoperative management of patients with PH, especially in the setting of CHD, should focus not only on optimization of the PH itself, but also other comorbidities. All attempts should be made to optimize any underlying systemic etiologies when possible. For example, medical management of inflammatory status in patients with rheumatologic diseases, respiratory status in patients with pulmonary etiologies, and coagulation status in patients with liver disease should be undertaken to minimize their impact on the patient's PH. Pharmacologic control of arrhythmias is generally warranted if associated risks are reasonable. Beta-blockers or calcium channel blockers should generally be avoided in the setting of RV dysfunction. Iron deficiency is common in children with idiopathic PH and in patients with cyanotic CHD and should be treated prior to elective procedures. Anticoagulation merits specific discussion, whether continuation of the thromboprophylaxis, or initiation of it during the periprocedural period. In the absence of renal dysfunction, low molecular weight heparin adjusted to the patient's weight should usually suffice once stable to transition off heparin infusion. Availability of essential equipment/therapy (i.e., iNO) needs to be in place, and back-up options, such as V-A ECMO, should be discussed prior to the procedure and provided if necessary. The overarching logistical considerations are summarized in Table 15.

Further studies are required as to whether preprocedural pulmonary vasodilators modify the risk or confer an advantage during the perioperative period given the conflicting evidence.[420,421,431]

Table 15 Preoperative Logistic Analysis

- Go/No go assessment
  - Is the procedure necessary? (i.e., do the risks outweigh the benefits). Are there alternative therapeutic options to consider?
  - Are additional consultations required to prepare for the procedure?
    - Would a scheduled, multi-disciplinary meeting improve communication among providers and allow for logistic optimization? To be encouraged, if time allows.
  - Have all preoperative assessments been completed?
  - If the procedure is to be done, where is the safest location (i.e., should a procedure routinely performed in an outpatient surgical-center or provider office be moved to a hospital location)?
- Medication assessment
  - If the patient is not on medication, should PH-specific therapy be initiated?
  - If the patient is on PH-specific therapy, has the dosing been stable for a reasonable amount of time or is further optimization required?
  - Will the patient receive their medications (PH-specific and others) preop?
    - If on anti-coagulation, when should it be stopped and/or how should it be bridged?
    - How will the medications be delivered intraop and postop?
- Procedure and postprocedure assessment
  - What (additional) staffing is required to perform the procedure in the safest manner?
    - Are sub-specialty cardiac anesthesiologists required?
    - Are multiple anesthesiologists or surgeons required to optimize safety and procedure time? Is a pharmacy consultation indicated?
  - Should the procedure be modified in the setting of PH?
  - Are there special considerations for the postop period?
    - Where should the patient recover, and should the final disposition be an inpatient or outpatient setting?
      - Is the patient an ECMO candidate?
      - If the patient is to be admitted, should they have a general care or ICU bed?
      - How long should the patient stay in intensive care unit/high dependency unit?
      - What early follow-up arrangements are in place?

Key Points

1. Preoperative risk assessment should include identification of hemodynamic, patient related, surgical and anesthetic risk factors.
2. All attempts should be made to optimize the patient's hemodynamic status and any underlying systemic conditions before surgery.
3. In some cases with unclear hemodynamic phenotype, for example, CpcPH, a preoperative cardiac catheterization at an experienced center may provide additional information to assist with perioperative planning and optimization, taking into account the risks of the procedure.
4. Non-urgent procedures should be performed at centers with intraoperative and postoperative expertise in managing pediatric PH patients.

Gaps in Knowledge

1. Studies to determine the best anesthetic technique in pediatric patients with PAH should be developed.
2. Studies should be developed to address which targeted PH therapies and inopressors are best utilized in pediatric PH patients undergoing surgery or cardiac catheterization.
3. Further studies are required as to whether preprocedural pulmonary vasodilators modify the risk or confer an advantage during the perioperative period given the conflicting evidence.

Perioperative considerations for cardiac and non-cardiac surgery in pediatric PH patients

Induction of GA and emergence from GA are 2 critical periods, because they may invoke an increased risk of PH related adverse events. As discussed in previous chapters, PVR, myocardial contractility, and systemic blood pressure are affected by the effects of anesthetic agents and mechanical ventilation. For these reasons, the use of local/regional anesthesia over GA should be considered for the older child whenever possible. There is currently no consensus regarding best anesthesia technique or ideal anesthetic agent for pediatric patients with PH. The overall goals involve avoidance of a PH crisis and RVF/ischemia and maintenance of the patient's hemodynamics close to their baseline, preoperative state. The chosen anesthesia technique/agents should:

(i) avoid conditions that increase PVR such as hypoxia, hypercarbia, acidosis, and noxious stimuli,

(ii) avoid decreases in SVR such as hypovolemia and systemic vasodilatation and

(iii) avoid arrhythmias and RV coronary ischemia.

To this end, oral or IV midazolam premedication is often administered. Midazolam, fentanyl, a small dose of propofol and/or a low concentration of sevoflurane may be used for induction of anesthesia. Anesthesia may be maintained with intermittent fentanyl doses and isoflurane or sevoflurane. Some anesthesiologists include ketamine for induction and maintenance. When paralysis is required, neuromuscular blocking agents with minimal hemodynamic effects are preferable (e.g., rocuronium and vecuronium).[445]

Patients who fall into the high-risk group should be considered for preoperative hospital admission and overnight IV maintenance hydration to avoid the potentially detrimental effects of fasting and volatile induction of GA on RV preload. Airway and ventilation management are similar to adults with PH. Intraoperative delivery of iNO or an inhaled prostanoid should be readily available in the event of PH crisis and should be considered for prophylactic use in high-risk cases. Invasive arterial pressure monitoring should be considered for high-risk PH cases. TEE can be used for ongoing assessment of ventricular function but is usually limited to cardiac surgeries. Use of an invasive PA catheter is typically limited to cases in which there is a need for continuous pressure monitoring.

Vigilant perioperative monitoring for changes in heart rate, rhythm, pulse oximetry and blood pressure is necessary in order to institute prompt treatment of impending RVF or PH crisis. Treatment of PH crisis/impending PH crisis should be prompt and includes pulmonary vasodilation with 100% oxygen, hyperventilation and iNO or an inhaled prostanoid and support of the RV with inotropes such as dopamine/epinephrine, and systemic vasoconstrictors such as vasopressin. Potential underlying causes should be addressed, for example,noxious stimulus, hypotension, hypovolemia etc. Mechanical cardio-pulmonary support with veno-arterial ECMO should be considered early for refractory PH crisis.

Postoperative disposition of the patient after surgery/cardiac catheterization should take into account risk factors for postoperative adverse events and should include intensive care level monitoring for high risk cases.[423,446] A recent single center study reported a 7-day postoperative cardiac arrest rate of 4.7%.[423]

Key Points

1. Perioperative management principles for the pediatric PH patient are similar to adults, as described in the previous chapter.
2. Local/regional anesthesia should be considered favorable over GA in older children to avoid GA, if possible, however this should not be done at the expense of increased patient agitation, anxiety, and pain.

Gaps in Knowledge

1. Studies to determine the best anesthetic technique in pediatric patients with PAH are needed.
2. Studies are needed to address which targeted PH therapies and inopressors may be best utilized in pediatric PH patients undergoing surgery or cardiac catheterization.

Post-operative considerations for pediatric patients undergoing cardiac surgery

PH may be anticipated during the immediate or subsequent postop period when children undergo cardiac surgeries due either to its preoperative presence, late timing of repaired palliated state, or its known association with certain forms of CHD. Such situations include obstructed total anomalous pulmonary venous return, truncus arteriosus, transposition of the great arteries, and mitral stenosis; or in the setting of various forms of acquired heart disease, most commonly cardiomyopathies. In some cases, PH may complicate cardiac surgery in both congenital and acquired heart disease without forewarning,[447] and on occasion, a patient with a seemingly straight-forward left-sided lesion (e.g., mitral stenosis) may have transient residual and quite reactive PH following repair.

In the cardiac surgery patient, PH and associated physiology, may be due purely to increased (1) PVR (i.e., precapillary), (2) pulmonary venous hypertension from left heart pressure elevation (post-capillary), (3) CO as seen in portal hypertension or severe anemia, or (4) a combination of the 3.

Regardless of etiology, the 2 main principles of perioperative management of PH are the prevention of systemic hypotension and the prevention of acute elevations in PAP.[448] When present, RVF and the associated impaired left ventricular filling, each contribute to the decreased systemic CO, decreased coronary perfusion and myocardial ischemia. Initial measures to prevent and/or treat PH include maintenance of adequate oxygenation, ventilation, sedation, acid base equilibrium, perfusion, volume status, and excessive systemic or pulmonary afterload. Table 16.

In cases where PH is expected or anticipated, surgical placement of monitoring lines including invasive central venous and systemic arterial pressure monitoring is standard of care for perioperative management. While placement of a left atrial catheter may assist in delineating pre- and post-capillary causes of PH in the presence of left heart disease or mixed pre- and post-capillary disease, it is not without added risk and our recommendations are against the use for most patients unless it will directly impact management. PA catheter monitoring is also generally not beneficial if one has a good understanding of the preop hemodynamics and physiology, though in select circumstances may provide necessary additional information. When monitoring lines are not in place, diagnosis of PH, especially when intermittent may be difficult. The clinician then needs to be vigilant about recognizing the clinical signs of a classic PH crisis evidenced by tachycardia, hypotension, and poor perfusion. A strong suspicion and use of additional diagnostic tests such as TTE, ABG analysis or serial NT-pro BNP measurements to assist in fluid management may prove useful. General recommendations for optimal volume status target a CVP of 8-15 mm Hg, allowing for sufficient preload for the RV with dysfunction while preventing the morbidities associated with fluid overload. Patients may display greater evidence of PH and the hemodynamic consequences as the effects of anesthesia wear off, and it must be managed expediently as discussed previously.

The use of inhaled agents, such as iNO, iloprost, milrinone, and epoprostenol, have demonstrated significant effects on perioperative pulmonary pressures/vascular resistance in pediatric post-cardiac surgery patients with PH as in adults, and similarly they are generally preferable to systemic agents, as the inhaled agents have less effect on SVR and blood pressure, with nitric oxide being the most studied and utilized.

In the setting of systemic hypotension, norepinephrine or vasopressin are typically used as first line therapies for patients with refractory shock,[449] as they are in adults with PH (see previous section). An additional benefit of systemic vasoconstriction in the postoperative setting is improving the ventricular septum's contribution to both the right and left heart's performance by pushing the interventricular

Table 16 Overview of General Postoperative Considerations in Pediatric Patients with PH

Encourage	Avoid
• Anatomic investigations	• Residual anatomic disease
• Opportunities for right to left shunt as pop off	• Intact atrial septum in right heart failure
• Sedation/Anesthesia	• Agitation/ pain
• Moderate hyperventilation	• Respiratory acidosis
• Moderate alkalosis	• Metabolic acidosis
• Adequate inspired oxygen	• Alveolar hypoxia
• Normal lung volumes	• Atelectasis or over-distention
• Optimal hematocrit	• Excessive hematocrit
• Inotropic support	• Low output and low coronary perfusion
• Pulmonary vasodilators	• Systemic vasodilators/low SVR

septum off the LV and enabling more filling. Epinephrine and dopamine may be less advantageous as they increase myocardial oxygen consumption. For patients who have been treated with targeted PAH therapy prior to surgery, for example a PDE-5I, the agent is usually not initiated in the immediate postoperative period until there is no longer a pressor requirement. IV prostanoid therapy may require dose adjustment if the patient is requiring high dose pressors.

Key Points

1. While perioperative placement of a left atrial catheter may assist in delineating pre- and post-capillary causes of PH in the presence of left heart disease or mixed pre- and post-capillary disease, it is not without added risk and our recommendations are against the use for most patients unless it will directly impact management.
2. General recommendations for optimal volume status target a CVP of 8 to 15 mm Hg, allowing for sufficient pre-load for the RV with dysfunction while preventing the morbidities associated with fluid overload.
3. Inhaled pulmonary vasodilators are the preferred agents to treat postoperative PH in pediatric PH and PH-ACHD patients because of their limited systemic effects on blood pressure.

Gaps in Knowledge

1. Data are lacking to form a consensus regarding the risk vs benefit of pulmonary arterial and left atrial catheters in the immediate postoperative course of patients with PH.

Peri-operative management in patients with single ventricle physiology and PH

Complex CHD with single ventricle physiology typically requires multiple palliative cardiac surgeries. Single ventricular physiology includes heart disease where there is one functional ventricle (i.e., tricuspid valve atresia, pulmonary valve atresia, hypoplastic left heart syndrome). The goals of the first palliative procedure are to establish secure pulmonary blood flow, systemic blood flow, or both. The second stage palliative procedure is an anastomosis of the SVC to the PA, commonly known as a bidirectional Glenn shunt or bi-directional cavopulmonary (BCPA). The third stage of palliation is an anastomosis of the IVC to the PA; a total cavopulmonary anastomoses (TCPA).[450-452]

PAH has been shown to increase mortality after BCPA/TCPA.[453,454] An understanding of the potential perioperative risks for these single ventricle patients is essential as more high-risk patients survive stage 1 palliative procedures and go on to complete palliation with BCPA and TCPA with elevated PAPs.

Pulmonary vasodilators may be useful in treatment of PH after BCPA/TCPA either early after surgical palliation (acute therapy) or as long-term chronic therapy. Short-term goals of therapy include: (1) treatment of RV dysfunction after surgery and (2) lowering PAP. From clinical experience, however, it seems that iNO is the most appropriate treatment in the acute setting early after BCPA and/or TCPA.[455,456] Other inhaled prostanoids may be preferred over systemic prostanoids given the lack of systemic effects on the blood pressure and data on the use of sildenafil in the immediate postoperative period is emerging. Further study is warranted to determine whether utilization of targeted PH therapies for single ventricle patients in between staged surgeries leads to less perioperative risk and better outcomes including enabling a patient with borderline PVR to become heart transplant eligible. In the interim, the use of these agents should be monitored in coordination with a PH specialist.

