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Acute Hemodynamic Responses to Supplemental Oxygen and Their Prognostic Implications in Pulmonary Hypertension

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Hemodynamic responses · Hypoxia · Oxygen saturation · Pulmonary hypertension · Supplemental oxygen

Abstract
Background: Pulmonary hypertension (PH) of various causes leads to a poor prognosis. Pulmonary vasoreactivity testing during right heart catheterization (RHC) has prognostic and therapeutic consequences. ***Objective:*** To characterize the acute hemodynamic response to short-term oxygen supplementation (SHOT) in adult PH patients and its impact on prognosis. ***Methods:*** After a stable baseline period, 104 patients with PH [pulmonary arterial hypertension (PAH; n = 56), chronic thromboembolic (PH; n = 22) or respiratory diseases (PH; n = 26)], who were mainly therapy-naïve (86.5%) (mean pO_2 64.5 ± 1.2 mm Hg), received a standardized SHOT during RHC and hemodynamic response was assessed for its prognostic potential. ***Results:*** SHOT significantly reduced heart rate (HR: 78.9 ± 1.5 to 74 ± 1.5 beats/min), cardiac output (4 ± 0.1 to 3.8 ± 0.1 l/min), pulmonary arterial pressure (46.4 ± 1.3 to 42.3 ± 1.3 mm Hg) and pulmonary vascular resistance (10.1 ± 0.5 to 9.6 ± 0.5 Wood units; all $p < 0.001$) compared to baseline. The magnitude of this effect varied between the different PH groups. During a median follow-up of 25.1 months (range: 0.2–73.3 months), HR <72 beats/min in response to SHOT was associated with a better prognosis in patients with PH due to chronic thromboembolism to the lung and PH from chronic lung disease. ***Conclusions:*** SHOT leads to characteristic hemodynamic responses across different forms of PH. The preserved capability to acutely respond to SHOT with HR reduction is of prognostic significance in patients with non PAH PH.

Introduction

Pulmonary hypertension (PH) develops in a variety of diseases and leads to functional impairment and a poor prognosis. Right heart catheterization (RHC) is warranted in every patient with suspect PH to facilitate therapeutic decision making [1]. Although invasive, RHC is a safe procedure in experienced hands [2] and is the gold standard to evaluate complete pulmonary hemodynamics. RHC is mandatory to establish the diagnosis of PH (i.e. mean pulmonary artery pressure, PAP, ≥25 mm Hg), differentiate between pre- and postcapillary forms (pulmonary capillary wedge pressure, PCWP, ≤15 or >15

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mm Hg) and to determine parameters of prognostic value [1]. Pulmonary arterial hypertension (PAH), PH due to chronic thromboembolism to the lung (CTEPH) or PH in the context of chronic lung disease with or without hypoxemia represent the majority of precapillary PH patients [3]. In order to identify a small subgroup of PAH patients with preserved pulmonary vasoreactivity with excellent prognosis who might benefit from high-dose calcium channel blockers [1], a vasoreactivity test with short-acting pulmonary vasodilators is recommended during RHC. In adults, vasoreactivity testing is usually done using intravenous epoprostenol or inhalatory approaches with inhaled nitric oxide or iloprost aerosol [4–6]. While vasoreactivity testing with inhaled oxygen is well established in pediatric PH patients [7–9], this approach has never been investigated systematically in an adult PH patient population.

We aimed to describe acute hemodynamic effects following a short-term application of oxygen (SHOT) during RHC in a group of patients with precapillary PH of different etiologies and to detect prognostic implications of SHOT-induced possible response patterns.

Methods

This study comprised 104 consecutive patients with suspected or established and clinically stable precapillary PH who were scheduled for RHC for clinical reasons. CTEPH patients with proximal disease who were assessed as operable in terms of pulmonary endarterectomy were excluded from the analysis.

Informed consent was obtained from all patients; the study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee.

Treatments at study entry varied. Twenty-three (n = 23) patients were already on domiciliary oxygen therapy. Most patients were naïve for specific PAH medications (n = 90). Otherwise, PAH patients included were treated with inhaled iloprost (n = 8), bosentan (n = 4), sildenafil (n = 1) and high-dose calcium channel blockers (n = 1). Except for oxygen therapy, all medications were discontinued 12 h before RHC. Oxygen therapy was paused at least 2 h before RHC. Since we did not perform a prospective therapeutic study with predefined treatment regimens, we were not able to evaluate different therapeutic effects.

