International Journal of Cardiology 283 (2019) 159–164

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Dexamethasone improves pulmonary hemodynamics in COPD-patients going to altitude: A randomized trial☆

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ARTICLE INFO

Article history:
Received 20 August 2018
Received in revised form 25 November 2018
Accepted 18 December 2018
Available online 28 December 2018

Keywords:
COPD
Dexamethasone
Hypobaric hypoxia
Altitude
Pulmonary artery pressure
Hemodynamics

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) may predispose to symptomatic pulmonary hypertension at high altitude. We investigated hemodynamic changes in lowlanders with COPD ascending rapidly to 3100 m and evaluated whether preventive dexamethasone treatment would mitigate the altitude-induced increase in pulmonary artery pressure.

Methods: In this placebo-controlled, double-blind trial, non-hypercapnic COPD patients living <800 m, were randomized to receive either dexamethasone (8 mg/day) or placebo tablets one day before ascent from 760 m and during a 3-day-stay at 3100 m. Echocardiography was performed at 760 m and after the first night at 3100 m. The trans-tricuspid pressure gradient (RV/RA, main outcome), cardiac output (Q) by velocity-time integral of left ventricular outflow, indices of right and left heart function, blood gases and pulse-oximetry (SpO_2) were compared between groups.

Results: 95 patients, 79 men, mean ± SD age 57 ± 8y FEV_1 89 ± 21% pred, SpO_2 95 ± 2% were included in the analysis. In 52 patients receiving dexamethasone, RV/RA, Q and SpO_2 at 760 and 3100 m were 19 ± 5 mm Hg and 26 ± 7 mm Hg, 4.9 ± 0.7 and 5.7 ± 1.1 l/min, SpO_2 95 ± 2% and 90 ± 3% ($P < 0.05$ all changes). In 43 patients receiving placebo the corresponding values were 20 ± 4 mm Hg and 31 ± 9 mm Hg, 4.7 ± 0.9 l/min and 95 ± 3% and 89 ± 3% ($P < 0.05$ all changes) between group differences of altitude-induced changes were (mean, 95% CI): RV/RA −4.8 (−7.7 to −1.8) mm Hg, Q 0.13 (−0.3 to 0.6) l/min and SpO_2 1 (−1 to 2) %.

Conclusions: In lowlanders with COPD travelling to 3100 m preventive dexamethasone treatment mitigates the altitude-induced rise in RV/RA potentially along with a reduced pulmonary vascular resistance and improved oxygenation.

1. Introduction

Despite an increasing prevalence of chronic obstructive pulmonary disease (COPD) in the general population, and an increasing number of people travelling to high altitude for professional and recreational activities, only few studies in COPD patients exposed to hypobaric hypoxia at altitude report about potential implications on health and preventive strategies [1,2]. Evidence for an altitude-associated increase in mortality in COPD underscores the need of research in this field [3,4].

COPD is the most common chronic respiratory disease worldwide. It is characterized by chronic airflow obstruction with airway inflammation, remodeling and in some patients parenchymal destruction of the lung (emphysema). Cardinal symptoms of COPD are chronic productive cough and dyspnea on exertion with limited exercise performance related to airflow obstruction, dynamic hyperinflation, exercise desaturation and increase in pulmonary artery pressure (PAP) [5]. Pulmonary hypertension

Abbreviation: 6MWD, six-minute-walking distance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eNOS, endothelial NO synthase; FAC, fractional area change; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, global Initiative for Chronic Obstructive Lung Disease; HAPE, high altitude pulmonary edema; HPV, hypoxic pulmonary vasoconstriction; mPAP, mean pulmonary arterial pressure; NO, nitric oxide; PaO2, partial pressure of oxygen in arterial blood; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; Q, cardiac output; RAP, right atrial pressure; RV, right ventricle; RV-ESPAR, right ventricular end-systolic pressure-area relation; sPAP, systolic pulmonary artery pressure; SpO2, oxygen saturation; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; RV/RA, trans-tricuspid or right ventricular to right atrial pressure gradient.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2018.12.052
0167-5273/

(PH) is a common complication in COPD with increasing prevalence with severity of the parenchymal lung destruction and airflow limitation due to increased hypoxic pulmonary vasoconstriction (HPV) and loss of the pulmonary capillary bed [6,7]. Exercise-induced PH usually precedes resting PH and a sustained PAP-elevation may ultimately lead to right ventricular (RV) failure, and reduced survival [6,8].

