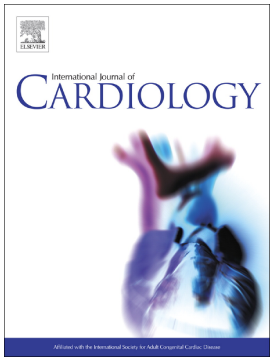

Decompensated right heart failure, intensive care and perioperative management in patients with pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018

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Decompensated right heart failure, intensive care and perioperative management in patients with pulmonary hypertension: Updated recommendations from the Cologne Consensus Conference 2018

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Abstract

In June 2016, members of the German Society of Cardiology (DGK), the German Society of Respiratory Medicine (DGP) and the German Society of Pediatric Cardiology (DGPK) met for a Consensus Conference in Cologne, Germany. Aim of this Conference was to compile consensus based practice recommendations based on the 2015 European Pulmonary Hypertension guidelines, aiming at their practical implementation, considering country-specific issues, and, and including new evidence, where available. This article summarizes the results and updated recommendations 2018 of the working group on decompensated right heart failure (RHF), intensive care and perioperative management in patients with pulmonary hypertension. The RHF section comprises definition and pathophysiology, diagnosis and monitoring, identification of triggering factors and supportive therapy of RHF, volume management as well as PAH targeting therapy, therapy with inotropic, inodilator and vasopressor drugs, extracorporeal support and transplantation. The second part of this article summarizes preoperative management, perioperative monitoring and choice of anesthesia.

Word count abstract: 150

Key words: pulmonary hypertension, decompensation, right heart failure, intensive care, perioperative management

Introduction

The first part of this article summarizes the updated recommendations from the 2016 Cologne Consensus Conference on the management of decompensated right heart failure (RHF) in patients with pulmonary hypertension (PH). RHF due to other causes such as acute pulmonary embolism or following cardiac surgery will not be addressed here. The second part of this manuscript provides recommendations on the perioperative management of patients with PAH undergoing major surgery.

Definition and pathophysiology of right heart failure in pulmonary hypertension

RHF in patients with PH can be defined as a "complex clinical syndrome caused by an inadequate cardiac output (CO) and/or an elevated central venous pressure (CVP) resulting from increased right ventricular afterload" [1].

Morphology and structure of the right ventricle (RV) are adapted to the physiological conditions of the pulmonary circulation, which are characterized by low resistance, high compliance and low impedance [2,3]. In this and other ways, the RV differs substantially from the left ventricle (LV), to which it is functionally connected via the interventricular septum and the pericardium [3,4].

In patients with PH, the chronically increased afterload leads to an increase in pulmonary arterial pressure (PAP) and, at least initially, concentric hypertrophy of the RV, through which cardiac function is maintained [5].

As the disease progresses, RV dilation occurs, along with deterioration in systolic function, increased end-diastolic volume, tricuspid regurgitation and decreased CO. This leads to impaired left ventricular filling and consecutive LV dysfunction resulting in a drop in systemic blood pressure, decreased coronary perfusion and myocardial ischemia, further impairing RV performance. RV fibrosis, another component of cardiac remodeling, also leads to impaired diastolic function and increased end-diastolic pressure. This results in increased right atrial (RA) pressure and enlargement of the right atrium along with the clinical symptoms of central venous congestion and fluid retention. The pathological processes that result in (or occur during) the transition from compensated to decompensated RHF are complex, and their temporal sequence cannot be reliably predicted [6].

There is no standard definition of the condition "decompensated RHF". The following definition is proposed here: Decompensated RHF is defined by World Health Organization functional class (WHO FC) IV symptoms with signs of reduced blood supply to other organs (e.g. increases in creatinine, troponin, lactate, and transaminase levels) and/or clinical signs of venous congestion (neck vein

congestion and liver capsule pain) with fluid retention (peripheral edema, ascites, weight gain) resulting from reduced RV function [7].

Management of decompensated RHF

Figure 1 provides an overview of the management of patients with decompensated RHF.