Key Points

1. iNO is the preferred pulmonary vasodilatory for the acute setting early after BCPA and/or TCPA. Other inhaled prostanoids may be preferred over systemic prostanoids given the lack of systemic effects on the blood pressure.
2. All secondary causes or contributors of PH in patients with single ventricle physiology should be identified and treated.

Gaps in Knowledge

1. Further studies to determine whether utilization of targeted PH therapies for single ventricle patients in between staged surgeries leads to less perioperative risk and better outcomes, including enabling a patient with borderline PVR to become heart transplant eligible, are warranted.

Heart transplantation in children with pulmonary hypertension

While primary graft failure (PGF) remains the leading cause of mortality within the first 30 days following pediatric orthotopic heart transplantation (OHT),[457] RV dysfunction due to underlying PVD plays a significant role, as it does in adults, and can lead to death in up to 15% of pediatric patients and is a major cause of early morbidity as well.[458-461] Recipient elevated PVR is a cause for early post-transplant RV dysfunction.[459, 461] Pediatric patients with cardiomyopathies and with CHD may develop high PVR due to exposure of the pulmonary vasculature to chronically elevated LAP. Ideally, transplant should occur early in the disease process to avoid fixed PVR, unfortunately patients commonly present further along in the process and with advanced changes. In order to achieve optimal outcomes a thorough evaluation of hemodynamics including assessment of any shunt, PVR, and pulmonary vascular reactivity by AVT is required.

In patients in whom PH is evident on echocardiogram, performance of a cardiac catheterization with calculation of PVR, indexed to body surface area (PVRI), is of paramount importance prior to listing for heart transplant. This is most

commonly true in patients with restrictive cardiomyopathy, but often in patients with dilated cardiomyopathy and forms of CHD as well. Historical literature suggests that PVRI > 6 Wood units (WU) x m^2 is considered a contraindication to transplant due to the risk of postoperative RVF.[458,461] Assessment of pulmonary vascular reactivity with AVT can help identify patients who have modifiable pulmonary vascular disease that may be more suitable for transplant. Several investigators have shown that post-transplant RVF is unlikely in recipients whose PVRI decreases with AVT to a value of 4 WU x m^2.[458,461,462] Newer data indicate a threshold of 9 WU x m^2 delineates high-risk status when controlling for recipient age and era of transplant, and define a positive response to vasoreactivity testing as 6 WU x m^2.[463,464]

Traditionally, AVT has been done with initiation of 100% oxygen challenge. If no change occurs, vasodilator administration with an intravenous agent such as nitroprusside is often used, especially when the left ventricular filling pressure is elevated.[463-465] The use of iNO for assessment of pulmonary vasoreactivity should be done with caution due to the risk of pulmonary edema in patients elevated LAP (majority of cases with advanced left heart disease), and the administration of iNO may lead to acute rises in LAP and the development of pulmonary edema. However, given the rapid onset/offset of action with iNO, in select cases and with careful management, it may be used in combination with an IV vasodilator to potentially assess maximized pulmonary vascular reactivity.

It is important that decisions not be made solely based on PVRI and vasoreactivity response. Hemodynamics such as PASP and TPG, as well as patient age, diagnosis and additional co-morbidities should all be taken into account when determining transplant candidacy and listing considerations should be undertaken only at centers with expertise to manage this highly complex patient population.

Much of the data regarding hemodynamics, AVT and transplant candidacy was gathered in the early days of pediatric heart transplantation. More recent reports occur in an era in which afterload-reducing inotropic agents such as milrinone and dobutamine are available for pretransplant patient management, and pulmonary vasodilators such as iNO and oral/intravenous sildenafil are now available post-transplant.

In pediatrics, heart transplantation is increasingly a treatment option for CHD and AHF. In these patients, abnormal pulmonary blood flow resulting in vascular remodeling may result in increased PVR.[466] CHD patients inherently have increased risk of post-transplant morbidity and mortality, and therefore accurate assessment of PVR pretransplant in these patients carries added importance. However, PVR assessment in palliated single ventricle patients and patients with other forms of complex CHD may be difficult or even impossible due to anomalies of the pulmonary vasculature, branch pulmonary artery stenosis, dual supplies of pulmonary blood flow including additional sources of flow from aortopulmonary collaterals, the presence of recruitable veno-venous vessels, and discrepant blood flow to lung segments may contribute to inaccurate assessment of the PVR. In addition, one group demonstrated post-transplant elevation of PVR and TPG in recipients transplanted for Fontan failure, concluding that this reflected an advanced element of PVR that was unmasked with the introduction of normal pulmonary blood flow post-transplant.[466,467]

For patients with elevated PVR and inadequate response to AVT, a longer course of afterload reduction can be employed with agents such as IV milrinone and/or dobutamine, and re-testing by catheterization should be performed after several weeks of therapy. In some cases, improvements in hemodynamics may allow for heart transplant listing. In patients that are refractory to medical therapy, use of LVAD should be considered. In these cases, LVAD may lead to decreased filling pressures, and by unloading the left heart, allow for aggressive treatment of elevated PVR with pulmonary vasodilators in an attempt to achieve transplant candidacy.[468-470]

In high PVR transplant recipients, the thin-walled donor RV must contend with high afterload due to the elevated recipient PVR and weaning from cardiopulmonary bypass might be challenging. Intensive care therapies to reduce PH in the postoperative period are similar to those employed after CHD repair, and include prolonged sedation, avoidance of hypercapnia, hypoxia and acidosis, and the preservation of a sufficient coronary perfusion pressure. Inotropic support for the RV as well as dilation of the pulmonary arterioles should be employed as well. Inhaled NO has improved outcomes for patients with RVF following pediatric heart transplant,[463] but is very costly and not suitable for long-term use. Newer reports have shown benefits of the use of sildenafil in the reduction of PVR post-transplant.[460]

Key Points

1. A PVR threshold of 9 WU x m^2 delineates high donor heart recipient risk status when controlling for recipient age and era of transplant, and a positive response to vasoreactivity testing is defined as a drop in PVRI to 6 WU x m^2.
2. The use of iNO for assessment of pre-cardiac transplant AVT should be done with caution in cardiomyopathy patients due to the risk of pulmonary edema in patients elevated left atrial pressure. IV nitroprusside is recommended for AVT in these cases.

Gaps in Knowledge

1. Further studies are needed to determine the best pulmonary vascular hemodynamic determinants that predict recovery of PH after heart transplantation.
2. Studies are needed to define the role of pulmonary vasodilators for pre-heart transplant preparation

Summary

PH has an adverse influence on patient outcomes. The preoperative assessment of a patient with PH must include input from the surgical team, anesthesiology, cardiologist/

pulmonologist expert in the care of patients with PH or the patient's primary PH team. RV function is central to the assessment and mitigation of risks. Every effort should be made to optimize patients prior to any planned surgery —even in the setting of emergent surgery. Perioperative and intraoperative management must allow for regular assessment of RV function and adequacy of tissue perfusion. The nuances of the type of surgery, surgical approach, merits of different anesthetic strategies must be balanced against the reserve of the RV. The tenants of management center upon maintenance of systemic pressure, optimization of RV preload and strategies to improve RV afterload. RV afterload may be modified by inhaled or systemic pulmonary vasodilators. Metabolic acidosis, hypercapnia, hypoxemia, atelectasis and high airway pressures may have a deleterious effect on the marginalized RV. Agents that cause direct myocardial depression need to be identified and avoided. Extracoporeal support may be required in patients who fail medical support or as a bridge to destination therapies. Although the inta-operative period is a high risk phase, the postoperative period is more commonly associated with decompensation of the patient with PH. Therefore the postoperative management plan must consider ongoing vigilance.

Author contributions

Project Leaders: Dana McGlothlin, MD, John Granton, MD, Walter Klepetko, MD. Writing Group Chairs: Maurice Beghetti, MD, Erika Berman-Rosenzweig, MD, Paul Corris, MD, Teresa De Marco, MD, Evelyn Horn, MD, Manreet Kanwar, MD, Karen McRae, MD, Antonio Roman, MD, Ryan Tedford, MD. Writing Group Members: Roberto Badagliaacca, MD, Sonja Bartolome, MD, Raymond Benza, MD, Marco Caccamo, MD, Rebecca Cogswell, MD, Celine Dewachter, MD, Laura Donahoe, MD, Elie Fadel, MD, Harrison Farber, MD, Jeffrey Feinstein, MD, Veronica Franco, MD, Robert Frantz, MD, Michael Gatzoulis, MD, Choon Hwa (Anne) Goh, MD, Marco Guazzi, MD, Georg Hansmann, MD, Stuart Hastings, MD, Paul Heerdt, MD, Anna Hemnes, MD, Antoine Herpain, MD, Chih-Hsin Hsu, MD, Kim Kerr, MD, Nicholas Kolaitis, MD, Jasleen Kukreja, MD, Michael Madani, MD, Stuart McCluskey, MD, Michael McCulloch, MD, Bernhard Moser, MD, Manchula Navaratnam, MD, Goran Radegran, MD, Cara Reimer, MD, Laurent Savale, MD, Oksana Shlobin, MD, Jana Svetlichnaya, MD, Keith Swetz, MD, Jessica Tashjian, MD, Thenappan Thenappan, MD, C. Dario Vizza, MD, Shawn West, MD, Warren Zuckerman, MD, Andreas Zuckermann, MD.

Disclosure statement

No specific funding was available for this project. During this project, the following authors reported the listed financial activities, all outside the submitted work. Andreas Zuckerman received institutional research funding from Mallincrodt, Biotest, and Chiesi; and honoraria from Mallincrodt, Paragonix, and Kohler; and fees from Novartis and Biotest for DSMB work. Anna Hemnes received institutional research funding from CMREF and Imara, and consulting fees from Bayer, Janssen, GossamerBio, United Therapeutics, and Acceleron; and stock ownership in Tenax therapeutics. Bernhard Moser received writing fees from Up-to-Date. Celine Dewachter received advisory board fees from Novartis, Actelion-Janssen, MDS-Bayer. Chih-Hsin Hsu received speaking honoraria from Bayer, Johnson-Johnson, Pfizer, Novartis, Servier, and AstraZeneca. Elie Fadel received speaking honoraria from MSD. Erika B. Rosenzweig received institutional research funding from Janssen, Bayer, SonVie, and United Therapeutics. Evelyn Horn received consulting fees from Biotronik; DSMB fees from AADi Biosciences and SoniVie; and clinical events committee fees from V-wave Ltd. Georg Hansmann received consulting fees from Janssen and honoraria from Ferrer. Goran Radegran received institutional research funding from Janssen and Nordic Infucare; speaking honoraria from Janssen; and advisory board fees from Janssen and Acceleron paid to his company. Harrison Farber has received speaking honoraria from Bayer and SAB fees from Actelion, Acceleron, Altavant, Aerovate, and United Therapeutics. Jeffrey Feinstein has received institutional research funding from United Therapeutics. John Granton has received institutional foundation and fellowship support from Janssen Canada and Bayer Canada, and speaking honoraria from Janssen. Kim Kerr has received institutional research funding from Bayer and consulting fees from Actelion. Laurent Savale has received institutional research funding from Acceleron, Janssen, GSK, MSD; speaker honoraria from Actelion and MSD; and advisory board fees from Janssen. Manreet Kanwar has received advisory board fees from Abiomed, Bayer, and CareDx; and speaker honoraria from Abiomed. Marco Caccamo has received speaker honoraria from Bayer. Maurice Beghetti has received institutional research funding, speaker honoraria, travel support; consulting fees from Actelion-Janssen, Bayer, Orpha, Altavant, Gossamer, and Acceleron; DSMB fees from Actelion-Janssen, Altavant, Bayer, GSK, Merck, and Gossamer. Michael Gatzoulis has received institutional research funding and speaker honoraria from Janssen. Michael Madani has received royalties from Wexler Surgical; consulting fees from Actelion-Janssen and Merk; and travel expenses from Bayer. Nicholas Kolaitis has received consulting fees from United Therapeutics, Acceleron, and Janssen; and Advisory Board fees from Janssen and Bayer. Okasana Shlobin has received consulting fees from United Therapeutics, Bayer, Janssen, and Acceleron. Paul Heerdt has received institutional research funding from NTT Research and consulting fees from Cardiage LLC and Baxter; and he was co-founder of RVMetrics, LLC. Raymond Benza received consulting fees from Bayer, Janssen, United Therapeutics, Acceleron, CERENO, Abbott, and Gossamer; and advisory board fees from Acceleron. Robert Frantz received writing fees from Up-to-Date; personal consulting fees from Janssen, Liquidia, Shouti, Altavent, and Tenax; consulting fees to his institution from Gossamer and Bayer; speaking fees to his institution from United Therapeutics; personal speaking honoraria from France Foundation and

Janssen; and DSMB fees from Janssen and Liquidia. Roberto Badagliacca received advisory board fees from MSD, Dompe, Janssen, United Therapeutics, and Ferrer; and speaker honoraria from Bayer, MSD, Ferrer, Dompe, Janssen, United Therapeutics, and AOP. Ryan Tedford received consulting fees from Merck, Actelion, Edwards, United Therapeutics, CareDx, Gradient, Abbott, Medtronic, Aria CV Inc, Itamar, Eidos, and Lexicon; travel support from Abiomed; DSMB fees from Edwards; and steering committee fees from Abbott, Acceleron, and Medtronic. Sonja Bartolome received consulting fees from Janssen and United Therapeutics, and travel support from Janssen. Teresa De Marco received institutional research funding from Acceleron and CareDx; consulting fees from Actelion-Janssen, Trio Health, Liquidia, Aerovate, Boston Scientific, NXT, Atara, and Acceleron; travel support from CareDx, and advisory board fees from BIAL and Acceleron. Thenappan Thenappan received institutional research funding from United Therapeutics, Aria CV, Acceleron, and Tenax; consulting and advisory board fees from Acceleron, Altavant, United Therapeutics, and Actelion-Janssen. Veronica Franco received institutional research funding from United Therapeutics, Acceleron, Aerovate, Aria CV, Cereno Scientific, Fluidda, and Gossamer.

