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ORIGINAL ARTICLE

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Impairment of left atrial mechanics does not contribute to the reduction in stroke volume after active ascent to 4559 m

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Hypoxia challenges left ventricular (LV) function due to reduced energy supply. Conflicting results exist whether high-altitude exposure impairs LV diastolic function and thus contributes to the high altitude-induced increase in systolic pulmonary artery pressure (sPAP) and reduction in stroke volume (SV). This study aimed to assess LV diastolic function, LV end-diastolic pressure (LVEDP), and LA mechanics using comprehensive echocardiographic imaging in healthy volunteers at 4559 m. Fifty subjects performed rapid (<20 hours) and active ascent from 1130 m to 4559 m (high). All participants underwent echocardiography during baseline examination at 424 m (low) as well as 7, 20 and 44 hours after arrival at high altitude. Heart rate (HR), sPAP, and comprehensive volumetric- and Doppler- as well as speckle tracking-derived LA strain parameters were obtained to assess LV diastolic function, LA mechanics, and LVEDP in a multiparametric approach. Data for final analyses were available in 46 subjects. HR (low: 64 ± 11 vs high: 79 ± 14 beats/min, $P < 0.001$) and sPAP (low: 24.4 ± 3.8 vs high: 38.5 ± 8.2 mm Hg, $P < 0.001$) increased following ascent and remained elevated at high altitude. Stroke volume (low: 64.5 ± 15.0 vs high: 58.1 ± 16.4 mL, $P < 0.001$) and EDV decreased following ascent and remained decreased at high altitude due to decreased LV passive filling volume, whereas LA mechanics were preserved. There was no case of LV diastolic dysfunction or increased LVEDP estimates. In summary, this study shows that rapid and active ascent of healthy individuals to 4559 m impairs passive filling and SV of the LV. These alterations were not related to changes in LV and LA mechanics.

KEYWORDS
cardiac imaging, high altitude pulmonary edema, hypoxia, speckle tracking echocardiography

1 | INTRODUCTION

Hypoxic conditions as during high-altitude exposure challenge LVdiastole by decreasing cardiac energy supply,[1] increasing sympathetic nervous activity[2] and pulmonary hypertension.[3] Impaired diastolic function and its main hemodynamic consequence, that is, an increased LV end-diastolic pressure (LVEDP), are of clinical importance at high altitude because a recently hypothesized deterioration[4,5] might increase pulmonary capillary pressure and thereby

increase the risk for high-altitude pulmonary edema (HAPE).[3] Furthermore, impaired diastolic function might contribute to the reduction in stroke volume (SV) at high altitude.[6] Two-dimensional (2D) transthoracic echocardiography (TTE) is the major non-invasive diagnostic tool for assessing LVEDP and diastolic LV function, especially under field conditions as at high altitude.[7] Recently, a multiparametric algorithm using volume- and Doppler-derived variables to estimate LVEDP and LV diastolic function has been shown to be feasible and accurate.[7,8] Still, these variables are angle- as well as load-dependent and fall short of sufficiently extracting and analyzing a main contributor of diastolic LV function, that is, the left atrium (LA) which has been suggested to compensate for LV diastolic alterations under acute hypoxia.[3] Advances in echocardiographic imaging and mainly the advent of 2D speckle tracking echocardiography (STE) myocardial strain assessment enabled a reliable and more independent insight into LA function by visualizing and calculating each of the atrial phases, that is, the *reservoir, conduit, and contraction phase*, separately.[9-11] Furthermore, LA reservoir strain has recently been shown to decrease with increasing LVEDP and to correlate with invasively obtained LVEDP even better than established Doppler-derived surrogates.[12] Subsequently, LA reservoir strain was proposed as an additional parameter in grading diastolic dysfunction.[13] In the light of rising interest in both recreational and occupational high-altitude activities and its potential for life-threatening high-altitude-associated complications, we aimed to retest the hypothesis of diastolic dysfunction at high altitude. Therefore, classic volumetric- and Doppler-derived estimates of diastolic function and LVEDP as well as novel STE-derived LA strain variables were assessed in healthy volunteers at low altitude (424 m) and after active rapid ascent to high altitude (4559 m).

2 | METHODS

2.1 | Study population

Fifty healthy, non-smoking native lowlanders were recruited via social media- and public postings. None of these subjects spent time at altitudes >2000 m within the last 4 weeks before the study, and none took any regular medication. Subjects with cardiovascular diseases were excluded from the study. All subjects provided written informed consent before study inclusion. This study was part of a trial showing that inhaled budesonide did not prevent acute mountain sickness (AMS)[14] and was registered at ClinicalTrials.gov (NCT02811016). The study was performed in accordance with the Declaration of Helsinki and its current amendments, and was approved by the Ethical Committee Salzburg, Austria, by the Ethical Committee of the University of Torino, Italy, and by the Competent Authority (BASG), Vienna, Austria.

2.2 | Study protocol

We performed baseline measurements including exercise testing and echocardiographic assessment at an altitude of 424 m (Salzburg, Austria). Subjects were then randomized to receiving 200 µg budesonide twice/d (group B200, n = 16), 800 µg budesonide twice/d (group B800, n = 17), or lactose-monohydrate (placebo group, n = 17). Inhalations (Cyclohaler®, PB Pharma, Meerbusch, Germany) were started 1 day prior to ascent and continued until the end of the study. Between 2 to 4 weeks after baseline examination, subjects travelled to Alagna (1130 m), Valsesia, Italy, and ascended in groups of 10 accompanied by licensed mountain guides to 4559 m within 20 hours. The ascent consisted of transport by cable car to 3275 m, and a 90-minutes climb to 3611 m (Capanna Giovanni Gnifetti), where they spent one night. On the next morning, subjects performed a 4- to 5-hours climb to 4559 m (Capanna Regina Margherita, Monte Rosa).

