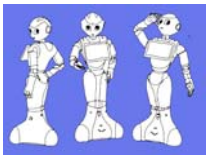
Baden, am 5.5.2017

Präkapilläre PH – bei welchen Patientinnen & Patienten ist intensivmedizinischer Support sinnvoll?



Diana Bonderman

Universitätsklinik für Innere Medizin II, Abteilung für Kardiologie

MEDIZINISCHE UNIVERSITÄT WIEN

Efficacy of intensive care unit management, balloon atrial septostomy & lung transplantation for PAH (Group 1)

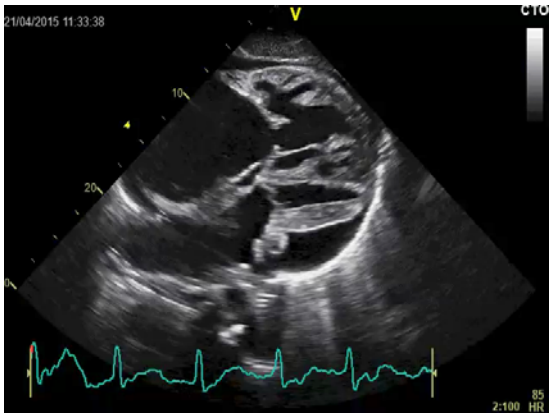
Recommendations	Class - Level					
Measure/treatment	WHO-FC II		WHO-FC III		WHO-FC IV	
Hospitalization in intensive care unit is recommended in PH patients with high heart rate (>110 b/min), low blood pressure (Systolic blood pressure <90 mmHg), low urine output and rising lactate levels due or not due to comorbidities.	-	-	-	-	I	C
Inotropic support is recommended in hypotensive patients.	-	-	I	C	I	C
Lung transplantation is recommended soon after inadequate clinical response on maximal medical therapy.	-	-	I	C	I	C
Ballon atrial septostomy may be considered where available after failure of maximal medical therapy.	-	-	IIb	C	IIb	C

ERS EUROPEAN RESPIRATORY SOCIETY

www.escardio.org

European Heart Journal 2016;37:67–119 doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015;46:903-975

- ALLE PATIENTINNEN UND PATIENTEN?
- WELCHES INTENSIVMEDIZINISCHE MANAGEMENT?



SMJ
SOUTHERN MEDICAL JOURNAL

Poor Outcomes Associated with Drainage of Pericardial Effusions in Patients with Pulmonary Arterial Hypertension

- 6 Patienten mit pulmonaler hypertension und Perikarderguss
- 5 Patienten mit therapeutischer Drainage
- 3 Patienten innerhalb von 13 Stunden nach Drainage verstorben

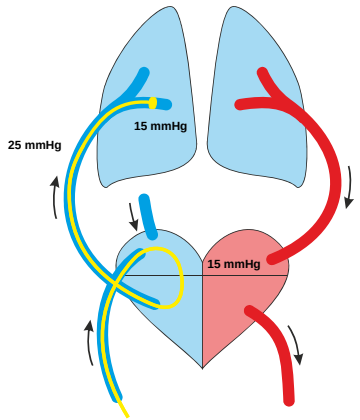


Table 3 Haemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

European Heart Journal

Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et al.[b])

1. Pulmonary arterial hypertension
- 1.1 Idiopathic
- 1.2 Heritable
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection
- 1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

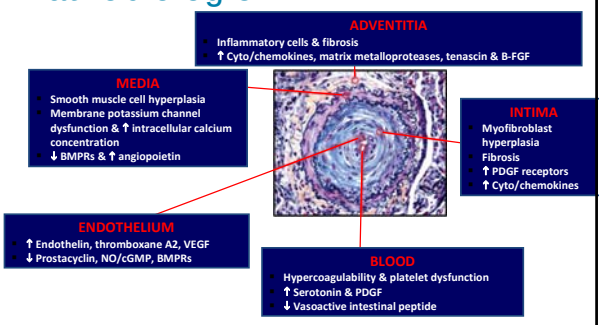
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

