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Ventricular structure, function and mechanics at high altitude: chronic remodelling in Sherpa verses short-term lowlander adaptation.

Mike Stembridge[1]; Philip N. Ainslie[2], Michael G. Hughes[1], Eric J. Stöhr[1], James D. Cotter[3], Amanda Q. X. Nio[1] and Rob Shave[1].

[1]Cardiff School of Sport, Cardiff Metropolitan University, Cardiff, UK. [2]School of Health and Exercise Sciences, University of British Columbia Okanagan Campus, Kelowna, Canada. [3]School of Sport and Exercise Sciences, University of Otago, Dunedin, New Zealand.

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Correspondence to: Mike Stembridge, Cardiff Metropolitan University, School of Sport, Cardiff, CF23 6XD, UK. Tel: +44 2920 416593. Email: mstembridge@cardiffmet.ac.uk

Author Contributions

M.S, P.N.A and R.S contributed to the conception and design of the experiment, interpretation and drafting of the manuscript. J.D.C, M.G.H, E.S and A.Q.X.N contributed to the data analysis, interpretation and critical revision of the manuscript. Data collection was performed by M.S, P.N.A and J.D.C. All authors have approved the final version of the manuscript.

Abstract

Short-term high altitude (HA) exposure raises pulmonary artery systolic pressure (PASP) and decreases left ventricular (LV) volumes. However, relatively little is known of the long-term cardiac consequences of prolonged exposure in Sherpa, a highly-adapted HA population. To investigate short-term adaptation and potential long-term cardiac remodelling, we studied ventricular structure and function in Sherpa at 5050 m (n=11; 31±13 y, mass 68±10 kg, height 169±6 cm) and lowlanders at sea level (SL) and following 10±3 d at 5050 m (n=9; 34±7 y, mass 82±10 kg, height 177±6 cm) using conventional and speckle-tracking echocardiography. At HA, PASP was higher in Sherpa and lowlanders when compared to lowlanders at SL (both $P<0.05$). Sherpa had smaller right ventricular (RV) and LV stroke volumes than lowlanders at SL with lower RV systolic strain ($P<0.05$) but similar LV systolic mechanics. In contrast to LV systolic mechanics, LV diastolic untwisting velocity was significantly lower in Sherpa when compared to lowlanders at both SL and HA. After partial acclimatization, lowlanders demonstrated no change in RV end-diastolic area, however both RV strain and LV end-diastolic volume were reduced. In conclusion, short-term hypoxia induced a reduction in RV systolic function that was also evident in Sherpa following chronic exposure. We propose this was consequent to a persistently higher PASP. In contrast to the RV, remodelling of LV volumes and normalization of systolic mechanics indicate structural and functional adaptation to HA. However, altered LV diastolic relaxation after chronic hypoxic exposure may reflect differential remodelling of systolic and diastolic LV function.

Key words:

Hypoxia; Cardiac Remodelling; Ventricular mechanics; Sherpa.

Introduction

High altitude (HA) exposure challenges the cardiovascular system to meet the metabolic demand for oxygen (O_2) in an environment where arterial O_2 content is markedly reduced. The drop in arterial O_2 has both direct and indirect consequences for the heart, including depressed inotropy of cardiac muscle (40, 44), changes in blood volume and viscosity and vasoconstriction of the pulmonary arteries (33). Despite these broad physiological changes, which have been previously reviewed (28, 49), there is evidence that the heart copes relatively well at high altitude (29, 34).

Short-term HA exposure in lowland natives is characterised by a decreased plasma volume, an increased sympathetic nerve activity and pulmonary vasoconstriction (17, 30, 37), all of which have considerable impact on cardiac function and, in time, could stimulate cardiac remodelling. Himalayan native Sherpa, who are of Tibetan lineage and have resided at HA for approximately 25,000 years (2), are well adapted to life at HA demonstrating greater lung diffusing capacity (11) and an absence of polycythaemia in comparison to acclimatised lowlanders (4). Previous studies have also reported Sherpa to have higher maximal heart rates and only moderate pulmonary hypertension in comparison to lowlanders at HA (11, 25). Due to their longevity at HA, Sherpa provide an excellent model to investigate the effects of chronic hypoxic exposure. Despite this, neither the acute nor life-long effects of HA on right *and* left ventricular structure and function have been fully assessed in lowlanders or the unique Sherpa population.

