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Deirdre Caffrey
Johns Hopkins University

J. Jaime Miranda
Universidad Peruana Cayetano Heredia

Robert H. Gilman
Johns Hopkins University

Victor G. Davila-Roman
Washington University School of Medicine in St. Louis

Lilia Cabrera
Johns Hopkins University

See next page for additional authors

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Authors
Deirdre Caffrey, J. Jaime Miranda, Robert H. Gilman, Victor G. Davila-Roman, Lilia Cabrera, Russell Dowling, Talia Stewart, Antonio Bernabe-Ortiz, Robert Wise, Fabiola Leon-Velarde, William Checkley, and CRONICAS Cohort Study Group
A cross-sectional study of differences in 6-min walk distance in healthy adults residing at high altitude versus sea level

Deirdre Caffrey1, J Jaime Miranda2,3, Robert H Gilman4,5, Victor G Davila-Roman6, Lilia Cabrera4, Russell Dowling6, Talia Stewart1, Antonio Bernabe-Ortiz2, Robert Wise1, Fabiola Leon-Velarde7, William Checkley1,2* and CRONICAS Cohort Study Group

Abstract

Background: We sought to determine if adult residents living at high altitude have developed sufficient adaptation to a hypoxic environment to match the functional capacity of a similar population at sea level. To test this hypothesis, we compared the 6-min walk test distance (6MWD) in 334 residents living at sea level vs. at high altitude.

Methods: We enrolled 168 healthy adults aged ≥35 years residing at sea level in Lima and 166 individuals residing at 3,825 m above sea level in Puno, Peru. Participants completed a 6-min walk test, answered a sociodemographics and clinical questionnaire, underwent spirometry, and a blood test.

Results: Average age was 54.0 vs. 53.8 years, 48% vs. 43% were male, average height was 155 vs. 158 cm, average blood oxygen saturation was 98% vs. 90%, and average resting heart rate was 67 vs. 72 beats/min in Lima vs. Puno. In multivariable regression, participants in Puno walked 47.6 m less (95% CI -81.7 to -13.6 m; p < 0.01) than those in Lima. Other variables besides age and height that were associated with 6MWD include change in heart rate (4.0 m per beats/min increase above resting heart rate; p < 0.001) and percent body fat (-1.4 m per % increase; p = 0.02).

Conclusions: The 6-min walk test predicted a lowered functional capacity among Andean high altitude vs. sea level natives at their altitude of residence, which could be explained by an incomplete adaptation or a protective mechanism favoring neuro- and cardioprotection over psychomotor activity.

Keywords: Six-minute walk test, High altitude adaptation, Hypoxia, Functional capacity
integrated systems of the body that are required during walking, the 6MWT provides information about how the cardiovascular and pulmonary systems function together. The exertion level achieved during the 6MWT is chosen by the participant and is usually less than their maximal exertion level [12]. However, activities of daily living are similarly performed at exertion levels chosen by the individual; therefore, the 6MWT is a good indicator of an individual’s ability to perform activities of daily living [18].

Results from the 6MWT related to ascent to altitude have been used as a measure of changes in functional capacity among lowlanders at various altitudes, as well as a method to predict who will be affected by acute altitude sickness [19,20]. However, the 6MWT has not been used as a method to compare functional capacities of high and low altitude populations. By testing participants at their residing altitudes, this study intends to determine whether long-term high altitude residents have adapted to their environments to achieve the same functional capacity as sea level residents. Thus, our primary objective was to investigate the functional capacity of a sea level and high altitude population by means of the 6MWT.

Methods

Study setting

The study population consisted of adults ≥35 years of age living in the cities of Lima and Puno. Lima is the highly urbanized capital of Peru located at sea level and with a population of more than ten million. We conducted our study in Pampas de San Juan de Miraflores, a peri-urban shanty town located 25 km south of the city center. Puno is an Andean City located at 3,825 m above sea level and with a population of approximately 150,000. The average temperature was 21.6°C in Lima and 16.1°C in Puno. The study protocol was approved by the Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health in Baltimore, USA and A.B. PRISMA in Lima, Peru. All participants provided verbal informed consent after our research team read the entire informed consent document to them and any questions were answered.

Study design

This is an ancillary study of a larger ongoing cohort study conducted in Lima and Puno. In preparation for study activities for this parent cohort study, we first conducted a door-to-door household census of the study areas from which an age-, sex- and site-stratified population-based cohort of approximately 1,000 participants per site was derived [21]. At baseline, participants responded to a face-to-face questionnaire regarding sociodemographics and medical history. Field workers measured weight, height, bioelectrical impedance, blood pressure, and spirometry before and after bronchodilators, and obtained a blood sample for analysis of cardiovascular and pulmonary biomarkers. We measured bioelectrical impedance using the TBF-300A body composition analyzer (TANITA Corporation, Itabashi-ku, Tokyo, Japan) to estimate lean mass, percent body fat, and water weight. Participants were asked to provide venous blood sample after 8 to 11 h of fasting. Blood was obtained by trained phlebotomists in the sitting position and using universal precautions. Plasma glucose was measured using an enzymatic colorimetric method (GOD-PAP; Modular P-E/Roche-Cobas, Grenzach-Whylen, Germany), serum insulin using electrochemiluminescence (Modular P-E/Roche-Cobas), hs-C reactive protein using Latex (Tina-quant CRP-HS Roche/Hitachi analyzer, Indianapolis, IN, USA), and hemoglobin A1C using high-performance liquid chromatography (D10, BioRad, Munich, Germany). We measured lung function using the Easy-On-PC spirometer (ndd, Zurich, Switzerland) following standard guidelines [22]. All patients underwent bronchodilator-response testing. We administered two puffs from a salbutamol inhaler (100 mcg/puff) via a spacer and repeated spirometry 10 to 15 min later.

