Do arterial oxygenation changes during exercise add prognostic value in patients with pulmonary arterial hypertension?

Short title: Arterial oxygenation in exercise and pulmonary arterial hypertension

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ABSTRACT

Background. The six-minute walking distance (6MWD) is often used to assess prognosis in pulmonary arterial hypertension (PAH) patients. Whether or not changes in arterial oxygen saturation (SpO_2) during exercise add prognostic value to the 6MWD in these patients is unclear. The objective of this study was to investigate if SpO_2 changes during exercise adds prognostic value to the 6MWD in PAH patients.

Methods. Ambispective study that includes 137 patients with PAH (38 idiopathic/heritable (I/H PAH), 42 with connective tissue disease (CTD-PAH), 34 with porto-pulmonary hypertension PoPH (24.8%), 21 with HIV-associated PAH (15.3%) and 2 with pulmonary venous occlusive disease (PVOD, 1.5%). Patients were characterized and, treated according to international recommendations, and were followed-up for 5 years. To integrate SpO_2 changes during exercise, we calculated the desaturation distance ratio (DDR) either in its original form (from a maximal theoretical value of 100%) or the actual resting SpO_2 value of the patient (new DDR) as well as the distance saturation product (DSP).

Results. *(1)* during follow-up, 40 patients died (29.2%); *(2)* results confirmed the prognostic value of the 6MWD (AUC 0.913 [IQR 0.868-0.958]; $p<0.0001$; and, *(3)* neither the original or new DDR or DSP added significant prognostic value to 6MWD in these patients.

Conclusions. Consideration of three different composite indices of arterial oxygenation changes during exercise does not add prognostic value to that of the 6MWD in patients with PAH.

Keywords: Six-minute walking test, pulmonary function tests, pulmonary arterial hypertension, prognosis.

Abbreviations: 6MWD: Six-minute walking distance; 6MWT: Six-minute walking test; AUC: Area under the curve; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; CTD-PAH: Pulmonary arterial hypertension associated with connective tissue disease; DDR: Desaturation distance ratio; DL_{CO}: Carbon monoxide lung diffusing capacity; DSP: Distance saturation product; FEV_1: Forced expiratory volume in the first second; FVC: Forced vital capacity; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; IRVP: Index pulmonary vascular resistance; i/h PAH: Idiopathic/heritable pulmonary arterial hypertension; mPAP: Mean pulmonary arterial pressure; mRAP: Mean right atrium pressure; PAH: Pulmonary arterial hypertension; PaO_2: Partial arterial oxygen pressure; PCWP: Pulmonary capillary wedge pressure; PoPH: Porto-pulmonary hypertension; PVOD: Pulmonary venous occlusive disease; PVR: Pulmonary vascular resistance; ROC: Receiver operating characteristics; RV: Right ventricular; SpO2: Arterial oxygen saturation; TLC: Total lung capacity.

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening condition characterized by increased pulmonary vascular resistance that leads to right ventricular (RV) failure [1]. PAH includes several different diseases such as PAH associated with connective tissue diseases (CTD-PAH), idiopathic pulmonary arterial hypertension (iPAH), heritable PAH (hPAH), and porto-pulmonary PAH (PoPH), among others [2]. The distance walked in the six-minute walking test (6MWD) is commonly used

in PAH patients to assess treatment response and prognosis [1,3–5]. Whether SpO_2 changes add predictive value to the 6MWD in patients with PAH at large (or in specific subgroups like CTD-PAH which can associate interstitial lung abnormalities) is unknown [6].

Several composite indices can integrate 6MWD and SpO_2 changes [7–9]. The desaturation distance ratio (DDR) integrates the 6MWD with the desaturation area (DA) calculated from either a maximal theoretical value of 100% (original DDR) [7] or the actual SpO_2 value of the patient measured at rest (new DDR) [10]. Alternatively, the distance saturation product (DSP) is the product of the 6MWD and the lowest SpO_2 value determined during test [11]. These composite indices predict mortality in chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and non-cystic fibrosis bronchiectasis [12–14], but they have not been explored in patients with PAH. Here, we sought to investigate if these composite indices add prognostic value to the 6MWD, which is currently considered the gold standard to assess prognosis in patients with PAH [1,3–5].

