Effect of Moderate Elevation above Sea Level on Blood Oxygen Saturation in Healthy Young Adults

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Key Words

Oxyhemoglobin saturation • Altitude • Normal value

Abstract

Background: Arterial hemoglobin oxygen saturation (SaO₂) decreases at an altitude of >1,500 m. There are no reports on normal SaO₂ at altitudes between 0 and 1,500 m. The clinical significance of decreased SaO₂ at such altitudes is unclear.

Objective: To test the hypothesis that in healthy volunteers normal SaO₂ at moderate altitude (MA; 725 m) is lower than that at almost sea level (SL; 43 m). **Methods:** SaO₂ was measured by transcutaneous pulse oximetry in young healthy volunteers at MA and was compared to equivalent measurements at SL. In addition, a 6-min walk test was performed and SaO₂ at the end of the walk was compared between the two locations. **Results:** 111 males were checked at MA and 101 at SL. At rest, nadir SaO₂ was 95% at MA compared to 97% at SL. Mean SaO₂ at rest was slightly higher at SL (98.53 ± 0.52) compared to MA (98.11 ± 0.8; p < 0.01). In subjects who completed the 6-min walk test, SaO₂ slightly decreased after the test in both locations, by 0.38 ± 0.65% in the SL group and by 0.37 ± 1.12% in the MA group. This difference is not statistically significant by univariate analysis; however, a

multiple regression analysis indicated that the drop in SaO₂ was higher at MA than at low altitude. **Conclusions:** We found a low but significant difference in SaO₂ between near-SL and at an altitude of 725 m. The clinical significance of this difference, in terms of human health, is probably minimal.

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Introduction

Pulse oximeters give a noninvasive estimation of arterial hemoglobin oxygen saturation (SaO₂). Measurements of SaO₂ have become a routine and been called the ‘fifth vital sign’ [1]. Normal blood SaO₂ is considered to be 97 ± 2% and hypoxemia is defined as SaO₂ lower than 90% [2, 3]. There are many potential sources of error in pulse oximetry measurements such as intravenous dyes, dys-hemoglobins, skin pigmentation or nail polish [4], as well as many other artifacts [5–7]. Also, SaO₂ may be affected by multiple physiologic variables. One of them is the partial pressure of oxygen in the inspired air, which is a function of the barometric pressure. The fraction of oxygen in the air is stable (21%), hence SaO₂ is predictably lower at high altitude than at sea level (SL) because of the lower

barometric pressure. Several studies have shown that the normal range of arterial SaO_2 at high altitudes is lower than that at SL. Many of these studies were collected and summarized recently and it appears that at altitudes of 1,500 m and above, normal SaO_2 decreases [8, 9]. Conversely, SaO_2 increases at depths below SL, which can be of benefit in patients with chronic lung disease [10]. To the best of our knowledge, there have been no studies of normal SaO_2 at elevations between 0 and 1,500 m above SL. Theoretically, normal SaO_2 should decrease at any altitude higher than SL, but the level at which this decrease is measurable is unknown.

The goal of this study was to measure SaO_2 in healthy volunteers at rest and after a 6-min walk at both an altitude of 725 m (moderate altitude, MA; Jerusalem) and at 48 m (near-SL; Rehovot). We tested the hypothesis that SaO_2 at rest at MA is lower than that at near-SL, and that the difference observed increases after the exercise test.

Methods

Measurements of SaO_2 were performed in young healthy male volunteers at MA and were compared to those taken in healthy volunteers at near-SL. Subjects were also requested to perform an additional measurement of SaO_2 after a 6-min walk test according to the guidelines of the American Thoracic Society [11]. Although this test is usually used for evaluation of patients with chronic heart or lung diseases [12, 13], we used it in this study in healthy volunteers since we could not perform a formal exercise test in the college area. Approximately half of the volunteers performed the 6-min walk tests. Most others refused to participate in it because of time restrictions and the need to attend the next lecture.

One investigator (E.B.) displayed a poster in each academic institution asking for volunteers for a noninvasive medical research study, explained the protocol to all potential volunteers and obtained their consent for the study. Volunteers who agreed only to the first part of the study but not to the 6-min walk test were not excluded. The same investigator (E.B.) administered a standard questionnaire in order to make sure that none of the volunteers included took any drugs that affect respiratory center drive such as benzodiazepines or sedatives, any sleep-inducing drugs, opioids, codeine derivatives, illicit drugs, carboanhydrase inhibitor, antibiotics (sulfonamides, trimethoprim, dapsone) or local anesthetics before or during the examination. Health status was evaluated by the questionnaire in order to exclude nonhealthy volunteers (by self-reporting). However, no physical examination or blood tests were performed. Thus, we only included young healthy male college students (18–35 years) from the 2 different academic institutions from each location of the study. We excluded all smokers, all subjects with any chronic disease and all subjects who reported any symptoms of acute disease such as fever or coryza on the day of the evaluation. We recorded demographic and anthropometric variables, such as the age, height and weight of each participant.

