Improvement in lung diffusion by endothelin A receptor blockade at high altitude

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During 1 wk. PVR was estimated by Doppler echocardiography, and may be in relation to different pulmonary vascular resistance (PVR). Twenty-two healthy volunteers were investigated at sea level and in May 2011; doi:10.1152/japplphysiol.00670.2011.—Lung diffusion capacities for nitric oxide (DLNO) and carbon monoxide (DLCO) were measured using a single-breath method before and 30 min after maximal exercise. The membrane component of DLCO (Dm) and capillary volume (Vc) was calculated with corrections for hemoglobin volume, alveolar volume, and barometric pressure. Altitude exposure was associated with unchanged DLCO, DLNO, and Dm but a slight decrease in Vc. Exercise at altitude decreased DLNO and Dm. Sitaxsentan intake improved VO2 max together with an increase in resting and postexercise DLNO and Dm. Sitaxsentan-induced decrease in PVR was inversely correlated to DLNO. Both DLCO and DLNO were correlated to VO2 max at sea level (r = 0.41–0.42, P < 0.1) and more so at altitude (r = 0.56–0.59, P < 0.05). Pharmacological pulmonary vasodilation improves the membrane component of lung diffusion in high-altitude newcomers, which may contribute to exercise capacity. Both the membrane and the capillary components of lung diffusion capacity have been shown to be increased in high-altitude residents (10, 13, 15, 25). Increased lung diffusion capacity at high altitude allows for the preservation of gas exchange in the presence of a decreased ventilatory response at exercise (15). High-altitude newcomers do not benefit from this adaptation (10, 15, 25) and, accordingly, depend on increased ventilation to maintain pulmonary gas exchange (15, 45).

Previous studies on lung diffusion capacity at high altitudes calculated the membrane and capillary components of alveolar-capillary transfer of carbon monoxide (CO) using measurements at ambient air and increased inspired PO2 (10, 13, 15, 25). This approach rests on the PO2 dependence of θ, the blood’s specific transfer conductance of CO, in the Roughton and Forster equation, which states that 1/DLCO = 1/Dm + 1/θVc where DLCO is the diffusing capacity of the lung for CO, Dm its membrane component, and Vc the capillary blood volume (37). Thus changing θ as by increasing or decreasing inspired PO2 allows for the calculation of Dm and Vc from a simple system of two equations with two unknowns. However, changing inspired PO2 might also change pulmonary vascular tone, cardiac output, and possibly the distribution of ventilation, all of which can be a cause of altered lung diffusion capacity. These pitfalls are avoided by the simultaneous measurements of CO and of nitric oxide (NO) transfer (24). Because the reaction of NO with hemoglobin is quasi-instantaneous, it has been assumed that θNO is infinite so that the transfer factor for NO with correction for the NO-to-CO ratio of diffusivity allows for the calculation of Dm, and hence Vc. Recent studies have shown that θNO has actually a finite value (6). However, it has been estimated that, for clinical applications in humans, measurements of the diffusing capacity for NO (DLNO) need adjustment only when the hemoglobin concentration is below 8 g/dl (51). The NO/CO transfer method has been applied to high-altitude residents, confirming a markedly increased lung diffusion capacity compared with recently acclimatized sojourners (12). The results showed a disproportionately increase in Vc with respect to Dm, suggesting an expanded pulmonary capillary bed. In the same study, the high-altitude sojourners presented with a decreased Dm compared with sea level, whereas Vc was unchanged. This was explained either by some degree of interstitial edema and/or decreased density of the air (12).