The structural alterations and functional abnormalities of pulmonary vessels resulting from HPV in patients with COPD might increase the risk of developing symptomatic PH when travelling to the hypoxic environment at altitude. In previous studies, we found that patients with COPD tolerated acute exposure to moderate altitude (2590 m) generally well although they suffered from a major reduction in exercise performance and pronounced dyspnea [9,10]. Effective means to prevent this limitation would therefore be desirable. To address this point, we designed a randomized trial evaluating the effectiveness of dexamethasone treatment in preventing altitude-related adverse health effects including acute mountain sickness, impairment in postural control, and cardiovascular impairment in COPD patients ascending to 3100 m. Dexamethasone was selected as preventive drug since glucocorticoids are used to treat airway inflammation and airflow obstruction in exacerbated COPD, and since it prevented the excessive rise in PAP and improved exercise capacity in otherwise healthy individuals susceptible to high altitude pulmonary edema (HAPE) after rapid ascend to 4559 m [11,12]. Whether preventive treatment with the glucocorticosteroid dexamethasone would similarly reduce PAP-increase in patients with COPD travelling to altitude has not been studied.

The purpose of the current study was thus to evaluate whether treatment with dexamethasone prevents or reduces an excessive rise in PAP and echocardiographic indices of cardiac performance in lowlanders with COPD travelling to 3100 m.

2. Methods

2.1. Design and setting

This current study was part of a randomized, placebo-controlled, double-blind, parallel-group trial evaluating efficacy of dexamethasone in preventing various altitude-induced adverse health effects. Power calculations were performed according to the study's overall primary outcome. Data on acute mountain sickness, safety endpoints, postural control and patient characteristics (spirometry, arterial blood gas analysis and 6 min walk distance) have been published recently [9,13]. The results of the detailed echocardiographic evaluation presented here have not been reported. The study was conducted from March 30th to August 6th, 2015 at the National Center for Cardiology and Internal Medicine, Bishkek (760 m) and the high-altitude clinic, Tuja Ashu (3100 m), Kyrgyzstan. Participants provided written informed consent and the protocol was approved by the Institutional Ethics Committee in Bishkek (01-8/405), endorsed by the Cantonal Ethics Committee Zurich (46-2015) and registered at www.clinicaltrials.gov NCT02450968.

2.2. Participants

Ninety-five lowlanders (43 in the placebo and 52 in the dexamethasone group) of both genders, aged 20 to 75 years, with COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 1–2 (post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 0.7 and FEV_1 > 50% predicted) living <800 m were recruited among outpatients of the National Center for Cardiology and Internal Medicine and surrounding hospitals. Patients with severe COPD (FEV_1 < 50% predicted), hypercapnia ($PaCO_2$ > 6 kPa), severe hypoxemia at low altitude baseline (pulse oximetry, SpO_2 < 92%) and unstable patients with COPD exacerbation, requiring systemic glucocorticoids, suffering from known PH, unstable cardiovascular disease, previous myocardial infarction or stroke were excluded.

2.3. Interventions

After undergoing baseline evaluations at the National Center of Cardiology and Internal Medicine, Bishkek (760 m) patients travelled by minibus within 3–5 h to the Tuja Ashu high altitude clinic at 3100 m and stayed there for 3 days. Dexamethasone (2 × 4 mg/day) or identically looking placebo capsules were given starting one day before ascent to and during the stay at 3100 m under supervision of investigators.

2.4. Randomization

Patients were randomized 1:1 to dexamethasone or placebo minimizing for age (≤ or >50 years), FEV_1 (< or ≥80% predicted) and gender using the STATA statistical software (plugin "rct_minim" [14]) and a probability of 80% to randomize patients to the favored group.

2.5. Blinding

Dexamethasone and placebo-mannitol were prepared in identical looking capsules prior to the study by a certified pharmacy and delivered in boxes with 7 pills each encrypted with a unique random 5-digit code. Investigators and patients were blinded during the study and data analysis.