Because of the many potential sources of error in pulse oximetry measurements, we used a strict protocol: all saturation measurements were performed by the same investigator (E.B.) using a single pulse oximeter (Mini O_2 Saturation Monitor, 4500 Scout, Invivo Research Inc., Orlando, Fla., USA), with the same probe on the index finger of the right hand. This instrument performs very well compared to other pulse oximeters [14] and in relation to simultaneously obtained arterial blood samples has a bias of 0.2% and a precision of 2.05% [15]. Before SaO_2 was measured subjects remained at rest in a sitting position for 10 min. The measurement was then taken with their palm resting on a table, and the radial artery free from compression. The reading was considered reliable after at least 30 s of stable signal. The 6-min walk test was conducted as follows: immediately after the SaO_2 measurement at rest, volunteers were asked to walk as fast as they could for 6 min in a straight 25-meter corridor with a flat floor. Immediately after the 6-min walk, the SaO_2 measurement was repeated, again in the sitting position, but without any rest period. No volunteer in this study used nail polish and they were uniformly Jewish Caucasians (no African subjects were included in this study in order to avoid an additional source of variation, i.e. major differences in skin pigmentation). The investigator (E.B.) only recorded the measurement if the signal (adequate visible pulse wave) was excellent.

Since acclimatization duration has an important impact on SpO_2 at a defined altitude [16–18], it was important that the recruited volunteers were residents of the college where they were studying, which was the case with each participant of this study. In both institutions, an air conditioning unit maintained the ambient temperature in the room at 23–25°C. This study was approved by our local human investigation committee and each volunteer was asked for his verbal agreement.

Statistical Analysis

In order to calculate the necessary sample size, we performed a theoretical calculation of the expected differences of SaO_2 between the two locations. To do so, we used an automated version of the Kelman equation [19], available on the internet (VentWorld, Amethyst Research LLC, <http://ventworld.com/resources/oxydisso/oxydisso.html>). This equation calculates blood oxygen saturation for any given blood oxygen pressure. We first calculated the alveolar oxygen pressure, using the alveolar gas equation: $P_{\text{AO}_2} = F_{\text{IO}_2} (P_{\text{B}} - P_{\text{H}_2\text{O}}) - P_{\text{ACO}_2} [F_{\text{IO}_2} + (1 - F_{\text{IO}_2})/R]$, where F_{IO_2} is the fractional concentration of oxygen (O_2) in inspired gas, P_{B} is the barometric pressure, $P_{\text{H}_2\text{O}}$ is the water vapor pressure (47 mm Hg), P_{ACO_2} is the partial pressure of carbon dioxide (CO_2) in the alveoli (40 mm Hg in a healthy subject) and R is the respiratory quotient (0.8) [20]. In order to calculate the arterial partial pressure of O_2 (P_{aO_2}) we assumed an alveolar to arterial pressure difference (A-a gradient) of 10 mm Hg. The barometric pressure in each location was obtained from the Israeli National Weather Service. According to these calculations the expected SaO_2 obtained were 97% at SL and 95.7% at MA. Thus, the expected SaO_2 difference between the two locations was 1.3%. Assuming a variability of $\pm 2\%$ in the SaO_2 measurements (from data published in the literature [3, 4]), we calculated that we would need a sample of 100 patients in each group to reach significance of <0.05 with a power of 80%.

For the purpose of analyses, we used the Minitab version 15.1 software (Minitab Inc., State College, Pa., USA). We used Student

t tests to analyze the difference between the MA and SL groups in mean SaO₂ at rest and after the 6-min walk. We used paired t tests to analyze the decrease in SaO₂ in each group after exercise. The χ^2 test was used for comparison of categorical variables between the two groups. The Pearson correlation was used to evaluate the relationship between SaO₂ and BMI or age. We used stepwise backward multiple regression analysis to evaluate the influence of independent variables such as age, height, weight and study site on SaO₂. Results are expressed as mean $\pm$ SD or as percentages. A p value of <0.05 was considered significant.