2. METHODS

2.1 Study Design, Patients and Ethics

This ambispective study includes patients older than 18 years with PAH, diagnosed, stratified and treated in our institution according to current ERS/ESC recommendations [1]. Data was obtained for clinical purposes, but its use for this analysis was approved by the Ethics Committee of our hospital (HCB/2017/0469).

2.2 Measurements

Forced spirometry (before and after bronchodilation), plethysmographic lung volumes and the carbon monoxide lung diffusing capacity (DL_{CO}) were determined (Medisoft body box 5500, Surennes, Belgium) in all participants according to international recommendations [15–17]. Reference values were those of Roca *et al* [18–20]. Pulmonary hemodynamics were measured by right heart catheterization following standard procedures [1]. A computed tomography (CT) of the thorax was obtained in all participants following standard clinical methodology. The six-minute walking test (6MWT) was determined indoors in a flat, straight, 30 meters walking course [21], using the reference values of Enright et al[22]. A dyspnea score was determined at rest and peak exercise using the Borg scale. Heart rate (HR) and SpO_2 were continuously monitored during exercise (PULSOX®-300; Minolta Co, Tokyo, Japan). Changes in dyspnea scores (ΔBorg) and SpO_2 (ΔSpO_2) were calculated by subtracting values determined immediately after walking for 6 minutes from resting ones. The original DDR [7], new DDR [10] and DSP [13] were calculated as described in the supplementary material. All evaluations were performed at the initial patients´ assessment, prior to therapy initiation.

2.3 Statistical analysis

Results are presented as number, range, and proportion for categorical variables, or as mean ± standard deviation or median (25–75% percentiles) for continuous variables. Groups were compared using ANOVA o Kruskal-Wallis test for normally or non-normally distributed continuous variables respectively, followed by post-hoc contrast if appropriate, or Chi-square test for categorical ones. For survival analysis, the date of the first 6MWT obtained was used as baseline and patients were

censored at their latest follow-up visit or after five years follow-up. Kaplan-Meier curves were used to investigate survival. The predictive value for mortality of the composite SpO2 indices was analysed by Cox proportional hazards regression. The C statistic (i.e., area under the curve [AUC] of the receiver-operating-characteristics [ROC] curve), was used to compare the predictive value for mortality of all composite indices versus 6MWD by the Bootstrap test. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics for Windows, Version 22.0 (IBM Corporation, Armonk, NY, USA) and Stata, Version 16 (Stata Corp, College Station, TX, USA).

3. RESULTS

3.1. Patient characteristics at recruitment

We included in the study 137 patients with PAH, 38 with idiopathic/heritable (i/h PAH, 27.7%), 42 with CTD-PAH (30.7%), 34 with PoPH (24.8%), 21 with HIV-associated PAH (15.3%) and 2 with pulmonary venous occlusive disease (PVOD, 1.5%). As detailed in Table 1, there were significant differences across disease groups in sex and age distributions, lung function and pulmonary hemodynamics at rest. We also observed significant differences between groups in the 6MWD and SpO_2 at the end of exercise. Accordingly, the original and new DDR as well as DSP were also significantly different across groups (Table 1).

Table 2 contrasts the characteristics of patients with CTD-PAH with and without associated interstitial lung disease (ILD) in CT. The latter included a lower proportion of females and had lower FVC, TLC, DL_{CO} and SpO_2 values (both at rest and peak

exercise). The original and new DDR were higher in patients with ILD, but differences in DSP did not reach statistical significance.