2.6. Assessments

Medical history was obtained, clinical examination performed, vital parameters and arterial oxygen saturation (SpO_2) measured by pulse oximetry at each altitude. Echocardiography and arterial blood gases (RapidPoint 405; Siemens, Zurich, Switzerland) were assessed at 760 m before treatment initiation and on the day after the first night at 3100 m [15].

Echocardiographic recordings were performed according to current guidelines (CX 50, Philips, Philips Respironics, Zofingen, Switzerland) [16]. The trans-tricuspid pressure gradient (RV/RA) was calculated from peak systolic velocity of the tricuspid regurgitation using the simplified Bernoulli equation: $\Delta P = 4 \times Vmax^2$. Right atrial pressure (RAP) was estimated by the diameter of the inferior vena cava and systolic PAP (sPAP) calculated as RV/RA + RAP. Areas of the right atrium and RV were manually traced and fractional area change (FAC) calculated (% systolic/diastolic RV-area). Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode and the RV free wall velocity by tissue Doppler. Mean PAP (mPAP) was calculated from sPAP according to the following formula: mPAP = sPAP * 0.61 + 2 [17]. Pulmonary artery wedge pressure (PAWP) was calculated as 1.24 * (E/e′) + 1.9 [18]. Cardiac output (Q) was calculated using the left ventricular (LV) outflow tract velocity time integral. The (RV/RA)/Q ratio was calculated as surrogates of the pulmonary vascular resistance (PVR) [19]. Right ventricular end-systolic pressure-area relation (RV-ESPAR) was calculated using sPAP/RV area at end-systole [20]. Pulmonary vascular resistance was calculated as (mPAP-PAWP)/CO. Left heart function was assessed according to the current guidelines [16].

2.7. Statistical analysis

Data was analyzed per protocol and presented as mean ± standard deviation (SD) and mean differences (95% confidence intervals [CI]). Differences in variables between the two altitudes and the two groups were compared by paired *t*-tests and mean differences with 95% CI. For the change in our main outcome a regression analysis was performed correcting for age. Analysis was performed with STATA 13. A *P*-value <0.05 or 95% CI not including zero were considered statistically significant.

3. Results

Of 294 screened patients, 124 fulfilled inclusion criteria and were randomized (Fig. 3, e-component). Twelve patients did not finish the study according to the protocol or did not meet inclusion criteria after randomization, 10 had insufficient echocardiographic quality, and 7 had echocardiography at one location only. Thus, 52 patients from the dexamethasone and 43 patients from the placebo group were included in the per-protocol analysis. Table 1 shows clinical characteristics: age,

Table 1
Baseline characteristics at 760 m.

	Placebo group ($n = 43$)	Dexamethasone group ($n = 52$)	*P* value
Age, years	59 ± 8	55 ± 9	0.041
Gender, m/f	38/5	41/11	ns
BMI, kg/m^2	25.2 ± 3.6	25.5 ± 4.2	ns
Height, cm	169 ± 7	168 ± 8	ns
Weight, kg	72 ± 11	71 ± 12	ns
Pack years, y	25 ± 22	20 ± 17	ns
GOLD 1	31 (72%)	32 (62%)	
GOLD 2	12 (28%)	20 (39%)	
FEV_1, % pred	92 ± 21	86 ± 21	ns
SpO_2, %	95 ± 3	95 ± 2	ns
Medication			
Inhaled anticholinergics, *n* (%)	2 (5%)	1 (2%)	
Inhaled beta-adrenergics or corticosteroids, *n* (%)	0 (0%)	0 (0%)	
Antihypertensive drugs, *n* (%)	7 (16%)	5 (10%)	
Beta-blocker, *n* (%)	2 (5%)	3 (6%)	
Antidiabetic drugs, *n* (%)	1 (2%)	0 (0%)	

Data are presented as No. (%) or mean ± SD. BMI = body mass index, GOLD = global initiative for chronic obstructive lung disease, FEV_1 = forced expiratory volume in 1 s, SpO_2 = oxygen saturation. ns = not significant.

Table 2
Echocardiography indices of the pulmonary artery pressure and the right heart.