We then invited a random subset of 400 participants (200 in Lima and 200 in Puno) from the parent cohort study to participate in this ancillary study. We defined healthy participants as those who did not have: a physical disability that impaired walking; self-reported diagnosis of heart failure, diabetes, asthma, COPD, active or a history of pulmonary tuberculosis; prior pulmonary or thoracic surgery, a self-reported history of daily smoking (i.e., ≥1 cigarette per day), a body mass index (BMI) ≥35 kg/m², systolic blood pressure (SBP) ≥140 mmHg, and diastolic blood pressure (DBP) ≥90 mmHg, pre-bronchodilator forced expiratory volume in 1 second (FEV₁) or pre-bronchodilator forced vital capacity (FVC) < 1 L (i.e., a marker of impaired lung function in our study population), post-bronchodilator FEV₁/FVC < 70% or excessive erythrocytosis (i.e., hemoglobin ≥19 g/dL in women and ≥21 g/dL in men) [23]. Of those who agreed to participate in this sub-study, we conducted a preliminary evaluation of eligibility criteria. The interview included a discussion of the study objectives, review of eligibility criteria, procedures, associated risks, and benefits, and consent. Enrollees were then invited to schedule an appointment to perform the 6MWT.

Six-minute walk test

The 6MWT was performed outdoors along a hard flat course measuring 30 m, following standard guidelines [24]. The 6MWT is a self-paced test and participants can choose their own intensity of exercise. It measures functional capacity as the majority of patients do not achieve maximal sustained exercise capacity. Before the test was performed, study staff measured height, weight, and vital signs including pulse oximetry, heart rate, blood pressure, and level of dyspnea and fatigue using the Borg
Biostatistical methods
The primary outcome was distance walked during the 6MWT (i.e., 6MWD). The primary risk factor was altitude of residence, defined as high altitude for participants in Puno and sea level for participants in Lima. We used t tests to compare continuous variables between groups if normally distributed and Mann–Whitney U tests if non-normally distributed. We used chi-square or Fisher exact tests whenever appropriate, if categorical variables. We used multiple linear regression to model 6MWD as a function of altitude of residence and adjusted for age, sex, height, resting heart rate, SBP, change in 6MWD as a function of altitude of residence and age, sex, height, resting heart rate, SBP, change in 6MWD as a function of altitude of residence and height-adjusted FVC (FVC/height2), self-reported for age, height, resting heart rate, SBP, change in 6MWD as a function of altitude of residence and height, percent body fat, water weight, education level, weekly exercise, FEV1/height2, and FVC/height2 (Table 2).

In Figure 1, we show single variable relationships between 6MWD and selected risk factors. In multivariable linear regression, however, variables that remained important were living at high altitude, age, height, percent body fat, and having completed high school (Table 3). Younger participants walked a greater 6MWD than did older participants with a decrease of 1.4 m per year of older age. Taller participants walked a greater 6MWD than shorter participants with an increase of 1.1 m more per cm increase in height. A greater increase in heart rate from baseline also corresponded to a greater 6MWD, with an increase 4.0 m more per beats/min increase above resting heart rate.

Differences in 6MWD between participants at altitudes of residence
In unadjusted analysis, living at high altitude was an important determinant of 6MWD. Specifically, average 6MWD was 415 m (SD = 65) in Puno vs. 475 m (SD = 81) in Lima (difference of 60 m, 95% CI 44 to 76; p < 0.001). In multivariable linear regression, this difference remained such that participants in Puno walked 47.6 m less than did those in Lima (95% CI 13.6 to 81.7 m; p = 0.006). There was no difference in 6MWD between those participants in Lima who were born at high altitude vs. born at sea level (p = 0.21) and the sample in Puno consisted almost entirely of participants born at high altitude. While we reported a difference in change in heart rate between the end of the 6MWT and baseline in Puno vs. Lima (mean 0.4 vs. 5.3 beats/min, respectively; p < 0.001), we did not find a difference in change in pulse oximetry (mean 0.54% vs. 0.41%; p = 0.27) or SBP (7.6 mmHg vs. 7.1 mmHg; p = 0.70) between the end of the 6MWT and baseline.

Reference equations for 6MWD in Lima and Puno, Peru
We defined site-specific reference equations for the 6MWD in Lima and Puno, adjusted for age, height, weight, sex, and change in heart rate between the end of test and baseline (Table 4). These models explained 54%
and 31% of the variation in 6WMD observed in Lima and Puno, respectively.