RHC and Hemodynamic Testing

RHC was performed as reported previously [10]. Briefly, a Swan-Ganz catheter (Criti-Cath; Becton-Dickinson; Temse, Belgium) and an arterial line were inserted into the femoral vein and artery, respectively. All measurements were performed in recumbent position. Hemodynamic parameters included systemic arterial (SAP) and right atrial pressure (RAP), PAP and PCWP. Cardiac output (CO) was assessed using the thermodilution method (Cardiac Output Computer; Edwards Laboratories; Santa Ana, Calif., USA). Arterial blood gases and mixed venous oxygen generation (S_vO_2) were measured. Pulmonary (PVR) and systemic vascular resistance (SVR) were calculated using standard formulas.

All measurements were taken at a stable baseline period without oxygen of at least 2 h (baseline). Standardized oxygen was given via standard commercial equipment at a flow rate of 5 l/min to achieve an oxygen saturation of at least 90% in every patient. Oxygen was applied for at least 10 min. Hemodynamic parameters were again recorded when stable parameters for oxygen saturation, heart rate (HR), breathing frequency and PAP and SAP had been noted.

Survival Estimates

The observation period started with the day of RHC and ended when the patient died or received transplantation. A total number of 8 patients received lung transplantation and were included as 'alive' until the day of transplantation and censored thereafter. All non-survivors died of cardiorespiratory failure. No patient was lost to follow up.

Statistical Analysis

Values are presented as means, medians, SEM and/or ranges, respectively. Comparisons were made based on the normal distribution of parameters using Student's t test or the non-parametric Mann-Whitney test. The effect of oxygen on hemodynamic parameters and blood gases was calculated in a paired fashion of the t test. One-factorial ANOVA with Bonferroni correction for multiple testing was performed when more than two groups were compared. The percentage of surviving patients at each time point was estimated with the Kaplan-Meier method.

A value of $p < 0.05$ was considered statistically significant. The statistical software used was SPSS 15.0 for Windows®.

Results

Patient Characteristics

Patient characteristics are listed in table 1. Arterial oxygen saturation (S_aO_2) was higher in PAH patients than in those with PH from chronic lung disease or CTEPH. All other parameters were not significantly different.

Hemodynamic Response to Supplemental Oxygen

Overall, SHOT did not cause any adverse events, but significantly increased oxygen partial pressure (pO_2; ΔpO_2 +54.8 ± 3.9 mm Hg), S_aO_2 (ΔS_aO_2 +8.8 ± 0.7%) and S_vO_2 (ΔS_vO_2 +8.8 ± 0.8 %), as expected (all $p < 0.001$; table 2). In response, HR (ΔHR –4.9 ± 0.7 beats/min), CO (ΔCO –252 ± 30 ml) and mean PAP (ΔPAP –4 ± 0.4 mm Hg), as well as PVR (ΔPVR –0.5 ± 0.1 Wood units, WU) decreased (all $p < 0.001$; fig. 1). While SAP and PCWP were mainly unchanged, RAP was reduced (ΔRAP –0.3 ± 0.1 mm Hg; $p < 0.05$) and SVR increased (ΔSVR