The authors would like to thank Teresa De Marco, MD for her inspiration and participation in the project; Megan Barrett for providing administrative support for the process, including invitation of the authors through the final approval by the ISHLT Board of Directors; expert reviewers Jean-Luc Vachiery, MD and David Jenkins, FRCS; Mardi Gomberg-Maitland for helping to shepherd the document through ISHLT channels; and members of the ISHLT who provided their valuable input on the manuscript while in preparation.

References

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53.
2. Meyer S, McLaughlin VV, Seyfarth H-J, et al. Outcomes of noncardiac, nonobstetric surgery in patients with PAH: an international prospective survey. Eur Respir J 2013;41:1302-7.
3. Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest 2014;146:449-75.
4. Fox DL, Stream AR, Bull T. Perioperative management of the patient with pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2014;18:310-8.
5. Olsson KM, Halank M, Egenlauf B, et al. Decompensated right heart failure, intensive care and perioperative management in patients with pulmonary hypertension: updated recommendations from the cologne consensus conference 2018. Int J Cardiol 2018;272S:46-52.
6. Tonelli AR, Minai OA. Saudi guidelines on the diagnosis and treatment of pulmonary hypertension: perioperative management in patients with pulmonary hypertension. Ann Thorac Med 2014;9 (Suppl 1):S98-S107.
7. Galie N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53.
8. Lai HC, Lai HC, Wang KY, Lee WL, Ting CT, Liu TJ. Severe pulmonary hypertension complicates postoperative outcome of non-cardiac surgery. Br J Anaesth 2007;99:184-90.
9. Price LC, Montani D, Jais X, et al. Noncardiothoracic nonobstetric surgery in mild-to-moderate pulmonary hypertension. Eur Respir J 2010;35:1294-302.
10. Kaw R, Pasupuleti V, Deshpande A, Hamieh T, Walker E, Minai OA. Pulmonary hypertension: an important predictor of outcomes in patients undergoing non-cardiac surgery. Respir Med 2011;105:619-24.
11. Ramakrishna G, Sprung J, Ravi BS, Chandrasekaran K, McGoon MD. Impact of pulmonary hypertension on the outcomes of noncardiac surgery: predictors of perioperative morbidity and mortality. J Am Coll Cardiol 2005;45:1691-9.
12. Meyer S, McLaughlin VV, Seyfarth HJ, et al. Outcomes of noncardiac, nonobstetric surgery in patients with PAH: an international prospective survey. Eur Respir J 2013;41:1302-7.
13. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J 2017;50.
14. Benza RL, Miller DP, Foreman AJ, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL) analysis. J Heart Lung Transplant 2015;34:356-61.
15. Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 2018;39:4175-81.
16. Lahm T, McCaslin CA, Wozniak TC, et al. Medical and surgical treatment of acute right ventricular failure. J Am Coll Cardiol 2010;56:1435-46.
17. Bedouch P, Roustit M, Quetant S, et al. Development of a pharmacist collaborative care program for pulmonary arterial hypertension. Int J Clin Pharm 2011;33:898-901.
18. Kingman MS, Tankersley MA, Lombardi S, et al. Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey. J Heart Lung Transplant 2010;29:841-6.
19. Watanabe K, Ito N, Ohata T, Kariya T, Inui H, Yamada Y. Preoperative balloon pulmonary angioplasty enabled noncardiac surgery of a patient with chronic thromboembolic pulmonary hypertension (CTEPH): a case report. Medicine (Baltimore) 2019;98:e14807.
20. McGlothlin D, Ivascu N, Heerdt PM. Anesthesia and pulmonary hypertension. Prog Cardiovasc Dis 2012;55:199-217.
21. Reimer CG. J. Pharmacology of the Pulmonary Circulation. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery, 2nd ed, Springer; 2019.
22. Pilkington SA, Taboada D, Martinez G. Pulmonary hypertension and its management in patients undergoing non-cardiac surgery. Anaesthesia 2015;70:56-70.
23. Steppan J, Diaz-Rodriguez N, Barodka VM, et al. Focused review of perioperative care of patients with pulmonary hypertension and proposal of a perioperative pathway. Cureus 2018;10:e2072.
24. Kondo U, Kim SO, Nakayama M, Murray PA. Pulmonary vascular effects of propofol at baseline, during elevated vasomotor tone, and in response to sympathetic alpha- and beta-adrenoreceptor activation. Anesthesiology 2001;94:815-23.
25. Ouedraogo N, Mounkaila B, Crevel H, Marthan R, Roux E. Effect of propofol and etomidate on normoxic and chronically hypoxic pulmonary artery. BMC Anesthesiol 2006;6:2.
26. Pensado A, Molins N, Alvarez J. Effects of propofol on mean arterial pressure and systemic vascular resistance during cardiopulmonary bypass. Acta Anaesthesiol Scand 1993;37:498-501.
27. Green DW. Cardiac output decrease and propofol: what is the mechanism? Br J Anaesth 2015;114:163-4.
28. Tweed WA, Minuck M, Mymin D. Circulatory responses to ketamine anesthesia. Anesthesiology 1972;37:613-9.
29. Gooding JM, Dimick AR, Tavakoli M, Corssen G. A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. Anesth Analg 1977;56:813-6.
30. Williams GD, Philip BM, Chu LF, et al. Ketamine does not increase pulmonary vascular resistance in children with pulmonary

hypertension undergoing sevoflurane anesthesia and spontaneous ventilation. Anesth Analg 2007;105:1578-84. table of contents.
31. Friesen RH, Twite MD, Nichols CS, et al. Hemodynamic response to ketamine in children with pulmonary hypertension. Paediatr Anaesth 2016;26:102-8.
32. Heller AR, Litz RJ, Koch T. A fine balance—one-lung ventilation in a patient with Eisenmenger syndrome. Br J Anaesth 2004;92:587-90.
33. Rees DI, Gaines GY 3rd. One-lung anesthesia—a comparison of pulmonary gas exchange during anesthesia with ketamine or enflurane. Anesth Analg 1984;63:521-5.
34. Burbridge MA, Brodt J, Jaffe RA. Ventriculoperitoneal shunt insertion under monitored anesthesia care in a patient with severe pulmonary hypertension. A A Case Rep 2016;7:27-9.
35. Colvin MP, Savege TM, Newland PE, et al. Cardiorespiratory changes following induction of anaesthesia with etomidate in patients with cardiac disease. Br J Anaesth 1979;51:551-6.
36. Nakayama M, Kondo U, Murray PA. Pulmonary vasodilator response to adenosine triphosphate-sensitive potassium channel activation is attenuated during desflurane but preserved during sevoflurane anesthesia compared with the conscious state. Anesthesiology 1998;88:1023-35.
37. Priebe HJ. Differential effects of isoflurane on regional right and left ventricular performances, and on coronary, systemic, and pulmonary hemodynamics in the dog. Anesthesiology 1987;66:262-72.
38. Kerbaul F, Bellezza M, Mekkaoui C, et al. Sevoflurane alters right ventricular performance but not pulmonary vascular resistance in acutely instrumented anesthetized pigs. J Cardiothorac Vasc Anesth 2006;20:209-16.
39. Schulte-Sasse U, Hess W, Tarnow J. Pulmonary vascular responses to nitrous oxide in patients with normal and high pulmonary vascular resistance. Anesthesiology 1982;57:9-13.
40. McCoy EP, Maddineni VR, Elliott P, Mirakhur RK, Carson IW, Cooper RA. Haemodynamic effects of rocuronium during fentanyl anaesthesia: comparison with vecuronium. Can J Anaesth 1993;40:703-8.
41. Searle NR, Thomson I, Dupont C, et al. A two-center study evaluating the hemodynamic and pharmacodynamic effects of cisatracurium and vecuronium in patients undergoing coronary artery bypass surgery. J Cardiothorac Vasc Anesth 1999;13:20-5.
42. Kaye AD, Hoover JM, Kaye AJ, et al. Morphine, opioids, and the feline pulmonary vascular bed. Acta Anaesthesiol Scand 2008;52:931-7.
43. Jin HK, Chen YF, Yang RH, McKenna TM, Jackson RM, Oparil S. Vasopressin lowers pulmonary artery pressure in hypoxic rats by releasing atrial natriuretic peptide. Am J Med Sci 1989;298:227-36.
44. Neal JM, Bernards CM, Hadzic A, et al. ASRA practice advisory on neurologic complications in regional anesthesia and pain medicine. Reg Anesth Pain Med 2008;33:404-15.
45. Bourne E, Wright C, Royse C. A review of local anesthetic cardiotoxicity and treatment with lipid emulsion. Local Reg Anesth 2010;3:11-9.
46. Vieillard-Baron A, Matthay M, Teboul JL, et al. Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. Intensive Care Med 2016;42:739-49.
47. Marini JJ, Culver BH, Butler J. Mechanical effect of lung distention with positive pressure on cardiac function. Am Rev Respir Dis 1981;124:382-6.
48. Strumpher J, Jacobsohn E. Pulmonary hypertension and right ventricular dysfunction: physiology and perioperative management. J Cardiothorac Vasc Anesth 2011;25:687-704.
49. Aguirre MA, Lynch I, Hardman B. Perioperative management of pulmonary hypertension and right ventricular failure during noncardiac surgery. Adv Anesth 2018;36:201-30.
50. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 1975;292:284-9.
51. Fischer LG, Van Aken H, Burkle H. Management of pulmonary hypertension: physiological and pharmacological considerations for anesthesiologists. Anesth Analg 2003;96:1603-16.
52. Pritts CD, Pearl RG. Anesthesia for patients with pulmonary hypertension. Curr Opin Anaesthesiol 2010;23:411-6.
53. Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: pathophysiology and anesthetic approach. Anesthesiology 2003;99:1415-32.
54. Roberts DH, Lepore JJ, Maroo A, Semigran MJ, Ginns LC. Oxygen therapy improves cardiac index and pulmonary vascular resistance in patients with pulmonary hypertension. Chest 2001;120:1547-55.
55. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Crit Care 2010;14:R169.
56. American Society of Anesthesiologists Task Force on Pulmonary Artery C. Practice guidelines for pulmonary artery catheterization: an updated report by the American society of anesthesiologists task force on pulmonary artery catheterization. Anesthesiology 2003;99:988-1014.
57. Ashes C, Roscoe A. Transesophageal echocardiography in thoracic anesthesia: pulmonary hypertension and right ventricular function. Curr Opin Anaesthesiol 2015;28:38-44.
58. Vieillard-Baron A, Naeije R, Haddad F, et al. Diagnostic workup, etiologies and management of acute right ventricle failure: a state-of-the-art paper. Intensive Care Med 2018.
59. Marik PE. Obituary: pulmonary artery catheter 1970 to 2013. Ann Intensive Care 2013;3:38.
60. De Backer D, Vincent JL. The pulmonary artery catheter: is it still alive? Curr Opin Crit Care 2018;24:204-8.
61. Kruthiventi SC, Kane GC, Sprung J, Weingarten TN, Warner ME. Postoperative pulmonary complications in contemporary cohort of patients with pulmonary hypertension. Bosn J Basic Med Sci 2019;19:392-9.
62. Hoeper MM, Benza RL, Corris P, et al. Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. Eur Respir J 2019;53.
63. Kwak YL, Lee CS, Park YH, Hong YW. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension*. Anaesthesia 2002;57:9-14.
64. Jin HK, Yang RH, Chen YF, Thornton RM, Jackson RM, Oparil S. Hemodynamic effects of arginine vasopressin in rats adapted to chronic hypoxia. J Appl Physiol 1989;66:151-60.
65. Currigan DA, Hughes RJ, Wright CE, Angus JA, Soeding PF. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: an in vitro study. Anesthesiology 2014;121:930-6.
66. Price LC, Dimopoulos K, Marino P, et al. The CRASH report: emergency management dilemmas facing acute physicians in patients with pulmonary arterial hypertension. Thorax 2017;72:1035-45.
67. Ichinose F, Roberts JD Jr., Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. Circulation 2004;109:3106-11.
68. Augoustides JG, Ochroch EA. Pro: inhaled prostaglandin as a pulmonary vasodilator instead of nitric oxide. J Cardiothorac Vasc Anesth 2005;19:400-2.
69. Atz AM, Wessel DL. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. Anesthesiology 1999;91:307-10.
70. Namachivayam P, Theilen U, Butt WW, Cooper SM, Penny DJ, Shekerdemian LS. Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children. Am J Respir Crit Care Med 2006;174:1042-7.
71. Singh R, Choudhury M, Saxena A, Kapoor PM, Juneja R, Kiran U. Inhaled nitroglycerin versus inhaled milrinone in children with congenital heart disease suffering from pulmonary artery hypertension. J Cardiothorac Vasc Anesth 2010;24:797-801.
72. Yurtseven N, Karaca P, Uysal G, et al. A comparison of the acute hemodynamic effects of inhaled nitroglycerin and iloprost in patients with pulmonary hypertension undergoing mitral valve surgery. Ann Thorac Cardiovasc Surg 2006;12:319-23.
73. Matamis D, Pampori S, Papathanasiou A, et al. Inhaled NO and sildenafil combination in cardiac surgery patients with out-of-proportion pulmonary hypertension: acute effects on postoperative gas exchange and hemodynamics. Circ Heart Fail 2012;5:47-53.