**Discussion**

It is well documented that high altitude natives in several settings around the world have made significant adaptations to life in a hypoxic environment [1-9,26,27]. The majority of these studies quantified these adaptations by testing the exercise capacity of highlanders and lowlanders at increasing altitudes and demonstrated highlanders had an overall lower decrease in exercise capacity than lowlanders. Instead of this approach, our study quantified the distance walked during a 6-min walk test by highlanders and lowlanders in their respective environments to determine to what extent high altitude adaptations have allowed high altitude natives to approach the functional capacity of a similar population at sea level. We found that, after controlling for multiple variables, highlanders at

| Table 1 Participant characteristics | Lima | Puno | P  |
|-----------------------------------|------|------|----|
| Sample size                       | 168  | 166  |    |
| Demographics                      |      |      |    |
| Male, %                           | 48%  | 43%  | 0.37|
| Age in years, mean (SD)           | 54 (11) | 54 (10) | 0.86|
| Clinical data, mean (SD)          |      |      |    |
| Height, cm                        | 154.8 (8.4) | 157.5 (9.3) | <0.01|
| Weight, kg                        | 67.3 (9.9) | 66.4 (10.9) | 0.47|
| Body Mass Index, kg/m²            | 28.0 (3.3) | 26.7 (3.4) | <0.001|
| Systolic blood pressure, mmHg     | 116 (11) | 107 (12) | <0.001|
| Diastolic blood pressure, mmHg    | 69 (8) | 69 (8) | 0.78|
| Pulse oximetry, %                 | 98.4 (1.2) | 89.5 (3.0) | <0.001|
| Resting heart rate, beats/min     | 66.9 (9.0) | 71.6 (9.3) | <0.001|
| Heart rate at the end of 6WMT, beats/min | 72.2 (10.6) | 72.0 (10.6) | 0.85|
| Change in heart rate, beats/min   | 5.3 (6.8) | 0.4 (6.2) | <0.001|
| Pre-bronchodilator FEV₁, L        | 2.8 (0.7) | 2.9 (0.8) | 0.19|
| Height-adjusted FEV₁, L/m²        | 1.1 (0.2) | 1.1 (0.3) | 0.79|
| Pre-bronchodilator FVC, L         | 3.6 (0.9) | 3.7 (1.0) | 0.12|
| Height-adjusted FVC, L/m²         | 1.5 (0.3) | 1.5 (0.3) | 0.51|
| Pre-bronchodilator FEV₁/FVC%      | 77.5 (4.9) | 76.7 (5.3) | 0.14|
| Difficulty breathing after 6MWT (Borg Scale) | 0.3 (0.6) | 0.6 (0.9) | <0.001|
| Fatigue after 6MWT (Borg Scale)   | 0.5 (0.9) | 0.8 (1.0) | <0.001|
| Laboratory data, mean (SD)        |      |      |    |
| hsCRP, mg/dL                      | 3.1 (4.0) | 2.1 (3.4) | 0.02|
| Insulin in uUnits/mL              | 104 (9.7) | 7.5 (4.8) | <0.001|
| Glucose, mg/dL                    | 91.6 (10.3) | 91.1 (19.9) | 0.78|
| Cholesterol, mg/dL                | 199.8 (38.8) | 199.5 (42.1) | 0.95|
| High density lipoprotein cholesterol, mg/dL | 41.0 (11.5) | 42.3 (12.0) | 0.33|
| Low-density lipoprotein cholesterol, mg/dL | 126.3 (35.2) | 125.2 (39.6) | 0.78|
| Triglycerides, mg/dL              | 162.1 (102.0) | 160.1 (107.6) | 0.86|
| Hemoglobin, g/dL                  | 13.5 (1.2) | 16.9 (1.5) | <0.001|
| Hemoglobin A1c, mmol/mol           | 5.6 (0.4) | 5.8 (0.4) | <0.001|
| Socioeconomic status data         |      |      |    |
| Completed high school,%            | 64%  | 83%  | <0.001|
| Percent employed,%                 | 68%  | 76%  | 0.13|
| People per household, mean (SD)    | 5.5 (2.3) | 4.0 (1.9) | <0.001|
## Table 2 Predictors of 6MWT

| Age (years) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|-------------|--------|----------------------|-----|--------|----------------------|-----|
| 35–44       | 42     | 507 (79)             | <0.001 | 32     | 414 (57)             | 0.08 |
| 45–54       | 44     | 494 (58)             |       | 60     | 427 (70)             |     |
| 55–64       | 46     | 469 (86)             |       | 44     | 416 (64)             |     |
| 65–85       | 36     | 421 (72)             |       | 30     | 389 (58)             |     |

**Gender (percent)**

| Gender | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|--------|--------|----------------------|-----|--------|----------------------|-----|
| Males  | 80     | 506 (83)             | <0.001 | 71     | 446 (68)             | <0.001 |
| Females| 88     | 446 (67)             |       | 95     | 392 (51)             |     |

**Height (cm)**

| Height (cm) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|-------------|--------|----------------------|-----|--------|----------------------|-----|
| 130–144     | 19     | 431 (60)             | <0.001 | 10     | 371 (39)             | <0.001 |
| 145–159     | 92     | 450 (73)             |       | 86     | 397 (53)             |     |
| 160–200     | 57     | 529 (70)             |       | 70     | 444 (69)             |     |

**Weight (kg)**

| Weight (kg) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|-------------|--------|----------------------|-----|--------|----------------------|-----|
| 40–59       | 41     | 440 (76)             | <0.001 | 45     | 396 (53)             | 0.06 |
| 60–79       | 107    | 478 (78)             |       | 100    | 423 (67)             |     |
| 80–101      | 20     | 529 (70)             |       | 21     | 417 (68)             |     |

**Body mass index (kg/m²)**

| Body mass index (kg/m²) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|-------------------------|--------|----------------------|-----|--------|----------------------|-----|
| 16–24                   | 32     | 473 (89)             | 0.88 | 51     | 428 (77)             | 0.02 |
| 25–29                   | 86     | 473 (80)             |       | 84     | 417 (57)             |     |
| 30–35                   | 50     | 479 (77)             |       | 31     | 387 (54)             |     |