We more recently reported on an improvement in exercise capacity that was correlated to decreased pulmonary vascular resistance (PVR) by the intake of the endothelin A receptor blocker sitaxsentan in lowlanders after a 1-wk hike to the altitude of 5,050 m (34). Part of this improvement in exercise capacity could have been related to improved lung diffusion capacity, either as a consequence of decreased pulmonary vascular pressures (34) or inhibition of some negative effect of endothelin-1 at the alveolocapillary membrane (32). The latter would be unlikely after sitaxsentan, since there is experimental evidence that endothelin inhibits the alveolar epithelial transport of sodium and water but through the specific interaction with endothelin B receptors (5, 11). We therefore here report on lung diffusion measurements at rest and after a maximal exercise test after the intake of sitaxsentan. The rationale of postexercise stress measurements was that exercise would be associated with increased capillary filtration and interstitial edema (7, 26, 49). Accordingly, lung diffusion capacity measured with the NO/CO transfer method has been reported previously to be altered after maximal exercise at sea level (31, 44).
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48). In the present study, we reasoned that maximal exercise in the presence of hypoxia-induced increase in PVR might further alter diffusing capacity with a decrease in Dm as a consequence of interstitial lung edema and that this might be improved by exclusive pulmonary vascular effects of an endothelin A receptor blocker.

METHODS

Subjects. Twenty two healthy nonsmoker European subjects, 12 men and 10 women, aged from 23 to 59 yr, mean 35 yr, gave an informed consent to the study, which was approved by the Ethical Committee of the Erasme University Hospital (Brussels). All of them were usually living in Belgium and the Netherlands, at sea level altitude.

Study design. All of the subjects underwent a clinical examination with measurements of blood pressure, heart rate (HR), and transthoracic pulse oximetry oxygen saturation (SpO2), successively followed by a lung diffusing capacity measurement, echocardiography, a cardiopulmonary exercise test (CPET), and again a lung diffusing capacity measurement 30 min after the CPET. This sequence of measurements was obtained at sea level, in Brussels, Belgium, and again during the first 48 h of arrival at the Pyramid International Laboratory Observatory at 5,050 m, in the Khumbu area of the Sagamartha National Park (Nepal). This setting is reached after a 1-wk hike at progressively increased altitudes following an airplane transportation from Kathmandu, at ~800 m, to Lukla, at 2,800 m. This hike is easy going and usually allows for a satisfactory acclimatization. Once at the Pyramid, the subjects rested or walked about in the surroundings, avoiding strenuous exercise activities. Meals were served by the local staff, and intake of water or hot lemon was allowed ad libitum. Altitude measurements were obtained at baseline, and repeated after 1 wk of 100 mg sitaxsentan or a placebo given in a prospective randomized, controlled double-blind fashion. Sitaxsentan was taken one time daily for 7 days to achieve steady state of plasma levels (4). The adaptation to high altitude was checked using the Lake Louise score, which is a self-reported acute mountain sickness questionnaire (36). A Lake Louise score above five is usually considered as diagnostic of acute mountain sickness.

Methods. The echocardiography and the incremental cycle ergometer CPET were performed as previously reported (34). The hemodynamic measurements relevant to the present study were cardiac output (Q) and pulmonary artery pressure (PAP), estimated, respectively, from the left ventricular outflow tract time-velocity integral and the maximal velocity of tricuspid regurgitation (TRmax). Mean PAP (mPAP) was calculated as 0.6 × systolic PAP + 2 mmHg, and systolic PAP as 4 × TRmax added to a standard estimate of right atrial pressure at 5 mmHg. PVR was calculated as mPAP/Q. Exercise capacity was estimated at standard incremental CPET with workload increased every minute until maximal, and increments were titrated for a 10- to 12-min duration of the test. Maximal oxygen uptake (VO2 max) and the ratio of ventilation (VE) to CO2 production (VCO2) at the anaerobic threshold were measured as previously described.

Alveolar volume (VA), DLNO, and DLCO were measured in the sitting position as previously reported (33). An automated apparatus for performing calibrations, extemporaneous mixing of gases, and online calculations was used (Hyp’Air compact; Medisoft, Dinant, Belgium). Measurements were repeated two to three times, with the aim of obtaining DLCO values within 5% and DLNO values within 10% of each other. VA was measured by helium dilution.