74. Vater Y, Martay K, Dembo G, Bowdle TA, Weinbroum AA. Intraoperative epoprostenol and nitric oxide for severe pulmonary hypertension during orthotopic liver transplantation: a case report and review of the literature. Med Sci Monit 2006;12:CS115-8.
75. Flondor M, Merkel M, Hofstetter C, Irlbeck M, Frey L, Zwissler B. The effect of inhaled nitric oxide and inhaled iloprost on hypoxaemia in a patient with pulmonary hypertension after pulmonary thrombarterectomy. Anaesthesia 2006;61:1200-3.
76. Haraldsson s A, Kieler-Jensen N, Ricksten SE. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. Anesth Analg 2001;93:1439-45. table of contents.
77. Rocca GD, Coccia C, Pompei L, et al. Hemodynamic and oxygenation changes of combined therapy with inhaled nitric oxide and inhaled aerosolized prostacyclin. J Cardiothorac Vasc Anesth 2001;15:224-7.
78. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American college of cardiology/American heart association task force on practice guidelines. Circulation 2014;130:e278-333.
79. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med 2021;384:325-34.
80. Olsson KM, Nickel NP, Tongers J, Hoeper MM. Atrial flutter and fibrillation in patients with pulmonary hypertension. Int J Cardiol 2013;167:2300-5.
81. Peacock A, Ross K. Pulmonary hypertension: a contraindication to the use of {beta}-adrenoceptor blocking agents. Thorax 2010;65:454-5.
82. Abrams DC, Brodie D, Rosenzweig EB, Burkart KM, Agerstrand CL, Bacchetta MD. Upper-body extracorporeal membrane oxygenation as a strategy in decompensated pulmonary arterial hypertension. Pulm Circ 2013;3:432-5.
83. Rosenzweig EB, Brodie D, Abrams DC, Agerstrand CL, Bacchetta M. Extracorporeal membrane oxygenation as a novel bridging strategy for acute right heart failure in group 1 pulmonary arterial hypertension. ASAIO J 2014;60:129-33.
84. Avriel A, Klement AH, Johnson SR, de Perrot M, Granton J. Impact of left ventricular diastolic dysfunction on lung transplantation outcome in patients with pulmonary arterial hypertension. Am J Transplant 2017;17:2705-11.
85. Strueber M, Hoeper MM, Fischer S, et al. Bridge to thoracic organ transplantation in patients with pulmonary arterial hypertension using a pumpless lung assist device. Am J Transplant 2009;9:853-7.
86. Punnoose L, Burkhoff D, Rich S, Horn EM. Right ventricular assist device in end-stage pulmonary arterial hypertension: insights from a computational model of the cardiovascular system. Prog Cardiovasc Dis 2012;55:234-43. e2.
87. Rosenzweig EB, Chicotka S, Bacchetta M. Right ventricular assist device use in ventricular failure due to pulmonary arterial hypertension: lessons learned. J Heart Lung Transplant 2016;35:1272-4.
88. Ammash NM, Connolly HM, Abel MD, Warnes CA. Noncardiac surgery in Eisenmenger syndrome. J Am Coll Cardiol 1999;33:222-7.
89. Deljou A, Sabov M, Kane GC, et al. Outcomes after noncardiac surgery for patients with pulmonary hypertension: a historical cohort study. J Cardiothorac Vasc Anesth 2020;34:1506-13.
90. Smilowitz NR, Armanious A, Bangalore S, Ramakrishna H, Berger JS. Cardiovascular outcomes of patients with pulmonary hypertension undergoing noncardiac surgery. Am J Cardiol 2019;123:1532-7.
91. Memtsoudis SG, Ma Y, Chiu YL, Walz JM, Voswinckel R, Mazumdar M. Perioperative mortality in patients with pulmonary hypertension undergoing major joint replacement. Anesth Analg 2010;111:1110-6.
92. Bennett JM, Ehrenfeld JM, Markham L, Eagle SS. Anesthetic management and outcomes for patients with pulmonary hypertension and intracardiac shunts and Eisenmenger syndrome: a review of institutional experience. J Clin Anesth 2014;26:286-93.
93. Kim D, Jules-Elysee K, Turteltaub L, et al. Clinical outcomes in patients with pulmonary hypertension undergoing total hip arthroplasty. HSS J 2014;10:131-5.
94. Minai OA, Venkateshiah SB, Arroliga AC. Surgical intervention in patients with moderate to severe pulmonary arterial hypertension. Conn Med 2006;70:239-43.
95. Ichinokawa M, Hida Y, Kaga K, Kawada M, Niizeki H, Kondo S. A case of primary pulmonary hypertension with pulmonary tumor. Ann Thorac Cardiovasc Surg 2010;16:270-2.
96. Kreider ME, Hansen-Flaschen J, Ahmad NN, et al. Complications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease. Ann Thorac Surg 2007;83:1140-4.
97. Ross AF, Ueda K. Pulmonary hypertension in thoracic surgical patients. Curr Opin Anaesthesiol 2010;23:25-33.
98. Nonaka DF, Grichnik KP, Whitener GB. Pulmonary hypertension and thoracic surgery: diagnostics and advances in therapy and intraoperative management. Current Anesthesiology Reports 2014;4:135-41.
99. Huang A, Marseu K. Pulmonary resection in the patient with pulmonary hypertension. In: Slinger P, ed. Principles and Practice of Anesthesia for Thoracic Surgery, Cham: Springer International Publishing; 2019:561-80.
100. Jung DM, Ahn HJ, Jung SH, et al. Apneic oxygen insufflation decreases the incidence of hypoxemia during one-lung ventilation in open and thoracoscopic pulmonary lobectomy: a randomized controlled trial. J Thorac Cardiovasc Surg 2017;154:360-6.
101. Lohser J, Slinger P. Lung injury after one-lung ventilation: a review of the pathophysiologic mechanisms affecting the ventilated and the collapsed lung. Anesth Analg 2015;121:302-18.
102. Heerdt PM, Stowe DF. Single-lung ventilation and oxidative stress: a different perspective on a common practice. Curr Opin Anaesthesiol 2017;30:42-9.
103. Misthos P, Katsaragakis S, Theodorou D, Milingos N, Skottis I. The degree of oxidative stress is associated with major adverse effects after lung resection: a prospective study. Eur J Cardiothorac Surg 2006;29:591-5.
104. Alfonsi P, Vieillard-Baron A, Coggia M, et al. Cardiac function during intraperitoneal CO2 insufflation for aortic surgery: a transesophageal echocardiographic study. Anesth Analg 2006;102:1304-10.
105. Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy. Anesth Analg 1993;76:1067-71.
106. Harris SN, Ballantyne GH, Luther MA, Perrino AC Jr. Alterations of cardiovascular performance during laparoscopic colectomy: a combined hemodynamic and echocardiographic analysis. Anesth Analg 1996;83:482-7.
107. Lestar M, Gunnarsson L, Lagerstrand L, Wiklund P, Odeberg-Wernerman S. Hemodynamic perturbations during robot-assisted laparoscopic radical prostatectomy in 45 degrees Trendelenburg position. Anesth Analg 2011;113:1069-75.
108. Hirvonen EA, Poikolainen EO, Paakkonen ME, Nuutinen LS. The adverse hemodynamic effects of anesthesia, head-up tilt, and carbon dioxide pneumoperitoneum during laparoscopic cholecystectomy. Surg Endosc 2000;14:272-7.
109. Perilli V, Sollazzi L, Bozza P, et al. The effects of the reverse trendelenburg position on respiratory mechanics and blood gases in morbidly obese patients during bariatric surgery. Anesth Analg 2000;91:1520-5.
110. Christie J, Robinson CM, Pell AC, McBirnie J, Burnett R. Transcardiac echocardiography during invasive intramedullary procedures. J Bone Joint Surg Br 1995;77:450-5.
111. Eriksson EA, Pellegrini DC, Vanderkolk WE, Minshall CT, Fakhry SM, Cohle SD. Incidence of pulmonary fat embolism at autopsy: an undiagnosed epidemic. J Trauma 2011;71:312-5.
112. Rothberg DL, Makarewich CA. Fat embolism and fat embolism syndrome. J Am Acad Orthop Surg 2019;27:e346-e55.
113. Lieberman JR, Cheng V, Cote MP. Pulmonary embolism rates following total hip arthroplasty with prophylactic anticoagulation: some pulmonary emboli cannot be avoided. J Arthroplasty 2017;32:980-6.

114. Duarte AG, Thomas S, Safdar Z, et al. Management of pulmonary arterial hypertension during pregnancy: a retrospective, multicenter experience. Chest 2013;143:1330-6.
115. Curry RA, Fletcher C, Gelson E, et al. Pulmonary hypertension and pregnancy—a review of 12 pregnancies in nine women. BJOG 2012;119:752-61.
116. Ma L, Liu W, Huang Y. Perioperative management for parturients with pulmonary hypertension: experience with 30 consecutive cases. Front Med 2012;6:307-10.
117. Rosengarten D, Blieden LC, Kramer MR. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 2012;40:1304-5.
118. Kiely DG, Condliffe R, Webster V, et al. Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. BJOG 2010;117:565-74.
119. Bendayan D, Hod M, Oron G, et al. Pregnancy outcome in patients with pulmonary arterial hypertension receiving prostacyclin therapy. Obstet Gynecol 2005;106(5 Pt 2):1206-10.
120. Sun X, Feng J, Shi J. Pregnancy and pulmonary hypertension: an exploratory analysis of risk factors and outcomes. Medicine (Baltimore) 2018;97:e13035.
121. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the registry of pregnancy and cardiac disease (ROPAC) of the European society of cardiology. Eur J Heart Fail 2016;18:1119-28.
122. Thomas E, Yang J, Xu J, Lima FV, Stergiopoulos K. Pulmonary hypertension and pregnancy outcomes: insights from the national inpatient sample. J Am Heart Assoc 2017;6.
123. Jais X, Olsson KM, Barbera JA, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 2012;40:881-5.
124. Kamp JC, von Kaisenberg C, Greve S, et al. Pregnancy in pulmonary arterial hypertension: midterm outcomes of mothers and offspring. J Heart Lung Transplant 2021;40:229-33.
125. Hemnes AR, Kiely DG, Cockrill BA, et al. Statement on pregnancy in pulmonary hypertension from the pulmonary vascular research institute. Pulm Circ 2015;5:435-65.
126. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256-65.
127. Duggan AB, Katz SG. Combined spinal and epidural anaesthesia for caesarean section in a parturient with severe primary pulmonary hypertension. Anaesth Intensive Care 2003;31:565-9.
128. Myles PS. Anaesthetic management for laparoscopic sterilisation and termination of pregnancy in a patient with severe primary pulmonary hypertension. Anaesth Intensive Care 1994;22:465-9.
129. Rodriguez RM, Pearl RG. Pulmonary hypertension and major surgery. Anesth Analg 1998;87:812-5.
130. Foresman RN, Connors CW. Severe pulmonary hypertension and right ventricular failure complicate a total abdominal hysterectomy. Semin Cardiothorac Vasc Anesth 2011;15:179-82.
131. Bessa Junior RC, Silva Filho AL, Maia PV, Quites LO, Triginelli SA. [Hemodynamic repercussions of exaggerated lithotomy position for vaginal hysterectomy in cardiac patient: case report.]. Rev Bras Anestesiol 2006;56:57-62.
132. Holte K, Kehlet H. Postoperative ileus: a preventable event. Br J Surg 2000;87:1480-93.
133. Martin JT, Tautz TJ, Antognini JF. Safety of regional anesthesia in Eisenmenger's syndrome. Reg Anesth Pain Med 2002;27:509-13.
134. Hsu CH, Gomberg-Maitland M, Glassner C, Chen JH. The management of pregnancy and pregnancy-related medical conditions in pulmonary arterial hypertension patients. Int J Clin Pract Suppl 2011: 6-14.
135. Bonnin M, Mercier FJ, Sitbon O, et al. Severe pulmonary hypertension during pregnancy: mode of delivery and anesthetic management of 15 consecutive cases. Anesthesiology 2005;102:1133-7. discussion 5A-6A.
136. Champaneria R, Shah L, Geoghegan J, Gupta JK, Daniels JP. Analgesic effectiveness of transversus abdominis plane blocks after hysterectomy: a meta-analysis. Eur J Obstet Gynecol Reprod Biol 2013;166:1-9.
137. Famuyide AO, Hopkins MR, El-Nashar SA, et al. Hysteroscopic sterilization in women with severe cardiac disease: experience at a tertiary center. Mayo Clin Proc 2008;83:431-8.
138. Ueda Y, Kamiya CA, Horiuchi C, et al. Safety and efficacy of a 52-mg levonorgestrel-releasing intrauterine system in women with cardiovascular disease. J Obstet Gynaecol Res 2019;45:382-8.
139. Berthelot E, Bauer F, Eicher JC, et al. Pulmonary hypertension in chronic heart failure: definitions, advances, and unanswered issues. ESC Heart Fail 2018;5:755-63.
140. Fang JC, DeMarco T, Givertz MM, et al. World health organization pulmonary hypertension group 2: pulmonary hypertension due to left heart disease in the adult—a summary statement from the pulmonary hypertension council of the international society for heart and lung transplantation. J Heart Lung Transplant 2012;31:913-33.
141. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. Anesth Analg 1999;89:814-22.
142. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:734-44. discussion 44-5.
143. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;24:881-2.
144. Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. JACC Cardiovasc Imaging 2015;8:83-99.
145. Tichelbacker T, Dumitrescu D, Gerhardt F, et al. Pulmonary hypertension and valvular heart disease. Herz 2019;44:491-501.
146. Capomolla S, Pozzoli M, Opasich C, et al. Dobutamine and nitroprusside infusion in patients with severe congestive heart failure: hemodynamic improvement by discordant effects on mitral regurgitation, left atrial function, and ventricular function. Am Heart J 1997;134:1089-98.
147. Maeder MT, Weber L, Buser M, et al. Pulmonary hypertension in aortic and mitral valve disease. Front Cardiovasc Med 2018;5:40.
148. Kumar N, Sevta P, Satyarthy S, Agarwal S, Betigeri VK, Satsangi DK. Early results of mitral valve replacement in severe pulmonary artery hypertension°TMan institutional prospective study. %J World Journal of Cardiovascular Surgery 2013;03(02):7.
149. Yang B, DeBenedictus C, Watt T, et al. The impact of concomitant pulmonary hypertension on early and late outcomes following surgery for mitral stenosis. J Thorac Cardiovasc Surg 2016;152:394-400. e1.
150. Fawzy ME, Hassan W, Stefadouros M, Moursi M, El Shaer F, Chaudhary MA. Prevalence and fate of severe pulmonary hypertension in 559 consecutive patients with severe rheumatic mitral stenosis undergoing mitral balloon valvotomy. J Heart Valve Dis 2004;13:942-7. discussion 7-8.
151. Fawzy ME, Osman A, Nambiar V, et al. Immediate and long-term results of mitral balloon valvuloplasty in patients with severe pulmonary hypertension. J Heart Valve Dis 2008;17:485-91.
152. Alexopoulos D, Lazzam C, Borrico S, Fiedler L, Ambrose JA. Isolated chronic mitral regurgitation with preserved systolic left ventricular function and severe pulmonary hypertension. J Am Coll Cardiol 1989;14:319-22.
153. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines. J Am Coll Cardiol 2014;63:e57-185.
154. Corciova F, Corciova C, Arsenescu Georgescu C, et al. Echocardiographic predictors of adverse short-term outcomes after heart surgery in patients with mitral regurgitation and pulmonary hypertension; 2012.
155. Bonow RO, Adams DH. The time has come to define centers of excellence in mitral valve repair. J Am Coll Cardiol 2016;67:499-501.

156. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a 'proof of concept' from the MITRA-FR and COAPT trials? Eur J Heart Fail 2019.
157. Al-Bawardy R, Vemulapalli S, Thourani VH, et al. Association of pulmonary hypertension with clinical outcomes of transcatheter mitral valve repair. JAMA Cardiol 2020;5:47-56.
158. Levy F, Bohbot Y, Sanhadji K, et al. Impact of pulmonary hypertension on long-term outcome in patients with severe aortic stenosis. Eur Heart J Cardiovasc Imaging 2018;19:553-61.
159. Kokkinidis DG, Papanastasiou CA, Jonnalagadda AK, et al. The predictive value of baseline pulmonary hypertension in early and long term cardiac and all-cause mortality after transcatheter aortic valve implantation for patients with severe aortic valve stenosis: a systematic review and meta-analysis. Cardiovasc Revasc Med 2018;19(7 Pt B):859-67.
160. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.
161. Zlotnick DM, Ouellette ML, Malenka DJ, et al. Effect of preoperative pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. Am J Cardiol 2013;112:1635-40.
162. Ben-Dor I, Goldstein SA, Pichard AD, et al. Clinical profile, prognostic implication, and response to treatment of pulmonary hypertension in patients with severe aortic stenosis. Am J Cardiol 2011;107:1046-51.
163. Weber L, Rickli H, Haager PK, et al. Haemodynamic mechanisms and long-term prognostic impact of pulmonary hypertension in patients with severe aortic stenosis undergoing valve replacement. Eur J Heart Fail 2018.
164. O'Sullivan CJ, Wenaweser P, Ceylan O, et al. Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation: insights from the new proposed pulmonary hypertension classification. Circ Cardiovasc Interv 2015;8:e002358.
165. Testa L, Latib A, De Marco F, et al. Persistence of severe pulmonary hypertension after transcatheter aortic valve replacement: incidence and prognostic impact. Circ Cardiovasc Interv 2016;9.
166. Gutmann A, Kaier K, Reinecke H, et al. Impact of pulmonary hypertension on in-hospital outcome after surgical or transcatheter aortic valve replacement. EuroIntervention 2017;13:804-10.
167. Khandhar S, Varadarajan P, Turk R, et al. Survival benefit of aortic valve replacement in patients with severe aortic regurgitation and pulmonary hypertension. Ann Thorac Surg 2009;88:752-6.
168. Bermejo J, Yotti R, Garcia-Orta R, et al. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. Eur Heart J 2018;39:1255-64.
169. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J 2016;37:67-119.
170. Vachiery JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. Eur Respir J 2019;53. https://doi.org/10.1183/13993003.01897-2018. Print 2019 Jan.
171. Subbotina I, Girdauskas E, Bernhardt AM, Sinning C, Reichenspurner H, Sill B. Comparison of outcomes of tricuspid valve surgery in patients with reduced and normal right ventricular function. Thorac Cardiovasc Surg 2017;65:617-25.
172. Chen Y, Liu JH, Chan D, et al. Prevalence, predictors and clinical outcome of residual pulmonary hypertension following tricuspid annuloplasty. J Am Heart Assoc 2016;5.
173. Farber G, Tkebuchava S, Dawson RS, et al. Minimally invasive, isolated tricuspid valve redo surgery: a safety and outcome analysis. Thorac Cardiovasc Surg 2018;66:564-71.
174. Civelek A, Ak K, Akgun S, Isbir SC, Arsan S. Tricuspid valve replacement: an analysis of risk factors and outcomes. Thorac Cardiovasc Surg 2008;56:456-60.
175. Buzzatti N, Iaci G, Taramasso M, et al. Long-term outcomes of tricuspid valve replacement after previous left-side heart surgery. Eur J Cardiothorac Surg 2014;46:713-9. discussion 9.
176. De Meester P, Van De Bruaene A, Voigt JU, Herijgers P, Budts W. Outcome and determinants of prognosis in patients undergoing isolated tricuspid valve surgery: retrospective single center analysis. Int J Cardiol 2014;175:333-9.
177. Di Mauro M, Foschi M, Tancredi F, et al. Additive and independent prognostic role of abnormal right ventricle and pulmonary hypertension in mitral-tricuspid surgery. Int J Cardiol 2018;252:39-43.
178. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119-26.
179. Calero Nunez S, Tercero Martinez A, Garcia Lopez JC, Jimenez-Mazuecos J. [Wild-type transthyretin-related cardiac amyloidosis and degenerative aortic stenosis: two inter-related pathologies in the elderly]. Rev Esp Geriatr Gerontol 2017;52:167-70.
180. Castano A, Bokhari S, Maurer MS. Could late enhancement and need for permanent pacemaker implantation in patients undergoing TAVR be explained by undiagnosed transthyretin cardiac amyloidosis? J Am Coll Cardiol 2015;65:311-2.
181. Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879-87.
182. Geske JB, Anavekar NS, Nishimura RA, Oh JK, Gersh BJ. Differentiation of constriction and restriction: complex cardiovascular hemodynamics. J Am Coll Cardiol 2016;68:2329-47.
183. Chowdhury MA, Cook JM, Moukarbel GV, et al. Pre-operative right ventricular echocardiographic parameters associated with short-term outcomes and long-term mortality after CABG. Echo Res Pract 2018;5:155-66.
184. Marui A, Nishiwaki N, Komiya T, et al. Comparison of 5-year outcomes after coronary artery bypass grafting in heart failure patients with versus without preserved left ventricular ejection fraction (from the CREDO-Kyoto CABG Registry Cohort-2). Am J Cardiol 2015;116:580-6.
185. Attaran S, Shaw M, Bond L, Pullan MD, Fabri BM. Do patients in congestive cardiac failure undergoing cardiac surgery demonstrate worse outcomes compared with those with a history of cardiac failure? Heart Surg Forum 2011;14:E178-82.
186. Adamson PB, Abraham WT, Stevenson LW, et al. Pulmonary artery pressure-guided heart failure management reduces 30-day readmissions. Circ Heart Fail 2016;9.
187. Costanzo MR, Stevenson LW, Adamson PB, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. JACC Heart Fail 2016;4:333-44.
188. Krahnke JS, Abraham WT, Adamson PB, et al. Heart failure and respiratory hospitalizations are reduced in patients with heart failure and chronic obstructive pulmonary disease with the use of an implantable pulmonary artery pressure monitoring device. J Card Fail 2015;21:240-9.
189. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading /clinical perspective. Circulation 2012;125:289-97.
190. Tampakakis E, Shah SJ, Borlaug BA, et al. Pulmonary effective arterial elastance as a measure of right ventricular afterload and its prognostic value in pulmonary hypertension due to left heart disease. Circulation: Heart Failure 2018;11.
191. Guazzi M, Vitelli A, Labate V, Arena R. Treatment for pulmonary hypertension of left heart disease. Curr Treat Options Cardiovasc Med 2012;14:319-27.
192. Argiriou M, Kolokotron SM, Sakellaridis T, et al. Right heart failure post left ventricular assist device implantation. J Thorac Dis 2014;6 (Suppl 1):S52-9.

193. Peters AE, Smith LA, Ababio P, et al. Comparative analysis of established risk scores and novel hemodynamic metrics in predicting right ventricular failure in left ventricular assist device patients. J Card Fail 2019.
194. Turner KR. Right ventricular failure after left ventricular assist device placement—the beginning of the end or just another challenge? J Cardiothorac Vasc Anesth 2019;33:1105-21.
195. Houston BA, Shah KB, Mehra MR, Tedford RJ. A new "twist" on right heart failure with left ventricular assist systems. J Heart Lung Transplant 2017;36:701-7.
196. Kalogeropoulos AP, Kelkar A, Weinberger JF, et al. Validation of clinical scores for right ventricular failure prediction after implantation of continuous-flow left ventricular assist devices. Special Issue: Mechanical Circulatory Support 2015;34:1595-603.
197. T. Sparrow C, J. LaRue S, Schilling J. Intersection of Pulmonary Hypertension and Right Ventricular Dysfunction in Patients on Left Ventricular Assist Device Support: Is There a Role for Pulmonary Vasodilators?; 2018.
198. Sabato LA, Salerno DM, Moretz JD, Jennings DL. Inhaled pulmonary vasodilator therapy for management of right ventricular dysfunction after left ventricular assist device placement and cardiac transplantation. Pharmacotherapy 2017;37:944-55.
199. Critoph C, Green G, Hayes H, et al. Clinical outcomes of patients treated with pulmonary vasodilators early and in high dose after left ventricular assist device implantation. Artif Organs 2016;40:106-14.
200. LaRue SJ, Garcia-Cortes R, Nassif ME, et al. Treatment of secondary pulmonary hypertension with bosentan after left ventricular assist device implantation. Cardiovasc Ther 2015;33:50-5.
201. Gulati G, Grandin EW, Kennedy K, et al. Preimplant phosphodiesterase-5 inhibitor use is associated with higher rates of severe early right heart failure after left ventricular assist device implantation. Circ Heart Fail 2019;12:e005537.
202. Ravichandran AK, LaRue SJ, Novak E, Joseph SA, Schilling JD. Sildenafil in left ventricular assist device is safe and well-tolerated. Asaio j 2017.
203. Tedford RJ, Hemnes AR, Russell SD, et al. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circ Heart Fail 2008;1:213-9.
204. Xanthopoulos A, Tryposkiadis K, Triposkiadis F, et al. Postimplant phosphodiesterase type 5 inhibitors use is associated with lower rates of thrombotic events after left ventricular assist device implantation. J Am Heart Assoc 2020;9:e015897.
205. Masri CS, Tedford RJ, Colvin MM, Leary PJ, Cogswell R. Pulmonary arterial compliance improves rapidly after LVAD implantation. ASAIO 2016. [In press] .
206. Frantz RP. First results of soprano: macitentan in patients (pts) with pulmonary hypertension (PH) post-left ventricular assist device (LVAD) implantation. J Heart Lung Transplant 2021;40:S12-S3.
207. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080-6.
208. Saeed D, Potapov E, Loforte A, et al. Transition from short-term to durable mechanical circulatory support systems. Outcome and patient selection. On behalf of ECMO-VAD study group. J Heart Lung Transplant 2019;38:S33-S4.
209. Anderson MB, Goldstein J, Milano C, et al. Benefits of a novel percutaneous ventricular assist device for right heart failure: the prospective RECOVER RIGHT study of the Impella RP device. J Heart Lung Transplant 2015;34:1549-60.
210. Schmack B, Weymann A, Popov A-F, et al. Concurrent left ventricular assist device (LVAD) implantation and percutaneous temporary RVAD support via cardiacassist protek-duo tandemheart to preempt right heart failure. Medical science monitor basic research 2016;22:53-7.
211. Guglin M, Zucker MJ, Bazan VM, et al. Venoarterial ECMO for adults: JACC scientific expert panel. J Am Coll Cardiol 2019;73:698-716.
212. Rich JD, Gosev I, Patel CB, et al. The incidence, risk factors, and outcomes associated with late right-sided heart failure in patients supported with an axial-flow left ventricular assist device. Theme Issue—Mechanical Circulatory Support 2017;36:50-8.
213. Takeda K, Takayama H, Colombo PC, et al. Incidence and clinical significance of late right heart failure during continuous-flow left ventricular assist device support. J Heart Lung Transplant 2015;34:1024-32.
214. Andersen KH, Schultz HH, Nyholm B, Iversen MP, Gustafsson F, Carlsen J. Pulmonary hypertension as a risk factor of mortality after lung transplantation. Clin Transplant 2016;30:357-64.
215. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: thirty-second official adult lung and heart-lung transplantation report—2015; focus theme: early graft failure. J Heart Lung Transplant 2015;34:1264-77.
216. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the pulmonary transplantation council of the international society for heart and lung transplantation. J Heart Lung Transplant 2015;34:1-15.
217. Castillo M. Anesthetic management for lung transplantation. Curr Opin Anaesthesiol 2011;24:32-6.
218. Schisler T, Marquez JM, Hilmi I, Subramaniam K. Pulmonary hypertensive crisis on induction of anesthesia. Semin Cardiothorac Vasc Anesth 2017;21:105-13.
219. Gordon C, Collard CD, Pan W. Intraoperative management of pulmonary hypertension and associated right heart failure. Curr Opin Anaesthesiol 2010;23:49-56.
220. Tomasi R, Betz D, Schlager S, et al. Intraoperative anesthetic management of lung transplantation: center-specific practices and geographic and centers size differences. J Cardiothorac Vasc Anesth 2018;32:62-9.
221. Feltracco P, Serra E, Barbieri S, et al. Anesthetic concerns in lung transplantation for severe pulmonary hypertension. Transplant Proc 2007;39:1976-80.
222. Hohn L, Schweizer A, Morel DR, Spiliopoulos A, Licker M. Circulatory failure after anesthesia induction in a patient with severe primary pulmonary hypertension. Anesthesiology 1999;91:1943-5.
223. de Boer WJ, Waterbolk TW, Brugemann J, van der Bij W, Huyzen RJ. Extracorporeal membrane oxygenation before induction of anesthesia in critically ill thoracic transplant patients. Ann Thorac Surg 2001;72:1407-8.
224. Tan Z, Roscoe A, Rubino A. Transesophageal echocardiography in heart and lung transplantation. J Cardiothorac Vasc Anesth 2019.
225. Bermudez CA, Shiose A, Esper SA, et al. Outcomes of intraoperative venoarterial extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation. Ann Thorac Surg 2014;98:1936-42. discussion 42-3.
226. Ius F, Sommer W, Tudorache I, et al. Five-year experience with intraoperative extracorporeal membrane oxygenation in lung transplantation: Indications and midterm results. J Heart Lung Transplant 2016;35:49-58.
227. Machuca TN, Collaud S, Mercier O, et al. Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2015;149:1152-7.
228. Pereszlenyi A, Lang G, Steltzer H, et al. Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support in patients with pulmonary hypertension. Eur J Cardiothorac Surg 2002;21:858-63.
229. Yu WS, Paik HC, Haam SJ, et al. Transition to routine use of venoarterial extracorporeal oxygenation during lung transplantation could improve early outcomes. J Thorac Dis 2016;8:1712-20.
230. Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Zacharoulis D. Extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation: a meta-analysis. Gen Thorac Cardiovasc Surg 2018;66:38-47.
231. Kuntz CL, Hadjiliadis D, Ahya VN, et al. Risk factors for early primary graft dysfunction after lung transplantation: a registry study. Clin Transplant 2009;23:819-30.

232. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527-34.
233. Porteous MK, Lee JC, Lederer DJ, et al. Clinical risk factors and prognostic model for primary graft dysfunction after lung transplantation in patients with pulmonary hypertension. Ann Am Thorac Soc 2017;14:1514-22.
234. Porteous MK, Ky B, Kirkpatrick JN, et al. Diastolic dysfunction increases the risk of primary graft dysfunction after lung transplant. Am J Respir Crit Care Med 2016;193:1392-400.
235. Gupta S, Torres F, Bollineni S, Mohanka M, Kaza V. Left ventricular dysfunction after lung transplantation for pulmonary arterial hypertension. Transplant Proc 2015;47:2732-6.
236. Birsan T, Kranz A, Mares P, et al. Transient left ventricular failure following bilateral lung transplantation for pulmonary hypertension. J Heart Lung Transplant 1999;18:304-9.
237. Moser B, Jaksch P, Taghavi S, et al. Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. Eur J Cardiothorac Surg 2018;53:178-85.
238. Tudorache I, Sommer W, Kuhn C, et al. Lung transplantation for severe pulmonary hypertension—awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation 2015;99:451-8.
239. Porter TR, Shillcutt SK, Adams MS, et al. Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American society of echocardiography. J Am Soc Echocardiogr 2015;28:40-56.
240. Sullivan B, Puskas F, Fernandez-Bustamante A. Transesophageal echocardiography in noncardiac thoracic surgery. Anesthesiol Clin 2012;30:657-69.
241. Bhabra MS, Hopkinson DN, Shaw TE, Onwu N, Hooper TL. Controlled reperfusion protects lung grafts during a transient early increase in permeability. Ann Thorac Surg 1998;65:187-92.
242. Hoetzenecker K, Schwarz S, Muckenhuber M, et al. Intraoperative extracorporeal membrane oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung transplantation. J Thorac Cardiovasc Surg 2018;155:2193-206. e3.
243. Kirshbom PM, Tapson VF, Harrison JK, Davis RD, Gaynor JW. Delayed right heart failure following lung transplantation. Chest 1996;109:575-7.
244. Chen F, Hanaoka N, Hasegawa S, et al. Right ventricular outflow tract obstruction after bilateral lung transplantation. Thorac Cardiovasc Surg 2009;57:48-50.
245. Mehra MR, Canter CE, Hannan MM, et al. The 2016 international society for heart lung transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35:1-23.
246. Lundgren J, Algotsson L, Kornhall B, Radegran G. Preoperative pulmonary hypertension and its impact on survival after heart transplantation. Scand Cardiovasc J 2014;48:47-58.
247. Costard-Jäckle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol 1992;19:48-54.
248. Murali S, Kormos RL, Uretsky BF, et al. Preoperative pulmonary hemodynamics and early mortality after orthotopic cardiac transplantation: the Pittsburgh experience. Am Heart J 1993;126:896-904.
249. Lindelow B, Andersson B, Waagstein F, Bergh CH. High and low pulmonary vascular resistance in heart transplant candidates. A 5-year follow-up after heart transplantation shows continuous reduction in resistance and no difference in complication rate. Eur Heart J 1999;20:148-56.
250. Delgado JF, Gómez-Sánchez MA, Sáenz de la Calzada C, et al. Impact of mild pulmonary hypertension on mortality and pulmonary artery pressure profile after heart transplantation. J Heart Lung Transplant 2001;20:942-8.
251. Klotz S, Deng MC, Hanafy D, et al. Reversible pulmonary hypertension in heart transplant candidates—pretransplant evaluation and outcome after orthotopic heart transplantation. Eur J Heart Fail. 2003;5:645-53.
252. Chang PP, Longenecker JC, Wang N-Y, et al. Mild vs severe pulmonary hypertension before heart transplantation: different effects on posttransplantation pulmonary hypertension and mortality. J Heart Lung Transplant 2005;24:998-1007.
253. Goland S, Czer LSC, Kass RM, et al. Pre-existing pulmonary hypertension in patients with end-stage heart failure: impact on clinical outcome and hemodynamic follow-up after orthotopic heart transplantation. J Heart Lung Transplant 2007; 26:312-8.
254. Klotz S, Wenzelburger F, Stypmann J, et al. Reversible pulmonary hypertension in heart transplant candidates: to transplant or not to transplant. Ann Thorac Surg 2006;82:1770-3.
255. Gude E, Simonsen S, Geiran OR, et al. Pulmonary hypertension in heart transplantation: discrepant prognostic impact of pre-operative compared with 1-year post-operative right heart hemodynamics. J Heart Lung Transplant 2010;29:216-23.
256. Chen JM, Levin HR, Michler RE, Prusmack CJ, Rose EA, Aaronson KD. Reevaluating the significance of pulmonary hypertension before cardiac transplantation: determination of optimal thresholds and quantification of the effect of reversibility on perioperative mortality. J Thorac Cardiovasc Surg 1997;114:627-34.
257. Lundgren J, Soderlund C, Radegran G. Impact of postoperative pulmonary hypertension on outcome after heart transplantation. Scand Cardiovasc J 2017;51:172-81.
258. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: international society for heart and lung transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant 2006;25:1024-42.
259. Vachiéry J-L, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. Eur Respir J 2018:1801897.
260. Lundgren J, Rådegran G. Pathophysiology and potential treatments of pulmonary hypertension due to systolic left heart failure. Acta Physiol (Oxf) 2014;211:314-33.
261. Koulova A, Gass AL, Patibandla S, Gupta CA, Aronow WS, Lanier GM. Management of pulmonary hypertension from left heart disease in candidates for orthotopic heart transplantation. J Thorac Dis 2017;9:2640-9.
262. Sahay S, Khirfan G, Tonelli AR. Management of combined pre- and post-capillary pulmonary hypertension in advanced heart failure with reduced ejection fraction. Respir Med 2017;131:94-100.
263. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the flolan international randomized survival trial (FIRST). Am Heart J 1997;134:44-54.
264. Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail 2005;11:12-20.
265. Packer M, McMurray JJV, Krum H, et al. Long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure: primary results of the ENABLE trials. JACC: Heart Failure 2017;5:317-26.
266. Vachiéry J-L, Delcroix M, Al-Hiti H, et al. Macitentan in pulmonary hypertension due to left ventricular dysfunction. Eur Respir J 2018;51:1701886.
267. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trialeffect of PDE-5 on exercise and clinical status in HFPEF. JAMA 2013;309:1268-77.
268. investigators SfIOaVC, González-Mansilla A, Fernández-Avilés F, Elízaga J, et al. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. Eur Heart J 2017;39:1255-64.
269. Bonderman D, Ghio S, Felix Stephan B, et al. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction. Circulation 2013;128:502-11.

270. Bonderman D, Pretsch I, Steringer-Mascherbauer R, et al. Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized, double-blind, placebo-controlled, single-dose study. Chest 2014;146:1274-85.
271. Gheorghiade M, Greene SJ, Butler J, et al. Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trialvericiguat and worsening chronic heart failurevericiguat and worsening chronic heart failure. JAMA 2015;314:2251-62.
272. Pieske B, Scalise A-V, Mueller K, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the soluble guanylate cyclase stimulator in heart failure patients with PRESERVED EF (SOCRATES-PRESERVED) study. Eur Heart J 2017;38:1119-27.
273. Guazzi M, Vicenzi M, Arena R, Guazzi Maurizio D. Pulmonary hypertension in heart failure with preserved ejection fraction. Circulation 2011;124:164-74.
274. Zimpfer D, Zrunek P, Roethy W, et al. Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates. J Thorac Cardiovasc Surg 2007;133:689-95.
275. Salzberg SP, Lachat ML, von Harbou K, Zünd G, Turina MI. Normalization of high pulmonary vascular resistance with LVAD support in heart transplantation candidates. Eur J Cardiothorac Surg 2005;27:222-5.
276. Martin J, Siegenthaler MP, Friesewinkel O, et al. Implantable left ventricular assist device for treatment of pulmonary hypertension in candidates for orthotopic heart transplantation-a preliminary study. Eur J Cardiothorac Surg 2004;25:971-7.
277. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 2001;38:923-31.
278. Carteaux JP, Roux S, Siaghy M, et al. Acute pulmonary hypertension after cardiopulmonary bypass in pig: the role of endogenous endothelin. Eur J Cardiothorac Surg 1999;15:346-52.
279. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008;117:1717-31.
280. Bittner HB, Chen EP, Biswas SS, Van Trigt P 3rd, Davis RD. Right ventricular dysfunction after cardiac transplantation: primarily related to status of donor heart. Ann Thorac Surg 1999;68:1605-11.
281. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. J Heart Lung Transplant 2014;33:327-40.
282. Costanzo MR, Dipchand A, Starling R, et al. The international society of heart and lung transplantation guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914-56.
283. Taghavi S, Zuckermann A, Ankersmit J, et al. Extracorporeal membrane oxygenation is superior to right ventricular assist device for acute right ventricular failure after heart transplantation. Ann Thorac Surg 2004;78:1644-9.
284. Marasco SF, Esmore DS, Negri J, et al. Early institution of mechanical support improves outcomes in primary cardiac allograft failure. J Heart Lung Transplant 2005;24:2037-42.
285. Chou NK, Chi NH, Ko WJ, et al. Extracorporeal membrane oxygenation for perioperative cardiac allograft failure. Asaio j 2006;52:100-3.
286. Shuhaiber JH, Jenkins D, Berman M, et al. The papworth experience with the levitronix centrimag ventricular assist device. J Heart Lung Transplant 2008;27:158-64.
287. Santise G, Petrou M, Pepper JR, Dreyfus G, Khaghani A, Birks EJ. Levitronix as a short-term salvage treatment for primary graft failure after heart transplantation. J Heart Lung Transplant 2006;25:495-8.
288. Gregoric ID, Bruckner BA, Jacob L, et al. Techniques and complications of tandemheart ventricular assist device insertion during cardiac procedures. Asaio j 2009;55:251-4.
289. Rossiter-Thornton M, Arun V, Forrest AP, Bayfield MS, Wilson MK. Left ventricular support with the impella® LP 5.0 for cardiogenic shock following cardiac surgery. Heart Lung Circ. 2008;17:243-5.
290. John R, Long JW, Massey HT, et al. Outcomes of a multicenter trial of the levitronix centrimag ventricular assist system for short-term circulatory support. J Thorac Cardiovasc Surg 2011;141:932-9.
291. Nersesian G, Hennig F, Müller M, et al. Temporary mechanical circulatory support for refractory heart failure: the German Heart Center Berlin experience. Ann Cardiothorac Surg 2018;8:76-83. 2018.
292. Anderson M, Morris DL, Tang D, et al. Outcomes of patients with right ventricular failure requiring short-term hemodynamic support with the Impella RP device. J Heart Lung Transplant 2018;37:1448-58.
293. Savale L, Watherald J, Sitbon O. Portopulmonary Hypertension. Semin Respir Crit Care Med. 2017;38:651-61.
294. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023-30.
295. Castro M, Krowka MJ, Schroeder DR, et al. Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients. Mayo Clin Proc 1996;71:543-51.
296. Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology 2003;37:401-9.
297. Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL Registry. Chest 2012;141:906-15.
298. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th world symposium on pulmonary hypertension. Eur Respir J 2019;53.
299. Fritz JS, Fallon MB, Kawut SM. Pulmonary vascular complications of liver disease. Am J Respir Crit Care Med 2013;187:133-43.
300. Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. Liver Transpl 2012;18:881-91.
301. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary hypertension: results from a 10-year screening algorithm. Hepatology 2006;44:1502-10.
302. De Wolf AM, Gasior T, Kang Y. Pulmonary hypertension in a patient undergoing liver transplantation. Transplant Proc 1991;23:2000-1.
303. Prager MC, Cauldwell CA, Ascher NL, Roberts JP, Wolfe CL. Pulmonary hypertension associated with liver disease is not reversible after liver transplantation. Anesthesiology 1992;77:375-8.
304. De Pietri L, Montalti R, Begliomini B, et al. Pulmonary hypertension as a predictor of postoperative complications and mortality after liver transplantation. Transplant Proc 2010;42:1188-90.
305. Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. Liver Transpl 2000;6:443-50.
306. Raevens S, Colle I, Reyntjens K, et al. Echocardiography for the detection of portopulmonary hypertension in liver transplant candidates: an analysis of cutoff values. Liver Transpl 2013;19:602-10.
307. Torregrosa M, Genesca J, Gonzalez A, et al. Role of doppler echocardiography in the assessment of portopulmonary hypertension in liver transplantation candidates. Transplantation 2001;71:572-4.
308. Cotton CL, Gandhi S, Vaitkus PT, et al. Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates. Liver Transpl 2002;8:1051-4.
309. Martin P, DiMartini A, Feng S, Brown R Jr., Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American association for the study of liver diseases and the american society of transplantation. Hepatology 2014;59:1144-65.
310. Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American heart association and the American college of cardiology foundation. J Am Coll Cardiol 2012;60:434-80.