**Systolic blood pressure (mmHg)**

| Systolic blood pressure (mmHg) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|--------------------------------|--------|----------------------|-----|--------|----------------------|-----|
| 75–89                          | 2      | 448 (106)            | 0.57 | 7      | 399 (36)             | 0.78 |
| 90–119                         | 95     | 480 (74)             |       | 135    | 415 (64)             |     |
| 120–139                        | 71     | 468 (89)             |       | 24     | 419 (74)             |     |

**Diastolic blood pressure (mmHg)**

| Diastolic blood pressure (mmHg) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|---------------------------------|--------|----------------------|-----|--------|----------------------|-----|
| 40–64                           | 43     | 458 (69)             | 0.24 | 52     | 408 (63)             | 0.64 |
| 65–79                           | 107    | 482 (82)             |       | 97     | 417 (65)             |     |
| 80–99                           | 18     | 468 (94)             |       | 17     | 422 (67)             |     |

**Resting heart rate (beats per minute)**

| Resting heart rate (beats per minute) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|---------------------------------------|--------|----------------------|-----|--------|----------------------|-----|
| 40–59                                 | 32     | 465 (67)             | 0.47 | 14     | 438 (67)             | 0.38 |
| 60–79                                 | 121    | 479 (82)             |       | 123    | 413 (64)             |     |
| 80–105                                | 15     | 458 (95)             |       | 29     | 412 (65)             |     |

**Active heart rate (beats per minute)**

| Active heart rate (beats per minute) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|--------------------------------------|--------|----------------------|-----|--------|----------------------|-----|
| 45–64                                | 38     | 451 (69)             | 0.05 | 50     | 398 (51)             | 0.08 |
| 65–84                                | 113    | 478 (78)             |       | 96     | 422 (69)             |     |
| 85–120                               | 17     | 504 (108)            |       | 20     | 422 (65)             |     |

**Delta heart rate (beats per minute)**

| Delta heart rate (beats per minute) | Number | 6MWD in m, mean (SD) | P   | Number | 6MWD in m, mean (SD) | P   |
|-------------------------------------|--------|----------------------|-----|--------|----------------------|-----|
| < 0                                 | 24     | 447 (49)             | <0.001 | 72     | 394 (55)             | <0.001 |
| 0–14                                | 131    | 470 (79)             |       | 92     | 431 (67)             |     |
| 15–35                                | 13     | 569 (87)             |       | 2      | 430 (35)             |     |
| Predictor                                      | 0      | 132 (80) | 0.65  | 88     | 420 (66) | 0.39  |
|-----------------------------------------------|--------|----------|-------|--------|----------|-------|
| Difficulty breathing after 6MWT (self-rating based on Borg Scale) | 0.5–2  | 25       | 487 (91) | 55     | 413 (63) |       |
| ≥ 3                                           | 11     | 462 (64) | 23     | 400 (62) |          |       |
| Fatigue after 6MWT (self-rating based on Borg Scale) | 0      | 107      | 470 (80) | 0.41  | 65       | 417 (65) | 0.80 |
| ≥ 2                                           | 34     | 491 (85) | 68     | 416 (63) |          |       |
| ≥ 3                                           | 27     | 474 (76) | 33     | 408 (68) |          |       |
| hsCRP (mg/dL)                                 | < 1    | 50       | 478 (86) | 0.03  | 76       | 412 (58) | 0.65 |
| 1–2                                          | 63     | 492 (81) | 63     | 414 (69) |          |       |
| 3–35                                         | 55     | 452 (70) | 27     | 425 (71) |          |       |
| Insulin (uUnits/mL)                           | 0–4    | 36       | 479 (90) | 0.92  | 63       | 427 (76) | 0.06 |
| 5–10                                         | 71     | 475 (85) | 64     | 400 (48) |          |       |
| 10–100                                       | 61     | 472 (70) | 39     | 419 (65) |          |       |
| Glucose (mg/dL)                               | 60–79  | 17       | 472 (78) | 0.57  | 30       | 405 (62) | 0.67 |
| 80–99                                        | 121    | 478 (83) | 110    | 418 (68) |          |       |
| 100–300                                      | 30     | 461 (71) | 26     | 414 (53) |          |       |
| High density lipoprotein cholesterol (mg/dL)  | 0–39   | 90       | 489 (89) | 0.04  | 80       | 424 (67) | 0.21 |
| 40–59                                        | 66     | 462 (68) | 72     | 405 (58) |          |       |
| 60–100                                       | 12     | 440 (57) | 14     | 413 (80) |          |       |
| Triglycerides (mg/dL)                         | 0–99   | 52       | 468 (79) | 0.60  | 37       | 396 (55) | 0.08 |
| 100–199                                      | 77     | 474 (78) | 92     | 417 (67) |          |       |
| 200–1,200                                    | 39     | 485 (89) | 37     | 429 (64) |          |       |
| Hemoglobin (g/dL)                             | 9–12   | 58       | 446 (70) | <0.001 | 2      | 416 (39) | <0.01 |
| 13–16                                        | 110    | 490 (85) | 86     | 398 (58) |          |       |
| 17–21                                        | 0      | NA (NA)  | 78     | 434 (67) |          |       |
| Hemoglobin A1c (mmol/mol)                     | 4–4.99 | 5        | 440 (58) | 0.37  | 2       | 397 (49) | 0.22 |
| 5–5.99                                       | 139    | 478 (84) | 110    | 415 (67) |          |       |
| 6–7                                          | 24     | 460 (64) | 54     | 416 (60) |          |       |
| Low-density lipoprotein cholesterol (mg/dL)   | 0–74   | 12       | 516 (69) | 0.21  | 12      | 446 (94) | 0.22 |
| 75–149                                       | 118    | 472 (82) | 119    | 413 (64) |          |       |
| 150–325                                      | 38     | 471 (77) | 35     | 411 (53) |          |       |
| Lean mass                                     | 30–44  | 88       | 442 (70) | <0.001 | 92     | 391 (47) | <0.001 |
| 45–54                                        | 52     | 496 (73) | 43     | 441 (69) |          |       |
| 55–75                                        | 28     | 536 (79) | 31     | 448 (76) |          |       |
Table 2 Predictors of 6MWT (Continued)

