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REVIEW

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Critical Care Management of Decompensated Right Heart Failure in Pulmonary Arterial Hypertension Patients – An Ongoing Approach

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Abstract

Despite substantial advancements in diagnosis and specific medical therapy in pulmonary arterial hypertension patients' management, this condition continues to represent a major cause of mortality worldwide. In pulmonary arterial hypertension, the continuous increase of pulmonary vascular resistance and rapid development of right heart failure determine a poor prognosis. Against targeted therapy, patients inexorable deteriorate over time. Pulmonary arterial hypertension patients with acute right heart failure who need intensive care unit admission present a complexity of the disease pathophysiology. Intensive care management challenges are multifaceted. Awareness of algorithms of right-sided heart failure monitoring in intensive care units, targeted pulmonary hypertension therapies, and recognition of precipitating factors, hemodynamic instability and progressive multisystem organ failure requires a multidisciplinary pulmonary hypertension team. This paper summarizes the management strategies of acute right-sided heart failure in pulmonary arterial hypertension adult cases based on recently available data.

Keywords: pulmonary arterial hypertension, acute right heart failure, hemodynamic, specific therapy, intensive care admission, management

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Introduction

Pulmonary hypertension (PH) is a cardiopulmonary condition with progressive discouraging evolution, defined by a resting value ≥25 mmHg of mean pulmonary arterial pressure (mPAP) measured by right heart catheterization (RHC) [1]. The value of 15 mmHg of the pulmonary artery wedge pressure (PAWP) along with mPAP discern two major forms of PH: precapillary (mPAP ≥25 mmHg, and PAWP ≤15 mmHg), and postcapillary PH (mPAP ≥25 mmHg, and PAWP >15 mmHg), respectively. A new definition proposed at The Sixth World Symposium in Pulmonary Hypertension consider a mPAP>20mmHg, and precapillary PH is defined as mPAP>20mmHg, PAWP≤15 mmHg and pulmonary vascular resistance (PVR) ≥3 WU [2].

Related to etiology, clinical presentation, hemodynamic data and pathological findings, PH is clinically classified into five groups and the therapeutic approach is patient-centred with common general measures and supportive therapies [1].

As a distinctive disease with multiple aetiologies, pulmonary arterial hypertension (PAH) is recognized as a cause of acute and chronic right-sided heart failure (RHF), but the clinical onset of the RHF is variable among different subgroups of PAH with similar degree of pulmonary pressure [3,4]. Data regarding admission, management, and outcomes of PAH patients in intensive care unit (ICU) are still limited, as a result of small number of diagnosed cases and lack of consisting data [5-7].

Intensive care unit admissions of acute decompensated right heart failure PAH patients present a complexity of disease pathophysiology and frequently a desolating short-term prognosis. The in-hospital mortality percentage is ranging from 26% up to 41% or higher in patients who require high doses of vasopressors and/or inotropes (50%) up to 70% in dialyzed cases [8-13].

Intensive care management challenges are multifaceted: trigger factors identification and treatment (case specific), volume optimization, right ventricular func-

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tion support, preserve cardiac output for adequate systemic perfusion, and pharmacological aspects (kinetics, molecular, biochemical, and effects) of PAH specific drugs [14-16]. Recognition of underlying cause, hemodynamic instability and progressive multisystem organ failure requires a multidisciplinary PH team.

This overview summarizes the management strategies of acute right-sided heart failure in pulmonary arterial hypertension adult cases based on recent available data.

Pulmonary Arterial Hypertension – A State Of Knowledge

Pulmonary arterial hypertension classified as group 1 in ESC/ERS guidelines, encompasses distinctive subgroups: 1.1-idiopathic, 1.2-heritable (*1.2.1-bone morphogenetic protein receptor type 2 (BMPR2) gene mutation, 1.2.2-other gene mutations (notable level of evidence for EIF2AK4, TBX4, ATP13A3, GDF2, SOX17, AQP1, ACVRL1, SMAD9, ENG, KCNK3, CAV1*), 1.3-drugs and toxins induced, and 1.4-associated with *1.4.1-connective tissue disease*, *1.4.2-human immunodeficiency virus infection*, *1.4.3-portal hypertension*, *1.4.4-congenital heart disease* and *1.4.5-schistosomiasis* [1, 17-19].

Real-life data related to PAH are derived from local, national and/or multinational registries, and observational studies [20,21]. The continuous increase of PVR and rapid development of RHF determines a poor prognosis, despite pulmonary vasodilator therapies development based on disease pathophysiology [22]. McLaughlin et al. exposed the survival rates of PAH patients at 1-, 3-, and 5-year follow-up; noticeable, the rates vary considerable in different subgroups of PAH, being especially related to the underlying etiology [23]. However, the outcomes analysis of an US cohort (REVEAL Registry) and a French study, advise a 69% and 83% respectively survival rate at 3-year follow-up in PAH patients on specific regimens combination [24, 25].