Table 1. Characteristics of the study cohort and subgroups

	All patients (n = 104)	PAH (n = 56)	non PAH PH (n = 48)
Gender (F/M)	57/47	40/16	17/31
Age, years	55.4 ± 1.5	54.6 ± 2.3	56.5 ± 2
Venice class I	56	56	–
iPAH	38	38	–
Scleroderma	11	11	–
PDA	2	2	–
PCH	2	2	–
ASD	1	1	–
VSD	1	1	–
Portopulmonary Hyp.	1	1	–
Venice class III	26	–	26
IPF	10	–	10
Unspecific PF	9	–	9
Post-TBC	3	–	3
COPD	2	–	2
CF	2	–	2
Venice class IV	22	–	22
Non-operable CTEPH	22	–	22
HR, beats/min	78.8 ± 1.4	76.8 ± 1.8	81.1 ± 2.1
CO, l/min	4 ± 0.1	4 ± 0.1	4 ± 0.1
Mean PAP, mm Hg	46.4 ± 1.3	47 ± 1.8	45.5 ± 1.8
PVR, WU	10.1 ± 0.5	10.2 ± 0.6	10 ± 0.7
Mean SAP, mm Hg	95.7 ± 1.5	95.5 ± 2.0	96.1 ± 2.3
PCWP, mm Hg	8.9 ± 0.4	9.1 ± 0.5	8.6 ± 0.5
S_vO_2, %	56.5 ± 1.0	57.6 ± 1.2	55.2 ± 1.6
FVC, liter	2.9 ± 0.1	2.9 ± 0.2	2.9 ± 0.2
FVC, %	82.8 ± 2.6	88.1 ± 3.3	76.7 ± 3.9
TLC, liter	5.1 ± 0.2	5 ± 0.2	5.2 ± 0.2
TLC, %	88.3 ± 2	92.1 ± 2.5	83.8 ± 3.1
FEV_1, liter	2.3 ± 0.1	2.2 ± 0.1	2.3 ± 0.1
FEV_1, %	78.7 ± 2.6	82.8 ± 3.2	74.6 ± 4.2
TLCO, %	54.0 ± 2.6	56.3 ± 2.9	51.2 ± 4.5
FEV_1/FVC, %	78.35 ± 1.0	78.17 ± 1.2	78.56 ± 1.6
pO_2, mm Hg	64.5 ± 1.7	66.5 ± 2.2	61.5 ± 2.4
S_aO_2, %	87.5 ± 0.8	89.4 ± 1.0	85.3 ± 1.3*
pCO_2, mm Hg	37.5 ± 0.8	37.6 ± 1.1	37.3. ± 1.2
Hb, mg/dl	14.7 ± 0.2	14.6 ± 0.3	14.9 ± 0.3

Means ± SEM. PAH includes idiopathic PAH (iPAH; n = 38); scleroderma-associated PAH (n = 11), corrected patent ductus arteriosus (PDA; n = 2); corrected atrial septal defect (ASD; n = 1); corrected ventricular septum defect (VSD; n = 1); portopulmonary hypertension (n = 1), and pulmonary capillary hemangiomatosis (PCH; n = 2). PH without PAH includes CTEPH (n = 22) and PH from chronic lung disease (n = 26). CF = Cystic fibrosis; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; Hb = hemoglobin; IPF = idiopathic pulmonary fibrosis; pCO_2 = carbon dioxide partial pressure; PCH = pulmonary capillary hemangiomatosis; PF = pulmonary fibrosis; TBC = tuberculosis; TLC = total lung capacity; T_LCO = transfer factor of the lung for carbon monoxide; * $p < 0.05$.

Table 2. Acute hemodynamic changes during oxygen supplementation (whole study population; means ± SEM)

	Baseline	Oxygen	p value
Mean SAP, mm Hg	95.4 ± 1.4	94.7 ± 1.5	NS
SVR, WU	23 ± 0.7	24.7 ± 0.8	<0.001
RAP, mm Hg	7.1 ± 0.4	6.8 ± 0.4	0.01
CO, l/min	4 ± 0.1	3.8 ± 0.1	<0.001
HR, beats/min	78.9 ± 1.5	74 ± 1.5	<0.001
Mean PAP, mm Hg	46.4 ± 1.3	42.3 ± 1.3	<0.001
PVR, WU	10.1 ± 0.5	9.6 ± 0.5	<0.001
pO_2, mm Hg	63.9 ± 1.6	118.7 ± 4.8	<0.001
S_vO_2, %	55.8 ± 1.0	64.5 ± 0.9	<0.001
S_aO_2, %	87.5 ± 0.8	96.2 ± 0.5	<0.001

+1.6 ± 0.3 WU; $p < 0.001$). All these effects disappeared 15 min after discontinuation of oxygen supplementation (data not shown).

In the PAH group, improved oxygenation (ΔpO_2 +61 ± 5.5 mm Hg, ΔS_aO_2 +7.4 ± 0.9%, ΔS_vO_2 +8.1 ± 1.1%; all $p < 0.001$) was paralleled by reductions in HR (ΔHR –3.5 ± 0.9 beats/min), CO (ΔCO –221 ± 37 ml) and mean PAP (ΔPAP –3.3 ± 0.5 mm Hg; all $p < 0.001$). PVR was not significantly affected.