| Predictor                        | 10–24 | 25–34 | 35–50 | Water weight (kg) | 20–29 | 30–39 | 40–55 | Education (level) | &lt; Secondary | Higher, non-university | University | Income per month (soles) | &lt; 550 | 550–1,499 | &gt; 1,500 | Not available | Number of people per household | 1–3 | 4–5 | 6–17 | Number of days walking for 10 min or more per week | 0 | 1 | &gt; 2 | 0 | 1 | &gt; 2 | Pre-bronchodilator forced expiratory volume in 1 s (liters) | 1.0–1.49 | 1.5–1.99 | &gt; 2.0 | Height-adjusted pre-bronchodilator forced expiratory volume in 1 s (L/m²) | 0.0–0.99 | 1.0–1.49 | &gt; 1.5 | Pre-bronchodilator forced vital capacity (liters) | 1.0–1.99 | 2.0–2.99 | &gt; 3.0 | Height-adjusted pre-bronchodilator forced vital capacity (L/m²) | 0.0–1.49 | 1.5–1.99 | &gt; 2.0 |
|----------------------------------|-------|-------|-------|------------------|-------|-------|-------|-------------------|----------------|------------------------|------------|--------------------------|---------|-------------|----------|----------------|-------------------|-----|-----|------|------------------|-----|-----|------|------------------|---------|-------------|------|------------------|---------|-----|------|------------------|---------|-------------|------|
| Percent body fat (%)            | 40    | 513   | 84    |                   | 53    | 453   | 72    |                   | 49             | 469                   | 78        | 79                        | 79      | 469         | 78        | 49             | 513     | 84    | 72    |                   | 65    | 475   | 74    | 85             | 475   | 74    | 85    |                   | 465    | 99        | 65    |                   | 465    | 99    | 65    |                   | 465    | 99        | 65    |                   |
| Water weight (kg)               |       |       |       |                   |       |       |       |                   | 53             | 438                   | 69        | 79                        | 79      | 469         | 78        | 49             | 513     | 84    | 72    |                   | 65    | 475   | 74    | 85             | 475   | 74    | 85    |                   | 465    | 99        | 65    |                   | 465    | 99    | 65    |                   | 465    | 99        | 65    |                   |
| Education (level)              |       |       |       |                   |       |       |       |                   | 60             | 430                   | 74        | 60                        | 60      | 430         | 74        | 60             | 430     | 74    | 72    |                   | 29             | 430 | 74 |                   | 29             | 430 | 74 |                   | 29             | 430 | 74 |                   |
| Income per month (soles)        |       |       |       |                   |       |       |       |                   | 27             | 429                   | 75        | 27                        | 27      | 429         | 75        | 27             | 429     | 75    | 72    |                   | 49             | 399 | 62 |                   | 49             | 399 | 62 |                   | 49             | 399 | 62 |                   |
| Number of people per household |       |       |       |                   |       |       |       |                   | 29             | 465                   | 99        | 29                        | 29      | 465         | 99        | 29             | 465     | 99    | 72    |                   | 65             | 416 | 62 |                   | 65             | 416 | 62 |                   | 65             | 416 | 62 |                   |
| Number of days of exercise per week |       |       |       |                   |       |       |       |                   | 12             | 508                   | 82        | 12                        | 12      | 508         | 82        | 12             | 508     | 82    | 82    |                   | 5               | 400 | 51 |                   | 5               | 400 | 51 |                   | 5               | 400 | 51 |                   |
| Pre-bronchodilator forced expiratory volume in 1 s (liters) |       |       |       |                   |       |       |       |                   | 4              | 303                   | 60        | 4              | 303 | 60 | 60 |                   | 3              | 303 | 60 | 4 |                   | 3              | 303 | 60 | 4 |                   | 3              | 303 | 60 | 4 |                   |
| Height-adjusted pre-bronchodilator forced expiratory volume in 1 s (L/m²) |       |       |       |                   |       |       |       |                   | 46             | 429                   | 76        | 46                        | 46      | 429         | 76        | 46             | 429     | 76    | 76    |                   | 49             | 393 | 64 |                   | 49             | 393 | 64 |                   | 49             | 393 | 64 |                   |
| Pre-bronchodilator forced vital capacity (liters) |       |       |       |                   |       |       |       |                   | 2              | 303                   | 60        | 2                        | 2       | 303         | 60        | 2             | 303     | 60    | 60    |                   | 5              | 383 | 60 |                   | 5              | 383 | 60 |                   | 5              | 383 | 60 |                   |
| Height-adjusted pre-bronchodilator forced vital capacity (L/m²) |       |       |       |                   |       |       |       |                   | 9              | 519                   | 78        | 9                        | 9       | 519         | 78        | 9             | 519     | 78    | 78    |                   | 16             | 451 | 78 |                   | 16             | 451 | 78 |                   | 16             | 451 | 78 |                   |

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their altitude of reference had a lower functional capacity than did lowlanders at sea level, i.e., a 48-m difference in 6-min walk distance. This difference was greater than the minimal clinically important difference for many chronic respiratory conditions (Table 5) [10,28,29].