311. Khaderi S, Khan R, Safdar Z, et al. Long-term follow-up of portopulmonary hypertension patients after liver transplantation. Liver Transpl 2014;20:724-7.
312. Massie AB, Caffo B, Gentry SE, et al. MELD exceptions and rates of waiting list outcomes. Am J Transplant 2011;11:2362-71.
313. Goldberg DS, Batra S, Sahay S, Kawut SM, Fallon MB. MELD exceptions for portopulmonary hypertension: current policy and future implementation. Am J Transplant 2014;14:2081-7.
314. Umgelter A, Hapfelmeier A, Kopp W, van Rosmalen M, Rogiers X, Guba M. Disparities in Eurotransplant liver transplantation wait-list outcome between patients with and without model for end-stage liver disease exceptions. Liver Transpl 2017;23:1256-65.
315. DuBrock HM, Goldberg DS, Sussman NL, et al. Predictors of wait-list mortality in portopulmonary hypertension. Transplantation 2017;101:1609-15.
316. Krowka MJ, Wiesner RH, Heimbach JK. Pulmonary contraindications, indications and MELD exceptions for liver transplantation: a contemporary view and look forward. J Hepatol 2013;59:367-74.
317. Krowka MJ, Fallon MB, Kawut SM, et al. international liver transplant society practice guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. Transplantation 2016;100:1440-52.
318. Savale L, Sattler C, Coilly A, et al. Long-term outcome in liver transplantation candidates with portopulmonary hypertension. Hepatology 2017;65:1683-92.
319. Rajaram P, Parekh A, Fisher M, Kempker J, Subramanian R. Comparison of post-liver transplantation outcomes in portopulmonary hypertension and pulmonary venous hypertension: a single-center experience. Transplant Proc 2017;49:338-43.
320. Reymond M, Barbier L, Salame E, et al. Does portopulmonary hypertension impede liver transplantation in cirrhotic patients? A French multicentric retrospective study. Transplantation. 2018;102:616-22.
321. Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. Lancet 2004;363:1461-8.
322. Reichenberger F, Voswinckel R, Steveling E, et al. Sildenafil treatment for portopulmonary hypertension. Eur Respir J 2006;28:563-7.
323. Melgosa MT, Ricci GL, Garcia-Pagan JC, et al. Acute and long-term effects of inhaled iloprost in portopulmonary hypertension. Liver Transpl 2010;16:348-56.
324. Awdish RL, Cajigas HR. Early initiation of prostacyclin in portopulmonary hypertension: 10 years of a transplant center's experience. Lung 2013;191:593-600.
325. Sakai T, Planinsic RM, Mathier MA, de Vera ME, Venkataramanan R. Initial experience using continuous intravenous treprostinil to manage pulmonary arterial hypertension in patients with end-stage liver disease. Transpl Int 2009;22:554-61.
326. Fix OK, Bass NM, De Marco T, Merriman RB. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. Liver Transpl 2007;13:875-85.
327. Schroeder RA, Rafii AA, Plotkin JS, Johnson LB, Rustgi VK, Kuo PC. Use of aerosolized inhaled epoprostenol in the treatment of portopulmonary hypertension. Transplantation 2000; 70:548-50.
328. Plotkin JS, Kuo PC, Rubin LJ, et al. Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. Transplantation 1998;65:457-9.
329. Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. Transplantation 1997;63:604-6.
330. Fisher JH, Johnson SR, Chau C, Kron AT, Granton JT. Effectiveness of phosphodiesterase-5 inhibitor therapy for portopulmonary hypertension. Can Respir J 2015;22:42-6.
331. Chua R, Keogh A, Miyashita M. Novel use of sildenafil in the treatment of portopulmonary hypertension. J Heart Lung Transplant 2005;24:498-500.
332. Cadden IS, Greanya ED, Erb SR, Scudamore CH, Yoshida EM. The use of sildenafil to treat portopulmonary hypertension prior to liver transplantation. Ann Hepatol 2009;8:158-61.
333. Hemnes AR, Robbins IM. Sildenafil monotherapy in portopulmonary hypertension can facilitate liver transplantation. Liver Transpl 2009;15:15-9.
334. Gough MS, White RJ. Sildenafil therapy is associated with improved hemodynamics in liver transplantation candidates with pulmonary arterial hypertension. Liver Transpl 2009;15:30-6.
335. Savale L, Magnier R, Le Pavec J, et al. Efficacy, safety and pharmacokinetics of bosentan in portopulmonary hypertension. Eur Respir J 2013;41:96-103.
336. Cartin-Ceba R ea. Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. PubMed - NCBI 2019.
337. Kuntzen C, Gulberg V, Gerbes AL. Use of a mixed endothelin receptor antagonist in portopulmonary hypertension: a safe and effective therapy? Gastroenterology 2005;128:164-8.
338. Grander W, Eller P, Fuschelberger R, Tilg H. Bosentan treatment of portopulmonary hypertension related to liver cirrhosis owing to hepatitis C. Eur J Clin Invest 2006;36(Suppl 3):67-70.
339. Hoeper MM, Halank M, Marx C, et al. Bosentan therapy for portopulmonary hypertension. Eur Respir J 2005;25:502-8.
340. Stahler G, von Hunnius P. Successful treatment of portopulmonary hypertension with bosentan: case report. Eur J Clin Invest 2006;36 (Suppl 3):62-6.
341. Sato A, Maie K, Ohno Y, et al. Efficacy and safety of bosentan treatment for portopulmonary hypertension associated with syncope. Int Heart J 2011;52:243-5.
342. Hinterhuber L, Graziadei IW, Kahler CM, Jaschke W, Vogel W. Endothelin-receptor antagonist treatment of portopulmonary hypertension. Clin Gastroenterol Hepatol 2004;2:1039-42.
343. Halank M, Miehlke S, Hoeffken G, Schmeisser A, Schulze M, Strasser RH. Use of oral endothelin-receptor antagonist bosentan in the treatment of portopulmonary hypertension. Transplantation. United States; 2004: 1775-6.
344. Krowka MJ, Frantz RP, McGoon MD, Severson C, Plevak DJ, Wiesner RH. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): a study of 15 patients with moderate to severe portopulmonary hypertension. Hepatology 1999;30:641-8.
345. Touma W, Nayak RP, Hussain Z, Bacon BR, Kudva GC. Epoprostenol-induced hypersplenism in portopulmonary hypertension. Am J Med Sci 2012;344:345-9.
346. Findlay JY, Plevak DJ, Krowka MJ, Sack EM, Porayko MK. Progressive splenomegaly after epoprostenol therapy in portopulmonary hypertension. Liver Transpl Surg 1999;5:362-5.
347. Chin KM, Channick RN, de Lemos JA, Kim NH, Torres F, Rubin LJ. Hemodynamics and epoprostenol use are associated with thrombocytopenia in pulmonary arterial hypertension. Chest 2009;135:130-6.
348. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809-18.
349. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-9.
350. Vercauteren M, Trensz F, Pasquali A, et al. Endothelin ETA receptor blockade, by activating ETB receptors, increases vascular permeability and induces exaggerated fluid retention. J Pharmacol Exp Ther 2017;361:322-33.
351. Sitbon O, Bosch J, Cottreel E, et al. Late breaking abstract - efficacy and safety of macitentan in portopulmonary hypertension: the PORTICO trial. Eur Respir J 2018;52:OA267.
352. Cartin-Ceba R, Halank M, Ghofrani HA, et al. Riociguat treatment for portopulmonary hypertension: a subgroup analysis from the PATENT-1/-2 studies. Pulm Circ 2018;8:2045894018769305.
353. Garcia-Pagan JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;362:2370-9.
354. Moreno A, Meneu JC, Moreno E, et al. Liver transplantation and transjugular intrahepatic portosystemic shunt. Transplant Proc 2003;35:1869-70.

355. Colombato LA, Spahr L, Martinet JP, et al. Haemodynamic adaptation two months after transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients. Gut 1996;39:600-4.
356. Boyer TD, Haskal ZJ. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009. Hepatology 2010;51:306.
357. Preston IR, Sagliani KD, Warburton RR, Hill NS, Fanburg BL, Jaffe IZ. Mineralocorticoid receptor antagonism attenuates experimental pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2013;304:L678-88.
358. Swanson KL, Krowka MJ. Screen for portopulmonary hypertension, especially in liver transplant candidates. Cleve Clin J Med 2008;75:121-2. 5-30, 33 passim.
359. Cosardereliogˇlu C, Cosar AM, Gurakar M, et al. Portopulmonary hypertension and liver transplant: recent review of the literature. Exp Clin Transplant 2016;14:113-20.
360. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. J Am Coll Cardiol 2003;41:1021-7.
361. Opotowsky AR, Clair M, Afilalo J, et al. A simple echocardiographic method to estimate pulmonary vascular resistance. Am J Cardiol 2013;112:873-82.
362. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American society of echocardiography endorsed by the European association of echocardiography, a registered branch of the European society of cardiology, and the Canadian society of echocardiography. J Am Soc Echocardiogr 2010;23:685-713. quiz 86-8.
363. Dorman T, Breslow MJ, Lipsett PA, et al. Radial artery pressure monitoring underestimates central arterial pressure during vasopressor therapy in critically ill surgical patients. Crit Care Med 1998;26:1646-9.
364. Rudnick MR, Marchi LD, Plotkin JS. Hemodynamic monitoring during liver transplantation: a state of the art review. World J Hepatol 2015;7:1302-11.
365. Fukazawa K, Poliac LC, Pretto EA. Rapid assessment and safe management of severe pulmonary hypertension with milrinone during orthotopic liver transplantation. Clin Transplant 2010;24:515-9.
366. Burger-Klepp U, Karatosic R, Thum M, et al. Transesophageal echocardiography during orthotopic liver transplantation in patients with esophagoastric varices. Transplantation 2012;94:192-6.
367. Li J, Zhuang Q, Zhang X, et al. Prevalence and prognosis of portopulmonary hypertension in 223 liver transplant recipients. Can Respir J 2018;2018:9629570.
368. Al-Naamani N, Roberts KE. Portopulmonary hypertension. Clin Chest Med 2013;34:719-37.
369. Yigla M, Fruchter O, Aharonson D, et al. Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. Kidney Int 2009;75:969-75.
370. Ramasubbu K, Deswal A, Herdejurgen C, Aguilar D, Frost AE. A prospective echocardiographic evaluation of pulmonary hypertension in chronic hemodialysis patients in the United States: prevalence and clinical significance. Int J Gen Med 2010;3:279-86.
371. Nakhoul F, Yigla M, Gilman R, Reisner SA, Abassi Z. The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. Nephrol Dial Transplant 2005;20:1686-92.
372. Sise ME, Courtwright AM, Channick RN. Pulmonary hypertension in patients with chronic and end-stage kidney disease. Kidney Int 2013;84:682-92.
373. Tang M ea. Pulmonary hypertension, mortality, and cardiovascular disease in CKD and ESRD patients: a systematic review and meta-analysis. - PubMed - NCBI 2019.
374. Abbasi M ea. End-stage renal disease. - PubMed - NCBI 2019.
375. O'Leary JM, Assad TR, Xu M, et al. Pulmonary hypertension in patients with chronic kidney disease: invasive hemodynamic etiology and outcomes. Pulm Circ 2017;7:674-83.
376. Zlotnick DM, Axelrod DA, Chobanian MC, et al. Non-invasive detection of pulmonary hypertension prior to renal transplantation is a predictor of increased risk for early graft dysfunction. Nephrol Dial Transplant 2010;25:3090-6.
377. Issa N, Krowka MJ, Griffin MD, Hickson LJ, Stegall MD, Cosio FG. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. Transplantation 2008;86:1384-8.
378. Wang SC, Garcia R, Torosoff M, et al. Influence of mildly and moderately elevated pulmonary artery systolic pressure on post-renal transplantation survival and graft function. Echocardiography 2019;36:22-7.
379. Jarmi T, Doumit E, Makdisi G, et al. Pulmonary artery systolic pressure measured intraoperatively by right heart catheterization is a predictor of kidney transplant recipient survival. Ann Transplant 2018;23:867-73.
380. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of pulmonary arterial hypertension. J Am Coll Cardiol 2015;65:1976-97.
381. Chou JA, Kalantar-Zadeh K. Volume balance and intradialytic ultrafiltration rate in the hemodialysis patient. Curr Heart Fail Rep 2017;14:421-7.
382. Clarkson MR, Giblin L, Brown A, Little D, Donohoe J. Reversal of pulmonary hypertension after ligation of a brachiocephalic arteriovenous fistula. Am J Kidney Dis 2002;40:E8.
383. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26.
384. Madani M, Ogo T, Simonneau G. The changing landscape of chronic thromboembolic pulmonary hypertension management. Eur Respir Rev 2017;26.
385. Madani M, Mayer E, Fadel E, Jenkins DP. Pulmonary endarterectomy. patient selection, technical challenges, and outcomes. Ann Am Thorac Soc 2016;13(Suppl 3):S240-7.
386. Madani MM, Jamieson SW. Technical advances of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Semin Thorac Cardiovasc Surg 2006;18:243-9.
387. Cannon JE, Su L, Kiely DG, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the United Kingdom National cohort. Circulation 2016;133:1761-71.
388. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest 1982;81:151-8.
389. Madani MM, Auger WR, Pretorius V, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. Ann Thorac Surg 2012;94:97-103. discussion.
390. Skoro-Sajer N, Hack N, Sadushi-Kolici R, et al. Pulmonary vascular reactivity and prognosis in patients with chronic thromboembolic pulmonary hypertension: a pilot study. Circulation 2009;119:298-305.
391. Suntharalingam J, Hughes RJ, Goldsmith K, et al. Acute haemodynamic responses to inhaled nitric oxide and intravenous sildenafil in distal chronic thromboembolic pulmonary hypertension (CTEPH). Vascul Pharmacol 2007;46:449-55.
392. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53.
393. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D92-9.
394. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Rev Esp Cardiol (Engl Ed) 2016;69:177.
395. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013;369:319-29.
396. Simonneau G, D'Armini AM, Ghofrani HA, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur Respir J 2015;45:1293-302.
397. Pepke-Zaba J, Jais X, Channick R. Medical therapy in chronic thromboembolic pulmonary hypertension. Ann Am Thorac Soc 2016;13 (Suppl 3):S248-54.