In the patients with PH from chronic lung disease and CTEPH, SHOT improved pO_2 (ΔpO_2 +45 ± 4.6 mm Hg), as well as S_aO_2 (ΔS_aO_2 +10.3 ± 1.2 %) and S_vO_2 (ΔS_vO_2 +9.7 ± 1.1 %; all $p < 0.001$). In response, HR (ΔHR –6.5 ± 1 beats/min), CO (ΔCO –290 ± 49 ml) and mean PAP (ΔPAP –4.9 ± 0.6 mm Hg) dropped (all $p < 0.001$). A mild reduction in PVR (ΔPVR –0.7 ± 0.2 WU) was also observed ($p = 0.001$).

Reductions in HR and mean PAP were more prominent in the PH patients than in the PAH group (all $p < 0.05$), while pO_2 increase was pronounced in the PAH group ($p < 0.05$).

Further subdivision of the PH group revealed that all parameters changed equally in these two subgroups (data not shown).

Influence of Baseline Hypoxemia on the Acute Hemodynamic Response to Oxygen

Oxygenation improved in all patients, as expected. Neither the reduction in mean PAP nor that of CO was related to the baseline pO_2. However, a significant reduction in HR was already observed in patients with mild baseline hypoxemia (pO_2 <65 mm Hg).

Table 3. Characteristics of survivors and non-survivors (means ± SEM)

	Survivors	Non-survivors	p value
Age, years	54.3 ± 1.9	57.7 ± 2.7	NS
BNP, pg/ml	165.7 ± 25.8	302.1 ± 76.5	<0.05
Baseline CO, l/min	4.1 ± 0.1	3.8 ± 0.2	NS
CO during SHOT, l/min	3.9 ± 0.1	3.5 ± 0.2	NS
Baseline HR, beats/min	77.2 ± 1.7	82.4 ± 2.5	NS
HR during SHOT, beats/min	72.2 ± 1.8	78.7 ± 2.5	<0.05
Mean baseline PAP, mm Hg	46.7 ± 1.6	45.7 ± 2.2	NS
Mean PAP during SHOT, mm Hg	42.5 ± 1.6	41.9 ± 1.9	NS
Baseline PVR, WU	9.8 ± 0.5	10.8 ± 0.9	NS
PVR during SHOT, WU	9.2 ± 0.5	10.5 ± 0.9	NS
Baseline pO_2, mm Hg	66.7 ± 2.0	60.5 ± 2.8	NS
pO_2 during SHOT, mm Hg	120.4 ± 6.3	107.5 ± 5.6	NS
Baseline S_aO_2, %	88.7 ± 1.0	85 ± 1.3	<0.05
S_aO_2 during SHOT, %	96.1 ± 0.7	96.6 ± 0.5	NS
Baseline S_vO_2, %	58.3 ± 1.1	52.2 ± 1.9	<0.01
S_vO_2 during SHOT, %	65.1 ± 0.9	63.1 ± 2.2	NS

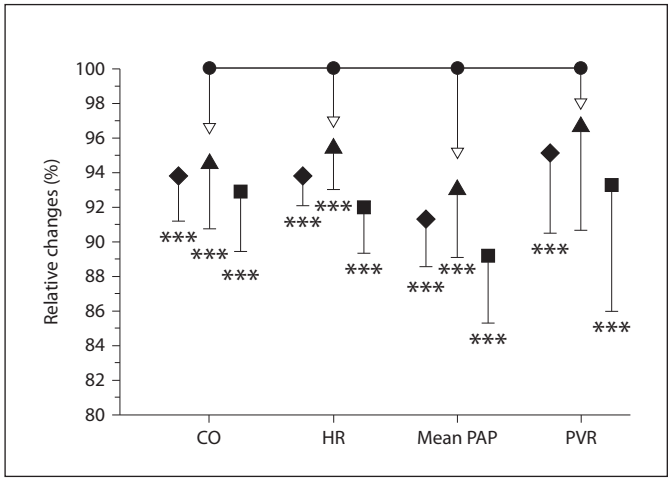

Fig. 1. Hemodynamic responses to supplemental oxygen. The 100% values reflect baseline parameters (one circle for each parameter, CO, HR, PAP and PVR). The development of each of the four parameters during SHOT is given for the whole study population (diamonds), PAH patients (triangles) and non-PAH patients (squares); *** $p < 0.001$.