A shorter 6-min walk distance we observed indicating a 13% lowered functional capacity is comparable to the previously reported decrease in marathon time performed by a trained high altitude native on a course ranging from 4,100 to 4,700 m in elevation. This time was 18.5% slower than the world record at sea level but still faster than the predicted time for a sea level native on a marathon course at this altitude [30]. Despite the superior oxygen uptake and pulmonary gas exchange, a 40% higher diffusing capacity and greater lactic acid buffering in high altitude natives [31,32], there is still a measurable impairment in functional capacity at their altitude of residence. It is unclear, however, whether the decrease in 6-min walk distance is an incomplete adaptation or a protective adaptation among Andean high altitude dwellers. The psychomotor slowing observed in European, Native American, and African altitude groups could be an adaptive rather than a deficient trait, perhaps enabling accuracy of cognitive activity in hypoxic conditions [33]. Hochachka et al. have shown that lower region-by-region brain glucose metabolic rates in high altitude Quechuas compared to lowlanders, which may be the result of a functional adaptation against chronic hypoxia [34]. The lower change in heart rate before and after the 6-min walk test in high altitude vs. sea level dwellers may also help explain the observed shorter 6-min walk distance. Heart rate is affected by both the sympathetic and parasympathetic nervous systems; a balance which is known to be different in hypoxic environments, even after prolonged exposure [35,36]. Some suggest that the lack of increase in heart rate may be a protective functional adaptation which prevents an excess of adrenergic stimulation during exercise [35-37].

The effects of high altitude on human health have been studied using various approaches ranging from its effects on athletic performance [5,6,26], to consequential functional adaptations that arise among highlanders including chronic mountain sickness and high-altitude pulmonary hypertension [38,39]. Maximal cardiopulmonary testing including peak VO2 has been shown to predict exercise capacity but has its limitations because the very sick are unable to undergo this testing. In several examples, a primary outcome of functional capacity has been adequately demonstrated using the 6MWT in

| Table 2 Predictors of 6MWT (Continued) |
|----------------------------------------|
| Pre-bronchodilator FEV1/FVC (%)         |
| 60–69                                  |
| 70–84                                  |
| ≥ 85                                   |
| Pulse oximetry (percent)               |
| 70–84                                  |
| 85–94                                  |
| 95–100                                 |

Figure 1 Single variable relationships between 6-min walk distance and selected risk factors.
Functions of age (in years), height (in cm), weight (in kg), sex, and change in heart rate between the end of 6MWT and baseline (beats/min).

In several instances whereby the study population that was unable to complete other means of maximal cardiopulmonary testing [10-13,15,16,18]. The 6-min walk test is simpler than full cardiopulmonary testing, and in this study, we demonstrate its simplicity in epidemiological studies to compare functional capacity of two healthy populations at different altitudes.

The results of this study suggest a lowered functional capacity among high altitude residents of Puno, Peru, vs. residents at sea level of Lima, Peru using a simple and noninvasive test. The study design does not allow us to conclude causation of the lowered functional capacity among high altitude natives due to its cross-sectional design. This study was also limited to a relatively homogeneous population from two Peruvian cities, which limits external validity. There are also limitations in the study’s high altitude population as it includes only decedents of Andean background, which differ in adaptations to hypoxia compared to Tibetan populations [40].

Conclusions

In summary, after stratifying for variables shown to be associated with the 6-min walk test, there was an important difference in the 6-min walk distance between healthy adult residents at high altitude versus sea level. This 48-m difference shown by multivariable regression is greater than the minimal important difference observed in previous studies for various chronic respiratory diseases, which varies between 24 and 45 m [10,28,29]. Based on the results of this study, measured differences in 6-min walk distance suggests that residents from the city of Puno, Peru, located at high altitude (3,825 m above sea level) have not developed the adaptations to their high altitude environment that are necessary to bring them to an equivalent functional capacity as similar residents of Lima, Peru, located at sea level. Alternatively, the shorter 6-min walk distance in healthy adults residing at high altitude versus sea level could be explained by protective mechanisms in which there is a lower psychomotor activity in favor of increased neuro- and cardioprotection.

Table 3 Multivariable linear regression of 6-min walk distance (6MWD) in meters

| Change in 6MWD, meters (95% CI) | P     |
|---------------------------------|-------|
| City (Lima is reference)        | −47.6 (−81.7 to −13.6) | <0.01 |
| Age (years)                     | −1.4 (−2.2 to −0.7)    | <0.001|
| Sex (male as reference)         | −13.5 (−39.8 to 12.8)  | 0.32  |
| Height (cm)                     | 1.1 (0.1 to 2.1)       | 0.04  |
| Percent body fat (%)            | −1.4 (−2.6 to −0.3)    | 0.02  |
| Systolic blood pressure (mmHg)  | 0.0 (−0.5 to 0.6)      | 0.87  |
| Pulse oximetry (%)              | 1.0 (−1.7 to 3.8)      | 0.45  |
| Log hsCRP (mg/dL)               | 5.0 (−1.7 to 11.3)     | 0.12  |
| Hemoglobin (g/dL)               | 2.4 (−4.5 to 53.3)     | 0.44  |
| Height-adjusted post-FVC (L/m²) | 24.4 (−41 to 52.9)     | 0.09  |
| Walks ≥10 min at least 1 day per week | 14.6 (−14 to 30.6) | 0.07  |
| Resting heart rate (beats/min)  | 0.6 (0.0 to 1.3)       | 0.07  |
| Change in heart rate between end of 6MWT and baseline (beats/min) | 4.0 (3.0 to 4.9) | <0.001|
| Completed high school           | 24.9 (10.1 to 39.7)    | <0.01 |
| Number of people per household  | −1.6 (−4.5 to 1.3)     | 0.28  |