Diagnosis and monitoring

Diagnosis and monitoring of patients with RHF should achieve three main objectives:

1) Identification of RHF

2) Evaluation of cardiac function,

3) Monitoring of end-organ function [7].

Identification of RHF

Timely identification of RHF is essential in order to administer treatment early, and, where possible, reverse the pathological changes and prevent further deterioration. Table 1 lists the clinical signs of overt RHF. An increase in biomarker levels (e.g. N-terminal pro-brain natriuretic peptide, NT-proBNP) and the presence of other high-risk markers as proposed by the recent European PH guidelines can be indicative of deteriorating RV function ("Traffic light table", see →[8]). Warning signs indicating a high risk of imminent death include rising lactate levels, drop in mixed or central venous oxygen saturation (SvO_2 or $ScvO_2$), and decreasing diuresis. Patients with decompensated RHF and secondary organ dysfunction should be monitored in an intensive care unit, at least as long intensive care is justified (see below).

Evaluation of cardiac function

Echocardiography is one of the key examinations in the acute disease phase and as the disease progresses; however, reliable and quantifiable monitoring is often difficult because of the asymmetrical anatomy of the RV. Suitable parameters for assessing the progression and severity of RHF are as follows:

Tricuspid annular plane systolic excursion (TAPSE), RA area, inferior vena cava diameter, pericardial effusion, eccentricity index ("D sign"), and parameters of LV filling [9].

Although the benefit of invasive cardiac function assessment is controversial in patients in cardiogenic or vasodilatory shock [10, 11], invasive cardiac monitoring including measurement of RA

pressure, CO, pulmonary artery pressure, SvO_2 and calculation of pulmonary vascular resistance is advised in patients with decompensated RHF to develop a therapeutic strategy and monitor success. Continuous measurement of CO can be useful in this context. A central venous catheter in the upper half of the body for monitoring of SvO_2 and CVP should, however, be a minimum requirement.

Monitoring of end-organ function

The declining CO seen in RHF leads to reduced blood flow to the organs and even to organ failure. To detect this early, the following parameters should be monitored:

- Kidney function: urinary excretion (urinary catheter), serum creatinine, urea, electrolytes
- Liver function: transaminases and bilirubin
- Oxygenation and tissue perfusion: SpO_2 (pulse oximetry), lactate, SvO_2 or $ScvO_2$, hemoglobin (Hb)
- Myocardial perfusion: electrocardiogram, troponin, systemic blood pressure [7]
- Cerebral function: neurological deficits / impaired vigilance in patients who are not under anesthesia

Management of triggering factors and supportive therapy

Besides the underlying disease, there are frequently triggering factors that can precipitate or aggravate RHF. With regard to successful treatment of decompensated RHF, it is essential to detect and treat these factors.

Arrhythmias

Supraventricular tachycardias are common in PAH patients (cumulative 5-year incidence: 25%; mostly atrial tachycardia, atrial flutter or atrial fibrillation) and can trigger right heart decompensation [12, 13] by loss of atrio-ventricular coupling, diastolic heart filling and negative RV-LV-interaction. In contrast, ventricular tachycardia occurs infrequently in PAH patients [14].

According to the data currently available, patients with supraventricular tachycardia benefit from the restoration of sinus rhythm (rhythm control) which can be achieved by radiofrequency ablation, electrical cardioversion or drug therapy (amiodarone) in accordance with current guidelines [12].

If sinus rhythm cannot be restored, rate control becomes of paramount importance. The negative inotropic properties of beta-blockers and calcium channel blockers (CCBs) should be considered in this context [12, 15, 16], especially in patients with advanced RHF.

Infections

A French study found that infections are one of the most common causes of RHF [17]. There is a high probability that the source of the infection is the bowel region (venous congestion with "leaky bowel" and translocation of intestinal bacteria) [14, 18]. A targeted search for the source of infection and prompt administration of appropriate empirical antibiotic therapy are essential.

Pulmonary embolism and **myocardial infarction** should be excluded or treated in accordance with current guidelines.