The incidence, prevalence, and phenotype of PAH display differences between studies, registries, presumably related to the design, structure biases, ranging from 2 to 52 cases per million inhabitants [1,26-30].

A remarkable registries derived result is related to the development of prognostic equations for survival probability and risk calculators. Currently available prognostic equations include hemodynamic data obtained at the moment of PH diagnosis – mPAP, mean right atrial pressure (mRAP), cardiac index (CI), and mixed venous oxygen saturation (SvO_2) which can be used as right ventricle function indicators as well as further guided management of PAH patients [31-33].

Main hemodynamic and oxygenation data normal values that are currently used in diagnosis, regular follow-up or ICU monitoring are depicted in table 1.

Different risk calculators used in present-day, built on multiple parameters (demographics, comorbidities, clinical, hemodynamic, functional, echocardiography, lab tests) are designed to offer practitioners valuable tools for an individualized treatment to obtain a low-risk profile of PAH patients [1,36-38].

Endothelial dysfunction and vascular fibrosis play a key-role in the development and disease advancement. Studies on angiogenesis, endothelial-mesenchymal transition, epigenetics, and voltage-gated ion channels biology are on-going [39].

Disease-specific and easily accessible biomarkers of PAH or aberrant pulmonary vascular remodelling-related are currently unavailable, mainly considering the heterogeneity of the PAH population [1,40,41]. N-terminal pro-brain natriuretic peptide (NT-proBNP), currently associated with disease severity and survival, is a non-specific PAH biomarker. Used in heart failure (HF) diagnosis and as predictor of mortality for decompensated HF, its levels can be influenced by multiple comorbidities [42-45]. At present, biomarkers associated with endothelin-1 pathway (ET-1), nitric oxide pathway (cGMP, ADMA, SDMA, nitrate, nitrite, S-nitrosothiol), galectin 3, soluble suppression of tumorigenicity (ST-2), troponins, osteopontin are studied, but the results must be validated by further research [1,11,46-48]. Promising data were published by Samokhin et al related to the NEDD9 plasma level role on pulmonary arterial remodelling, abnormal hemodynamic, and clinical events in PAH patients [49].

The complex and multifactorial pathophysiology of PAH, the presence of three different pathways contributed to the development of approved specific treatment options since 1995. Acute vasoreactivity testing using a short-acting pulmonary vasodilator (intravenous epoprostenol or adenosine, inhaled nitric oxide, inhaled iloprost) should be performed after PAH diagnosis confirmation. A decrease in mean PAP≥10mmHg to reach a value <40mmHg with an unchanged or increased cardiac index confirm channel blocker (CCB) responders. In patients with CI <2L/min/m^2 or RAP >15mmHg treatment with CCB should be considered useless [3].

Table 1. The main hemodynamic and oxygenation parameters considered in diagnosis and monitoring PAH patients (adapted from [34, 35])

Hemodynamic parameters	Equation	Normal range
Systolic blood pressure (SBP)		90-140 mmHg
Diastolic blood pressure (DBP)		60-90 mmHg
Mean arterial pressure (MAP)	[SBP + (2 x DBP)]/3	70–100 mmHg
Heart rate (HR)		60–100 bpm
Right atrial pressure (RAP)		≤6 mmHg
Right ventricular systolic pressure (RVSP)		15-30 mmHg
Right ventricular diastolic pressure (RVDP)		1-8 mmHg
Pulmonary artery systolic pressure (PASP)		15-30 mmHg
Pulmonary artery diastolic pressure (PADP)		6-12 mmHg
Mean pulmonary artery pressure (mPAP)	[PASP + (2 x PADP)]/3	9-18 mmHg
Pulmonary capillary wedge pressure (PCWP)		≤12 mmHg
Cardiac output (CO)	HR x SV/1000	4-8 L/min
Cardiac index (CI)	CO/BSA	2.6-4.2 L/min/m^2
Stroke volume (SV)	CO/HR x 1000	60-120 mL/beat
Stroke volume index (SVI)	CI/HR x 1000	40-50 mL/beat/m^2
Systemic vascular resistance (SVR)	(MAP-mean RA/CO) x 80	800-1200 dynes x s/cm^5 10-15 WU
Systemic vascular resistance index (SVRI)	80 x (MAP- RAP)/CI	1970-2390 dynes x s/cm^5/m^2 24.6-29.8 WU
Pulmonary vascular resistance (PVR)	(mPAP-mean PCWP/CO) x 80	120-250 dynes x s/cm^5 1.5-3.1 WU
Pulmonary vascular resistance index (PVRI)	80 x (MPAP- PAWP)/CI	255-285 dynes x s/cm^5/m^2 3.2-3.6 WU
Partial pressure of arterial oxygen (PaO_2)		80-100 mmHg
Partial pressure of arterial CO_2 ($PaCO_2$)		35-45 mmHg
Bicarbonate (HCO_3)		22-28 mEq/L
pH		7.38-7.42
Arterial oxygen saturation(SaO_2)		95-100%
Mixed venous saturation (SvO_2)		60-80%
Oxygen delivery (DO_2)	CaO_2 x CO x 10	950-1150 mL/min
Oxygen delivery index (DO_2I)	CaO_2 x CI x 10	500-600 mL/min/m^2
Oxygen consumption (VO_2)	$(C(a- v)O_2$ x CO x 10	200-250 mL/min
Oxygen consumption index (VO_2I)	$(C(a- v)O_2$ x CI x 10	120-160 mL/min/m^2
Oxygen extraction ratio (O_2ER)	[(CaO2- CvO_2)/CaO_2] x 100	22-30%
Oxygen extraction Index (O_2EI)	[SaO2- SvO_2)/SaO_2 x 100	20-25%