	Placebo group ($n = 43$)	Dexamethasone group ($n = 52$)	Treatment effect
	Mean ± SD	Mean ± SD	ΔMean differences (95% CI)
Pulmonary artery pressure indices			
RV/RA (trans-tricuspid pressure gradient), mm Hg			
760 m	20 ± 4	19 ± 5	
3100 m	31 ± 9*	26 ± 7*	-4.8 (−7.7 to −1.8)** $P = 0.0014$ age corrected: −4.8 (−7.7 to −1.9)** $P = 0.001$
Systolic pulmonary artery pressure, mm Hg			
760 m	23 ± 4	22 ± 5	
3100 m	36 ± 10*	29 ± 7*	−5.0 (−8.0 to −2.1)** $P = 0.0009$
Mean pulmonary artery pressure, mm Hg			
760 m	16 ± 3	15 ± 3	
3100 m	24 ± 6*	20 ± 4*	−3.1 (−5.0 to −1.3)** $P = 0.0009$
RV and RA indices			
Right atrial pressure, mm Hg			
760 m	3 ± 1	3 ± 0	
3100 m	4 ± 2*	4 ± 2*	−0.3 (−1.0 to 0.5)
Main pulmonary artery diameter, cm			
760 m	2.0 ± 0.3	1.9 ± 0.2	
3100 m	2.1 ± 0.3*	2.1 ± 0.3*	−0.1 (−0.2 to 0.0)
Right atrial area, cm^2			
760 m	12.7 ± 2.3	13.0 ± 2.4	
3100 m	15.2 ± 3.0*	15.6 ± 3.1*	−0.9 (−2.0 to 0.3)
RV end-diastolic area A4C, cm^2			
760 m	14.0 ± 2.9	14.0 ± 3.0	
3100 m	17.3 ± 3.1*	16.8 ± 2.8*	−0.5 (−1.7 to 0.8)
RV end-systolic area A4C, cm^2			
760 m	7.9 ± 1.9	7.8 ± 1.7	
3100 m	10.8 ± 2.6*	10.3 ± 2.1*	−0.4 (−1.3 to 0.5)
RV fractional area change, %			
760 m	43.6 ± 6.8	44.2 ± 6.1	
3100 m	37.6 ± 6.8*	38.6 ± 7.4*	0.4 (−2.5 to 3.2)
Eccentricity Index end-diastolic			
760 m	1.07 ± 0.1	1.05 ± 0.1	
3100 m	1.14 ± 0.1*	1.12 ± 0.1*	0.0 (−0.0 to 0.1)
Eccentricity Index end-systolic			
760 m	1.05 ± 0.85	1.03 ± 0.11	
3100 m	1.11 ± 0.11*	1.10 ± 0.12*	0.0 (−0.0 to 0.1)
RV anterior wall diameter, cm			
760 m	0.46 ± 0.1	0.42 ± 0.1	
3100 m	0.52 ± 0.1*	0.50 ± 0.1*	0.0 (−0.0 to 0.1)
RV diameter end-diastolic, cm			
760 m	3.1 ± 0.4	2.9 ± 0.4	
3100 m	3.2 ± 0.4*	3.2 ± 0.3*	0.1 (−0.1 to 0.3)
Tricuspid annular plane systolic excursion, cm			
760 m	2.3 ± 0.4	2.3 ± 0.3	
3100 m	2.5 ± 0.4	2.5 ± 0.4*	0.1 (−0.1 to 0.2)
TDI tricuspid annular systolic velocity, cm/s			
760 m	3.1 ± 0.4	2.9 ± 0.4	
3100 m	3.2 ± 0.4*	3.2 ± 0.3*	1.5 (0.2 to 2.8)**
RV end-systolic pressure-area relation, mm Hg/m^2			
760 m	3.1 ± 0.8	2.9 ± 0.8	
3100 m	3.5 ± 1.4	2.9 ± 0.8	−0.4 (−0.8 to −0.0)**
Heart rate, cardiac output, stroke volume and resistance			
Heart rate, min^{-1}			
760 m	68 ± 9	67 ± 9	
3100 m	74 ± 11*	70 ± 8.7	−2.3 (−6.6 to 1.9)
Stroke volume, ml			
760 m	74 ± 12	71 ± 12	
3100 m	77 ± 12	80 ± 13*	4.6 (0.0 to 9.2)**
Cardiac output, l/min			
760 m	4.9 ± 0.7	4.7 ± 0.9	
3100 m	5.7 ± 1.1*	5.7 ± 1.1*	0.13 (−0.3 to 0.6)
Cardiac index, l/min/m^2			
760 m	2.7 ± 0.3	2.6 ± 0.5	
3100 m	3.1 ± 0.5*	3.1 ± 0.5*	0.08 (−0.2 to 0.3)
(RV/RA)/Q			
760 m	4.1 ± 1.1	4.0 ± 1.1	
3100 m	5.6 ± 1.6*	4.6 ± 1.1*	−1 (−1.5 to −0.5)**
Pulmonary vascular resistance, WU			
760 m	1.5 ± 0.8	1.3 ± 1.0	
3100 m	2.4 ± 0.9	1.8 ± 0.8	−0.5 (−0.9 to −0.1)**
SpO_2, %			
760 m	95 ± 3	95 ± 2	
3100 m	89 ± 3*	90 ± 3*	1 (−1 to 2)
Blood gas analysis			
$PaCO_2$, kPa			
760 m	5.2 ± 0.4	5.1 ± 0.5	
3100 m	4.6 ± 0.4*	4.42 ± 0.4*	−0.2 (−0.4 to −0.03)**
PaO_2, kPa			
760 m	9.8 ± 1.0	9.7 ± 1.0	
3100 m	7.9 ± 0.6*	8.2 ± 0.7*	0.4 (0.0 to 0.8)**
Hematocrit, %			
760 m	0.4 ± 0.05	0.43 ± 0.04	
3100 m	0.4 ± 0.05	0.4 ± 0.04	0.004 (−0.0 to 0.01)
Hemoglobin, g/L			
760 m	144 ± 17	147 ± 15	
3100 m	145 ± 16	149 ± 15	1.1 (−1.1 to 3.3)