3.2. Mortality during follow-up

During follow-up, 40 of the 137 patients included in the study (29.2%) died (Figure 1, left panel). Survival for the entire study population at 1, 3, and 5-yr follow-up were 92.7%, 78.8% and 68.1%, respectively. This is similar to previous reports [23,24]. By disease, mortality was 21.1% in i/h PAH, 28.6% in patients with CTD-PAH, 44.1% in PoPH and 21.7% in the remaining patients (Figure 1, right panel). In keeping with previous reports, we found that patients with PoPH had worse mortality [23]. The presence of ILD in patients with CTD-PAH worsened their survival, but differences did not reach statistical significance.

3.3 Prediction of mortality during follow-up

The 6MWD (HR: 1.003; 95% CI: 1.000–1.005, p=0.033), original DDR (HR: 1.022; 95% CI: 1.005–1.040, p=0.024) and DSP (HR: 1.003; 95% CI: 1.000–1.006, p=0.032) significantly predict mortality, but the new DDR (HR: 1.028; 95% CI: 0.996–1.061, p=0.118) failed to reach statistical significance.

Figure 2 presents the ROC curves for predicting mortality during follow-up in the entire study population using the four variables tested here. The 6MWD, original DDR, and DSP had a similar capacity to predict mortality in the entire study population, with AUC values that ranged from 0.913 (6MWD) to 0.923 (original DDR) (Table 3). The Bootstrap test comparing pairwise the AUC of the 6MWD, original DDR, new DDR, and DSP showed that there was no significant difference between them (p=0.666) indicating similar predictive power. Using as a cut-off point the value

with the best sensitivity and specificity determined in the ROC curves, Figure 3 presents the Kaplan-Meier survival curves for the entire study population by the 6MWD, original DDR, new DDR and DSP.

In the subgroup of 42 patients with CTD-PAH, the integration of the 6MWD with SpO_2 changes produced slightly lower results than those seen in the population of PAH patients at large. Table 3 shows that the AUC values in patients with CTD-PAH ranged from 0.811 (6MWD) to 0.881 (original DDR), all of them reaching statistical significance ($p<0.001$), and not being different across them ($p=0.390$). Finally, Figure 4 presents the Kaplan-Meier survival curves in patients with CTD-PAH by the threshold value derived from the respective ROC curves for 6MWD, original DDR, new DDR and DSP, all of which predict mortality significantly.

4. DISCUSSION

This study explores if any of three different composite indices that integrate arterial oxygenation changes during exercise adds prognostic value to that of the distance walked in 6 minutes in patients with PAH at large and/or with CTD-PAH only, who may have associated ILD. Results show that integration of SpO_2 changes during exercise does not improve the prognostic value of the 6MWD in any case.

The 6MWD is recommended to assess treatment response and prognosis in PAH patients [1,3–5]. Our study confirmed the prognostic value ($p<0.001$) of the 6MWD in the entire population of PAH patients investigated with an AUC of 0.913 [0.868-0.958], a value higher than that reported by previous authors. Chen *et al*., reported an AUC value of 0.672 [0.494-0.849] in 54 patients with PAH[25], whereas Lee *et*

199 *al*., found an AUC of 0.74 [0.63–0.86] in 137 PAH patients [26]. These differences
200 may relate to the fact that these two previous studies followed patients for only 2-
201 years while we did it for more than 5 years.
202
203 On the other hand, previous studies have reported lower 6MWD cut-off points (331
204 and 295 meters, respectively) [25,26] than ours (437 m) This is likely related to the
205 fact that the previous studies recruited patients before 2013 while the
206 pharmacological management of PAH has improved significantly over the past ten
207 years [27].
208
209 A few studies have previously investigated the prognostic value of composite SpO_2
210 indices in other chronic respiratory diseases [8,10,14]. In ILD and COPD, the DDR
211 (both original and new) are significantly associated with DL_{CO} and emphysema
212 [8,10]. The prognostic value for mortality of DDR was not explored in these other
213 respiratory diseases but DSP has been shown to be a predictor of mortality in IPF,
214 non-CF bronchiectasis and COPD [12–14]. Particularly, in the case of COPD
215 patients, the DSP is a good predictor of mortality, although it does not offer better
216 prognostic ability than 6MWD [14], similarly with our observations here in patients
217 with PAH.
218
219 Our results render further support to the current recommendation of using the
220 6MWD as a prognostic index in PAH patients [1] since we showed that the dynamic
221 integration of 6MWD with arterial oxygenation changes during exercise yielded
222 similar, but not better results. Of not, however, changes in arterial oxygenation

during exercise are clinically relevant since they may merit potential treatment (oxygen therapy) in individuals patients.