Currently, there are 14 drugs approved for PAH specific treatment, delivered using 4 administration routes [50]. Approved drugs for use in PAH patients, usual dosage and administration route are depicted in table 2.

Specific medications used in PAH treatment primarily target the pulmonary vasculature, with minimal effects on right ventricle [53]. The lack of long-term improvement in PA pressures even by using modern specific PAH therapies (prostanoids) may be related to the progression of the disease [54].

Despite PAH-specific combination regimens, patients still deteriorate over time and other treatment options (balloon atrial septostomy, surgical or transcatheter Potts shunt, pulmonary artery denervation) should be considered before lung or heart-lung transplantation [55].

In order to avoid late diagnosis with displayed RHF symptoms and signs, disease increased awareness, early referrals to PH reference centers and a well-precise initial treatment is required.

With disease advance, PAH patients need frequent hospitalizations for repeated decompensations and admission in intensive care units in acute episodes of right ventricular failure (RVF).

The Right Ventricle –The Forgotten Chamber of the Heart

Advocate by the Cologne Consensus Conference 2018 and 6th World Symposium on Pulmonary Hypertension, although there is no standard definition, the right-sided heart failure is characterised by the two statements:

- systolic and/or diastolic right ventricular dysfunction drives to low cardiac output and/or elevated right-sided filling pressures (increased right ventricular afterload)
- right-sided HF is severe if it leads to secondary dysfunction of other organs and tissues, in particular liver, kidneys, and gut [4,5,56,57].

Fundamental definitions of the components of the right heart system, distinction between RHF and RVF and what represents RHF were proposed by the International Right Heart Foundation Working Group [58]. Mehra et al recommend RHF as "*a clinical syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to sub-optimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures at rest or with exercise*" [58].

Pathophysiology

By clinical perspective, RHF is a complex syndrome with signs and symptoms' resulting from impaired RV structure or function and both appears to be common in severely ill patients [3].

Systolic RHF and diastolic RHF may present as isolated systolic or isolated diastolic RHF, however combined forms frequently require patient's admission and treatment to the ICU. Tissue perfusion and oxygenation detriment is consequential to left ventricular underfilling and low cardiac output in systolic RHF. In diastolic RHF altered tissue perfusion and oxygenation as well, is the consequence of elevated systemic venous pressure [59]. Detailed pathophysiology mechanisms of right ventricular failure, ventricular interdependence, shifting of interventricular septum, pericardial mechanical involvement in RVF are detailed discussed elsewhere [5,60,61] (figure 1).

The Patient with Pulmonary Arterial Hypertension and Acute Decompensated Right Heart Failure

Intensive care unit management

Facing with a PAH patient with clinical signs of acute decompensated RHF failure including signs of low CO, congestion in the setting of RV failure reworking to pressure or volume overload, impaired venous return should be detected [62].