1. LUNGEN-GEFÄß-ERKRANKUNG

4. LUNGEN-GEFÄß-GERINNSEL

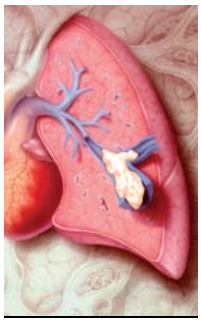
European Heart Journal

Pathobiologie



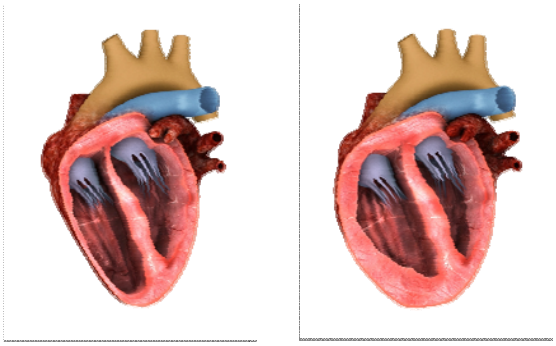
Galiè N, *et al. Eur Heart J* 2010; 31:2080-6.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

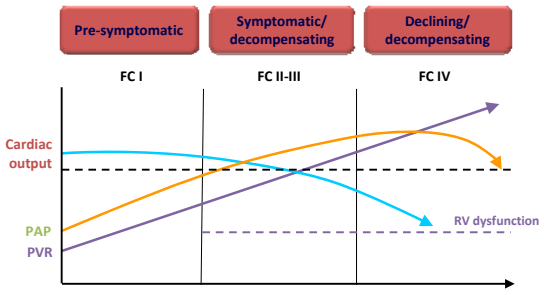


- Characterized by organized thrombotic obstructions in the pulmonary arteries
- Can be associated with small vessel vasculopathy indistinguishable from idiopathic PAH
- CTEPH is associated with increased risk of mortality
  - In one study, the 5-year survival rate in patients with CTEPH was 30% with mPAP >40 mm Hg, and 10% with mPAP >50 mm Hg[1]
  - 62 out of 679 patients in a registry died in <10 months[2]
  - Right ventricular heart failure is the most common cause of death

RV-Anatomie: Normal versus PAH



PH verläuft progressiv



Domenighetti G. *Swiss Med Wkly* 2007; 137:331-6.

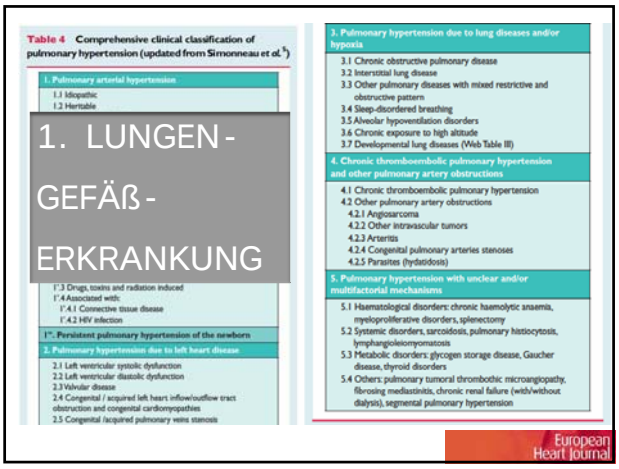


Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et al.[5])

1. Pulmonary arterial hypertension
- 1.1 Idiopathic
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  - 1.4.2 HIV infection

1'. Persistent pulmonary hypertension of the newborn

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- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

1. LUNGEN-GEFÄß-ERKRANKUNG

European Heart Journal

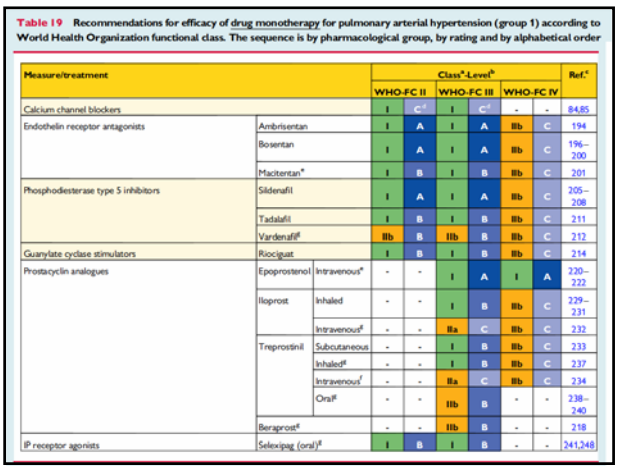

Table 19 Recommendations for efficacy of drug monotherapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. The sequence is by pharmacological group, by rating and by alphabetical order