Table 4 Reference equations for 6-min walk distance in Lima and Puno, Peru

| 6MWD (m) | Lima (n = 168) | Puno (n = 166) |
|----------|----------------|---------------|
| 496.8–2.7× (age−53.9) + 1.6 |
| x(height−156.0) + 0.9 |
| x(weight−66.8)−38.8 |
| x(female) | 36.2% | 106.8 |
| 468.8–2.4× (age−53.9) + 1.1 |
| x(height−156.0) + 0.7 |
| x(weight−66.8)−37.5 |
| x(female) + 5.1 |
| x(Δ Heart rate) | 54.1% | 90.9 |
| 433.0–0.9× (age−53.9) + 2.4 |
| x(height−156.0)−1.3 |
| x(weight−66.8)−37.8 |
| x(female) | 24.6% | 92.9 |
| 434.3–1.2× (age−53.9) + 2.0 |
| x(height−156.0)−1.3 |
| x(weight−66.8)−40.8 |
| x(female) + 2.68 |
| x(Δ Heart rate) | 30.5% | 89.6 |

Functions of age (in years), height (in cm), weight (in kg), sex, and change in heart rate between the end of 6MWT and baseline (beats/min).

Table 5 Minimal clinical important differences (MCID) of 6-min walk distance (6MWD) for various chronic respiratory diseases

| Condition                                           | MCID for 6MWD (m) |
|-----------------------------------------------------|-------------------|
| Chronic obstructive pulmonary disease [28]          | 25 to 35          |
| Idiopathic pulmonary fibrosis [10]                  | 24 to 45          |
| Pulmonary arterial hypertension [29]                | 33                |
Abbreviations
6MWD: 6-min walk distance; 6MWT: 6-min walk test; BMI: body mass index; DBP: diastolic blood pressure; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; SBP: systolic blood pressure; VO2 max: maximal oxygen consumption.

Competing interests
Sponsor had no role in study design, conduct, analysis, interpretation of results, or manuscript writing. The authors declare that they have no competing interests.

Authors’ contributions
DC, JM, RG, ABO, and WC conceived the original study design. DC, LC, RD, TS, and WC were responsible for conduct of the study. RW, FLV, and VDR provided expert guidance in the interpretation of results. All authors contributed equally to the writing of the manuscript. All authors read and approved the final manuscript.

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Author details
1Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, 1800 Orleans St, Suite 9121, Baltimore, MD 21205, USA.
2CRONICAS Center of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima 31, Peru. 3Department of Medicine, Escuela de Medicina, Universidad Peruana Cayetano Heredia, Lima 31, Peru. 4Program in Global Disease Epidemiology and Control, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore 21205, USA. 5A.B. PRSMA, Lima 32, Peru. 6Cardiovascular Imaging and Clinical Research Core Laboratory, Cardiovascular Division, Washington University School of Medicine, St. Louis 63110, USA. 7Department of Ciencias Biológicas y Fisiológicas, Laboratorio de Adaptación a la Altura, Universidad Peruana Cayetano Heredia, Lima 31, Peru.