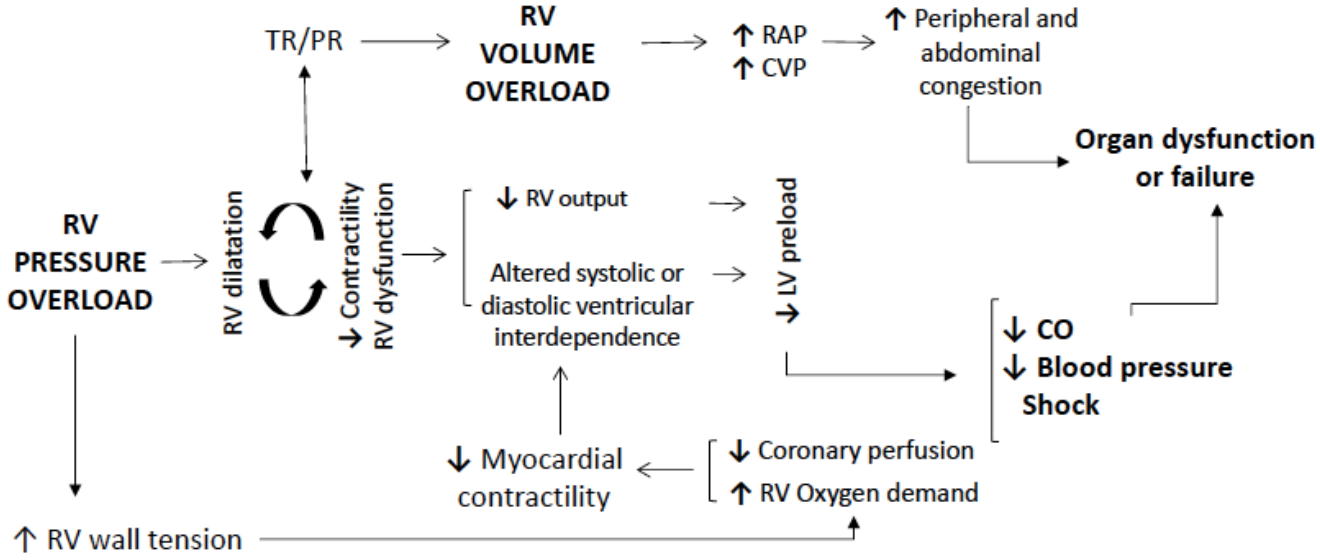

Fig. 1. Schematic pathophysiology of right ventricular failure. Abbreviations: CO-cardiac output, CVP-central venous pressure, LV-left ventricle, TR-tricuspid regurgitation, PR-pulmonary regurgitation, RAP-right atrial pressure, RV-right ventricle.

Table 2. Currently approved agents for PAH patients (adapted after [14,51,52]). Abbreviations: PDE-5-phosphodiesterase-5, ERA-endothelin receptor antagonist, sGC-soluble guanilat cyclase, OD-omne in die (once daily), BID-bis in die (twice daily), TID-ter in die (three times a day)

Administration route	Class	Drug	Acute settings	Dosing	Major side-effects	Important precautions
Oral	PDE-5 inhibitor	Sildenafil	N/A	20mg TID	Hypotension, headache, epistaxis, visual changes, diziness	Contraindicated with nitrates and sGC stimulators
	PDE-5 inhibitor	Tadalafil	N/A	40mg OD	Headache, flushing, hypotension, epistaxis, visual changes	Contraindicated with nitrates and sGC stimulators
	ERA	Bosentan	N/A	Initial 62.5mg BID then up-titration to 125mg BID	Anemia, fluid retention	Potential hepatotoxicity, decrease in hemoglobin concentrations, teratogenicity, avoid administration with CYP3A4 and CYP2C9 inhibitors
	ERA	Macitentan	N/A	10mg OD	Anemia, edema, nasopharyngitis, moderate elevation in liver tests	Teratogenicity
	ERA	Ambrisentan	N/A	Initial 5mg OD then up-titration to 10mg OD	Edema, headache, migraine, nasopharyngitis, moderate elevation in liver test	Severe hepatic impairment (with or without cirrhosis), teratogenicity
	Stimulator of sGC	Riociguat	N/A	Initial 0.5mg TID then up-titration to 2.5mg TID	Hypotension, anemia, gastrointestinal distress, headache, gastritis, hemoptysis	Contraindicated with nitrates and PDE-5 inhibitors, teratogenicity
	Synthetic analogue of prostacyclin	Treprostinil	N/A	Initial 0.25mg BID or 0.125mg TID, then up-titration to 0.25–0.5mg BID or 0.125mg TID every 3–4 days to the highest tolerated dose	Hypotension, gastrointestinal distress, headache	
	Selective prostacyclin receptor agonist	Selexipag	N/A	Initial 200mcg BID, then up-titration weekly with 200mcg BID to a maximum tolerated dose of 1600mcg BID	Hypotension, gastrointestinal distress, myalgias	