AMS was evaluated using the Lake Louise score (cumulative self-report plus clinical scores) and the AMS-C score of the abbreviated version of the Environmental Symptoms Questionnaire.[15] Individuals were diagnosed AMS-positive when they had a Lake Louise score ≥5 in combination with an AMS-C score ≥0.70 points.[16,17] Peripheral oxygen saturation (SpO_2) was measured by pulse oximetry (Covidien Nellcor, Mansfield, USA), and mean arterial blood pressure (MAP) was measured non-invasively by analyzing brachial artery waveforms (Pulsecor, Auckland, New Zealand).

In order to account for the impact of intravascular volume status on echocardiographic variables, hydration status was assessed from hematocrit (Htc) and hemoglobin concentration [Hb] from capillary blood samples with the participant in a seated position. Changes in plasma volume (%ΔPV) were estimated using the Dill and Costill equation.[18]

2.3 | Transthoracic echocardiography

TTEs were performed during baseline examination as well as 7, 20, and 44 hours after arrival at 4559 m. After participants rested for five min in supine position, TTE was conducted using a commercially available ultrasound system (Philips CX50, Phillips Medical Systems, Andover, MA, USA) with a 1.0-5.0 MHz sector array transducer (Philips S5-1, Phillips Medical Systems, Andover, MA, USA) made by the same experienced cardiac sonographer with the subject lying in the left lateral decubitus position. Image acquisition was performed from standard transducer positions and analyzed in accordance with existing recommendations.[19] An electrocardiogram connected to the ultrasound system recorded heart

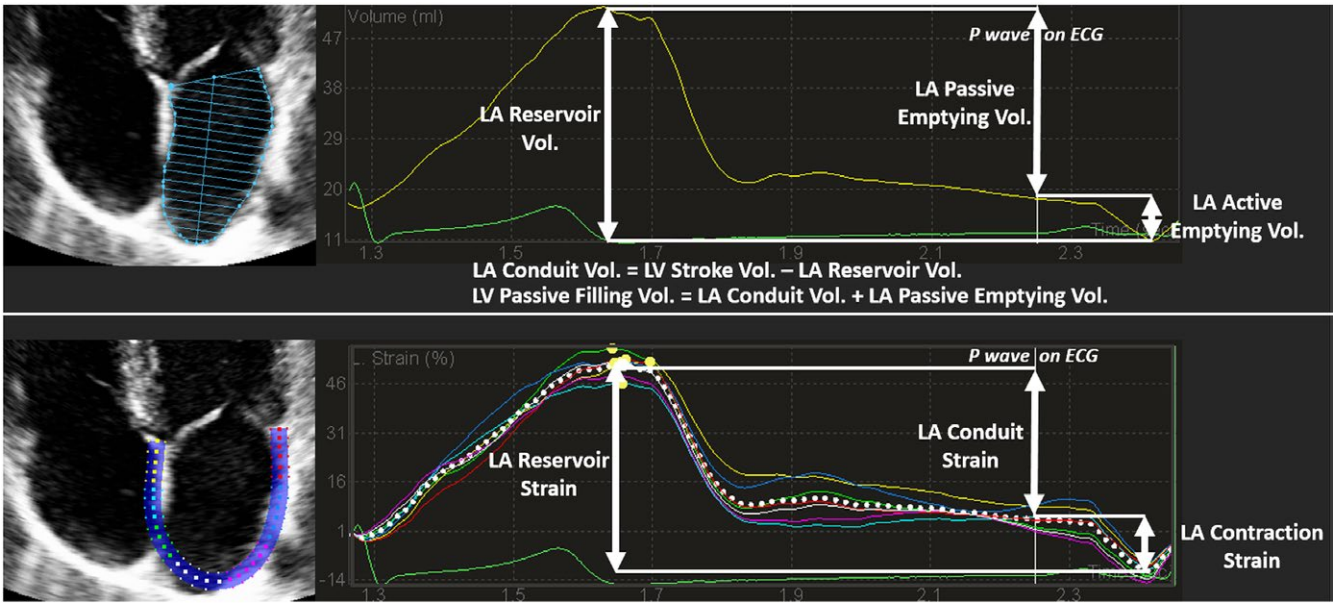

FIGURE 1 Illustration of volumetric- and speckle tracking-derived strain analysis of phasic left atrial function

rate (HR) during the examination. All images were saved in a raw Digital Imaging and Communications in Medicine (DICOM) format on a mass storage device and analyzed offline using commercially available software (Philips Xcelera, Phillips Medical Systems, Andover, MA, USA).