Hypoxia, hypercapnia and **acidosis** can increase pulmonary vascular resistance (PVR) and should be avoided or treated [2, 19].

The ideal Hb value in patients with RHF is unknown. However, as **anemia** has the potential to further worsen oxygen supply and thus RV function, the aim is to achieve an Hb value ≥10 g/dl [20].

Iron deficiency, at an incidence rate of 43%, is a widespread phenomenon in idiopathic PAH (IPAH) and is also associated with deterioration in RV function and reduced exercise capacity [20]. Intravenous iron supplementation is recommended whenever iron deficiency is present in patients with RHF.

Hyper- and **hypothyroidism** should be excluded as potential trigger factors and treated accordingly [21, 22].

Diarrhea with dehydration, **discontinuation of targeted PAH medication** or **diuretics** as well as **pregnancy** can cause or aggravate RHF and require appropriate management.

With associated forms of PAH and other forms of PH, **control of the underlying disease** is frequently a precondition for controlling RHF (e.g. immunosuppressive therapies in SLE) [23].

Volume management

Adequate volume management is a difficult but crucial task in the management of RHF. Both hypovolemia and hypervolemia can have negative effects on cardiac pump function and thus on blood pressure and organ perfusion [7].

Early studies indicated that volume loading could have positive effects on hemodynamics in patients with acute pulmonary embolism and patients with RV infarction [24]. However, this observation should not be extrapolated to patients with decompensated PH, the majority of whom have RHF associated with fluid overload. Fluid overload leads to increased RV wall tension and to compression

of the LV by the RV [2]. The impairment of LV filling is potentiated by an increase in pericardial pressure [25,26] and promotes reduced perfusion of the right coronary artery and a further reduction in RV contractility (Fig. 2) [27].

This explains why decompression of the RV by volume reduction can lead to improved RV function, better filling of the LV, better coronary perfusion, and increased CO.

Parameters that can be used to estimate volume status are as follows:

- RA filling pressure
- Diameter and variability of the inferior vena cava
- RA diameter and area, atrial septum shift to the left.

Fluid removal should be performed under careful monitoring, because it can result in deterioration of systemic blood pressure, organ perfusion, and cardiac function. As a rule, RA filling pressures should be kept between 8 and 12 mmHg to optimize CO [28]. Intravenous diuretics are the treatment of choice to remove fluid. If this is not successful, hemofiltration may be considered.

Targeted PAH medication in the intensive care unit – Reduction of RV afterload

Reducing RV afterload is a critical factor in the treatment of RHF. How rapidly the chronically overloaded RV can regenerate becomes evident after lung transplantation or pulmonary endarterectomy [7,29-32]. Targeted PAH therapies, i.e. prostacyclin analogues (PCA), endothelin receptor antagonists (ERA), and phosphodiesterase 5-inhibitors (PDE5-I) or soluble guanylate cyclase stimulators, are useful in many cases in patients with RHF, although their use has never been studied systematically in these patients.

Intravenous PCAs (epoprostenol, treprostinil) are the treatment of choice for patients with decompensated RHF [33]. To prevent systemic hypotension, an initial combination with an inotropic agent, e.g. dobutamine (see below), is often necessary. Inhaled vasodilators, such as nitric oxide (NO) or iloprost, are less efficacious but may occasionally present an alternative for patients who cannot tolerate intravenous PCA administration because of systemic hypotension [34-36]. NO is frequently used after cardiac surgery, particularly in intubated patients with RHF [37, 38]. Sildenafil is available for intravenous administration but has not been studied in patients with RHF.

Based on current data and increasing clinical experience with initial triple combination therapy (PCA, ERA and PDE5-I) in patients with severe PAH [39], the recommendation for initial combination therapy in PAH also appears to be justified for patients presenting with severely decompensated RHF as their initial disease manifestation. In patients who are already receiving advanced PAH therapy when admitted to the ICU, therapeutic success essentially depends on supportive measures and on

whether trigger factors are present and treatable [7]. If this is not the case, extra-corporal membrane oxygenation (ECMO) and lung transplantation should be considered early on as therapeutic procedures, provided that this appears to be a sound and promising approach in the clinical context.