Parenteral	Synthetic analogue of prostacyclin	Epoprostenol (Flolan®)	YES	Continuous intravenous, in acute setting starting at 1-2ng/kg/min, step by step dose escalation at an interval of minimum 15 minutes 1- to 2- ng/kg/min depending on clinical response	Tachycardia, flushing, hypotension, headache, diarrhoea, jaw pain, muscle aches, dizziness	Short half-time (3-5 minutes) At 25°C old formula is stable for only 8 hours; new formula is stable for up to 72h
	Synthetic analogue of prostacyclin	Epoprostenol (Veletri®)	YES	Continuous intravenous, in acute setting: 1-2 ng/kg/min and increased by increments of 2 ng/kg/min every 15 minutes or longer depending on clinical response	Hypotension, headache, jaw pain, muscle aches, agitation, anxiety, flushing, anorexia, photosensitivity, catheter-related infection	Stable at 25°C for 48h at concentrations of 3000≤60000 ng/mL and for 72h at concentrations ≥60000 ng/mL
	Synthetic analogue of prostacyclin	Treprostinil	N/A	Continuous intravenous or subcutaneously initiated at 1.25ng/kg/min, rising the dose by 1.25 ng/kg/min per week during the first month and then 2.5ng/kg/min per week, depending on the clinical response	Flushing, hypotension, headache, gastrointestinal distress, diarrhoea, jaw pain, myalgias; infusion site pain (subcutaneously administration)	Stable at room temperature
	PDE-5 inhibitor	Sildenafil	YES	In acute setting bolus 0.05-0.43mg/kg, usually 10-20mg, then continuous infusion starts at 1.25 mg/hour with a maximum effect in 20 minutes	Similar as in orally administration	Similar as in orally administration
Inhaled	Synthetic analogue of prostacyclin	Epoprostenol	YES	In acute setting 30-40ng/kg/min, over 10–20 minutes, inhaled or nebulisation		
	Synthetic analogue of prostacyclin	Iloprost	YES	In acute setting 2.5-5 mg 6-9 times per day	Cough, headache, hemoptysis, gastrointestinal distress	
	Synthetic analogue of prostacyclin	Treprostinil	N/A	18-54 mg 4 times a day	Cough, headache, hemoptysis, gastrointestinal distress	

The greatest importance to the ICU monitoring of PAH and severe right-sided heart failure patients are clinical signs, cardiac and organ's functions [16] (figure 2).

Basic ICU monitoring and laboratory tests

Monitoring clinical signs is the first step in PAH patients admitted in ICU. WHO functional class improvement, maintaining sinus rhythm, reducing tachycardia, a negative fluid balance, decrease of jugular venous pressure, preserving a SBP over 90 mmHg with a MAP>70 mmHg, avoiding acute renal and hepatic injuries are mandatory. Urinary output measured by continuous catheterization must be >0.5mL/kg/hour. Commonly lab tests are depicted in figure 2. Serial checks of natriuretic peptides (BNP or/and NT-proBNP) levels should be completed.

Echocardiography

Against the RV difficult anatomy, cardiac function evaluation and valve assessment by echocardiographic parameters is an essential key examination in monitoring the continuity of RV evolution. The right ventricle worsening, determining the ventricular dyssynchrony by time to peak strain is a good parameter to evaluate the interdependence of left and right ventricle [63].