The following biplane volumetric indices of LV and LA function were calculated according to current recommendations[20,21]: LV volumes were measured at end-diastole (LVEDV) and end-systole (LVESV) allowing for calculation of LV SV and ejection fraction (EF). LA volumes were measured at three time points (see Figure 1): (a) the maximal volume (LAV_{max}) just before the opening of the mitral valve, (b) pre-atrial contraction volume (LAV_{preA}), obtained at the onset of the P-wave on surface electrocardiogram, and (c) the minimal volume (LAV_{min}) at the closure of the mitral valve. LA reservoir volume (ie, LA stroke volume (LASV)) was calculated as the difference between LAV_{max} and LAV_{min}, LA passive emptying volume as the difference between LAV_{max} and LAV_{preA}, and LA active emptying (ie, LV active filling volume) volume as the difference between LAV_{preA} and LAV_{min}, respectively. We calculated conduit volume, representing the flow from the pulmonary veins to the LV, as the difference between LVSV and LA reservoir volume. The sum of LA passive emptying volume and LA conduit volume was calculated to define LV passive filling volume. LAV_{max} indexed (LAVI) to body surface area (BSA) was measured and used as a surrogate for increased LV filling pressure.[7] BSA was derived from the formula of Mostseller: $BSA = 0.01666667 \text{ body height}^{-0.5} \text{ body weight}^{-0.5}$.

Conventional Doppler and Tissue Doppler Images (TDI) were obtained from the apical 4-chamber view. At least three cardiac cycles were averaged for assessment of all peak indices. Maximum tricuspid regurgitation velocity was obtained in the RV inflow projection of the parasternal long-axis view, the parasternal short-axis view, and the apical 4-chamber view. The best Doppler envelope was used to calculate the right atrial to right ventricular pressure gradient using the modified Bernoulli Equation.[22] For calculation of sPAP, 5 mm Hg for the estimated RA were added to tricuspid pressure gradients.[23] For pulsed-wave Doppler assessment of trans-mitral flow, the ultrasound beam was placed between the mitral leaflet tips in order to obtain peak early (E) and late diastolic (A) flow velocities. For TDI assessment of peak early diastolic (e'), late diastolic (a'), and systolic (s') myocardial velocities, ultrasound beam was aligned to the longitudinal motion of the basal septum and basal lateral wall of the LV. The E/e' ratio was used as an additional surrogate for the multiparametric approach of LVEDP estimation.[7]

Longitudinal STE-derived strain measurements for LV and LA derived from the apical 4-chamber view. The researcher optimized image quality by positioning the focus at the region of interest and adjusting sector depth and width to include as little as possible outside the region of interest in order to maintain a frame rate between 50-80/min. The same researcher performed offline analyses using a commercially available acoustic tracking software package (QLAB 9 (cardiac motion quantification (CMQ); Phillips Medical Systems, Andover, MA, USA)). Thereby, the region of interest was set at the myocardium using a point-and-click technique and the software divided the LV and LA walls into six equidistant segments. Orifices of the pulmonary veins and segments in which inadequate tracing was observed were excluded from further analysis, and the remaining segments were averaged. Before processing, a cine loop preview was

used to confirm that speckles remained within the myocardium throughout the cardiac cycle, and additional manual adjustment was performed when myocardial tracking was unsatisfactory. The frame at the onset of the R-wave was used as the reference frame. Peak, pre-atrial contraction, and minimal strain values were derived from the maximal inflection point, the point correlating with the onset of the P-wave on surface ECG and the minimal inflection point on the LA strain curve, respectively. Consequently, 2D-STE-derived atrial reservoir-, conduit-, and contractile-strains were calculated as illustrated in Figure 1. We already demonstrated high intra- as well as interobserver reliability of these variables in our laboratory.[11]

Increased LVEDP was defined using recommended variables and cutoffs using a multiparametric approach: (a) LAVI>34 mL/m2, (b) E/e'>14, (c) e' med <7 cm/s or e' lat <10 cm/s. Increased sPAP could not be used as an estimate for increased LVEDP as recommended at sea level because in hypoxic conditions, its increase is considered physiologic. Therefore, (d) STE-derived LA reservoir strain was calculated as an additional parameter and <29% defined as the cutoff.[13] As recommended in individuals with normal EF, if <50% of the parameters were positive, LVEDP diastolic function were assessed as normal, if 50% were positive as indeterminate, and in case >50% of the parameters were positive as diastolic dysfunction and increased LVEDP.[7]

2.4 | Statistical analysis

Continuous variables are presented as means±SD. Effects of altitude and treatments were analyzed by 2-way repeated-measures ANOVA with altitude and treatment as within-subject factors, after confirmation of normal distribution using the Shapiro-Wilk test. Partial eta squared (ηp^2) was calculated to estimate effect sizes for ANOVA calculations. The relationship between pairs of variables was expressed with the Pearson (r) Correlation Coefficient, and effect sizes of correlation were defined as follows: trivial, 0.0; small, 0.1-0.3; moderate, 0.3-0.5; large, 0.5-0.7; very large 0.7-0.9; nearly perfect 0.9, and perfect 1.0.[24] A P-value ≤ 0.05 (two-sided) was considered to be significant. All statistical analyses were performed using SPSS 19 for Windows (SPSS, Inc, Chicago, IL).

3 | RESULTS

Baseline characteristics of the participants are outlined in Table 1. In 62% of the subjects, AMS developed of which four developed severe AMS and were excluded from the study because of necessary oxygen treatment and its potential effect on sPAP and LV function. Thus, data of 46 participants were available for final analyses.