Results

Two hundred and twenty-two male volunteers were approached for enrollment. Ten of them were excluded; 7 because of bronchial asthma and 3 because of other chronic diseases. Thus 212 subjects were enrolled. Among the 111 participants at MA, 60 were examined both at rest and after a 6-min walk, and 51 at rest only. Of the 101 subjects enrolled at SL, 55 were examined both at rest and after a 6-min walk, and 46 at rest only.

All measurements were performed in August 2009 over a period of 2–3 consecutive days in each location. The barometric pressure during the study period happened not to change during the study period at each site, remaining at 697 mm Hg at MA and 755 mm Hg at SL.

The characteristics and anthropometric measurements of the subjects are summarized in table 1. There were no significant differences between the groups in terms of age and height. However, both weight and BMI were significantly higher in the SL location.

Mean SaO₂ at rest was significantly higher at SL (98.53 $\pm$ 0.52%) compared to MA (98.11 $\pm$ 0.8%; $p < 0.01$; table 1). Saturations ranged from 97 to 99% at SL and from 95 to 99% at MA. Since weight (and subsequently BMI) differed significantly between the 2 groups, we performed a stepwise backward multiple regression analysis to evaluate the possible influence of age, height, weight (or BMI) and study site on SaO₂ at rest. Only the study site was found to significantly influence the baseline SaO₂ at rest while taking into account the above-mentioned potential confounding variables.

After a 6-min walk, mean SaO₂ decreased slightly by 0.38 $\pm$ 0.65% in the SL group and by 0.37 $\pm$ 1.12% in the MA group. Thus, the difference in SaO₂ observed prior to exercise between the 2 groups remained nearly constant (table 2). No significant correlation was found between age, height, weight or BMI and SaO₂ at rest, but weight and BMI differed significantly between the 2 groups. The SL group walked a significantly shorter distance and had

Table 1. Patient data at rest

	SL	MA	p value
n	101	111	
Age, years	25.1 $\pm$ 3.2	24.0 $\pm$ 4.4	0.42
Height, cm	175.6 $\pm$ 6.9	175.1 $\pm$ 6.3	0.55
Weight, kg	73.1 $\pm$ 13.8	68.6 $\pm$ 10.3	<0.02
BMI	23.7 $\pm$ 3.9	22.3 $\pm$ 3.0	0.004
Heart rate, bpm	66.7 $\pm$ 9.6	66.0 $\pm$ 10.1	0.65
SaO ₂ , %	98.53 $\pm$ 0.52	98.11 $\pm$ 0.8	<0.01

Table 2. Comparison of SaO₂ between SL and MA at rest and after exercise

	SL (n = 55)	MA (n = 60)	p value
Mean SaO ₂ at rest, %	98.64 $\pm$ 0.49	97.97 $\pm$ 0.80	<0.01
Mean heart rate at rest, bpm	66.9 $\pm$ 10.0	67.5 $\pm$ 10.1	0.72
Mean walking distance, m	595.4 $\pm$ 136	721.5 $\pm$ 153.9	<0.001
Mean SaO ₂ after			
6-min walking, %	98.25 $\pm$ 0.64	97.6 $\pm$ 0.87	<0.01
Mean heart rate after			
6-min walking, bpm	89.9 $\pm$ 19.2	102.6 $\pm$ 24.3	0.002
Mean drop in SaO ₂ between rest and after exercise, %	-0.38 $\pm$ 0.65	-0.37 $\pm$ 1.12	0.93

a lower increase in heart rate. Thus, we conducted a multiple regression analysis in which the dependent variable was difference in SaO₂ before and after exercise and the independent variables were the group, heart rate after exercise, saturation at rest, distance walked and BMI. In this analysis, only saturation at rest, group and postexercise heart rate remained significant (R^2 for the equation = 0.3641, $p = 0.02$), indicating that the drop in SaO₂ was greater when the saturation was higher at rest, greater at MA than at low altitude, and greater when the heart rate after exercise was higher.

Discussion

In this study we evaluated SaO₂ in young volunteers at two locations, one at SL and one at MA. We found that SaO₂ at SL (98.53% $\pm$ 0.52) was higher by a mean of 0.42% than SaO₂ at MA (98.11% $\pm$ 0.80). Interestingly, SaO₂ decreased in a similar fashion after mild exercise in the two locations. However, in multiple regression analysis taking

into account altitude group, heart rate after exercise, saturation at rest, distance walked and BMI, the drop in saturation after exercise correlated significantly with location (a greater drop at higher altitude), saturation at rest, and postexercise heart rate. We speculate that faster oxygen extraction from hemoglobin occurs at MA because of the fact that the oxygen saturation curve gets steeper as the SaO_2 decreases. Apparently, when the 6-min walk test is performed by volunteers at much higher altitude (4,365 m), the decrease in saturation is much greater and ranges between 3.9 and 9.1% [21].