Lung blood Vc and Dm were calculated following the method described by Glénét et al. (21). The coefficient relating DLNO and Dm was set at 1.97 according to the solubility and molecular weights of both gases (3). To solve the Roughton and Forster equation (37), we used an equation proposed by Forster (17) expressing the conductance of CO with hemoglobin (θCOG) as a function of capillary PO2:

\[ \frac{1}{\theta_{COG}} = 1.3 + 0.0041 \times P_{capO2} \]

where \( P_{capO2} \) is the capillary partial pressure of O2 estimated as: alveolar PO2 – V̇O2/(DLCO × 1.23) with partial pressures in millimeters mercury, V̇O2 in milliliters per minute, and DLCO in milliliters per minute per millimeter mercury. Alveolar PO2 was calculated at 58 mmHg from a barometric pressure measured on average at 412 mmHg and the expired fraction of O2. Capillary PO2 was calculated at 108 ± 12 mmHg at sea level and 46.7 ± 22.7 mmHg at altitude. Oxygen uptake was calculated by taking the mass balance of oxygen between inspiration and expiration during the maneuver. The fraction of oxygen in the residual volume preceding the inspiration was supposed to be similar to that found in the expired sample (mean 16.4%). We used DLCO × 1.23 as a surrogate for the diffusing capacity for oxygen (17). Hemoglobin concentrations were measured from venous blood samples, and Vc and DLCO values were corrected accordingly for an inspired PO2 of 150 mmHg and for standard concentrations of hemoglobin of 14.6 g/dl for men and 13.4 g/dl for women (29). The percent predicted values were calculated using previously reported equations (3).

Results are expressed as mean values ± SE, except when indicated differently. The statistical analysis was performed using the Statistica 5.1 package (Statsoft, Tulsa, OK) and consisted of a two-way repeated-measures ANOVA. The normality of the data was checked by a Kolmogorov-Smirnov test. When the F value of the ANOVA reached a critical P < 0.05 value, Scheffé’s tests were used for post hoc comparisons (45). Linear regressions were calculated using the Braivais-Pearson’s least-squares method.

RESULTS

Effects of altitude. The sea level measurements could be obtained in only 18 of the 22 subjects. Altitude exposure was associated with mild headache and fatigue, causing the Lake Louise score to increase to 7 ± 1 corresponding to the diagnosis of a mild degree of acute mountain sickness. The score remained at 8 ± 1 in the placebo group but decreased to 5 ± 1 with sitaxsentan intake. The hemoglobin concentration changed from 14.2 ± 0.2 to 14.7 ± 0.4 g/dl [P = not significant (NS)], SpO2 from 98 ± 0.2 to 82 ± 1.1% [P < 0.001], resting HR from 66 ± 3 to 67 ± 3 beats/min [P = NS], 30 min postexercise HR from 81 ± 4 to 78 ± 4 beats/min [P = NS], maximal HR (HRmax) from 177 ± 6 to 151 ± 6 [P < 0.05], maximal workload (Wmax) from 280 ± 18 to 150 ± 10 W, VO2 max from 45 ± 2 to 28 ± 1 ml·kg−1·min−1 [P < 0.001], VE/VO2 max from 116 ± 7 to 121 ± 10 l/min [P = NS], VE/VO2 from 30 ± 1 to 49 ± 1 [P < 0.001], and PVR from 3.4 ± 0.2 to 4.6 ± 0.3 Wood units [P < 0.05].

The lung diffusing capacity measurements at rest and 30 min postexercise, at sea level, and at altitude are shown in Table 1. At sea level at rest, DLCO and DLNO were 94 ± 10 to 167 ± 13 W (P <
SUMMARIZED IN TABLE 2. THE MEASUREMENT OF DIFFUSING CAPACITY.

0.05) AND V̇O₂ max FROM 27 ± 1 TO 29 ± 1 ML·KG⁻¹·MIN⁻¹, WHEREAS V̇E MAX, V̇E/V̇CO₂, AND HR max WERE UNCHANGED, AND PVR DECREASED FROM 4.3 ± 0.4 TO 3.5 ± 0.2 WOOD UNITS (P < 0.05). THE EFFECTS OF 1 WK INTAKE OF SITAXSENTAN VS. PLACEBO ARE SUMMARIZED IN TABLE 2.