TABLE 1 Physical characteristics of the study population

Variables	n = 46
Male	34
Age (y)	36 ± 11
Body height (cm)	176 ± 9
Body weight (kg)	72 ± 10
BMI (kg/m^2)	20.3 ± 2.3
BSA (m^2)	1.9 ± 2.2
HR at rest (beats/min)	64 ± 11
Systolic BP at rest (mm Hg)	123 ± 12
Diastolic BP at rest (mm Hg)	72 ± 7
Maximal exercise capacity (W/kg)	4.2 ± 0.5

BMI, body mass index; BSA, Body surface area; HR, heart rate; BP, blood pressure; W, Watt.
Values are presented as arithmetic mean ±SD or number of participants.

3.1 | Inhaled budesonide and echocardiographic variables of cardiac function

Inhalation of budesonide did not have any systemic effects (assessed by plasma cortisol and ACTH levels)[14] nor did it affect physiological variables (Table S1, online supplement). At baseline, and thus before administration of the study drug, there was a statistically significant group difference in some Doppler-derived LV diastolic filling (E, E/A ratio, and e') estimates (Table S1, online supplement). These differences persisted at high altitude and were not affected by budesonide (all P$tx group \geq 0.388$). Volumetric- and LA strain parameters did not differ between study groups, neither regarding treatment nor interaction effects (Table S1, online supplement). Therefore, hemodynamic and echocardiographic data of the three study groups were pooled for final analyses.

3.2 | Physiological characteristics

SpO_2 decreased significantly at high altitude, whereas sPAP, HR, and MAP increased significantly following ascent and remained elevated at high altitude (Table 2). %PV was significantly reduced 20 hours after arrival at high altitude compared to baseline (Table 2).

3.3 | Echocardiographic characteristics

3.3.1 | Left ventricular characteristics

Stroke volume decreased and CO increased on arrival at high altitude due to the HR increase. SV remained significantly reduced at subsequent analyses at high altitude (Figure 2), whereas HR and consequently CO remained elevated (Table 3). TDI (s')- and STE-derived longitudinal

TABLE 2 Physiological and hydration parameters at low- and high altitude

	Low Alt	High Alt-7 h	High Alt-20 h	High Alt-44 h	ηp^2
SpO_2 (%)	97 ± 2	78 ± 7*	81 ± 6*	81 ± 7*	0.812
sPAP (mm Hg)	24 ± 4	39 ± 8*	38 ± 9*	38 ± 8*	0.615
HR (beats/min)	64 ± 11	79 ± 14*	77 ± 15*	75 ± 15*	0.425
MAP (mm Hg)	89 ± 6	92 ± 7*	91 ± 6*	92 ± 5*	0.160
% PV change vs baseline	—	+1.8% ± 9.8%	−2.9% ± 8.4%*	−2.0% ± 9.5%	0.092

ηp^2, partial eta square (effect size); HR, heart rate; MAP, mean arterial blood pressure; SpO_2, peripheral oxygen saturation; sPAP, systolic pulmonary artery pressure.
Values are presented as arithmetic mean ± SD
*Significant difference compared to low altitude ($P < 0.05$)

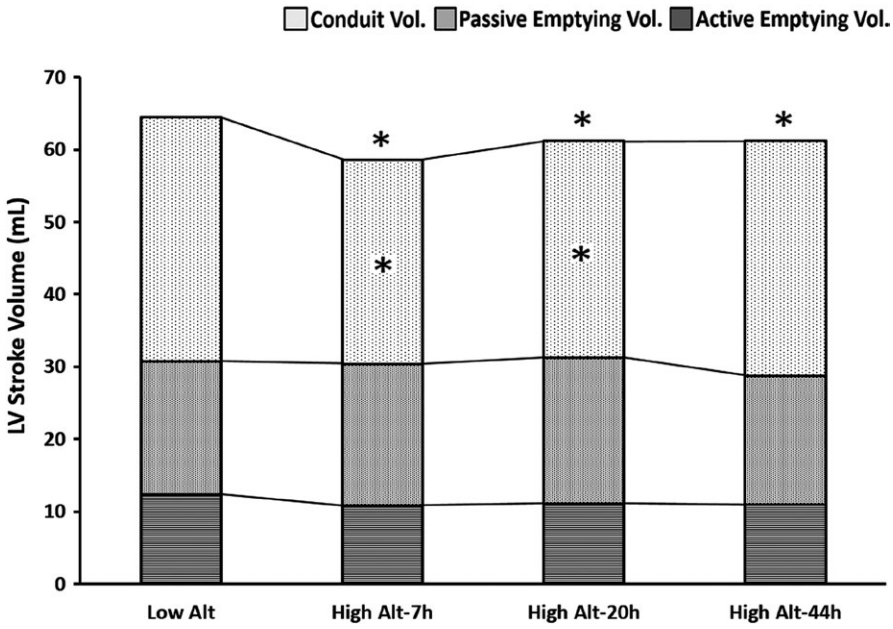

FIGURE 2 Diastolic left atrial volume contribution to left ventricular (LV) stroke volume from baseline examinations at low altitude (Low Alt), 7 h (High Alt-7 h), 20 h (High Alt−20 h), and 44 h (High Alt-44 h) after arrival at high-altitude, respectively. *Significant difference compared to low altitude ($P < 0.05$)

LV contractility indices increased at high altitude, whereas LV EF did not change. The spectral Doppler-derived early to late diastolic LV filling (E/A) ratio decreased significantly due to a significant increase in late diastolic filling (Table 3). TDI-derived E/e' and medial as well as lateral e' as estimates of LVEDP did not change (Table 3).