Because, patients with CTD-PAH can have associated ILD which, in turn, can worsen pulmonary gas exchange during exercise [28], we explored if the addition of changes in oxygenation indices during 6MWT can add prognostic value in CTD-PAH with ILD. Our analysis did not identify significant differences in terms of ability to prognosticate death during follow-up in these patients either. Again, however, the considerations made above on the potential clinical relevance of SpO_2 changes during exercise hold here too in terms of individualized treatment.

Our study has strengths and limitations. Among the former, the 5-year follow-up of a group of well characterized patients with a rare disease (PAH). Among the latter, we acknowledge that sample size was relatively small and that results need validation in other cohorts.

5. Conclusion

Changes during exercise of three different composite SpO_2 indices do not add prognostic value to that of the 6MWD in patients with PAH.

Author contributions

All investigators contributing to the study are listed as authors. All listed authors contributed to the study. In particular: Study conception or design: XAR, RTC, AA, IB; Data acquisition: XAR, YTG, IB; Data analysis or interpretation: XAR, RTC, YTG, FB, JAB, AA, IB; Manuscript drafting: XAR, RTC, YTG, FB, JAB, AA, IB; Critical manuscript revision: XAR, RTC, YTG, FB, JAB, AA, IB; Final manuscript approval: XAR, RTC, YTG, FB, JAB, AA, IB.

Conflict of interests

The authors declare no conflict of interest in this study.

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Table 1. Characteristics of patients at study entry. Results are presented as mean±SD, n (%) or median (25–75% percentiles).

Demographics	**All (n=137)**	**i/h (n=38)**	**CTD-PAH (n=42)**	**PoPH (n=34)**	**Others (n=23)**	**p-value***
Age (years)	65 ± 14	62 ± 17	69 ± 14	65 ± 11	53 ± 10	0.001 *
Females n (%)	86 (63%)	21(55%)	39(93%)	15(44%)	10(44%)	0.001 +
Body mass index (Kg/m^2)	27 ± 5	26 ± 5	27 ± 5	27 ± 4	24± 6	0.086
Lung function						
FVC (% predicted)	89 ± 17	87 ± 18	81 ± 17	89 ± 18	94 ± 14	0.028 ‡
FEV_1 (% predicted)	81 ± 18	83 ± 17	82 ± 15	80 ± 18	85 ± 17	0.767
FEV_1/FVC	73 ± 8	76 ± 8	77 ± 8	70 ± 7	76 ± 7	0.171
TLC (% predicted)	96 ± 14	94 ± 13	84 ± 15	96 ± 15	105 ± 10	0.001 +
DL_{CO} (% predicted)	52 ±18	61 ± 20	47 ±14	55 ±11	56 ±12	0.004 **
Pulmonary hemodynamics						
mPAP (mmHg)	45 ±12	45 ±10	40 ±15	47±10	46 ±12	0.066
mRAP (mmHg)	8 ± 5	8 ± 4	7 ± 5	7 ± 4	7 ± 5	0.683
PCWP (mmHg)	9 ± 3	9 ± 3	9 ± 3	10 ± 4	8± 3	0.315
Cardiac output (L/min)	4.2 ± 1.35	3.9±1.09	3.88± 0.95	5.32± 1.34	4.54 ± 1.66	0.001 ++
Cardiac index (L/min·m^2)	2.38 ± 0.72	2.21±0.58	2.30 ± 0.52	2.95± 0.77	2.57 ± 0.88	0.001 ‡‡
PVR Pulmonary vascular resistance (Wood unit)	10 ± 6	11± 5	9 ± 6	7 ± 3	10 ± 6	0.089
IRVP (dyn·s/cm^5·m^2)	15 ± 8	17± 8	12 ± 7	14 ± 6	14 ± 9	0.215
6MWT						
6MWD (m)	395±136	433±134	378±125	456±98	490±89	0.002 §
6MWD (%predicted)	74±22	76±22	78±22	85±14	77±12	0.180
Initial Borg score	2 (1-3)	2(1-3)	1(0-2)	1(0-2)	1(0-2)	0.759
Final Borg score	4 (3-6)	4(3-5)	5(3-6)	3(2-4)	4 (2-6)	0.121
SpO_2 at rest (%)	96 (94-97)	96(95-97)	97(94-98)	97(94-98)	96(95-97)	0.867