RV = right ventricle, RA = right atrium, A4C = apical 4-chamber view, TDI = Tissue Doppler Image, (RV/RA)/Q = tricuspid pressure gradient/cardiac output.
* $P < 0.05$ low vs high altitude.
** $P < 0.05$ Placebo vs Dexamethasone at altitude.

gender, body mass index (BMI), smoking habits, medication, lung function and SpO_2 were similar in both groups. Seven patients in the placebo and 5 patients in the dexamethasone group were diagnosed with systemic hypertension and one patient was treated with oral antidiabetics for diabetes mellitus. Blood analysis after lunch revealed higher serum glucose concentrations in the dexamethasone group. In total 15 patients (29%) in the dexamethasone group but only 2 (5%) in the placebo group were measured with a glucose concentration above 11.1 mmol/l indicating a blood sugar imbalance.

3.1. Pulmonary artery pressure

Both groups had normal low-altitude baseline values of RV/RA and mPAP that increased significantly with ascent from 760 m to 3100 m (Table 2, Fig. 1). The altitude-induced RV/RA-increase in the dexamethasone group was significantly less pronounced than that in the placebo group (treatment effect, Δmean difference (95% CI): −4.8 (−7.7 to −1.8), $P < 0.01$), even when controlled for age (treatment effect controlled for age, Δmean difference (95% CI): −4.8 (−7.7 to −1.9), $P < 0.01$).

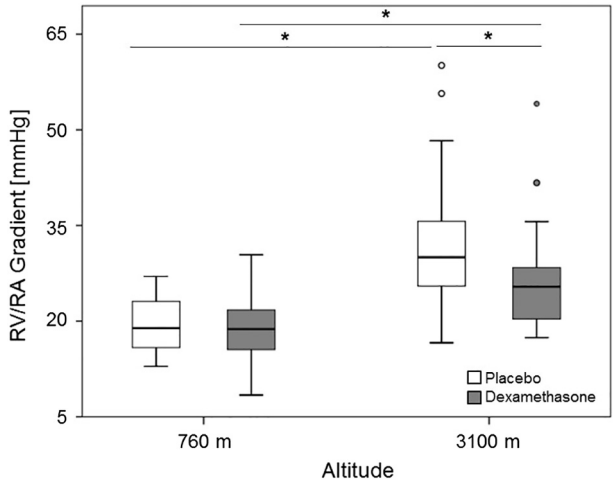

Fig. 1. Change in trans-tricuspid pressure gradient from lowland (760 m) to high altitude (3100 m) in patients receiving dexamethasone and placebo. Boxplot horizontal lines represent median values, box borders display quartiles, upper and lower whiskers display the last value that is in between 1.5× interquartile range. Symbols represent individual values that fall outside this range. *$P < 0.01$.