Measure/treatment			Class[a]-Level[b]						Ref.[c]
			WHO-FC II		WHO-FC III		WHO-FC IV		
Calcium channel blockers			I	C[d]	I	C[d]	-	-	84,85
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C	194
	Bosentan		I	A	I	A	IIb	C	196–200
	Macitentan[e]		I	B	I	B	IIb	C	201
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C	205–208
	Tadalafil		I	B	I	B	IIb	C	211
	Vardenafil[f]		IIb	B	IIb	B	IIb	C	212
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C	214
Prostacyclin analogues	Epoprostenol	Intravenous[g]	-	-	I	A	I	A	220–222
	Iloprost	Inhaled	-	-	I	B	IIb	C	229–231
		Intravenous[g]	-	-	IIa	C	IIb	C	232
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C	233
		Inhaled[g]	-	-	I	B	IIb	C	237
		Intravenous[f]	-	-	IIa	C	IIb	C	234
		Oral[g]	-	-	IIb	B	-	-	238–240
	Beraprost[g]		-	-	IIb	B	-	-	218
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-	241,248

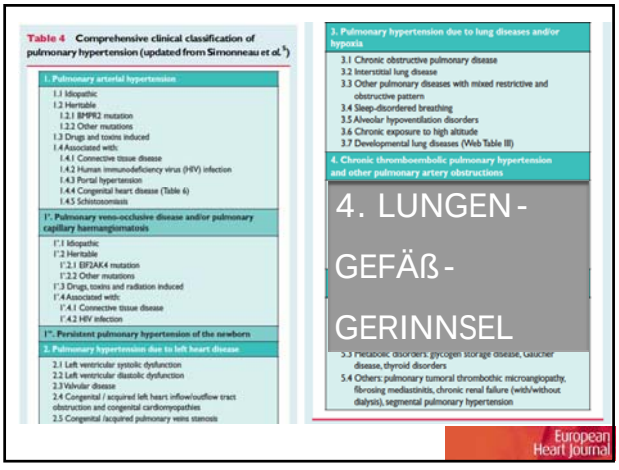

Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et al.[5])

1. Pulmonary arterial hypertension
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

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4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4. LUNGEN-GEFÄß-GERINNSEL

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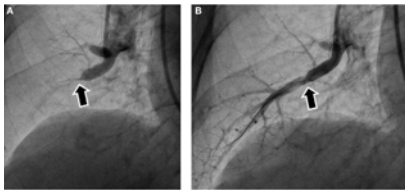
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

European Heart Journal

Treating CTEPH: lifelong anticoagulation and PEA in eligible patients

Only proven therapy is surgery (PEA)

Keogh AM *et al. J Am Coll Cardiol* 2009;54:S67–77. 2. Mayer E. *Eur Respir Rev* 2010;19:64–7.



Triggerfaktoren für Rechtsherzversagen	Anzahl an Patienten (n=19)
Ungeplante Modifikation oder Unterbrechung der PH-Medikation	3
Ungeplante Unterbrechung der diuretischen Therapie	1
Sepsis	5
Pneumonie	3
Purulenter Perikarderguss	1
Septisches Zustandsbild ohne mikrobiologischem Keimnachweis	2
Arrhythmie	3
Ungeplante Schwangerschaft	1

Sztrymf B et al, Eur Respir J. 2010

TABLE 2 Baseline characteristics of patients according to survival in the intensive care unit