3.3.2 | Left atrial characteristics

Among the volumetric LA indices, LA conduit volume decreased and remained decreased until the last examination, whereas LA passive emptying volume did not change (Figure 2). Overall, these changes lead to a reduced LV passive filling volume during the first examination at high-altitude (−8.5%; $P = 0.05$), with a trend toward reduced LV passive filling 20 hours after arrival (−5.6%; $P = 0.08$) but was not significantly reduced 44 hours after arrival (−2.9%; $P = 0.20$; Figure 2). Active emptying volumes did not change significantly (Figure 2).

LA reservoir strain increased significantly following ascent and remained elevated at high-altitude. Increase in LA reservoir strain was accompanied by a significant increase in LA conduit strain starting at 20 hours after arrival at high-altitude, whereas LA contraction strain did not change significantly (Table 3).

Using the multiparametric approach for assessing increased LVEDP, only 1 out of 46 participants could be classified as indeterminate diastolic function and none of the participants as LV diastolic dysfunction or increased LVEDP.

3.4 | Correlation analysis

sPAP correlated with moderate effect size with E/A ($r = 0.30$, $P < 0.001$) and A ($r = 0.39$, $P < 0.001$). HR

TABLE 3 Echocardiographic parameters of left ventricular function at low- and high altitude

	Low Alt	High Alt-7 h	High Alt-20 h	High Alt-44 h	ηp^2
LV parameters					
CO (L/min)	4.1 ± 1.1	4.5 ± 1.2*	4.6 ± 1.5*	4.5 ± 1.3*	0.045
LVEDV (mL)	110.2 ± 27.1	100.3 ± 26.9*	100.4 ± 29.8*	104.2 ± 16.1*	0.142
LVESV (mL)	46.2 ± 15.5	42.4 ± 13.3	40.3 ± 13.8*	43.6 ± 16.1	0.096
EF (%)	58.6 ± 6.3	58.2 ± 6.4	60.1 ± 6.1	58.4 ± 7.1	0.040
av LV s'(cm/s)	9.9 ± 1.3	10.9 ± 1.7*	11.1 ± 2.1*	11.0 ± 1.8*	0.150
med LV s'(cm/s)	8.5 ± 1.2	9.4 ± 1.5*	9.7 ± 1.8*	9.8 ± 1.6*	0.203
lat LV s'(cm/s)	11.3 ± 1.9	12.3 ± 2.4*	12.5 ± 2.8*	12.3 ± 2.5*	0.079
LV Long Strain (%)	21.3 ± 2.4	21.4 ± 2.6	21.8 ± 2.4*	22.0 ± 1.9*	0.067
E (cm/s)	70.4 ± 15.8	69.4 ± 15.0	71.7 ± 16.6	68.6 ± 17.3	0.029
E-wave DT (ms)	158.0 ± 17.5	154.9 ± 18.7	154.8 ± 18.5	158.8 ± 17.6	0.029
A (cm/s)	43.4 ± 9.0	53.1 ± 12.2*	52.7 ± 13.8*	49.9 ± 12.1*	0.296
E/A	1.7 ± 0.5	1.4 ± 0.4*	1.4 ± 0.4*	1.5 ± 0.5*	0.211
av LV e' (cm/s)	14.2 ± 2.3	14.8 ± 2.5*	14.5 ± 2.1	14.3 ± 2.0	0.045
med LV e' (cm/s)	12.1 ± 2.0	12.6 ± 2.5	12.3 ± 1.9	11.9 ± 1.8	0.039
lat LV e' (cm/s)	16.2 ± 3.3	17.1 ± 3.4	16.7 ± 2.5	16.7 ± 2.9	0.032
E/e'	5.0 ± 1.0	4.7 ± 0.9*	5.0 ± 0.9	4.8 ± 1.0	0.056
LA parameters					
$LAVI_{max}$ (mL/m^2)	25.7 ± 7.1	23.1 ± 5.8*	23.9 ± 6.0	23.2 ± 6.3*	0.091
LA_{max} volume (mL)	49.0 ± 15.0	43.6 ± 12.9*	45.7 ± 14.2*	44.0 ± 14.5*	0.093
LA_{preA} volume (mL)	30.6 ± 11.9	24.6 ± 9.3*	26.2 ± 9.5*	26.2 ± 11.7*	0.229
LA_{min} volume (mL)	18.2 ± 7.8	13.8 ± 5.5*	15.2 ± 6.4*	15.2 ± 7.4*	0.258
LA stroke volume (mL)	30.8 ± 9.6	29.9 ± 8.7	30.4 ± 9.8	28.8 ± 8.5	0.009
LA reservoir strain (%)	44.6 ± 9.4	49.6 ± 12.6*	51.0 ± 11.7*	50.2 ± 10.6*	0.081
LA conduit strain (%)	27.3 ± 6.9	29.3 ± 9.5	31.7 ± 8.7*	32.4 ± 7.8*	0.122
LA contraction strain (%)	17.2 ± 5.3	20.3 ± 10.2	19.9 ± 7.0	17.8 ± 4.9	0.063

A, pulsed-wave-derived peak late trans-mitral diastolic filling velocity; CO, cardiac output; DT, Deceleration time; E, pulsed-wave-derived peak early trans-mitral diastolic filling velocity; e', pulsed-wave Doppler tissue imaging (DTI)-derived peak early diastolic myocardial velocity; EF, ejection fraction; High alt, high-altitude (4559 m); LA_{max}, Left atrial maximal volume; $LAVI_{max}$, maximal left atrial volume indexed to body surface area; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; Low Alt, low altitude (424 m); min, minimal volume; preA, Volume at the onset of the P-wave on surface electrocardiogram (ie, pre-atrial contraction); s', pulsed-wave Doppler tissue imaging (DTI)-derived peak systolic myocardial velocity.