THE MEASUREMENT OF DIFFUSING CAPACITY FAILED FOR TECHNICAL REASONS IN ONE OF THE SITAXSENTAN-TREATED SUBJECTS. THE ONLY EFFECT ASSOCIATED WITH PLACEBO INTAKE WAS AN INCREASE IN POSTEXERCISE DLCO, WHICH WAS ATTRIBUTABLE TO AN INCREASE IN VC. SITAXSENTAN INCREASED RESTING AND POSTEXERCISE DLNO, SO THAT DM WAS INCREASED, AT REST AND AFTER EXERCISE. THESE CHANGES PERSISTED AFTER CORRECTION FOR VA. SITAXSENTAN DID NOT AFFECT DLCO.

CORRELATIONS. BOTH DLCO AND DLNO WERE CORRELATED WITH V̇O₂ max WITH A P < 0.1 LEVEL OF SIGNIFICANCE AT SEA LEVEL BUT A P < 0.05 LEVEL OF SIGNIFICANCE AT ALTITUDE (FIGS. 1 AND 2). NEITHER DLNO NOR DLCO WERE CORRELATED WITH V̇E/V̇CO₂.

THERE WERE NO CORRELATIONS BETWEEN DLCO OR DLNO AND ECHOCARDIOGRAPHIC MEASUREMENTS OF THE PULMONARY CIRCULATION WHEN CORRECTED FOR BODY SIZE (INDEXED CARDIAC OUTPUT), NEITHER AT SEA LEVEL NOR AT ALTITUDE.

CHANGES IN PVR ASSOCIATED AFTER THE INTAKE OF SITAXSENTAN WERE CORRELATED TO DLNO (P < 0.05) BUT NOT DLCO (P = NS). THERE WAS NO CORRELATION BETWEEN CHANGES IN PVR AND DLNO OR DLCO AFTER THE INTAKE OF PLACEBO.

DISCUSSION

THE MAIN RESULT OF THE PRESENT STUDY IS THAT A PHARMACOLOGICAL DECREASE IN PVR BY SELECTIVE ENDOTHELIN A RECEPTOR BLOCKADE (SITAXSENTAN) IN HEALTHY SUBJECTS AT HIGH ALTITUDE WAS ASSOCIATED WITH AN IMPROVEMENT OF THE MEMBRANE COMPONENT OF LUNG DIFFUSING CAPACITY, AT REST AND AT EXERCISE. ALTITUDE IN THESE ACCLIMATIZED SOJOURNERS HAD NO EFFECT ON LUNG DIFFUSING CAPACITY AT REST, BUT DECREASED CAPILLARY BLOOD VOLUME, AND WAS ASSOCIATED WITH A DECREASE IN THE MEMBRANE COMPONENT OF DIFFUSION AFTER MAXIMAL EXERCISE. LUNG DIFFUSING CAPACITY FOR BOTH NO AND CO WAS CORRELATED TO EXERCISE CAPACITY AT SEA LEVEL AND AT HIGH ALTITUDE. THESE RESULTS SUGGEST THAT IMPROVED LUNG DIFFUSING CAPACITY MAY PARTICIPATE TO PREVIOUSLY REPORTED IMPROVEMENT IN AEROBIC EXERCISE CAPACITY ASSOCIATED WITH A PHARMACOLOGICAL PULMONARY VASODILATION AT HIGH ALTITUDE.

LUNG DIFFUSING CAPACITY HAS BEEN REPORTED VARIABLY IN HIGH-ALTITUDE SOJOURNERS, WITH AN OVERALL PATTERN OF MINIMAL CHANGES OR A SLIGHT TRANSIENT INITIAL INCREASE OR DECREASE, IN CONTRAST WITH MARKED INCREASES REPORTED IN HIGH-ALTITUDE RESIDENTS (10, 12–15, 25, 45). IN HIGH-ALTITUDE RESIDENTS, DM AND VC ESTIMATED FROM MEASUREMENTS AT VARIABLE PO₂ (10, 13, 25) OR FROM THE NO/CO TRANSFER METHOD (12) HAVE BOTH BEEN SHOWN TO CONTRIBUTE TO AN INCREASE IN DLCO, EITHER WITH PARALLEL CHANGES (13, 25) OR A PRONOMINATE INCREASE OF DM (10) OR VC (12). WHILE A DISPROPORTIONATE INCREASE IN DM WOULD BE DIFFICULT TO EXPLAIN (10), A PRONOMINATE INCREASE IN VC HAS BEEN SPECULATED TO BE RELATED TO LONG-TERM HYPOXIA-INDUCED ANGIOGENESIS (12).