398. Manecke GR Jr., Parimucha M, Stratmann G, et al. Deep hypothermic circulatory arrest and the femoral-to-radial arterial pressure gradient. J Cardiothorac Vasc Anesth 2004;18:175-9.
399. Banks DA, Pretorius GV, Kerr KM, Manecke GR. Pulmonary endarterectomy: part II. Operation, anesthetic management, and postoperative care. Semin Cardiothorac Vasc Anesth 2014;18:331-40.
400. Adams A, Fedullo PF. Postoperative management of the patient undergoing pulmonary endarterectomy. Semin Thorac Cardiovasc Surg 2006;18:250-6.
401. Dittrich HC, Nicod PH, Chow LC, Chappuis FP, Moser KM, Peterson KL. Early changes of right heart geometry after pulmonary thromboendarterectomy. J Am Coll Cardiol 1988;11:937-43.
402. Menzel T, Wagner S, Kramm T, et al. Pathophysiology of impaired right and left ventricular function in chronic embolic pulmonary hypertension: changes after pulmonary thromboendarterectomy. Chest 2000;118:897-903.
403. Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. J Thorac Cardiovasc Surg 2011;141:702-10.
404. Freed DH, Thomson BM, Berman M, et al. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. J Thorac Cardiovasc Surg 2011;141:383-7.
405. de Perrot M, Thenganatt J, McRae K, et al. Pulmonary endarterectomy in severe chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2015;34:369-75.
406. Kramm T, Eberle B, Guth S, Mayer E. Inhaled iloprost to control residual pulmonary hypertension following pulmonary endarterectomy. Eur J Cardiothorac Surg 2005;28:882-8.
407. Imanaka H, Miyano H, Takeuchi M, Kumon K, Ando M. Effects of nitric oxide inhalation after pulmonary thromboendarterectomy for chronic pulmonary thromboembolism. Chest 2000;118:39-46.
408. Levinson RM, Shure D, Moser KM. Reperfusion pulmonary edema after pulmonary artery thromboendarterectomy. Am Rev Respir Dis 1986;134:1241-5.
409. Kerr KM, Auger WR, Marsh JJ, et al. The use of cylexin (CY-1503) in prevention of reperfusion lung injury in patients undergoing pulmonary thromboendarterectomy. Am J Respir Crit Care Med 2000;162:14-20.
410. Bates DM, Fernandes TM, Duwe BV, et al. Efficacy of a low-tidal volume ventilation strategy to prevent reperfusion lung injury after pulmonary thromboendarterectomy. Ann Am Thorac Soc 2015;12:1520-7.
411. Kerr KM, Auger WR, Marsh JJ, et al. Efficacy of methylprednisolone in preventing lung injury following pulmonary thromboendarterectomy. Chest 2012;141:27-35.
412. Thistlethwaite PA, Madani MM, Kemp AD, Hartley M, Auger WR, Jamieson SW. Venovenous extracorporeal life support after pulmonary endarterectomy: indications, techniques, and outcomes. Ann Thorac Surg 2006;82:2139-45.
413. Berman M, Tsui S, Vuylsteke A, et al. Successful extracorporeal membrane oxygenation support after pulmonary thromboendarterectomy. Ann Thorac Surg 2008;86:1261-7.
414. Boulate D, Mercier O, Mussot S, et al. Extracorporeal life support after pulmonary endarterectomy as a bridge to recovery or transplantation: lessons from 31 consecutive patients. Ann Thorac Surg 2016;102:260-8.
415. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123:1788-830.
416. Hsieh PC, Wang SS, Ko WJ, Han YY, Chu SH. Successful resuscitation of acute massive pulmonary embolism with extracorporeal membrane oxygenation and open embolectomy. Ann Thorac Surg 2001;72:266-7.
417. Fukuda I, Daitoku K. Surgical embolectomy for acute pulmonary thromboembolism. Ann Vasc Dis 2017;10:107-14.
418. Carmosino MJ, Friesen RH, Doran A, Ivy DD. Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. Anesth Analg 2007;104:521-7.
419. Taylor CJ, Derrick G, McEwan A, Haworth SG, Sury MR. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. Br J Anaesth 2007;98:657-61.
420. Williams GD, Maan H, Ramamoorthy C, et al. Perioperative complications in children with pulmonary hypertension undergoing general anesthesia with ketamine. Paediatr Anaesth 2010;20:28-37.
421. Taylor K, Moulton D, Zhao XY, Laussen P. The impact of targeted therapies for pulmonary hypertension on pediatric intraoperative morbidity or mortality. Anesth Analg 2015;120:420-6.
422. Bobhate P, Guo L, Jain S, et al. Cardiac catheterization in children with pulmonary hypertensive vascular disease. Pediatr Cardiol 2015;36:873-9.
423. Bernier ML, Jacob AI, Collaco JM, McGrath-Morrow SA, Romer LH, Unegbu CC. Perioperative events in children with pulmonary hypertension undergoing non-cardiac procedures. Pulm Circ 2018;8:2045893217738143.
424. Faraoni D, Vo D, Nasr VG, DiNardo JA. Development and validation of a risk stratification score for children with congenital heart disease undergoing noncardiac surgery. Anesth Analg 2016;123:824-30.
425. Zuckerman WA, Turner ME, Kerstein J, et al. Safety of cardiac catheterization at a center specializing in the care of patients with pulmonary arterial hypertension. Pulm Circ 2013;3:831-9.
426. Karangelis D, Mazine A, Narsupalli S, Mendis S, Veldtman G, Nikolaidis N. Morbidity after cardiac surgery in patients with adult congenital heart disease in comparison with acquired disease. Heart Lung Circ 2018;27:739-44.
427. Kurth CD, Tyler D, Heitmiller E, Tosone SR, Martin L, Deshpande JK. National pediatric anesthesia safety quality improvement program in the United States. Anesth Analg 2014;119:112-21.
428. Ramamoorthy C, Haberkern CM, Bhananker SM, et al. Anesthesia-related cardiac arrest in children with heart disease: data from the pediatric perioperative cardiac arrest (POCA) registry. Anesth Analg 2010;110:1376-82.
429. Bennett D, Marcus R, Stokes M. Incidents and complications during pediatric cardiac catheterization. Paediatr Anaesth 2005;15:1083-8.
430. Odegard KC, Bergersen L, Thiagarajan R, et al. The frequency of cardiac arrests in patients with congenital heart disease undergoing cardiac catheterization. Anesth Analg 2014;118:175-82.
431. O'Byrne ML, Glatz AC, Hanna BD, et al. Predictors of catastrophic adverse outcomes in children with pulmonary hypertension undergoing cardiac catheterization: a multi-institutional analysis from the pediatric health information systems database. J Am Coll Cardiol 2015;66:1261-9.
432. Hansmann G, Apitz C, Abdul-Khaliq H, et al. Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European paediatric pulmonary vascular disease network, endorsed by ISHLT and DGPK. Heart 2016;102(Suppl 2):ii86-ii100.
433. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American heart association and American thoracic society. Circulation 2015;132:2037-99.
434. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J 2016;37:67-119.
435. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European pediatric pulmonary vascular disease network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38:879-901.
436. Hansmann G, Apitz C. The need for comprehensive cardiac catheterization in children with pulmonary hypertension. J Am Coll Cardiol 2016;67:1009-10.

437. Lopes AA, Barst RJ, Haworth SG, et al. Repair of congenital heart disease with associated pulmonary hypertension in children: what are the minimal investigative procedures? Consensus statement from the congenital heart disease and pediatric task forces, pulmonary vascular research institute (PVRI). Pulm Circ 2014;4:330-41.
438. Beghetti M, Schulze-Neick I, Berger RM, et al. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: Insights from the Global TOPP Registry (tracking outcomes and practice in paediatric pulmonary hypertension). Int J Cardiol 2016;203:325-30.
439. Beghetti M, Berger RM, Schulze-Neick I, et al. Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice. Eur Respir J 2013;42:689-700.
440. Zuckerman WA, Turner ME, Kerstein J, et al. Safety of cardiac catheterization at a center specializing in the care of patients with pulmonary arterial hypertension. Pulm Circ 2013;3:831-9.
441. Hoeper MM, Lee SH, Voswinckel R, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006;48:2546-52.
442. Ginoux M, Cottin V, Glerant JC, et al. Safety of right heart catheterization for pulmonary hypertension in very elderly patients. Pulm Circ 2018;8:2045894018799272.
443. Hansmann G. Pulmonary hypertension in infants, children, and young adults. J Am Coll Cardiol 2017;69:2551-69.
444. Latham GJ, Yung D. Current understanding and perioperative management of pediatric pulmonary hypertension. Paediatr Anaesth 2018.
445. Friesen RH, Williams GD. Anesthetic management of children with pulmonary arterial hypertension. Paediatr Anaesth 2008;18:208-16.
446. Chau DF, Gangadharan M, Hartke LP, Twite MD. The post-anesthetic care of pediatric patients with pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2016;20:63-73.
447. Adatia I, Beghetti M. Early postoperative care of patients with pulmonary hypertension associated with congenital cardiac disease. Cardiol Young 2009;19:315-9.
448. Opotowsky AR. Clinical evaluation and management of pulmonary hypertension in the adult with congenital heart disease. Circulation 2015;131:200-10.
449. Siehr SL, Feinstein JA, Yang W, Peng LF, Ogawa MT, Ramamoorthy C. Hemodynamic effects of phenylephrine, vasopressin, and epinephrine in children with pulmonary hypertension: a pilot study. Pediatr Crit Care Med 2016;17:428-37.
450. Glenn WW. Circulatory bypass of the right side of the heart. IV. Shunt between superior vena cava and distal right pulmonary artery; report of clinical application. N Engl J Med 1958;259:117-20.
451. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240-8.
452. Kreutzer G, Galindez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg 1973;66:613-21.
453. Hussain A, Arfi AM, Hussamuddin M, et al. Comparative outcome of bidirectional Glenn shunt in patients with pulmonary vascular resistance >or = 3.5 woods units versus < 3.5 woods units. Am J Cardiol 2008;102:907-12.
454. Alsoufi B, Manlhiot C, Awan A, et al. Current outcomes of the Glenn bidirectional cavopulmonary connection for single ventricle palliation. Eur J Cardiothorac Surg 2012;42:42-8. discussion 8-9.
455. Gamillscheg A, Zobel G, Urlesberger B, et al. Inhaled nitric oxide in patients with critical pulmonary perfusion after Fontan-type procedures and bidirectional Glenn anastomosis. J Thorac Cardiovasc Surg 1997;113:435-42.
456. Agarwal HS, Churchwell KB, Doyle TP, et al. Inhaled nitric oxide use in bidirectional Glenn anastomosis for elevated Glenn pressures. Ann Thorac Surg 2006;81:1429-34.
457. Rossano JW, Cherikh WS, Chambers DC, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: twenty-first pediatric heart transplantation report-2018; focus theme: multiorgan transplantation. J Heart Lung Transplant 2018;37:1184-95.
458. Addonizio LJ, Gersony WM, Robbins RC, et al. Elevated pulmonary vascular resistance and cardiac transplantation. Circulation 1987;76 (5 Pt 2):V52-5.
459. Hoskote A, Carter C, Rees P, Elliott M, Burch M, Brown K. Acute right ventricular failure after pediatric cardiac transplant: predictors and long-term outcome in current era of transplantation medicine. J Thorac Cardiovasc Surg 2010;139:146-53.
460. Singh RK, Richmond ME, Zuckerman WA, et al. The use of oral sildenafil for management of right ventricular dysfunction after pediatric heart transplantation. Am J Transplant 2014; 14:453-8.
461. Gajarski RJ, Towbin JA, Bricker JT, et al. Intermediate follow-up of pediatric heart transplant recipients with elevated pulmonary vascular resistance index. J Am Coll Cardiol 1994;23:1682-7.
462. Kimberling MT, Balzer DT, Hirsch R, Mendeloff E, Huddleston CB, Canter CE. Cardiac transplantation for pediatric restrictive cardiomyopathy: presentation, evaluation, and short-term outcome. J Heart Lung Transplant 2002;21:455-9.
463. Ofori-Amanfo G, Hsu D, Lamour JM, et al. Heart transplantation in children with markedly elevated pulmonary vascular resistance: impact of right ventricular failure on outcome. J Heart Lung Transplant 2011;30:659-66.
464. Chen JM, Levin HR, Michler RE, Prusmack CJ, Rose EA, Aaronson KD. Reevaluating the significance of pulmonary hypertension before cardiac transplantation: determination of optimal thresholds and quantification of the effect of reversibility on perioperative mortality. J Thorac Cardiovasc Surg 1997;114:627-34.
465. Chiu P, Russo MJ, Davies RR, Addonizio LJ, Richmond ME, Chen JM. What is high risk? Redefining elevated pulmonary vascular resistance index in pediatric heart transplantation. J Heart Lung Transplant 2012;31:61-6.
466. Gazit AZ, Canter CE. Impact of pulmonary vascular resistances in heart transplantation for congenital heart disease. Curr Cardiol Rev 2011;7:59-66.
467. Mitchell MB, Campbell DN, Ivy D, et al. Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure. J Thorac Cardiovasc Surg 2004;128:693-702.
468. Yilmaz B, Zuckerman WA, Lee TM, et al. Left ventricular assist device to avoid heart-lung transplant in an adolescent with dilated cardiomyopathy and severely elevated pulmonary vascular resistance. Pediatr Transplant 2013;17:E113-6.
469. Zimpfer D, Zrunek P, Roethy W, et al. Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates. J Thorac Cardiovasc Surg 2007;133:689-95.
470. Tsukashita M, Takayama H, Takeda K, et al. Effect of pulmonary vascular resistance before left ventricular assist device implantation on short- and long-term post-transplant survival. J Thorac Cardiovasc Surg 2015;150:1352-60. 61.e1-2.