Values are presented as arithmetic mean ± SD.

*Statistical significance defined as $P < 0.05$.

correlated with moderate effect size with E/A ($r = 0.39$; $P < 0.001$), A ($r = 0.52$; $P < 0.001$), and SpO_2 ($r = 0.42$; $P < 0.001$). Other correlations between changes of physiologic (sPAP, HR, MAP, and PV) and echocardiographic parameters for LV diastolic function (E, e', E/e', LAVI) or LA strain mechanics (LA reservoir, conduit and contraction strain) were trivial or small at best (data not shown). Among echocardiographic variables, longitudinal STE-derived LV strain correlated significantly and with moderate effect size with longitudinal STE-derived LA reservoir strain ($r = 0.30$; $P < 0.001$) and significantly with small effect size with LA conduit- ($r = 0.27$ $P = 0.001$) and LA contraction strain ($r = 0.17$ $P = 0.037$).

4 | DISCUSSION

The main findings of the study are that active and rapid ascent of healthy individuals to 4559 m is associated (a) with reduced SV secondary to reduced LV passive filling volume; (b) consistent LA performance as described by STE-derived LA strain mechanics; and (c) does not increase surrogates of LVEDP.

4.1 | Stroke volume at high altitude

In our study, LVEDV and SV were significantly reduced by 9% and 10% after arrival at high altitude and stayed reduced during the 44-hours stay at4559 m. Three possible mechanisms have

been proposed for the reduction of LV filling and SV at high altitude: (a) impaired LV diastolic and/or systolic function by altered cardiac energy supply,[25] (b) impaired LV diastolic function by altitude-induced pulmonary hypertension,[26] and (c) lower ventricular preload secondary to decreased plasma volume.[27]

With regard to LV systolic function, despite an unaffected *global* systolic function (EF) at high altitude, we observed an increased *longitudinal* motion of the mitral annular plane (s', longitudinal LV strain) that was related to increased HR. These changes are in line with recent and comprehensive studies of LV mechanics in hypoxic conditions.[6,28] Systolic function affects diastolic filling by creating restoring forces. In addition, diastolic filling is affected by LV relaxation and active LA active emptying. Thereof, LV relaxation is the main driving force for blood flow from the LA into the LV during early diastole and is directly challenged in hypoxic conditions due to its energy-dependency. LV relaxation can be assessed non-invasively by assessment of early volumetric filling, Doppler-derived LV filling and tissue displacement analysis. Our results showed a reduction of LV passive filling volume, which in the light of normal systolic LV function, might be due to impaired LV relaxation. In addition, altitude-induced pulmonary hypertension and/or reduction in PV are discussed to cause LV passive filling reduction. Doppler-derived early to late diastolic LV filling (E/A) ratio was reduced at high altitude due to a significant increase in late diastolic filling velocity (A) while early diastolic filling velocity (E), an estimate of LV relaxation, remained unaffected. Doppler-derived LV filling alterations were largely related to an increase in HR while additional variables of early diastolic filling (E-wave deceleration time, e') were not affected suggesting that impaired LV relaxation plays a minor role in the reduction of ventricular filling at high altitude. Of note, Stembridge et al reported an increase in resting systolic as well as diastolic LV mechanics at 5050 m and hypothesized the increase as a mechanism by which further SV reduction is defended.[6] Still, volumetric and speckle tracking-derived phasic LA function were not assessed, and the SV reduction seen in that study was hypothesized to be related to the increased pulmonary artery pressure.

As expected, sPAP increased by 58% in our study. The underlying mechanisms of pulmonary hypertension-related LV diastolic challenge are discussed to be LV myocardial interstitial edema[29] and a shift of the ventricular septum toward the LV.[30] In the present study, we could not demonstrate an impact of altitude-induced pulmonary hypertension at volumetric- and speckle tracking-derived LV filling data by means of correlation analysis.

It is well established that PV is reduced by diuresis when lowlanders are acutely exposed to high altitude in order to rapidly restore arterial oxygen concentration by the resultant hemoconcentration.[31] In contrast, PV expansion occurs with rapid onset following endurance exercise as ascent to high altitude.[32] Recently, in another comprehensive study by Stembridge et al, the decrease in PV (−11% PV change vs baseline) was attributed a major role in regulating LV filling during passive ascent to 3800 m.[27] In our study, PV increased after ascent and was significantly reduced at 20 hours after arrival at high altitude. The magnitude of the reduction (−3% PV change vs baseline) was smaller than predicted for this altitude.[33] This difference can be explained by the impact of PV expansion due to the active ascent in our study and analytical variation as we used the Dill and Costill approach to estimate PV changes while Stembridge et al used the carbon monoxide rebreathing method. Furthermore, water was readily available in our study and our participants refrained from any exercise during the stay at high altitude. Considering the small changes in PV we observed, dehydration and intravascular volume deficit probably played a minor role in LV filling and SV changes.