RECENT HIGH-ALTITUDE NEWCOMERS, DLCO HAS BEEN FOUND TO BE ESSENTIALLY UNCHANGED (10, 12, 13, 15, 45), WITH, HOWEVER, SOMETIMES A SLEIGHT TRANSIENT INCREASE (14) OR DECREASE (25). THE LATTER WAS RECENTLY CONFIRMED BY THE NO/CO TRANSFER METHOD IN ACCLIMATIZED SOJOURNERS ON THE BOLIVIAN ALTIPLANO, ALTHOUGH LIMITED TO DM (12). A TRANSIENT INCREASE IN DLCO IN HIGH-ALTITUDE SOJOURNERS WOULD BE EXPLAINED BY CAPILLARY RECRUITMENT ON INCREASED CARDIAC OUTPUT AND PAP IN (14). AT HIGH ALTITUDE, A REDUCTION IN PO₂ MAY ITSELF INCREASE DLCO BECAUSE OF LESS COMPETITION BY O₂ FOR THE HEMOGLOBIN-BINDING SITE. WHEN RECALCULATED WITH SEA LEVEL θ IN THE PRESENT STUDY, DLCO AT ALTITUDE DECREASED FROM 33 ± 2 TO 31 ± 2 ML·MIN⁻¹·MMHG⁻¹ AT REST AND FROM 33 ± 2 TO 20 ± 2 ML·MIN⁻¹·MMHG⁻¹ AFTER EXERCISE. A DECREASE IN DM COULD BE EXPLAINED EITHER BY A DECREASED DENSITY OF THE AIR AND/OR SOME DEGREE OF INTERSTITIAL LUNG EDEMA (12), AS REPORTED IN SUBJECTS WITH ACUTE MOUNTAIN

Table 1. Resting and postexercise lung diffusion variables in healthy volunteers at sea level (n = 18) and at high altitude (n = 22)

<table>
<thead>
<tr>
<th></th>
<th>Sea Level</th>
<th>Altitude</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>30 min PE</td>
</tr>
<tr>
<td>DLCO, ml·min⁻¹·mmHg⁻¹</td>
<td>32 ± 2</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>DLNO, ml·min⁻¹·mmHg⁻¹</td>
<td>147 ± 8</td>
<td>145 ± 8</td>
</tr>
<tr>
<td>Dm, ml·min⁻¹·mmHg⁻¹</td>
<td>75 ± 4</td>
<td>74 ± 5</td>
</tr>
<tr>
<td>Vc, ml</td>
<td>100 ± 6</td>
<td>97 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. DLCO, lung diffusing capacity for carbon monoxide; DLNO, lung diffusing capacity for nitric oxide; Dm, membrane component of DLCO; Vc, pulmonary capillary blood volume; 30 min PE, 30 min postexercise. P < 0.05, exercise vs. rest at the same altitude (*) and altitude vs. sea level at rest or after exercise (#).

Table 2. Lung diffusion variables at high altitude before and after 7 days of treatment with either placebo or sitaxsentan, before and 30 min after a maximal exercise test