SpO_2 at the end (%)	88 (83-92)	90(85-92)	87(83-92)	92(87-95)	91(88-93)	0.090
ΔSpO_2 (%) (range)	7 (4-12)	7 (4-10)	8 (4-13)	5 (3-8)	5 (3-6)	0.098
Original DDR	0.160 (0.094-0.270)	0.128(0.087-0.229)	0.161(0.092-0.279)	0.103(0.059-0.156)	0.109(0.072-0.135)	0.027 §
New DDR	0.095 (0.045-0.166)	0.080(0.037-0.152)	0.105(0.046-0.147)	0.059(0.031-0.096)	0.055(0.037-0.070)	0.010 §
DSP	397(322-465)	392(312-462)	349(268-420)	419(349-467)	433(395-497)	0.002 §

* ANOVA or Kruskal-Wallis test. Abbreviations: CTD-PAH: Pulmonary arterial hypertension associated with connective tissue diseases; I/H: Idiopathic and heritable pulmonary arterial hypertension; PoPH: Porto-pulmonary hypertension; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; TLC, total lung capacity; DL_{CO}, diffusing capacity of the lung carbon monoxide; PaO_2, partial arterial oxygen pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrium pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; IRVP, index pulmonary vascular resistance; 6MWT: Six-minute walking test; 6MWD: Six-minute walking distance; SpO_2: Arterial oxygen saturation; DDR: Distance desaturation ratio; DSP: Distance saturation product.

Symbols: * Significant between Others and CTD-PAH, PoPH, Idiopathic/hereditary; + Significant differences between CTD-PAH and PoPH, Others, Idiopathic/hereditary; ‡ Significant differences between CTD-PAH and Others; § Significant differences between CTD-PAH and Others, PoPH; ** Significant differences between Idiopathic/hereditary and CTD-PAH; ++ Differences between Idiopathic/hereditary and PoPH; ‡‡ Differences between PoPH and CTD-PAH, Idiopathic/hereditary

Table 2. Characteristics of patients CTD-PAH with and without interstitial lung disease (ILD). Results are presented as mean±SD, n (%) or median (25–75% percentiles).

Demographics	**All CTD-PAH (n=42)**	**with ILD (n=10)**	**without ILD (n=32)**	**p-value***
Age (years)	69 ± 14	76 ± 10	67 ± 15	0.066
Females n (%)	39 (63%)	7(70%)	32(100%)	0.001
Body mass index (Kg/m^2)	27 ± 5	26 ± 4	28 ± 6	0.273
Lung function				
FVC (% predicted)	81 ± 19	71 ± 16	84 ± 16	0.026
FEV_1 (% predicted)	82 ± 15	75 ± 13	85 ± 15	0.061
FEV_1/FVC	77 ± 8	77 ± 7	76 ± 8	0.691
TLC (% predicted)	84 ± 15	74 ± 17	88 ± 12	0.010
DL_{CO} (% predicted)	47 ±14	39 ±10	50 ± 14	0.024
Pulmonary hemodynamics				
mPAP (mmHg)	40 ±15	33 ±9	42 ±15	0.070
mRAP (mmHg)	7 ± 5	6 ± 3	8 ± 5	0.159
PCWP (mmHg)	9 ± 3	8 ± 3	9 ± 3	0.357
Cardiac output (L/min)	3.88 ± 0.95	3.90± 1.02	3.88±0.95	0.966
Cardiac index (L/min·m^2)	2.29 ± 0.51	2.32 ± 0.50	2.29±0.53	0.910
PVR (Wood units)	9 ± 6	98± 6	9± 6	0.756
IRVP (dyn·s/cm^5·m^2)	12 ± 7	12± 5	12± 5	0.861
Exercise response				
6MWD (m)	378±125	366±157	382±117	0.733
6MWT (%predicted)	78±22	79±27	78±21	0.884
SpO_2 at rest (%)	97 (94-98)	94(93-96)	97(95-98)	0.045