Characteristics of Survivors and Non-Survivors

Overall, during a mean follow-up of 27.7 ± 6 months (median 25.1; range 0.2–73.3), 32 patients died (31%). Those patients had higher brain natriuretic peptide (BNP) levels, higher HR during oxygen treatment and a lower S_aO_2 (each $p < 0.05$) and S_vO_2 ($p < 0.01$) at baseline (table 3)

There was no significant difference in the studied parameters between survivors and non-survivors (n = 12) in the PAH subgroup.

In patients with PH from chronic lung disease or CTEPH, non-survivors (n = 20; 41.7%) had a higher BNP level and HR during oxygen supplementation ($p < 0.05$), while baseline pO_2 and S_vO_2 were lower in the patients who died ($p < 0.05$). In addition, the surviving patients had a better PVR response to SHOT ($p < 0.05$).

Risk Estimates of Mortality

In univariate analysis of the whole study population (table 4), BNP >180 pg/ml, S_aO_2 <88% and S_vO_2 <58% at baseline were predictors of mortality. During SHOT, HR >72 beats/min was the only parameter that predicted mortality. During multivariate analysis BNP >180 pg/ml (hazard ratio 2.2; range 1.1–4.5; $p < 0.05$) and HR >72 beats/min during oxygen application (hazard ratio 2.1; range 1–4.6; $p < 0.05$) remained predictors of death.

In the PAH group, univariate analysis revealed that S_vO_2 <56% (hazard ratio 3.3; range 1–11; $p < 0.05$) at baseline was associated with mortality.

In PH from chronic lung diseases or CTEPH, univariate analysis showed that a BNP level >160 pg/ml (hazard ratio 3.4; range 1.4–8.4; $p < 0.01$), baseline values of pO_2 <65 mm Hg (hazard ratio 3.2; range 1.3–7.8; $p < 0.05$),

S_aO_2 <88% (hazard ratio 4; range 1.2–13.6; $p < 0.05$) and S_vO_2 <58% (hazard ratio 2.8; range 1.1–6.9; $p < 0.05$) were predictive of death. During SHOT, HR >72 beats/min (hazard ratio 4.3; range 1.4–12.8; $p < 0.01$) was the only prognostic hemodynamic parameter.

During multivariate analysis of PH from chronic lung diseases or CTEPH, HR >72 beats/min during SHOT (hazard ratio 3.3; range 1.1–10.8; $p < 0.05$) remained an indicator of mortality.

Survival Estimates Based on the Hemodynamic Response to Supplemental Oxygen

Ten of 45 patients with HR <72 beats/min during SHOT (mean survival 58 months; 95% confidence interval 49.37–65.53) and 22 of 59 patients with a higher HR died during the follow-up (mean survival time 42.3 months; 95% confidence interval 33.5–51; $p < 0.05$; fig. 2).

Impact of Treatment on Survival

Since we did not perform a prospective therapeutic study with predefined treatment regimens, we are not able to evaluate different therapeutic effects. Twenty-three patients (10 survivors) were on long-term oxygen therapy before study entry and an additional 3 patients were treated with oxygen after completion of the hemodynamic study.

Table 4. Predictors of mortality in univariate analysis in the whole study population

Variable	Hazard ratio	p value
BNP >180 pg/ml	2.5 [1.2–5]	<0.05
HR with O_2 >72 b.p.m.	2.4 [1.1–5.2]	<0.05
S_aO_2 <88%	2.1 [1–4.5]	<0.05
S_vO_2 <58%	2.3 [1.1–4.6]	<0.05

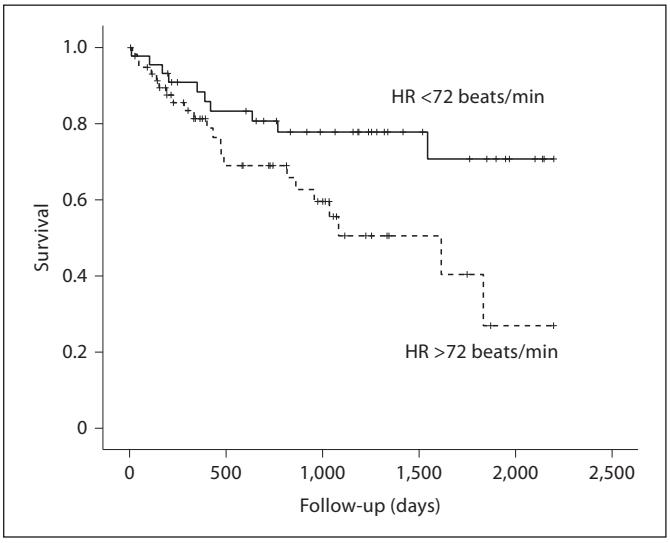

Fig. 2. Effect of risk stratification by HR during SHOT (Kaplan-Meier).