Due to the unique arrangement of myofibres, cardiac form and function are intrinsically linked as reflected in the cardiac mechanics (left ventricular twist and rotation and ventricular strain) that underpin ventricular function. In response to altered physiological demand, ventricular mechanics acutely change (16, 41) and chronically remodel (31, 42) in order to reduce myofibre stress and achieve efficient ejection (5, 47). Therefore, concomitant examination of myocardial mechanics and ventricular structure in both the acute and chronic HA setting will provide novel insight into human adaptation to hypoxia.

To investigate the effects of chronic hypoxic exposure, we compared ventricular volumes and mechanics in Sherpa at 5050 m with lowlanders at sea level. In addition, to reveal potential stimuli for remodelling and to examine the time course of adaptation, we also compared Sherpa to lowlanders after short-term HA exposure.

We hypothesised that (i) Sherpa would exhibit smaller left ventricular (LV) volumes and a higher right (RV) to left ventricular ratio (RV/LV) than lowlanders at sea level, (ii) LV mechanics in Sherpa will closely resemble those of lowlanders at sea level and (iii) following partial acclimatization to HA, LV volumes would be reduced in lowlanders and LV mechanics acutely increased.

Methods

Study Participants and Design

All experimental procedures and protocols were approved by the Clinical Research Ethics Board at the University of British Columbia and the Nepal Health Medical Research Council, and conformed with the Declaration of Helsinki. Eleven Caucasian male lowlanders (34±7 years) and eleven Nepalese male highland Sherpa (31±13 years) provided informed consent and volunteered to participate in the study. Four weeks prior to departure, Caucasian participants underwent a thorough transthoracic echocardiographic assessment (TTE) close to sea level (SL; Kelowna, Canada; 344 m) and then after 10 ± 3 days at the Ev-K2-CNR Pyramid Laboratory (Lobuche, Nepal; 5050 m). One lowlander was excluded due to poor acoustic windows and a second due to significant non-altitude related illness. Sherpa were assessed at 5050 m only. All participants were free from respiratory and cardiovascular disease and were not taking any prescription medications. The native Sherpa participants originated from, and were residents of the Khumbu Valley at an altitude greater than 3000 m and self-identified to be of Sherpa ethnicity. None of the Sherpa had travelled below 3000 m for at least 6-months prior to testing. Although it was not possible to rigorously assess physical activity, it is our belief that Sherpa and lowlander participants were relatively comparable in this regard, with Sherpa making their living through expedition trekking and lowlanders engaging in frequent recreational activity.

Stature, mass, blood pressure and oxygen saturation (SaO_2) were recorded prior to each TTE. Venous blood samples were taken from lowlanders to assess total haemoglobin (HemoCue®, Ängelholm, Sweden) concentration and haematocrit (Micro Haematocrit Reader) to approximate changes in plasma volume (PV) (9), assuming that erythropoiesis would have only minor effects in the timeframe of our study (37). After travel to Nepal and four nights in Kathmandu (1400 m), the participants flew to Lukla (2800 m) and began a ten-day ascent to the Pyramid Research Centre (5050 m). During the following nine days, a cautious ascent profile was adopted with no more than 300 m net gain in altitude per day. To aid acclimatization, three full rest days with no net change in altitude were included in the ten-day ascent.