3.2. Right and left heart function

The results of the echocardiographic evaluation are displayed in Tables 2 and 3 (e-component). In association with the increase in PAP from 760 to 3100 m, there were significant increases in the diameter of the pulmonary artery, the RV (cavity and wall), the RV-FAC, RA-area and RAP in both groups to a similar extent. The TAPSE did not change with altitude in the placebo group but increased in the dexamethasone group. With exception of a slightly reduced LV ejection fraction in the placebo group and a minimal increase in PAWP in both groups, indices of LV function and dimensions and systemic blood pressure remained unchanged at 3100 m and differences in altitude-induced changes between groups were non-significant (Table 3).

In both groups the Q increased significantly with ascent to 3100 m. While this was predominantly related to an increase in HR in the placebo group, the altitude-induced increase in Q was mostly achieved by an increased SV in the dexamethasone group while to increase in HR was not significant.

The effect of altitude and of dexamethasone was further evaluated by plotting changes in RV/RA and Q induced by altitude exposure. As shown in Fig. 2, the increase in RV/RA and in pressure/flow ratio ((RV/RA)/Q), a surrogate for PVR was less pronounced in the

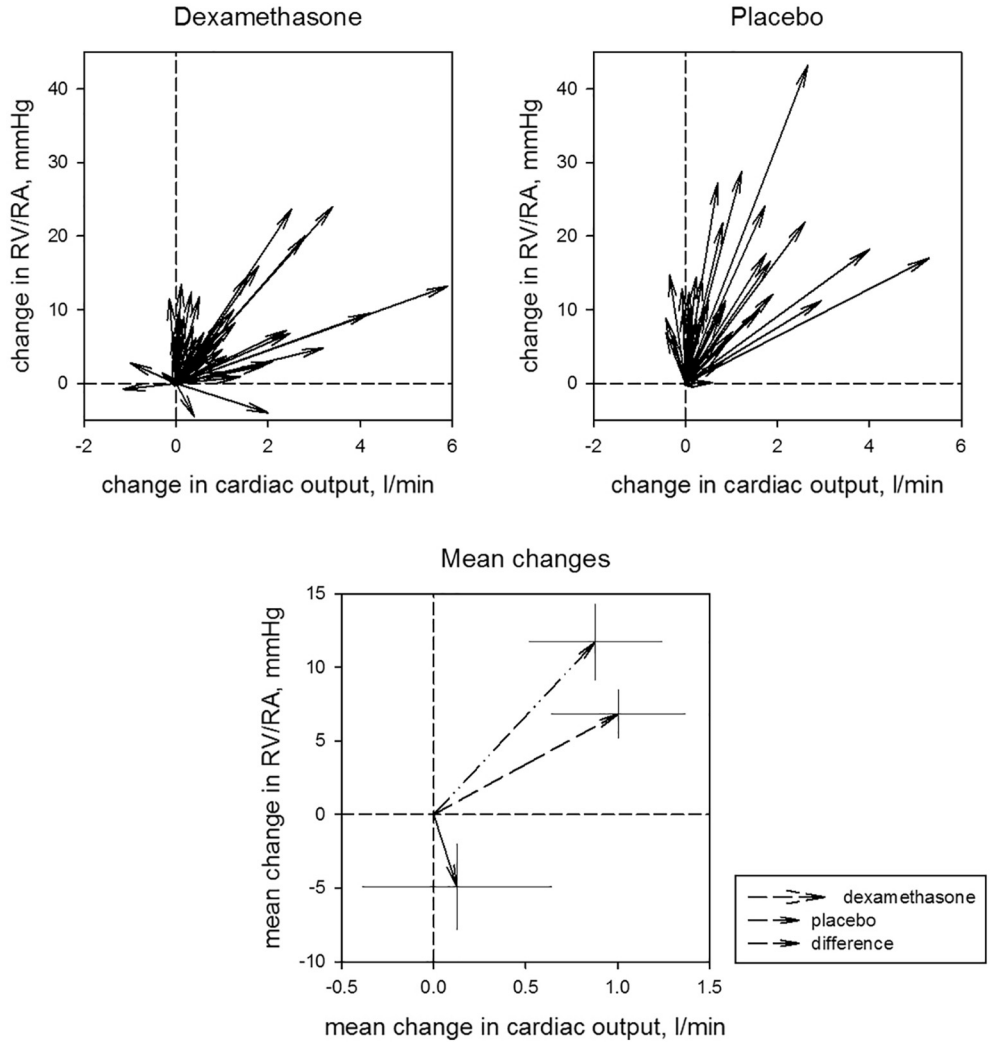

Fig. 2. Changes in trans-tricuspid pressure gradient (RV/RA) and cardiac output (Q) induced by ascent from 760 m to 3100 m in patients receiving dexamethasone and placebo. The vector lines with arrows start at zero corresponding to values measured at 760 m and point to values measured at 3100 m. The slopes of the lines reflect the (RV/RA)/Q ratio, a surrogate of pulmonary vascular resistance. The upper panels show individual changes for each patient. The lower panel shows mean changes in the dexamethasone and the placebo group, the mean between-group difference and 95% confidence intervals. Altitude-induced changes in RV/RA and Q were significant ($P < 0.05$) in both groups and the between-group difference was significant for RV/RA and for the (RV/RA)/Q ratio.