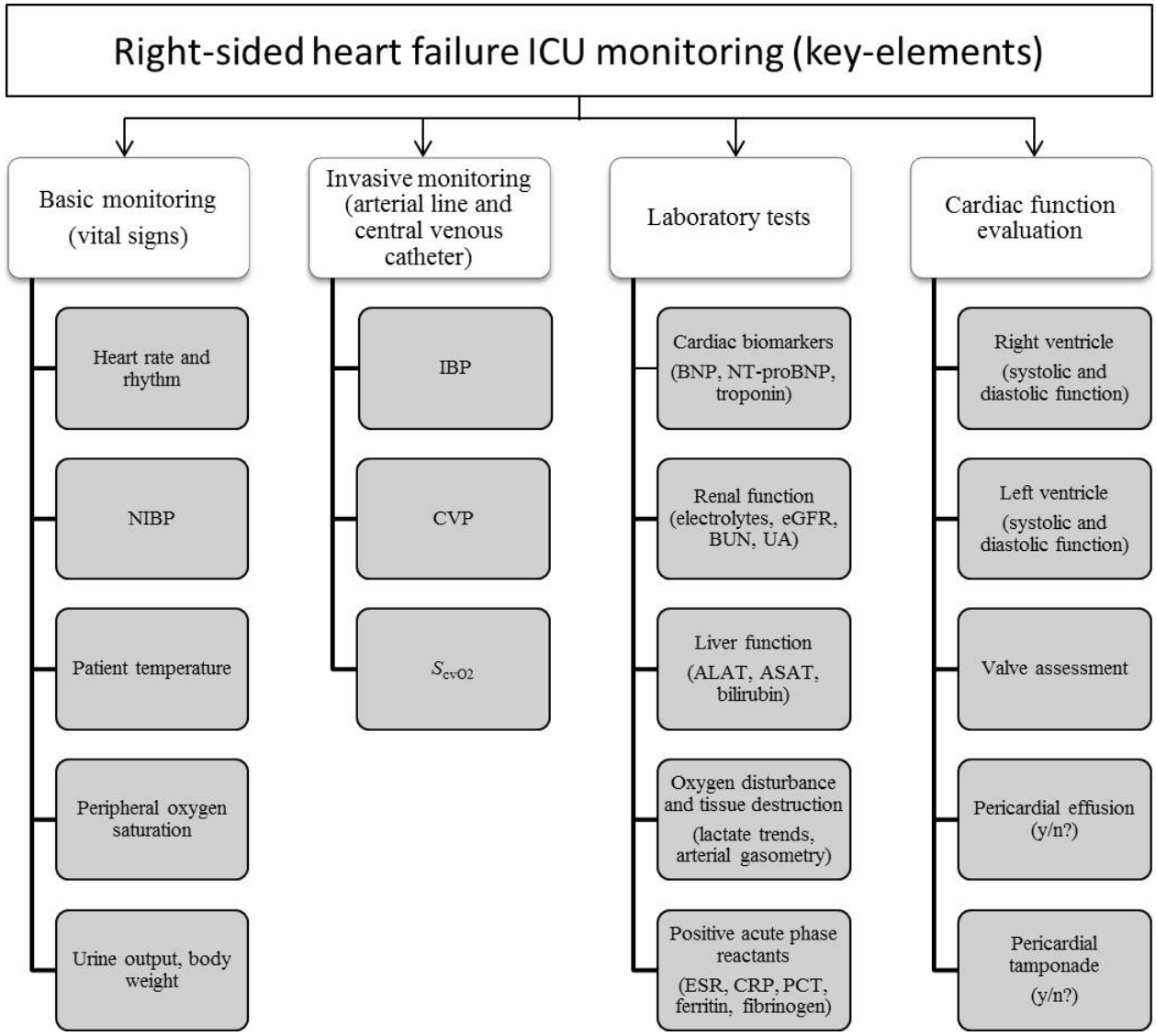

Fig. 2. Algorithm of right-sided heart failure monitoring in ICU. Abbreviations: ICU-intensive care unit, NIBP-non-invasive blood pressure, IBP-invasive blood pressure, CVP-central venous pressure, ScvO2-central venous oxygen saturation, BNP-brain natriuretic peptide, NT-proBNP-N-terminal pro-brain natriuretic peptide, eGFR-estimated glomerular filtration rate, BUN- blood urea nitrogen, UA-uric acid, ALAT-alanine transaminase, ASAT-aspartate transaminase, ESR-erythrocyte sedimentation rate, CRP-C-reactive protein, PCT-procalcitonin, LV-left ventricle, RV-right ventricle.

In critically ill patients, serial quantitative RV function by tricuspid annular plane systolic excursion (TAPSE), S′ velocity of the tricuspid annulus, RV index of myocardial performance (RIPM) and/or fractional area change (FAC) assessment are supported by contemporary management of acute RVF [59]. Other parameters, such as right atrium area, inferior vena cava diameter, RV/LV ratio, and LV eccentricity index, pericardial effusion, and parameters of LV filling or advance use of the three-dimensional (3D) imaging studies, enhance the non-invasive evaluation of the RV dysfunction progression [64].

Management of PAH patients admitted in the ICU with acute RHF should target the reduction of pulmonary vascular resistance [52]. This could be achieved primary by identifying and prompt treatment of the triggering factors.

Hemodynamic monitoring

Invasive hemodynamic monitoring (arterial and central venous lines) is essential to guide therapy. The main goals are maintaining a normal blood pressure for each case, a CVP of 8–12 mm Hg and tailor drugs administration for a normal CO. Standard placement of a pulmonary artery catheter or a Swan-Ganz one to monitor PCWP, PVR, CO, and transpulmonary pressure gradient is attributable in complex patients [65]. An adequate titration of prostanoid therapy, inotropes, diuretics can be driven by the real-time data obtained, but these catheters are carrying-out the risk of arrhythmias [66]. Advanced hemodynamic monitoring can be performed using minimally/non-invasive systems such as pulse index continuous cardiac output device (PiCCO), lithium dilution techniques (LiDCO) [67,68]. In special conditions (extended hemodynamic evaluation or severe PAH patients) right heart catheterization can be considered.

Intensive care unit therapy aims

Management of treatable triggering factors

Common treatable triggering factors who determine ICU admission of PAH patients are represented by infection, arrhythmias, anaemia, pulmonary embolism, systemic hypotension, or specific medication withdrawal/noncompliance [16].

Infection

Infections (including sepsis, infective endocarditis, cerebral abscesses, confirmed HIV) are important negative prognostic factors for mortality in PAH patients admitted in the ICU. They are substantial evidence in favour of connections between gut pathology and PAH [69,70]. The presence of biofilms on indwelling medical devices is another important source of infection. When are diagnosed (isolation of microorganism or high clinical suspicion, radiologic findings, blood samples), prompted targeted treatment decision should be taken by a multidisciplinary team (including infection diseases advocacy). Removal the possibly infected line should be performed, but an alternative route (preferably a central line) must be commenced before (caution related to short half-time of prostacyclins).