Non-specific vasodilators such as CCBs are obsolete in patients with RHF, even though prior CCB therapy should not be discontinued in patients with IPAH and documented positive vasoreactivity during RHC.

Therapy with inotropic, inodilator and vasopressor drugs

If decompensated RHF manifests with reduced CO and hypotension, the use of positive inotropic agents and/or vasopressors is often indicated. Increasing CO by inotropic compounds frequently improves hypotension; if this is not the case, particularly in patients with low systemic vascular resistance, vasopressor drugs are also used to ensure adequate perfusion pressure of the end organs and of the coronary arteries.

See Table 2 for an overview of the most widely used inotropic drugs and vasopressors together with their desired and unwanted effects.

Inotropics, inodilators:

The β_1-agonist dobutamine remains the inotropic agent of choice for patients with RHF. At doses up to 5 µg/kg/min, dobutamine improves myocardial contractility and reduces RV afterload. β_1-Agonists can, however, also lead to tachycardia which can have a negative effect by shortening diastolic filling time, particularly in patients with PH [7,8,17,40,41]

PDE-3 inhibitors may offer an advantage in this respect. They exert direct inotropic effects by increasing endogenous cyclic adenosine monophosphate, as well as positive indirect effects on cardiac function by reducing afterload. However, the critical disadvantage of these compounds is systemic vasodilation (inodilators), which limits their use, or makes simultaneous vasopressor use necessary.

There is a limited number of small experimental and clinical studies on the efficacy of the calcium sensitizer levosimendan in RHF, but there is currently insufficient clinical experience for a recommendation in this regard [42, 43].

Vasopressors

Norepinephrine is a vasoconstrictor that acts on the α_1-and β_1-adrenoceptors and is frequently used in persistent hypotension due to low systemic vascular resistance. However, norepinephrine may also increase PVR [44].

Vasopressin offers a possible alternative to norepinephrine acting as a systemic vasoconstrictor and pulmonary vasodilator. Beyond favorable clinical experience, however, there are few data in this respect on the use of vasopressin in patients with RHF [7, 45]

Extracorporeal support

Various supportive extracorporeal procedures are available to treat RHF. Veno-arterial ECMO is probably the most commonly used form of extracorporeal support for these patients as it provides rapid and reliable support of the RV [7]. Implantable RV assist devices are used predominantly in the area of cardiac surgery in patients with RHF as a result of LV failure (e.g. after implantation of a left heart support system). Central procedures involving implantation of pump-free systems into the pulmonary circulation are occasionally used as bridge to transplantation [46].

The decision to use extracorporeal life support to treat patients with RHF has to be made on a case-by-case basis. The best-established use for this technique is as bridge to transplantation, particularly in what is known as the “awake ECMO” concept, i.e. in non-intubated, spontaneously breathing patients. In individual cases, “awake ECMO” can be used to facilitate recovery (bridge to recovery), for example when a treatable trigger of RHF or PH is present or when severe RHF occurs in hitherto untreated patients [47-49].

Early identification of patients who may need ECMO therapy is critical, so that intubation can be avoided, and patients can be promptly transferred to an appropriate center [47,48]. If necessary, a transportable ECMO implanted on site by an experienced ECMO-Team may be provided.

Lung transplantation

The question of the need for an urgent lung transplantation arises in individual cases of patients with PH and refractory RHF who are treated in an intensive care setting. A quick decision on whether this option applies can generally be made if the patient has already been fully evaluated and listed for transplantation [50]. A thorough evaluation for transplantation is problematic under the conditions of intensive care and should be avoided as far as possible. Individual cases which deviate from this rule must be discussed on a case-by-case basis with the transplantation team. As the lung allocation score criteria might not reflect clinical severity in patients with PAH in this situation, exceptional

criteria for this patient group have been implemented (see **Table 3** for exceptional lung allocation score criteria for patients with PAH).