Final dyspnea, Borg Scale	5 (3-6)	5(4-6)	5(2-6)	0.423
SpO_2 at the end (%)	87 (83-92)	82(77-85)	91(85-94)	0.001
ΔSpO_2 (%)	8 (4-13)	12(10-17)	6 (3-10)	0.001
Original DDR	0.160 (0.092-0.279)	0.269(0.160-0.444)	0.133(0.070-0.240)	0.016
New DDR	0.104 (0.046-0.147)	0.137(0.119-0.184)	0.070(0.037-0.127)	0.008
DSP	349(269-420)	307(153-441)	356 (285-412)	0.358

* ANOVA or Kruskal-Wallis test (between CTD-PAH with or without ILD). Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; TLC, total lung capacity; DL_{CO}, diffusing capacity of the lung carbon monoxide; PaO_2, partial arterial oxygen pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrium pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; IRVP, index pulmonary vascular resistance; 6MWT: Six-minute walking test; 6MWD: Six-minute walking distance; SpO_2: Arterial oxygen saturation; DDR: Distance desaturation ratio; DSP: Distance saturation product.

Table 3. AUC for 6MWD, original DDR, new DDR, and DSP for entire population and CTD-PAH patients

	6MWD	Original DDR	New DDR	DSP
All patients	0.913 [0.868-0.958]*	0.923 [0.881-0.966]*	0.917 [0.872-0.961]*	0.914 [0.869-0.959]*
CTD-PAH	0.811 [0.682-0.941]*	0.881 [0.777-0.984]*	0.847 [0.732-0.962]*	0.817 [0.690-0.943]*

Abbreviations: 6MWD: Six-minute walking distance; AUC: Area under the curve; DDR: Distance desaturation ratio; DSP: Distance saturation product; CTD-PAH: Pulmonary arterial hypertension associated with connective tissue disease. *p<0.001

FIGURE LEGENDS

Figure 1. Kaplan Meier survival curves of the entire study population (left), by subtypes disease (right) and by presence of ILD in patients with CTD-PAH (bottom). For further explanations, see text.

Abbreviations: i/h: Idiopathic/hereditary; CTD-PAH: Pulmonary arterial hypertension associated with connective tissue disease;; PoPH: Porto-pulmonary hypertension.

Figure 2. Receiving operating characteristic (ROC) curves to predict mortality in the entire study population for 6MWD, original DDR, new DDR and DSP. For further explanations, see text.

Abbreviations: 6MWD: Six-minute walking distance; DDR: Distance desaturation ratio; DSP: Distance saturation product.

Figure 3. Kaplan Meier survival curves of the entire study population of 6MWD, original DDR, new DDR and DSP. Cut-off values were derived from the ROC curves. For further explanations, see text.

Abbreviations: 6MWD: Six-minute walking distance; DDR: Distance desaturation ratio; DSP: Distance saturation product.

Figure 4. Receiving operating characteristic (ROC) curves to predict mortality in patients with CTD-PAH for 6MWD, original DDR, new DDR and DSP. For further explanations, see text.

Abbreviations: CTD-PAH: Pulmonary arterial hypertension associated with connective tissue disease; 6MWD: Six-minute walking distance; DDR: Distance desaturation ratio; DSP: Distance saturation product.

Figure 5. Kaplan Meier survival curves in patients with CTD-PAH of 6MWD, original DDR, new DDR, and DSP. Cut-off values were derived from the ROC curves. For further explanations, see text.