Arrhythmias

With limited and various patients study population, the burden of arrhythmias in PAH mostly supraventricular (tachycardias, atrial fibrillation, atrial flutter, and atrioventricular nodal re-entry tachycardia), and ventricular arrythmias is less clear [71]. Supraventricular arrythmias (SVA), with a cumulative incidence ranging from 13.2% to 25.1%, are linked to a marked clinical deterioration, and considered to be a negative prognostic marker of evolution to the end-stage [72-75]. The onset of SVA is associated with right ventricle failure and death [76]. The maintenance or restoring sinus rhythm should be pursued; rhythm control is another option. Among medications used in the treatment of arrythmias, the first choice is Amiodarone; other drugs (Digoxin, Sotalol, Dronedaron, beta-blockers, CCBs) are less studied and they should be used in well-definite scenarios, carrying-out a high-risk in patients with severe RV dysfunction. Alternative procedures - direct electric cardioversion (DCCV) or electrophysiologic therapies (ablations, AAD's, overdrive pacing) must be also individualized and performed in specialized centers [77]. DCCV requires anaesthetic support, carries out a significant risk, and should be ordered before irreversible haemodynamic changes occur. There are no clear indications for prophylactic implantation of ICD in PAH patients [78]. Anticoagulation should be initiated in all patients accordingly to individual patterns. The CHA2DS2-VASc score is not validated in PAH.

Anaemia can precipitate acute RHF in PAH patients, encompasses different etiologies and, therefore, should be carefully corrected [79]. The real incidence of iron-deficiency anemia is not well-known in PAH subgroups, but represents a common comorbidity in HF. Iron replacement using intravenous ferric car-

boxymaltose may be used in acute episodes of HF in PAH patients, reducing hospitalization but the effect on 1-year mortality is still in debate [80,81].

Haemoptysis represent a potentially cause of acute anemia in acute RHF PAH patients. Depending on etiology (including previous anticoagulation), severity, and source of bleeding, it can negative impact the patients management. Severity of haemoptysis can be closely related to the underlying mechanisms: pulmonary embolism, and/or the sequence of elevated PAP, development of functional microvascular networks and association of changes in the structural and functional bronchial arteries.

Bleedings related to anticoagulants address their withholding, the use of traditional reversal agents including prothrombin concentrate in case of vitamin K antagonists or novel reversal agents for DOACs (Idarucizumab, Adexanet alfa) [82,83]. Particular cases of bleedings in PAH-Eisenmenger syndrome-related should be prudentially treated with tranexamic acid. In abundant haemoptysis, tranexamic acid represents an option for rapid resolution of bleeding in case of multiple bronchial artery embolization is unavailable [84,85]. Specific PAH cases with major haemoptysis should grant the use of desmopressin [86].

In PAH patients with acute RVF related to an of acute pulmonary embolism episode, treatment should be initiated accordingly to current guidelines, but the effect of thrombolysis can be unpredictable [59,87].

Ventilation issues

Oxygen inhalations reduce PVR hypoxia-related, mPAP and improve cardiac output [88]. As is stated by Price et al, inadequate oxygenation can exacerbate pulmonary vasoconstriction via hypoxia, hypercapnia and acidosis [89]. Oxygen saturations (SaO_2) should be kept above 90% in rest, and when sleeping [79]. As a general warning mechanical ventilation possess a high-risk during induction and ventilation itself with potential negative haemodynamic effect (systemic vasodilation, increasing PVR); thus auto or low (≤10 cmH_2O) PEEP, a 6 mL/kg/min tidal volume if tolerated, a plateau pressure lower than 30 cmH_2O are recommended in PAH patients who experienced ARDS [60,90]. For patients with refractory hypoxemia, alternative support methods such as high-flow nasal oxygen cannula, continuous positive airways pressure (CPAP) and non-invasive ventilation can be used [91].

Optimising fluid balance

Fluid management is challenging in PAH patients with acute right heart failure. Usually PAH patients who experience an acute episode of decompensation are hypervolemic, but optimal filling point is variable [66]. Tailored dosage of loop diuretics (such as furosemide) in continuous infusion will determine volume depletion with reduction of RV preload, RV wall tension, augmentation of ventricular interdependence and LV diastolic compliance [76]. In selected patients a combination of loop diuretics and thiazides or ultrafiltration may be needed. Diuretic therapy supplementation by adding spironolactone in higher doses may be successful in acute decompensated episodes of HF in PAH patients as they are susceptible for secondary hyperaldosteronism [92,93].Management of hypervolemia by venovenous ultrafiltration is retained in particular cases of hypervolemic PAH patients [16,93].