Perioperative management in patients with PH

PH is a significant risk factor for increased perioperative morbidity and mortality. Stress, pain, mechanical ventilation and the trauma-induced inflammatory reaction can result in a further increase in PVR and thus promote the development of RHF.

In the current literature, a perioperative mortality of 3-18% has been reported among patients with severe PH, depending on the severity of the underlying disease, and the nature and urgency of the surgical procedure. The highest risk is allocated to pregnant women and patients with concomitant coronary heart disease. Emergency procedures are also associated with a high risk of complications [51,52].

Preoperative preparation

Patient-related and surgery-related factors can be taken into consideration when assessing perioperative risk (see Table 4). Because of the complex underlying disease, interdisciplinary care (pneumology, cardiology, surgery, anesthesiology) of patients may be necessary at, or in consultation with, the expert PH center. In the case of elective procedures, current examination findings (Table 5) should be available to be able to assess the severity of PH, and to evaluate the perioperative risk in order to allow the best possible individual preoperative preparation. Where possible, the patient's supportive and targeted PH medication should be optimized at an appropriate interval to achieve the best possible hemodynamic baseline conditions. Prophylaxis for thromboembolism should be considered [53-55].

Intra-operative monitoring

There is currently no evidence that the intraoperative application of special monitoring has any influence on survival of PH patients. Nonetheless, most authors recommend extended hemodynamic monitoring that includes at least continuous invasive blood pressure measurements and a central venous catheter [1,9-12]. In patients with severely impaired hemodynamics, intra-operative trans-esophageal echocardiography and, if necessary, pulmonary artery catheterization for continuous hemodynamic monitoring after careful benefit/risk assessment, may also be useful [53, 55-57].

Anesthesia: Choosing a procedure

At present, there are no evidence-based data to recommend which anesthetic procedure (regional, general or combined anesthesia) should be used preferentially in patients with PH. However, in elective surgical procedures, experts (as well as the current PH guidelines) recommend that preference is given to regional anesthesia procedures because controlled mechanical ventilation contributes to an increase in RV afterload. If general anesthesia is urgently required, the majority of authors recommend a balanced technique with higher opioid doses and low-dosed volatile anesthetics [58].

If a neuraxial procedure is used, it is important to remember that a reduction in systemic resistance with hypotension may be caused by sympathicolysis; suitable monitoring and slow titration of continuously administered anesthesia to control the extent of the drug's distribution are recommended [53,55,56].

Anesthesia: Dealing with intraoperative increases in PAP

The aim of perioperative management is to prevent further increases in RV afterload which carries the risk of associated RHF. Hypotension, hypothermia, hypoxemia, hypercapnia and acidosis should be categorically prevented by low-dose administration of vasopressors, consistent temperature management, suitable ventilation and adequate fluid therapy. Intravenous and inhaled vasodilators are suitable for reducing intraoperative increases in PAP [53,54,59,60].

Postoperative follow-up care and pain therapy

In the postoperative period, further monitoring should be conducted in an intensive or intermediate care unit for a period appropriate for the individual patient. Because postoperative pain can also contribute to an increase in PVR, adequate pain management should be provided, if possible favoring continuous regional anesthetic procedures and/or non-opioid analgesics. The PAH medication regimen should be resumed as soon as possible post-surgery or not interrupted [53,55,59].

Conflicts of interests:

KMO: received fees for talks and consulting work from Actelion, Bayer, GSK, Pfizer and United Therapeutics.

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CK: received fees for consulting and/or lectures and conference sponsorship from Actelion, Bayer, GSK, Novartis and Pfizer.

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TK: received fees for consulting and lectures from Bayer, GSK and Actelion.

ML: No conflicts of interests.

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Figure Legends

Figure 1: Algorithm on the treatment of acute right heart failure [7]

ECMO: extracorporeal membrane oxygenation, NO: nitric oxide, PH: pulmonary hypertension, RV: right ventricle Tx: transplant

* licensed for PAH (group 1 of the classification) only

Figure 2: Volume management and RV-LV interaction.