Transthoracic Echocardiography

All echocardiographic images were recorded on a commercially available portable ultrasound system (Vivid q, GE Medical Systems, Israel Ltd) using a 1.5-4 MHz phased array transducer. Images were captured by the same highly trained cardiac sonographer with the participant lying in the left lateral decubitus position. Following 10 minutes of supine rest, parasternal long- and short-axis images and apical four chamber views were recorded at end-expiration and three consecutive cardiac cycles were stored for offline analysis (Echopac, GE Medical, Horten, Norway). Heart rate (HR) was recorded via ECG.

Ventricular Structure

Left ventricular wall thickness and internal diameter were measured from the 2D parasternal long-axis view. Left ventricular mass was calculated using the current American Society of Echocardiography guidelines and relative wall thickness was defined as [(2 x LV posterior wall thickness)/LV internal diameter] (26). Systolic and diastolic eccentricity index was calculated from the parasternal short-axis view at the mitral valve level to assess the impact of RV pressure increase on LV shape (39). Left ventricular end-systolic volume (ESV), end-diastolic (EDV) volume and LV ejection fraction were calculated from planar tracings of the LV endocardial border in the apical four- and two-chamber views (Simpson's biplane approach) (26). Left ventricular end-diastolic length was also measured using an apical four-chamber view and defined as the distance from the mitral valve hinge point plane to the most distal endocardium at the apex of the LV. Right ventricular end-diastolic area (EDA) was calculated by tracing the endocardial border from a modified apical four-chamber orientation. Right Ventricular basal diameter was also recorded from an apical four-chamber view (38) and divided by LV basal diameter to obtain the ratio of RV/LV diameter (RV/LV).

Scaling of Cardiac Parameters

To account for the potential influence of body size, cardiac parameters were allometrically scaled for height. The data were tested for the appropriateness of ratiometric scaling (3) and discounted if the coefficient of variation for height divided by the coefficient of variation for the cardiac parameter was not equal to the Pearson's product moment correlation between the two variables (43). To determine whether the data could be grouped to derive a single exponent, an analysis of covariance (ANCOVA) was performed. As the exponents for

lowlanders and Sherpa were similar, a common exponent was calculated for each parameter and used to scale structural and volume parameters.

Systolic Function

Left ventricular stroke volume (SV) was calculated as EDV-ESV and multiplied by HR for cardiac output. Right ventricular SV was obtained by placing a sample volume in the RV outflow tract (RVOT) from a parasternal short axis to obtain the velocity time integral. This was then multiplied by the cross sectional area of the RVOT measured from the same view. Tissue Doppler imaging (TDI) was used to assess peak LV and RV myocardial velocity during systole (S') with the sample volume placed in the basal septum and RV free wall, respectively. M-mode echocardiography was used to assess the tricuspid annular plane systolic excursion (TAPSE) (22). The pulmonary vascular response was quantified as the peak systolic tricuspid regurgitation jet velocity (V) recorded in an apical 4-chamber view using continuous wave Doppler and the right ventricle (RV) to right atrium (RA) pressure gradient was calculated using the simplified Bernoulli equation ($4V^2$). With the addition of RA pressure, estimated using collapsibility index of the inferior vena cava, pulmonary artery systolic pressure (PASP) was also calculated (38).

Diastolic Function

Pulsed-wave Doppler recordings were obtained to assess transmitral early (E) and late (A) diastolic filling velocities from an apical 4-chamber view with the sample volume placed between the tips of the open mitral valve. From the TDI traces described above, peak early diastole (E') and late diastole (A') were identified and isovolumic relaxation time (IVRT) was assessed as previously described (1).