dexamethasone group compared to the placebo group (mean between-group difference −1 (−1.5 to 0.5)). The reduced altitude-induced increase in the (RV/RA)/Q ratio in the dexamethasone group was mainly related to a minor increase in the RV/RA compared to the placebo group while the greater increase in cardiac output was not statistically significant (Fig. 2). An estimation of PVR by echo measurements shows a significant amelioration of altitude related increase in resistance in the dexamethasone group (Table 2).

4. Discussion

The current study provides a detailed account of changes in PAP and cardiac function in lowlanders with COPD ascending acutely to 3100 m, an elevation corresponding to that of many settlements and tourist destinations worldwide. Our observations in the placebo group indicate that COPD patients, GOLD grade 1–2, who are non-hypercapnic and only mildly hypoxemic at low altitude (760 m) experience a moderate mean rise in RV/RA of 11 mm Hg when travelling to 3100 m. The randomized, double-blind comparison among patients using preventive dexamethasone and placebo before and during the stay at 3100 m confirms our hypothesis that dexamethasone mitigated the altitude-induced RV/RA increase by about one half (5 mm Hg). Since patients revealed a mild increase in Q that was at least as large in the dexamethasone as in the placebo group the findings suggest that dexamethasone reduced the PVR. These novel insights into the cardiovascular adaptation of COPD patients to acute hypobaric hypoxia might help to counsel the increasing number of such patients travelling to high altitude.

In healthy lowlanders acutely exposed to 3450 m an increase in RV/RA of 8 mm Hg has been reported [21], i.e., less than the mean increase of 11 mm Hg observed in the current COPD patients using placebo at 3100 m. The findings are consistent with an impairment of the pulmonary vascular bed due to COPD. In a previous study in COPD-patients, GOLD grade 2–3 (FEV_1 50–80% predicted) travelling to 2590 m we found a mean altitude-induced RV/RA increase of 9 mm Hg [22]. In the current study in comparably milder COPD patients, GOLD grade 1–2 (FEV_1 > 70% predicted), who however were exposed to a higher altitude of 3100 m, the RV/RA increase in the placebo group was slightly greater (11 mm Hg). This rise in RV afterload induced by the exposure to hypobaric hypoxia resulted in a decrease in the RV-FAC, and an increase in the eccentricity index of the LV, the right atrium and RV area, and in the main pulmonary artery diameter (Table 2). Moreover, the (RV/RA)/Q ratio reflecting the PVR increased significantly (Fig. 2).