CO: cardiac output, LV: left ventricle, RV: right ventricle, RVEDP: right ventricular end-diastolic pressure, TI: tricuspid valve insufficiency

Table 1: Clinical signs of acute right heart failure

Forward heart failure / low cardiac output	**Backward heart failure / congestion**
Drowsiness/sleepiness	Neck vein congestion
Pallor, peripheral cyanosis	Abdominal distension
Hypotension	Ascites
Decreasing diuresis	Edema

Table 2: Overview of inotropic, inodilator and vasopressor drugs [41]

	CO	PVR	SVR	PVR/SVR	Tachycardia	Diuresis/metabolic effects
Inotropics						
Dobutamine <5 ng/kg/min	↑↑	↓	↓	↓	↑	
Dopamine	↑	↑/↓	↑	↑	↑↑	Natriuresis
Epinephrine	↑↑	↓	↑↑	↓	↑↑	Lactic acidosis
Inodilators						
PDE-3 inhibitors	↑↑	↓	↓	↓	(↑)	
Levosimendan	↑↑	↓	↓	↓		
Vasopressors						
Noradrenaline	↑	↑	↑↑	↑/↓*	↑	Lactic acidosis
Vasopressin	↑/↓	↑/↓	↑↑	↓		Diuresis ↑↑

CO: cardiac output, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance

* dose-dependent

Table 3: Exceptional lung allocation score (eLAS) criteria for patients with PAH

eLAS criteria PH group I	**+ at least 1 of the following criteria**	**eLAS aligned with**
• Cardiac index < 2 L/min/m^2 determined by current right heart catheterization (≤ 3 months)	• RAP > 15 mmHg in the last 12 months • Bilirubin > 1 mg/dL and increase > 50% • Creatinine > 1 mg/dL and increase > 50% • 6-minute walk distance < 300 m and deterioration > 100 m	• 95% percentile of all listed (ECMO 99% percentile)

ECMO: extracorporeal membrane oxygenation, PH: pulmonary hypertension, RAP: right atrial pressure (Eurotransplant Thoracic Committee P-ThAC01.14 – eLAS business rules).

Table 4: Perioperative risk factors in PAH

Patient-related perioperative risk factors in PAH	**Surgery-related perioperative risk factors**
• Functional class > II • Reduced 6-minute walk distance • Coronary heart disease • Previous pulmonary embolism • Chronic renal insufficiency • Advanced right ventricular strain	• Emergency surgery • Duration of anesthesia > 3 hours • Intraoperative requirement for vasopressors

PAH: pulmonary arterial hypertension

Table 5: Preoperative check list for patients with PAH

Perioperative check list in PAH
• History and examination • Medication • Functional status • 6-minute walk distance • Pulmonary function, blood gas analysis • Laboratory tests (incl. creatinine, GFR, NT-proBNP) • ECG • Chest X-ray • Echocardiography • Right heart catheterization (optional)

ECG: electrocardiogram, GFR: glomerular filtration rate, NT-proBNP: N-terminal pro-brain natriuretic peptide, PAH: pulmonary arterial hypertension