4.2 | LA mechanics at high altitude

The abovementioned Doppler-derived increase in A has previously been described as *augmented atrial contraction* at high altitude.[3,34] Limitations of the Doppler technique include angle-dependency, dependence on loading conditions and cardiac translational motion. As a result, Doppler-derived late diastolic filling does not necessarily reflect functional atrial properties.[35] Thus, the hypothesis of *augmented atrial contraction* based on Doppler- and volume-derived parameters not only must be questioned but may be answered by assessment of intrinsic myocardial properties, as can be performed with STE-derived strain assessment.[9] To this end, this is the first study using STE-derived strain imaging for the assessment of LA contractile function at high altitude and the results complement existing Doppler-derived data. We did not observe a significant increase in LA contractile performance and our volumetric LA data did not show any change in LA stroke volume and active emptying volume. Thus, in contrast to previous high-altitude studies which described an augmented atrial contraction during Doppler examinations,[3] the LA STE-derived strain and volumetric results of our study point to a consistent LA workload.

4.3 | LVEPD at high altitude

At high altitude, increased LVEDP may add to the physiological increase in PAP and thus contribute to life-threatening HAPE in otherwise healthy individuals. Recently, a multiparametric approach for the echocardiographic assessment of LVEDP has been proposed.[7] In our study, not a single participant reached the criteria for elevated LVEDP at any of the three measurements at high altitude even after adding new STE-derived atrial strain parameters, which has previously been shown to strongly correlate

with invasively measured LVEDP.[12] Our LVEDP results are in line with a study by Maggiorini et al who performed pulmonary artery catheter-derived measurements at 4559 m and reported no change of LVEDP in *non-HAPE*-susceptible individuals, whereas HAPE susceptibles showed a significant increase, that, however, was still within normal range.[36] This observation may be explained by the exaggerated hypoxia-induced pulmonary hypertension of HAPE-susceptible individuals which might impact diastolic mechanics. Still, another explanation might be a silent diastolic dysfunction unmasked at high altitude and thus contributing to increased pulmonary capillary pressure that leads to edema formation.[36] Considering that none of our subjects developed HAPE, future trials may wish to assess to which extent diastolic dysfunction adds to the exaggerated increase in pulmonary capillary pressure present in HAPE-susceptible individuals by using comprehensive echocardiographic imaging.

4.4 | Limitations

This study has several limitations: Invasive right-heart catheterization is considered to be the gold standard method for the assessment of sPAP, LVEDP, and LV diastolic function. In the present study, these data were assessed by comprehensive echocardiography. However, it has repeatedly been shown that echocardiographic and invasive measurements of these parameters are in good agreement.[12,37] Our participants were healthy, physically fit, and only few showed an exaggerated sPAP increase at high altitude without developing HAPE. Thus, our results cannot be extended to individuals with underlying structural heart disease and/or with marked increase in sPAP. In addition, even though it did not occur at rest, LV diastolic dysfunction might occur during exercise like mountaineering at high altitude, which we did not address in this study.

5 | PERSPECTIVE

High-altitude mountaineering and even speed ascents are getting more popular, and in parallel, the number of high-altitude-associated incidents increases. Cardiac function is not only challenged by endurance sports as indicated by the SV reduction following prolonged exercise but also in hypoxic conditions as at high altitude. However, its integrity is of utmost importance in order to adjust cardiac output to atmospheric changes and peripheral metabolic demands. This is the first study investigating alterations in left ventricular diastolic filling as well as atrial mechanics following active and rapid ascent to high altitude of healthy mountaineers. The data provide new evidence for maintained left ventricular diastolic function and left ventricular end-diastolic pressure at high altitude and demonstrate that left ventricular passive filling and stroke volume are reduced. Considering that LV and LA mechanics were not impaired the underlying mechanisms remain speculative but the data indicate that a functional left atrial reserve might be required to maintain diastolic integrity and consequently cardiac output at high altitude. Cardiac function assessment prior to high altitude ascents may have the potential to reduce life-threatening incidents at high altitude and may be indicated for mountaineers who are at increased risk for impaired LV diastolic reserve, as advanced age and cardiac comorbidities like arterial hypertension and atrial fibrillation.

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CONFLICT OF INTEREST

There is no conflict of interest to report. The project was not supported by external funding.

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REFERENCES

1. Holloway C, Cochlin L, Codreanu I, et al. Normobaric hypoxia impairs human cardiac energetics. *FASEB J*. 2011;25(9):3130-3135.
2. Naeije R. Physiological adaptation of the cardiovascular system to high altitude. *Prog Cardiovasc Dis*. 2010;52(6):456-466.
3. Allemann Y, Rotter M, Hutter D, et al. Impact of acute hypoxic pulmonary hypertension on LV diastolic function in healthy mountaineers at high altitude. *Am J Physiol Heart Circ Physiol*. 2004;286(3):H856–H862.
4. Rao M, Li J, Qin J, et al. Left ventricular function during acute high-altitude exposure in a large group of healthy young Chinese men. *PLoS ONE*. 2015;10(1):e0116936.
5. Kjaergaard J, Snyder EM, Hassager C, Olson TP, Oh JK, Johnson BD. The effect of 18 h of simulated high altitude on left ventricular function. *Eur J Appl Physiol*. 2006;98(4):411-418.
6. Stembridge M, Ainslie PN, Hughes MG, et al. Impaired myocardial function does not explain reduced left ventricular filling and stroke volume at rest or during exercise at high altitude. *J Appl Physiol (1985)*. 2015;119(10):1219-1227.
7. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17(12):1321-1360.
8. Andersen OS, Smiseth OA, Dokainish H, et al. Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol*. 2017;69(15):1937-1948.
9. Blume GG, Mcleod CJ, Barnes ME, et al. Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr*. 2011;12(6):421-430.