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 11)</th>
<th>Sitaxsentan (n = 11)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 7 Days</td>
</tr>
<tr>
<td></td>
<td>Rest 30 min PE</td>
<td>Rest 30 min PE</td>
</tr>
<tr>
<td>DLCO, ml·min⁻¹·mmHg⁻¹</td>
<td>34 ± 2</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>DLNO, ml·min⁻¹·mmHg⁻¹</td>
<td>146 ± 9</td>
<td>140 ± 9</td>
</tr>
<tr>
<td>Dm, ml·min⁻¹·mmHg⁻¹</td>
<td>74 ± 5</td>
<td>71 ± 5</td>
</tr>
<tr>
<td>Vc, ml</td>
<td>94 ± 7</td>
<td>97 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. P < 0.05, 30 min PE different from rest (*) sitaxsentan different from baseline (#).
In the present study, DLNO and DLCO were correlated to $V_{O2\text{, max}}$ with only a $P < 0.1$ level of significance in normoxia. The diffusing capacities of both gases predicted $V_{O2\text{, max}}$ more significantly in hypoxia. Lung diffusing capacity has been shown to predict aerobic exercise capacity in patients with chronic heart failure (1, 35) or with lung diseases (43), but less constantly in healthy subjects with the exception of smokers (41). In healthy subjects, aerobic exercise capacity is generally better predicted by DLNO than DLCO, indicating a predominant effect on the membrane component of lung diffusion (51). The same was shown in a study on patients with heart failure (35), although not clearly confirmed (1). The superior prediction of $V_{O2\text{, max}}$ by DLNO compared with DLCO in healthy subjects who are smokers would suggest a predominant role of early vascular disease or ventilation/perfusion mismatch is limiting maximal pulmonary gas exchange. In the present study, changes in DLNO but not DLCO were correlated to changes in PVR in sitaxsentan-treated subjects, which is in keeping with the notion that a lower pulmonary vascular tone improves lung diffusion in healthy subjects at altitude. However, there were no correlations between DLNO or DLCO with the ventilatory responses to exercise, underscoring that larger increases in lung diffusing capacity are needed to allow for improved gas exchange at a lower level of ventilation like reported in high-altitude dwellers (15).

Most recently, Borland et al. (6) reported on membrane oxygenator and experimental animal preparations showing that the replacement of whole blood by hemolyzed blood and cell-free hemoglobin solution actually increased DLNO, with demonstration of a finite value for $\Theta_{NO}$ of $-4.5$ ml NO/ml blood-min-mmHg$^{-1}$ (6). This is similar to that initially reported by Carlsen and Comroe in 1958 (8). However, it has been estimated that DLNO would not need to be adjusted unless the hemoglobin concentration is $<8$ g/dl (50). This is apparent in the data reported by Borland et al. (6) and in keeping with previous observation that changes in hemoglobin concentrations like measured in the present study would not be expected to affect DLNO (42).

In the present study, the coefficient of DLNO and Dm was set at 1.97. This value is derived from the solubility and the molecular weight of the gases (3). Others have determined a ratio of 2.2 to 2.4 (9, 47). It has been determined that a ratio of
2.42 (48) more closely reflects the two-step method reported by Zanen et al. (47) when the initial Roughton and Forster (37) equation is used. However, the value of 2.42 was derived from experiments performed at higher than physiological pH, which led to the equation $1/\theta_{\text{CO}} = 0.7 + 0.0061 \times \text{Po}_2$. Forster (17) later on expressed preference for the equation $1/\theta_{\text{CO}} = 1.3 + 0.0041 \times \text{Po}_2$. Using 2.42 instead of 1.97 would have decreased Dm and increased Vc by 23%, and thus introduced an unlikely discrepancy between the two measurements. We therefore preferred to use 1.97 as previously reported in our reference equations (3).

The idea that pulmonary vasodilating interventions might affect lung diffusing capacity has been tested previously with administration of the phosphodiesterase-5 inhibitor sildenafil. In patients with congestive heart failure, sildenafil improved the membrane component of lung diffusion without affecting pulmonary capillary pressure or Vc, which the authors explained by a yet unclear NO-dependent effect on the alveolocapillary membrane (23). In healthy acutely hypoxic volunteers at exercise, sildenafil attenuated the hypoxia-induced increase in PAP and did not affect DlCO but was associated with an increased Dm and increased Vc by 23%, and thus introduced an unlikely discrepancy between the two measurements. We therefore preferred to use 1.97 as previously reported in our reference equations (3).

Measurements during exercise would be needed to confirm our study is a small change, of uncertain clinical significance. While this report was in progress, Agostoni et al. (2) reported on an improvement in lung diffusing capacity with a 1-wk longer acclimatization to 5,400 m than in the present study, in relation to more marked increases in hemoglobin, VA, and the membrane component of lung diffusion. Differences with the present results have to be explained by different polycythemic responses, hydration, lung volume, different correction equations, and the use of variable Po2 to determine the components of lung diffusing capacity. How the findings reported by Agostoni et al. relate to exercise capacity or to the functional state of the pulmonary circulation would be interesting to explore.

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