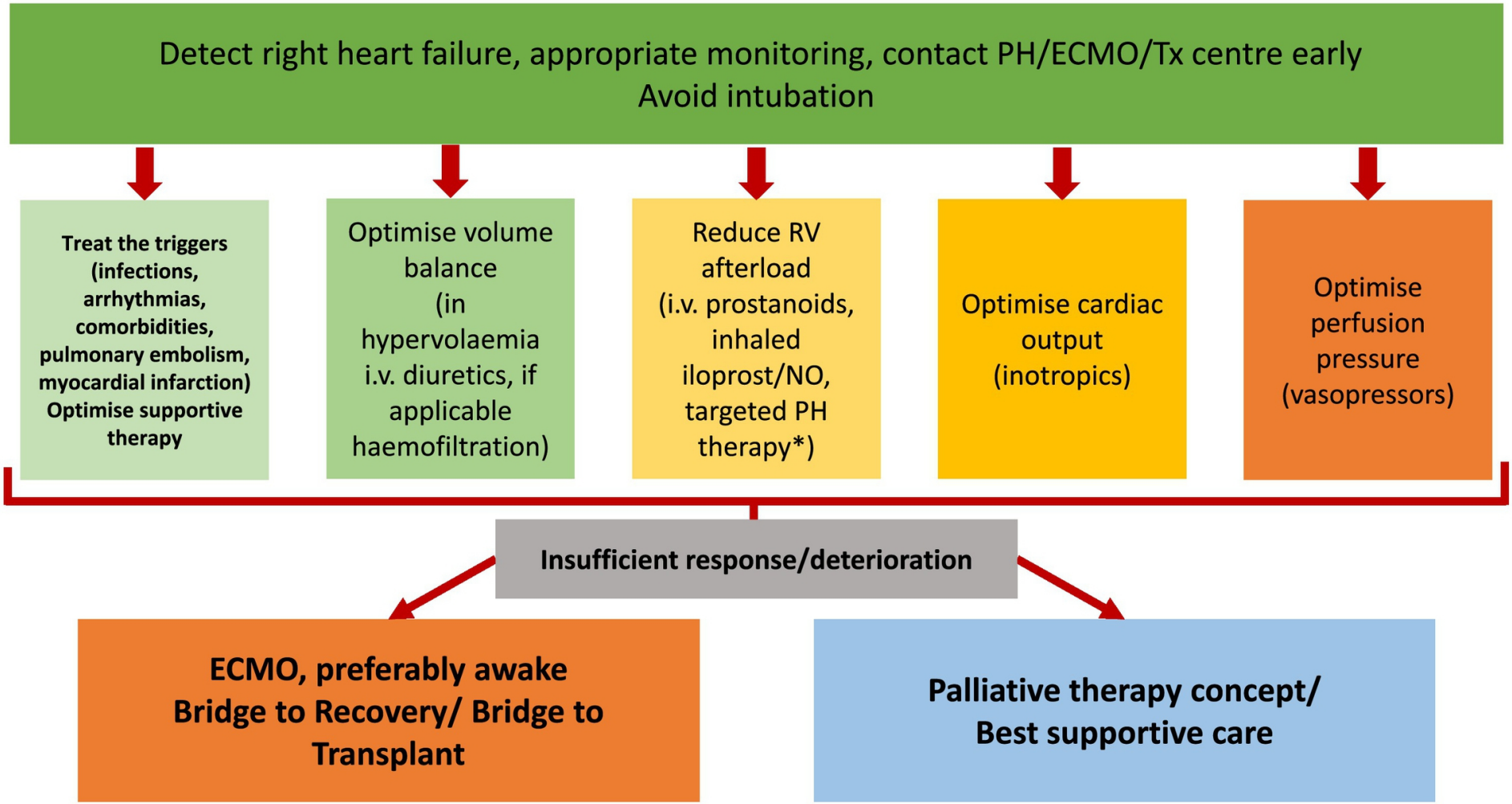
Detect right heart failure, appropriate monitoring, contact PH/ECMO/Tx centre early
Avoid intubation
Treat the triggers (infections, arrhythmias, comorbidities, pulmonary embolism, myocardial infarction) Optimise supportive therapy
Optimise volume balance (in hypervolaemia i.v. diuretics, if applicable haemofiltration)
Reduce RV afterload (i.v. prostanoids, inhaled iloprost/NO, targeted PH therapy*)
Optimise cardiac output (inotropics)
Optimise perfusion pressure (vasopressors)
Insufficient response/deterioration
ECMO, preferably awake Bridge to Recovery/ Bridge to Transplant
Palliative therapy concept/ Best supportive care