	Nonsurvivors	Survivors	p-value
Subjects n	19	27	
Age yrs	52.9 (20.4–77.4)	42.5 (16.2–76.3)	0.07
Sex F/M n	2.3/1	2.2/1	0.7
BMI kg·m^{-2}	21.7 (16.7–30.8)	20.3 (15.9–33.6)	0.7
Type of PAH n			
Idiopathic PAH	8	16	ND
Inoperable CTEPH	3	4	ND
Systemic sclerosis-associated PAH	4	1	ND
PAH associated with connective tissue diseases other than scleroderma	1	1	ND
HIV-related PAH	1	2	ND
Portopulmonary hypertension	1	2	ND
PAH associated with congenital heart disease	1	1	ND
NYHA functional class when last stable n			
II	2	3	0.5
III	9	17	0.5
IV	8	7	0.5
Pulmonary haemodynamic data when last stable			
P_{pa} mmHg	52 (32–87)	52 (40–103)	0.6
PVR dyn·s·cm^{-5}	1054 (623–2400)	990 (525–2315)	0.5
P_{ra} mmHg	12 (3–32)	10 (0–21)	0.7
CI L·min^{-1}·m^{-2}	2.14 (1.48–3.10)	2.26 (1.47–5.0)	0.4

Data are presented as median (min–max), unless otherwise stated. F: female; M: male; BMI: body mass index; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association; P_{pa}: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; P_{ra}: right atrial pressure; CI: cardiac index; ND: not determined.

Sztrymf B et al, Eur Respir J. 2010

TABLE 3 Clinical and biochemical data at admission according to survival in the intensive care unit

	Nonsurvivors	Survivors	p-value
Patients n	19	27	
Triggering factor (yes/no) n	9/19	14/27	0.8
Mean systemic arterial pressure mmHg	64 (32–95)	67 (43–91)	0.9
Cardiac frequency beats·min^{-1}	112 (42–144)	110 (82–151)	0.9
Diuresis mL day^{-1}	1500 (100–8500)	1550 (500–3900)	0.7
Furosemide dose mg·day^{-1}	250 (60–1500)	170 (40–1000)	0.04
Serum level of creatinine µmol·L^{-1}	112 (76–446)	95 (53–204)	0.04
BNP pg mL^{-1}	1415 (449–3550)	628 (87–1460)	0.0007
C-reactive protein mg·L^{-1}	40 (0–277)	12 (0–200)	0.01
Troponin Ic ng mL^{-1}	0 (0–7.35)	0 (0–1.14)	0.4
SAPS II	32 (11–49)	22 (6–43)	0.001

BNP: brain natriuretic peptide; SAPS II: simplified acute physiology score II.

Sztrymf B et al, Eur Respir J. 2010

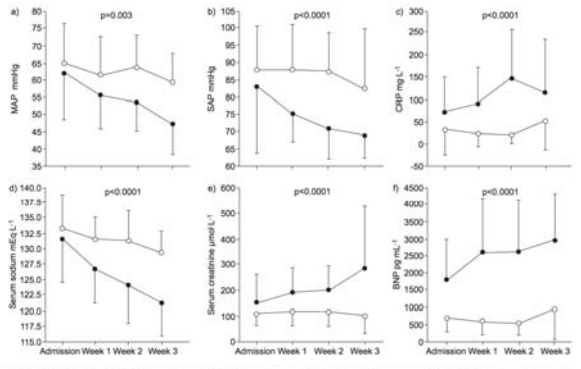


FIGURE 2. Clinical and biochemical data during intensive care unit (ICU) stay according to survival in ICU: patients discharged from the ICU (survivors: ○) or patients who died in the ICU (nonsurvivors: ●). a) Changes in mean systemic arterial pressure (MAP), b) systolic systemic arterial pressure (SAP), c) C-reactive Protein (CRP) serum levels, d) sodium serum levels, e) creatinine serum levels, and f) brain natriuretic peptide (BNP) serum levels, during ICU stay.

Sztrymf B et al, Eur Respir J. 2010

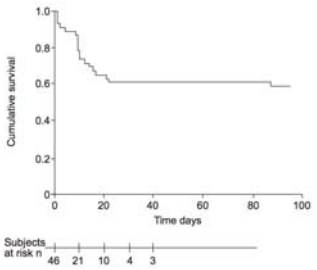
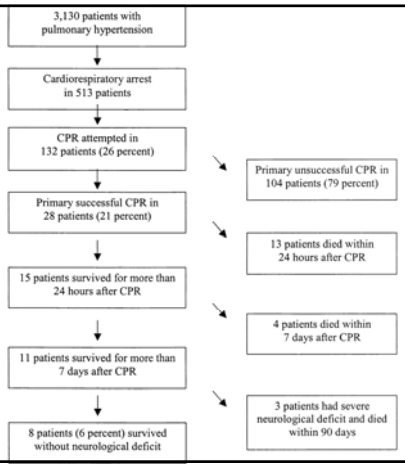


FIGURE 1. Survival in overall population.