Discussion

In this study, hemodynamic response patterns to SHOT were characterized across different etiologies of precapillary PH. In addition, we identified that a part of this response, namely a HR <72 beats/min, was of prognostic significance.

In contrast to the pediatric PH patient population in whom vasoreactivity testing with oxygen during RHC is well established [7–9], this has never been investigated in a comparable cohort of adult PH patients. Therefore, the identification of any hemodynamic response pattern was of interest.

In our current study, SHOT lowered HR, CO and pulmonary artery pressure across all PH subgroups. In patients with PH from chronic lung disease or CTEPH, an additional small but significant reduction in PVR was detectable during acute testing. Neither a reduction in HR nor PVR reduction was restricted to a certain level of hypoxemia. Of note, we observed these hemodynamic effects in a population with no proven effects of long-term oxygen therapy [1]. In fact, patients were only mild hypoxemic (mean pO_2 64.5 mm Hg) at baseline.

Our interpretation of this hemodynamic response is that supplementary oxygen decreased the sympathetic drive, leading to a reduction in HR, CO and, consequently, PAP. The potential of oxygen to decrease HR as a sign of less adrenergic drive may be of interest, since tachycardia and a decreased HR variability have been interpreted as signs of RH insufficiency and autonomic dysfunction in PH and have been associated with a worse outcome [11–13]. Naturally, it remains to be determined whether a reduction in HR induced by oxygen (or any other substance) could improve outcome in PH patients. However, a reduction in HR may be a therapeutic target in PH, particularly when considering the previously shown beneficial effects of β-adrenoceptor antagonists in left heart failure inhibiting the β-adrenergic stimulus [14]. However, β-blockers can have deleterious effects in PH patients [15]. Recently, it has been shown that in patients

with left ventricular dysfunction HR reduction is a therapeutic target beyond the use of β-adrenergic blockade [16]. Therefore, it is of interest that a reduction in HR can be achieved by SHOT in PH patients, presumably by an alleviation of the adrenergic stimulus.

Even if the extent of PVR reduction was minor and of questionable clinical benefit, it was still statistically significant and diverging between PH subgroups. In fact, PVR reduction was not seen in the PAH group, suggesting a compensable alveolar hypoxia in CTEPH and PH from chronic lung disease. Combined with the effects on HR, the question of when oxygen should be administered in patients with CTEPH and PH from chronic lung disease may be raised. Currently, recommendations for long-term oxygen therapy in PH patients are based on studies in patients with chronic lung disease, including patients with and without PH [1].

Typically, vasoreactivity testing is used in order to identify a subgroup of PAH patients with preserved pulmonary vasodilatory reserve who show a favorable response to calcium channel blocker therapy. In this setting, the prognostic significance of hemodynamic responses has already been characterized for patients with idiopathic PAH. Classically, patients acutely respond with pulmonary vasodilation and either unchanged or increasing CO (depending on the agent). However, in our study, we tried to characterize a different hemodynamic pattern to SHOT besides pulmonary vasodilation, i.e. the reductions in CO and HR, but only minimal pulmonary vasodilation. Based on this, we would not call SHOT a true pulmonary vasoreactivity test at all. This might be in contrast to the pediatric population.

The observation that part of this hemodynamic response to oxygen has prognostic implications is of special interest. A reduction in HR during oxygen inhalation to <72 beats/min turned out to be a predictor of survival in the whole study population, and during subgroup analysis in patients with underlying chronic lung disease or CTEPH. Comparably, HR >70 beats/min was a negative prognostic parameter in patients with left ventricular dysfunction [17]. In addition, tachycardia and reduced HR variability have been associated with a worse outcome in PH patients [11–13]. The potential to lower HR while breathing oxygen may be a sign of preserved autonomic function. Peripheral oxygen shortage in PH mainly results from circulatory insufficiency, which is potentially aggravated by gas exchange disturbances and anemia, depending on the respective comorbidities. In order to overcome this shortage, compensatory circulatory mechanisms are activated. These include neurohumoral upregulation via β-adrenergic stimulation but also the activation of the natriuretic peptide system which is acutely [18] and chronically [19] regulated to counterregulate fluid retention in order to alleviate RH strain [20–23]. An overt clinical sign of such a situation is an increased HR, which is in part thought to compensate threatening heart failure [24–26].