10. Sirbu C, Herbots L, D'hooge J, et al. Feasibility of strain and strain rate imaging for the assessment of regional left atrial deformation: a study in normal subjects. *Eur J Echocardiogr*. 2006;7(3):199-208.
11. Sareban M, Perz T, Macholz F, et al. Reliability of echocardiographic speckle-tracking derived bi-atrial strain assessment under different hemodynamic conditions. *Int J Cardiovasc Imaging*. 2017;33(11):1685-1692.
12. Cameli M, Sparla S, Losito M, et al. Correlation of left atrial strain and doppler measurements with invasive measurement of left ventricular end-diastolic pressure in patients stratified for different values of ejection fraction. *Echocardiography*. 2016;33(3):398-405.
13. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA strain categorization of LV diastolic dysfunction. *JACC Cardiovasc Imaging*. 2016;10(7):735-743.
14. Berger MM, Macholz F, Sareban M, et al. Inhaled budesonide does not prevent acute mountain sickness after rapid ascent to 4559 m. *Eur Respir J*. 2017;50(3):1700982.
15. Beidleman BA, Muza SR, Fulco CS, Rock PB, Cymerman A. Validation of a shortened electronic version of the environmental symptoms questionnaire. *High Alt Med Biol*. 2007;8(3):192-199.
16. Roach RC, Bartsch P, Hackett PH, Oelz OLake Louise AMS Scoring Consensus Committee. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G eds. Hypoxia and Molecular Medicine. Proceedings of the 8th International Hypoxia Symposium Held at Lake Louise, Canada, February 9–13, 1993. Burlington, VT: Queen City Printers; 1993:272–274. 1993.
17. Bailey DM, Dehnert C, Luks AM, et al. High-altitude pulmonary hypertension is associated with a free radical-mediated reduction in pulmonary nitric oxide bioavailability. *J Physiol*. 2010;588(Pt 23):4837-4847.
18. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol*. 1974;37(2):247-248.
19. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr*. 2011;12(3):167-205.
20. Todaro MC, Choudhuri I, Belohlavek M, et al. New echocardiographic techniques for evaluation of left atrial mechanics. *Eur Heart J Cardiovasc Imaging*. 2012;13(12):973-984.
21. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270.
22. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685–713; quiz 786–688.
23. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation*. 1984;70(4):657–662.
24. Hopkins WG. Measures of reliability in sports medicine and science. *Sports Medicine*. 2000;30(1):1–15.
25. Alexander JK, Grover RF. Mechanism of reduced cardiac stroke volume at high altitude. *Clin Cardiol*. 1983;6(6):301–303.
26. Stembridge M, Ainslie PN, Hughes MG, et al. Ventricular structure, function, and mechanics at high altitude: chronic remodeling in Sherpa vs. short-term lowlander adaptation. *J Appl Physiol (1985)*. 2014;117(3):334–343.
27. Stembridge M, Ainslie PN, Boulet LM, et al. The independent effects of hypovolaemia and pulmonary vasoconstriction on ventricular function and exercise capacity during acclimatisation to 3800 m. *J Physiol*. https://doi.org/10.1113/JP275278. [Epub ahead of print].
28. Dedobbeleer C, Hadefi A, Naeije R, Unger P. Left ventricular adaptation to acute hypoxia: a speckle-tracking echocardiography study. *J Am Soc Echocardiogr*. 2013;26(7):736–745.
29. Davis KL, Mehlhorn U, Laine GA, Allen SJ. Myocardial edema, left ventricular function, and pulmonary hypertension. *J Appl Physiol (1985)*. 1995;78(1):132–137.
30. Morris-Thurgood JA, Frenneaux MP. Diastolic ventricular interaction and ventricular diastolic filling. *Heart Fail Rev*. 2000;5(4):307–323.
31. Siebenmann C, Hug M, Keiser S, et al. Hypovolemia explains the reduced stroke volume at altitude. *Physiol Rep*. 2013;1(5):e00094.
32. Fellmann N. Hormonal and plasma volume alterations following endurance exercise. *A brief review. Sports Med*. 1992;13(1):37–49.
33. Beidleman BA, Staab JE, Muza SR, Sawka MN. Quantitative model of hematologic and plasma volume responses after ascent and acclimation to moderate to high altitudes. *Am J Physiol Regul Integr Comp Physiol*. 2017;312(2):R265–R272.
34. Boussuges A, Molenat F, Burnet H, et al. Operation Everest III (Comex ' 97): modifications of cardiac function secondary to altitude-induced hypoxia. An echocardiographic and Doppler study. *Am J Respir Crit Care Med*. 2000;161(1):264–270.
35. Mitter SS, Shah SJ, Thomas JD. A test in context: E/A and E/e' to assess diastolic dysfunction and LV filling pressure. *J Am Coll Cardiol*. 2017;69(11):1451–1464.
36. Maggiorini M, Mélot C, Pierre S, et al. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation*. 2001;103(16):2078–2083.
37. Allemann Y, Sartori C, Lepori M, et al. Echocardiographic and invasive measurements of pulmonary artery pressure correlate closely at high altitude. *Am J Physiol Heart Circ Physiol*. 2000;279(4):H2013–H2016.
38. Fritzsche RG, Switzer TW, Hodgkinson BJ, Coyle EF. Stroke volume decline during prolonged exercise is influenced by the increase in heart rate. *J Appl Physiol*. 1999;86(3):799–805.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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