In the dexamethasone group, the altitude-induced increase in RV/RA was significantly less pronounced than that in the placebo group in association with a similar rise in Q (Fig. 2). As the Q increased in the dexamethasone group at least as much as in the placebo group, the findings suggest that dexamethasone prevented a major increase in pulmonary vascular resistance and maintained a higher RV-ESPAR, a surrogate for RV-arterial coupling. A significant amelioration of PVR increase with altitude (calculated from echo measurements) in the dexamethasone group underlines these suggestions. Many other altitude-effects were similar as those in the placebo group.

A favorable effect of dexamethasone on PAP and an improvement of exercise capacity at altitude has been observed in those with HAPE-susceptibility [11,12]. Several mechanisms have been suggested to explain the effect of dexamethasone on the pulmonary vascular system. Thus, the inhibition of hypoxia-induced endothelial dysfunction by dexamethasone as well as enhanced nitric oxide (NO) availability via direct activation of endothelial NO synthase (eNOS) and possibly by increase in eNOS messenger ribonucleic acid and new protein expression might prevent excessive hypoxic pulmonary vasoconstriction [23]. Second, hypoxic sympathetic nervous system excitation, reflected in the altitude-induced HR rise in the placebo group (Table 2), may be inhibited by dexamethasone thereby contributing to a reduction in PVR and consequently a lower PAP. [24,25]. Furthermore, dexamethasone is known to reduce vascular permeability and enhance alveolar fluid clearance and might consequently prevent altitude associated interstitial edema, improving arterial oxygenation and reducing HPV [26–28]. It has further been suggested that dexamethasone enhances ventilatory acclimatization and thereby improves oxygenation according to experimental data obtained in 8 subjects exposed to isocapnic hypoxia [29]. Consistently, the current patients receiving preventive dexamethasone revealed a lower $PaCO_2$ and a higher PaO_2 at 3100 m than the patients receiving placebo which may also have contributed to the observed reduction in the PVR. No change in lung function as a possible mechanism for better oxygenation has been detected [9]. Furthermore, dexamethasone did not improve exercise capacity, measured by 6 min walking distance, in this patient cohort [9].

We found a significant increase in Q with exposure to acute hypoxia in both the placebo and the dexamethasone group (Table 2). This was related to the expected increase in the HR but no significant increase in SV in the placebo group. In contrast, in the dexamethasone group, HR did not change significantly while SV increased. The sympatholytic activity of dexamethasone [11,24,25] that prevented an increase in HR and reduced the HPV might have led to the increase in SV by prolonging diastolic filling time.

In patients with COPD, echocardiography can be challenging due to acoustic interference in the hyperinflated thorax. Thus, right heart catheterization would have been the investigation of choice to assess pulmonary hemodynamics but was not feasible due to its invasive nature. Nevertheless, the robust design of our study as a placebo-controlled trial applying the same measurement technique to all participants allowed conclusions on the effect of dexamethasone. This was the first study to systematically take patients with COPD to an altitude of 3′100 m and no safety data were available so far, we included only patients with COPD GOLD stage I–II and thus our results apply only for this group. The fact that only patients with COPD GOLD 1 and 2 were accepted into the study for safety reasons might have contributed to the relatively good echo quality in our subjects but limits our findings to relatively mild COPD when going to moderate levels of high altitude.

5. Conclusion

In lowlanders with COPD, GOLD grade 1–2, travelling to 3100 m induces a mild increase in PAP. The current randomized, placebo-controlled trial shows for the first time that dexamethasone prophylaxis mitigates this altitude-induced PAP-increase and may be associated with a lower pulmonary vascular resistance due to a preserved cardiac output. The findings are important as they identify a potentially clinically useful means to prevent hemodynamic compromise in COPD patients exposed to hypobaric hypoxia at high altitude.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.052.

Financial disclosures

The study was supported by the Swiss National Science Foundation [grant numbers 320030_143875, 32003B_172980] and Zurich Lung [grant 2015].

Acknowledgements and authors' contributions

ML, KEB, SU: substantial contributions to the conception and design of the study, interpretation of the data, critical revision for important intellectual content, final approval of the version to be published. SU is the guarantor of the work.

MF, SA, MB, StU, SS, US, NM, BO, BE, TS: data acquisition, critical revision for important intellectual content, final approval of the version to be published.

KEB, SU: substantial contributions to the conception and design of the study, interpretation of the data, critical revision for important intellectual content, final approval of the version to be published.

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