Despite the observation that oxygen inhalation improved a variety of hemodynamic parameters, HR <72 beats/min remained the only variable with prognostic implications in our cohort. Notably, HR without oxygen was not of prognostic significance. This underlines the merit of a test in order to disclose a subclinical oxygen deficit. Very recently, Minai et al. [27] have shown that a reduced HR recovery after moderate exercise (6-min walk test) is a predictor of clinical worsening in PAH patients. Our results are in line with these observations. However, in contrast to their study, we defined an absolute cutoff value (72 beats/min) instead of a relative HR reduction.

The preserved cardiac ability to actively regulate the mentioned compensatory mechanisms could be the rationale for the observation that a physiologic HR during oxygen inhalation was of prognostic significance in the group of patients with PH. In this context, the failure to increase HR in response to a submaximal exercise test was also of prognostic value [28]. However, the prognostic value of a preserved cardiac capability to respond to alleviated cardiac stress has not been investigated. Nevertheless, during subgroup analysis, HR <72 beats/min was no longer a predictor of mortality in the PAH group. One reason for this observation may be the pronounced chronic hypoxemic stress in PH compared to PAH patients and the higher compensatory HR at baseline. Another explanation is a better compensated PAH status despite otherwise almost identical hemodynamic variables, leaving more space for improvement in the PH patients.

Naturally, HR variability can be assessed noninvasively. However, this variability is different from what we investigated in this study and is typically not based upon a defined stimulus or withdrawal of a stimulus, respectively. However, although this acute trial increases our pathophysiological understanding, future assessments can be made without RHC.

Our study clearly has limitations. First, we can only speculate on mechanisms that caused clinically questionable significant improvements in hemodynamics during oxygen inhalation, especially the reduction in PVR. One potential explanation is the antagonizing effect of oxygen on hypoxic pulmonary vasoconstriction [29], which is at

least in part mediated via the oxygen-dependent production of endogenous nitric oxide, a potent pulmonary vasodilator. Moreover, experimental and clinical data suggest an impairment in the catabolism of asymmetric dimethylarginine in chronic hypoxia-induced PH [30]. This may be of importance since asymmetric dimethylarginine is an endogenous inhibitor of nitric oxide synthesis and related to the severity of PH [31]. The fact that in PAH patients a PVR reduction was not observed is in line with this observation, since usually these patients do not have alveolar hypoxia. Nevertheless, even PAH patients responded to SHOT with reductions in HR, CO and PAP.

Although BNP is a well-established parameter of neurohumoral activation, it may not be sufficient to rely on one marker alone to describe neurohumoral activation. However, adrenergic activation is mainly regulated in a paracrine fashion and we might have missed such pathways by measuring catecholamine levels anyway. We did not perform a dose-response curve for supplemental oxygen. Applying 5 l/min of oxygen was a pragmatic approach in order to standardize dosing. Therefore, a conclusion cannot be drawn regarding the threshold of oxygen tension and/or arterial oxygen saturation that would cause a significant reduction in the oxygen deficit. However, the value of the additional information of such a dose-response curve is questionable. Instead, we performed a stepwise statistical analysis in order to identify a threshold for hypoxemia. As a matter of fact, our study population was too small to allow further subgroup analysis, especially in terms of further subdivision of the non-PAH PH group. Finally, we cannot conclude on the long-term effects of chronic oxygen therapy, since we only characterized the acute response to supplemental oxygen.

Despite these limitations, we were able to demonstrate that SHOT provokes a characteristic hemodynamic response with a reduction in HR, CO and, consequently, PAP in patients with different forms of precapillary PH. In addition, we evidenced that the ability to reduce HR <72 beats/min in response to SHOT may confer a survival benefit in PH.

Financial Disclosure and Conflicts of Interest

The authors declare that they have no competing interests.

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