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References
1. Baker PT: Human adaptation to high altitude. Science 1969, 163:1149–1156.
2. Kollas J, Buskirk ER, Akers RF, Prokop EK, Baker PT, Picon-Reategui E: Work capacity of long-time residents and newcomers to altitude. J Appl Physiol 1968, 24:792–799.
3. Monge C: Acclimatization in the Andes. Baltimore: Johns Hopkins Press; 1948.
4. Hochachka PW: Mechanism and evolution of hypoxia-tolerance in humans. J Exp Biol 1998, 201:1243–1254.
5. Brutsaert TD: Do high-altitude natives have enhanced exercise performance at altitude? Appl Physiol Nutr Metab 2008, 33:58–592.
6. Buskirk ER, Kollas J, Aker RF, Prokop EK, Reategui EP: Maximal performance at altitude and on return from altitude in conditioned runners. J Appl Physiol 1967, 23:259–267.
7. Brutsaert TD, Spielvogel H, Soria R, Caiores E, Buzenet G, Haas JD: Effect of developmental and ancestral high-altitude exposure on VO2peak of Andean and European/North American natives. Am J Phys Anthropol 1999, 110:45–455.
8. Frisancho AR, Velasquez T, Sanchez J: Influence of developmental adaptation on lung function at high altitude. J Appl Physiol 1996, 81:376–383.
9. Caffrey JP, Haggard TS, Abo WC, Buddeke W, Caffrey JP, Haggard TS: Work performance of high-altitude Aymara males. Ann Hum Biol 1984, 10:227–233.
10. Bois RM, Weyder D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Sahn SA, Szwarzberg J, Thomeer M, Valeyre D, King TE Jr: Six-minute-walk test in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011, 183:1231–1237.
11. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DMA: Two-, six-, and 12-minute walking tests in respiratory disease. Br Med J (Clin Res Ed) 1982, 84:1607–1608.
12. Demir R, Kucukoglu MS: Evaluation of exercise capacity in pulmonary arterial hypertension. Turk Kardiyol Dern Ars 2010, 38:580–588.
13. Divo M, Pitta-Pirani V: Role of exercise in testing and in therapy of COPD. Med Clin North Am 2012, 96:753–766.
14. Enright PL: The six-minute walk test. Respir Care 2003, 48:783–785.
15. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB: The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985, 132:919–923.
16. Miyamoto S, Nagaya N, Sato H, Koyanagi S, Sakamaki F, Fujita M, Nakashima N, Miyatake K: Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000, 161:487–492.
17. Balke B: A simple field test for the assessment of physical fitness. Rep 63–64. Rep Cvr Anermed Res Inst US 1963, 1–8.
18. Solway S, Brooks D, Lacasse Y, Thomas S: A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001, 119:256–270.
19. Lazio MP, Van Roo JD, Pesce C, Malik S, Courtney DW: Postexercise peripheral oxygen saturation after completion of the 6-minute walk test predicts successfully reaching the summit of Aconcagua. Wilderness Environ Med 2010, 21:309–317.
20. Mazzuero G, Mazzuero A: Six-minute walking test at high altitude. Wilderness Environ Med 2011, 22:97–98.
21. Miranda JJ, Barbene-Ortiz A, Smeeth L, Gilman RH, Checkley W: Addressing geographical variation in the progression of non-communicable diseases in Peru: the CRONICAS cohort study protocol. BMJ Open 2012, 2:e000610.
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Vegi G, Wagner J, ATS/ERS Task Force: Standardisation of spirometry. Eur Respir J 2005, 26:319–38.
23. León-Velarde F, Maggiorni M, Reeves JT, Aldashev A, Amsu I, Bernardi L, Ge RL, Hackett P, Kobayashi T, Moore LG, Penalosa D, Richea JP, Roach R, Wu T, Vargas E, Zubieta-Castillo G, Zubieta-Calleja G: Consensus statement on chronic and subacute high altitude diseases. High Alt Med Biol 2005, 6:147–157.
24. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002, 166:111–117.
25. Siegel P, Schultz K: The Borg Scale as an instrument for the detection of subjectively experienced stress in industrial medicine laboratory and field studies. Z Gesamte Hyg 1984, 30:383–386.
26. Cunin LS, Zhang J, Droma T, Moore GC: Superior exercise performance in lifelong Tibetan residents of 4,400 m compared with Tibetan residents of 3,658 m. Am J Phys Anthropol 1998, 105:21–31.
27. Frisancho AR, Frisancho HG, Milotch M, Brutsaert T, Albakir H, Spielvogel H, Villena M, Vargas E, Soria R: Developmental, genetic, and environmental components of aerobic capacity at high altitude. Am J Phys Anthropol 1995, 96:431–442.
28. Holland AE, Nici L: The return of the minimum clinically important difference for 6-minute-walk distance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013, 187:335–336.
29. Mathai SC, Puhani MA, Lam D, Wise RA: The minimal important difference in the 6-minute-walk test for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2012, 186:426–433.
30. Comoto J, Bruniquel JV, Macarulpa JL, Privat C, León-Velarde F, Richea JP: Autonomic adaptations in Andean trained participants to a 4,220-m altitude marathon. Med Sci Sports Exerc 2005, 21:48–53.
31. Lundby C, Calbet JA, van Hall G, Saltin B, Sander M: Pulmonary gas exchange at maximal exercise in Danish lowlanders during 8 wk of acclimatization to 4,100 m and in high-altitude Aymara natives. Am J Phys Regul Integr Comp Physiol 2004, 287:R1202–1208.
32. Wagner PD, Arozzi M, Bouhelier R, Calbet JA, Jensen BJ, Rådegran G, Spielvogel H, Sandegaard H, Wagner H, Saltin B: Pulmonary gas exchange and acid-base balance at 5,260 m in high-altitude Bolivians and acclimatized lowlanders. J Appl Physiol 2002, 92:1293–1300.
33. Hogan AM, Virus-Ortega J, Botti AB, Bucks R, Holloway JW, Rose-Zerilli MJ, Palmer LJ, Webster RJ, Baldegowd T, Kirkham FJ: Development of aptitude at altitude. Dev Sci 2010, 13:53–54.
34. Hochachka PW, Clark CM, Brown WD, Stanley C, Stone CK, Nickles RJ, Zhu GG, Allen PS, Holden JE: The brain at high altitude: hypometabolism as a defense against chronic hypoxia. J Cereb Blood Flow Metab 1994, 14:671–9.
35. Hansen J, Sander M: Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. J Physiol 2003, 546:921–929.
36. Zhuang J, Droma T, Sutton JR, McCullough RE, McCullough RG, Groves BM, Rapmund G, James C, Sun S, Moore LG: Autonomic regulation of heart rate response to exercise in Tibetan and Han residents of Lhasa (3,658 m). J Appl Physiol 1993, 75:1968–73.
37. Antezana AM, Richalet JP, Antezana G, Spielvogel H, Kacimi R: Adrenergic system in high altitude residents. Int J Sports Med 1992, 13:S96–S100.
38. Penaloza D, Arias-Stella J: The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation 2007, 115:1132–1146.
39. Leon-Velarde F, Villafuerte FC, Richalet JP: Chronic mountain sickness and the heart. Prog Cardiovasc Dis 2010, 52:540–549.
40. Beall CM, Brittenham GM, Strohl KP, Blangero J, Williams-Blangero S, Goldstein MC, Decker MJ, Vargas E, Villena M, Soria R, Alarcon AM, Gonzalez C: Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. Am J Phys Anthropol 1998, 106:385–400.

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