Vasopressors, inotropes and PAH specific drugs used in ICU settings

Optimizing the cardiac output, myocardial contractility, and preserving systemic blood pressures with direct effect of coronary arteries perfusion pressure by increasing systemic vascular resistance are in close conjunction with above mentioned measures. The effects of commonly vasopressors and inotropes used in ICU admitted PAH patients are presented in table 3 (abbreviations are same as above). The use of these drugs should be well individualised.

Afterload pressure decreasing is important to enhance RV function via mechanisms targeting RV wall tension, rebalancing oxygen delivery-consumption, improving coronary perfusion, increasing RV stroke volume and LV filling [60]. All approved drugs for PAH treatment can be used (see table 2). Typically, due to rapid onset, shorter half-time, titratability, pronounced afterload reduction and reduction in mortality, continuous infusion of epoprostenol is the first option [94]. A special attention must be conferred to selexipag (a prostacyclin receptor agonist) which was not studied in acute care settings, but treatment should not be discontinued in already treated patients [95]. The rapid onset (15 minutes), peak effects (60 minutes) and a 4-6 hour duration of action of Sildenafil determine an increase of CO and decrease of mPAP and PVR; it can be used in ICUs orally and/or intravenously with caution due to side-effects [10,96]. Initiation of up-front triple therapy with epoprostenol, ERA's and PDE-5 is also suitable for critically ill PAH patients [97].

Table 3. Vasopressors and inotropes effects on hemodynamics

Effect	CO	HR	SVR	PVR
↑↑	Dobutamine Milrinone Levosimendan Epinephrine	Dopamine Epinephrine	Epinephrine Norepinephrine Vasopressin	-
↑	Dopamine Norepinephrine	Dobutamine Norepinephrine	Dopamine	Dopamine Norepinephrine
↑/↓	Vasopressin	-	-	Epinephrine Vasopressin
↓	-	-	Dobutamine Milrinone Levosimendan	Dobutamine Milrinone Levosimendan

The usual dosage and duration of action of agents used to optimize preload, myocardial contractility and diminishing right ventricular afterload, including pulmonary vasodilator therapy are presented in table 4.

- Other therapeutic options

Small and moderate pericardial effusions should be managed conservatively. In cardiac tamponade, immediate pericardiocentesis or surgical drainage is confirmed by echocardiographic parameters assessed during one respiratory cycle, using pulse wave velocity (PWV) in both mitral inflow and hepatic venous flow [98].

In particular situations of non-responsive to acute therapies cases is crucial to include the right ventricular mechanical circulatory support. Mechanical support of RV failure (i.e. extracorporeal membrane oxygenation membrane ECMO veno/venous or veno/arterial, or pumpless membrane oxygenators PA-LA, right ventricular assist device-RVAD) can be proposed as a bridge to recovery in acute decompensated naïve PAH patients, in treatable causes of acute decompensation of RHF, or overpassing to lung transplantation [16,60]. Survival of PAH patients admitted in ICU assessed with veno/venous ECMO can be predicted by the SAVE score [99].

CONCLUSIONS

Pulmonary arterial hypertension is a progressive disease with an inexorable advance to death, irrespective

Table 4. Pharmacological options in acute right heart failure PAH patients

Drugs	Dosage	Duration of action (t1/2)
Vasopressors		
Noradrenaline	0.2- 1.0 µg/kg/min	1-2 min
Vasopressin	20 units/ml dose 1-4 units/hour	4- 20 min
Sympathicomimetic inotropics		
Dopamine	2 – 20 µg/kg/min	2 min
Dobutamine	2 – 20 µg/kg/min	2-3 min
Inodilators		
Milrinone	0.375- 0.75 µg/kg/min	1-2 hours
Levosimendan	0.1–0.2 µg/kg/min (Optional bolus of 6–12 µg/kg bolus in 10 min; not recommended if SBP<90 mmHg)	1 hour
Reduction of afterload		
Inhaled		
Epoprostenol	5 – 20 µg/kg/min	2-3 min
Iloprost	2.5 – 5 µg 6-9 times/day	30 min
Intravenous		
Epoprostenol	Titrate upward in 2 ng/kg/min increments according to effect	2-3 min
Iloprost	1 – 5 ng/kg/min	30 min

of advances in diagnosis and medical approach. In time right heart failure develops as a consequence of the disease progress. Understanding the pathophysiology of the right ventricle, the ventricular interdependence and hemodynamic, advocate the monitoring and the treatment, and expert center team management should be the therapeutic approach of severe right-sided heart decline PAH patients. Intensive care support goal is focused on optimising the fluid status, cardiac output and blood pressure, reduce the right ventricle afterload, ward off the intubation, and avoiding development of multisystem organ failure.

Author contribution

All authors made substantial contributions to conceptualization, acquisition, analysis and interpretation of presented information; writing and original draft preparation and revising it for important intellectual content; agreed submission to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Conflict of interest

All authors declare that they have no conflicts of interest related to this study.

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