Several studies have reported decreased oxygen saturation at altitudes above 1,500 m [8, 9]. The results of several such studies were used by Subhi et al. [8] to predict mean oxygen saturation at every altitude between SL and 4,000 m. The mean predicted oxygen saturation at an altitude of 725 m according to that study was 96.6%, which is also lower than the value measured in our current study. We suspect that this difference might be due to a selection bias, since our patient population consisted exclusively of young healthy male individuals.

The SaO_2 values measured in this study were higher than the values we calculated using the alveolar gas equation and the hemoglobin dissociation curve according to the Kelman equation. Indeed, according to these calculations, the SaO_2 at MA should be 95.7% (instead of 98.11% as measured) and at SL should be 97% (instead of 98.53% as measured). Thus, the SaO_2 levels measured in our study were higher than expected by 2.41% at MA and 1.53% at SL. These differences between the expected and measured SaO_2 might be due to a combination of several factors. (1) Increased SaO_2 in MA due to acclimatization. Acclimatization involves an involuntary increase in ventilation, which lowers the alveolar PaCO_2 and increases the alveolar PO_2 as the 2 are inversely related according to the alveolar gas equation [22, 23]. It is possible that this process is already in effect at moderate altitude. (2) Accuracy of the pulse oximeter used in the study. This specific pulse oximeter has a bias of 0.2% [15], which indicates an overestimation of SaO_2 in blood by 0.2%. (3) Incorrect assumption concerning the A-a difference or body temperature of 37°C. (4) Imprecision in barometric pressure measurements at the exact site of SaO_2 measurement. We suspect that arterial samples, which are much less practical to obtain, may have provided us with measurements much closer to the calculated values.

There are several limitations to our study. The first one is that it was performed exclusively on young adult male volunteers and the results do not necessarily apply to oth-

er subjects such as females, children or elderly individuals. Indeed, it has been shown that during rest at SL, SaO_2 is slightly higher (nearly 1%) in women than in men [24]. Additionally, altitude may differently affect SaO_2 at different ages in a gender-dependent fashion. Indeed, it has been shown that native Tibetans living at high altitude (3,800–4,200 m) have a steady increase in mean SaO_2 during the first decade of life [25], followed by a stabilization during the second decade and a decrease starting between 20 and 29 years in males and 50 and 59 years in females. Thus, the SaO_2 differences that we report between SL and MA in this specific group of patients are not necessarily applicable to females or to other age groups. Therefore, we suggest that additional studies be conducted on such groups of subjects in order to quantify the potential effect of moderate altitude on them.

Another limitation of our study was that all measurements were conducted on healthy individuals. It is possible that diseases, even mild upper respiratory tract infection, may affect the altitude-dependent changes that we report here. Indeed, Beebe et al. [26] have demonstrated that mean SaO_2 levels of children with upper respiratory tract infection are significantly lower (by approx. 1.5%) than in healthy children. The latter study was conducted in Salt Lake City, at a moderate altitude of 1,500 m. No such studies have been conducted at SL.

It is also possible that season is another confounding variable that may also affect the relationship between SaO_2 and altitude. Indeed, at a given altitude the barometric pressure changes with local variations in weather and to a greater extent with the season, such that in midsummer the barometric pressure may be significantly higher than in winter [27].

Another limitation of our study resides in the fact that the exercise test we selected was the 6-min walk test. As stated by the American Thoracic Society [11], the 6-min walk test is a practical simple test that does not require any exercise equipment or advanced training. However, most patients do not achieve maximal exercise capacity during the test. It is possible that after more strenuous exercise the decrease in SaO_2 would be greater and the difference in SaO_2 between the two locations would be higher.

Finally, although our study gives us an idea of the effect of moderate altitude on SaO_2 , the exact values of SaO_2 that we report here are only applicable to the type of pulse oximeter used in our study. It is known that there could be some variability between pulse oximeters and measurements might vary slightly depending on which device is used [14, 15, 28, 29]. However, it is unlikely that the

difference in SaO₂ observed between the two locations would be affected by the type of oximeter used.

In summary, in this prospective study we found a statistically significant difference in SaO₂ between near-SL and an altitude of 725 m. The clinical significance of this

difference, in terms of human health, is probably minimal. However, one may wonder what the effect of such a small difference could be when strict SaO₂ limits are applied in the context of a clinical protocol or algorithm that would involve medical decisions.

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