Sztrymf B et al, Eur Respir J. 2010



Hoeper MM et al., Am J Respir Crit Care Med 2002;165: 341–344.

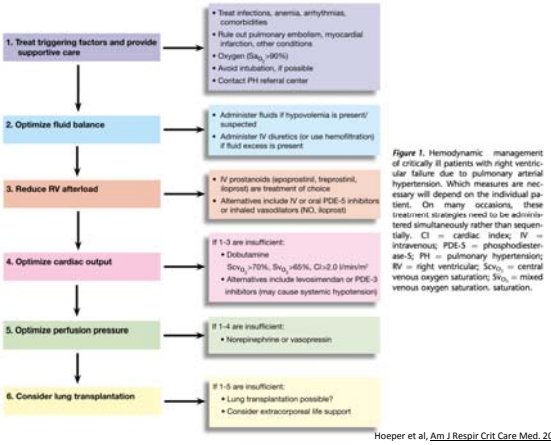


Figure 1. Hemodynamic management of critically ill patients with right ventricular failure due to pulmonary arterial hypertension. Which measures are necessary will depend on the individual patient. On many occasions, these treatment strategies need to be administered simultaneously rather than sequentially. CI = cardiac index; IV = intravenous; PDE-5 = phosphodiesterase-5; PH = pulmonary hypertension; RV = right ventricular; Scv_{O_2} = central venous oxygen saturation; Sv_{O_2} = mixed venous oxygen saturation. saturation.

Hoeper et al, Am J Respir Crit Care Med. 2011

TABLE 2. RECOMMENDED MONITORING OF THE CRITICALLY ILL PATIENT WITH SEVERE PULMONARY ARTERIAL HYPERTENSION

Parameter	Modality	Treatment Goal
Renal function	Urinary catheter Serum creatinine	Maintain kidney function and diuresis. In general a net negative fluid balance is required
Liver function	AST, ALT, bilirubin	Reduce hepatic congestion Maintain hepatic perfusion
Cardiac function	Central venous line (central venous pressure, Scv_{O_2})	Improvement in cardiac function demonstrated by an increase in cardiac output with improvement (reduction) in right atrial pressures
	Pulmonary arterial catheter (RA pressure, cardiac index, PAPm, PVR, Si_{O_2})	Scv_{O_2} > 70% Si_{O_2} > 65%
	Echocardiography	Improve LV filling
Tissue perfusion/oxygenation	Lactate	<2.0 mmol/L
Neurohormonal markers	Brain natriuretic peptides (BNP or NT-proBNP)	Reduction in BNP levels
Myocardial perfusion	Systemic blood pressure (noninvasive or invasive)	Ensure adequate systemic diastolic pressure (>60 mm Hg)
	ECG	Avoid/treat tachycardia/tachyarrhythmia
	Troponin	Optimize myocardial perfusion (negative troponin)

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; ECG = electrocardiogram; LV = left ventricle; NT-proBNP = N-terminal fragment of brain natriuretic peptide; PAPm = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; RA = right atrial; Scv_{O_2} = central venous oxygen saturation; Si_{O_2} = mixed venous oxygen saturation.

Hoeper et al, Am J Respir Crit Care Med. 2011

ZUSAMMENFASSUNG

WELCHE PATIENTINNEN UND PATIENTEN?

- Nicht ausgeschöpfte therapeutische Optionen in Bezug auf Pulmonalgefäßbett (parenterales Prostazyklin, PEA, BPA)
- Reversible interkurrente Ursachen (Infektionen, Rhythmusstörungen, Gravidität)
- Medikamentöse/interventionelle Therapie ausgeschöpft, Kandidatinnen für LuTX

INTENSIVSTATION MIT EXPERTISE IN BETREUUNG VON PAH-PATIENTEN