Figure 1

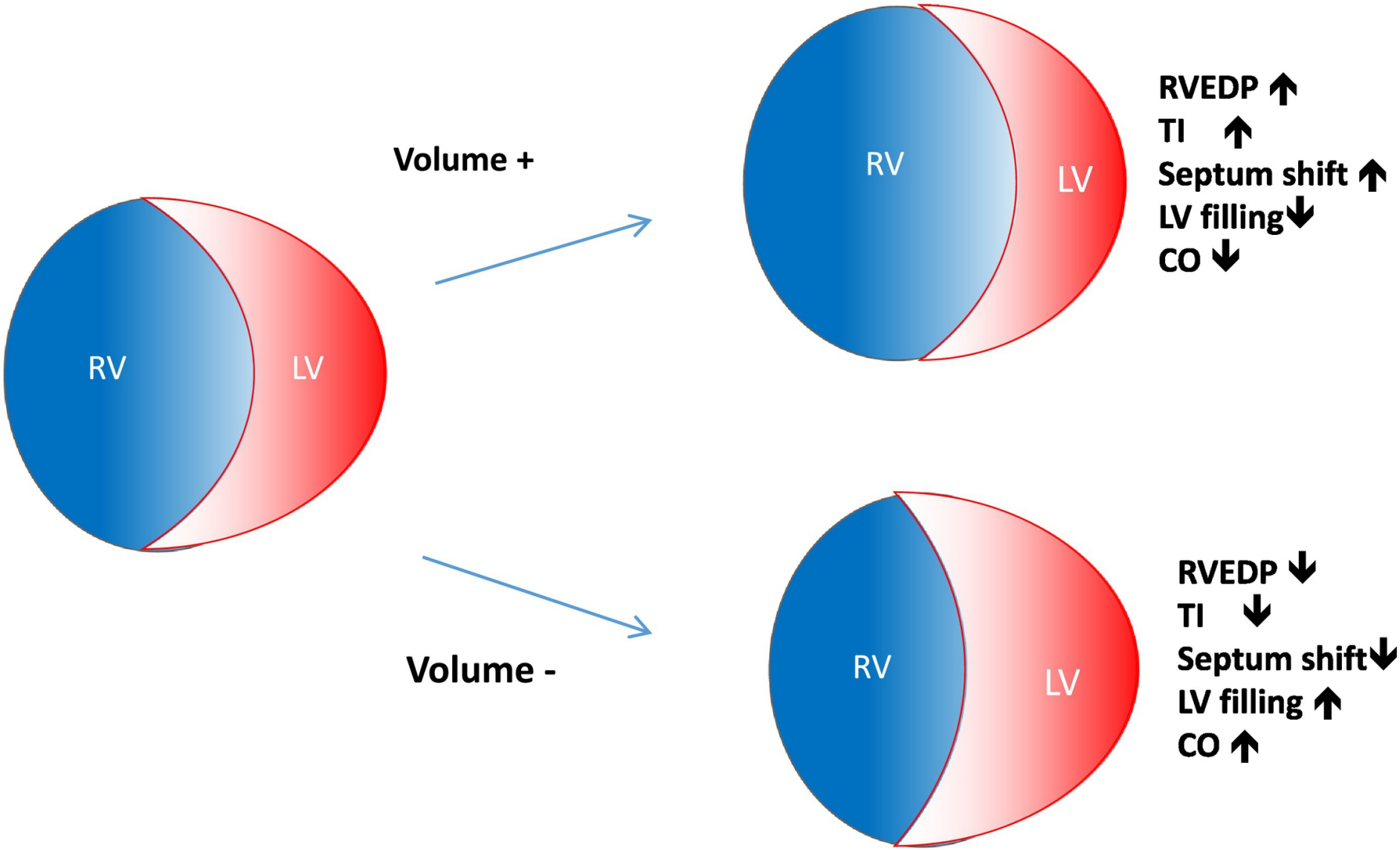
RV
LV
Volume +
RV
LV
RVEDP ↑
TI ↑
Septum shift ↑
LV filling ↓
CO ↓
Volume -
RV
LV
RVEDP ↓
TI ↓
Septum shift ↓
LV filling ↑
CO ↑

Figure 2