Ventricular Mechanics: Strain, Rotation and Twist

Left ventricular circumferential strain, LV rotation and their time derivatives strain rate and rotational velocity were assessed from parasternal short-axis views obtained from the LV base at the level of the mitral valve and the LV apex. The LV apex was defined as the point

just above end-systolic luminal obliteration and obtained by moving the transducer 1-2 inter-costal spaces caudally from the basal position to align with the apical short-axis (46), keeping the LV cross-section as circular as possible. Left ventricular and RV longitudinal strain and strain rate were analyzed from an apical 4-chamber view. Images were acquired with the highest possible frame rate (>70 frames per second) and kept constant for repeat examinations. All images were analyzed off-line using 2-D speckle tracking analysis to assess global rotation, rotational velocity, strain, strain rate and to calculate LV twist and untwist ('LV mechanics') (Echopac, GE Medical, Horten, Norway, V110.1.1). In order to time align and adjust for inter- and intra-individual variability of heart rate and frame rate, post-processing was completed as previously described (41, 42). Briefly, raw frame-by-frame data were exported to bespoke software (2D Strain Analysis Tool, Stuttgart, Germany) and cubic spline interpolation was applied. Twist variables were calculated by subtracting the apical frame-by-frame data from the basal data. The time it took to achieve peak: twist, twisting velocity, rotation, rotational velocity, strain and strain rate from the onset of systole was expressed as a percentage of the cardiac cycle. Peak basal rotation during isovolumic contraction was defined as the peak counter clockwise basal rotation during early systole. For analysis and interpretation of diastolic mechanics, untwist was expressed as the percentage of peak twist to normalise for differences in absolute peak twist (32). Peak untwisting velocity has previously been shown to provide an accurate and reproducible measure of diastolic function, and has been validated against invasive measures of LV chamber stiffness (50). Untwist data were analyzed up to 50% diastole as previously reported (45). To account for differences in absolute (ms) and relative (% diastole) differences in IVRT, percentage untwist was expressed relative to IVRT.

Statistical Analyses

Comparison of lowlander and Sherpa was performed using independent samples *t*-test. The two lowlander conditions were analyzed using paired samples *t*-tests. For detailed analysis of untwisting mechanics, a mixed-design repeated measures analysis of variance (ANOVA) was used. Alpha was set *a priori* to 0.05. All statistical analyses were performed using the Statistical Package for Social Science software (SPSS for Windows 19.0, Chicago, Il, USA).

Results

Hemodynamics

Sherpa exhibited higher systemic and pulmonary systolic pressure and a lower SaO_2 in comparison to lowlanders at sea level (Table 1). Heart rate was higher in Sherpa than lowlanders at sea level and HA. Once lowlanders had partially acclimatised to HA, differences in hemodynamics and oxygen saturation were no longer evident (Table 1). High altitude exposure in lowlanders was associated with a significant increase in haematocrit (47 ± 2 vs. 59 ± 5 %, $P<0.01$) and haemoglobin concentration (15.1 ± 0.7 vs. 15.9 ± 0.6, $P<0.05$), from which a 20 ± 7 % decrease in PV was estimated.

Ventricular Structure

Following scaling, Sherpa demonstrated smaller wall thicknesses, LV mass and ventricular volumes in comparison to lowlanders at sea level with no between-group differences in relative wall thickness observed (Table 2). Sherpa had a similar eccentricity index to lowlanders at HA, however both were moderately higher than lowlanders at sea level ($P<0.05$). After exposure to HA, lowlanders reported a reduced LV EDV and LV mass, meaning differences observed between lowlanders at sea level and Sherpa were no longer evident. Despite a reduction in LV EDV and PV, lowlanders reported no change in RV EDA.

Systolic Function

When compared to lowlanders at sea level, Sherpa demonstrated a lower SV ($P<0.05$) however there were no significant differences in ejection fraction or cardiac output. Right ventricular systolic performance, as measured by TAPSE, was lower in Sherpa compared to lowlanders at sea level. There were no differences in RV or LV SV between Sherpa and lowlanders at 5050 m.

Diastolic Function

Sherpa exhibited a lower early transmitral velocity, elevated atrial contribution to LV filling and lower E' compared to lowlanders at sea level. Additionally, both LV and RV IVRT were longer in Sherpa and lowlanders at 5050 m (Table 3) compared to lowlanders at sea level.

Ascent to HA reduced the ratio of early to late transmitral filling (E/A ratio) and tissue (E'/A') velocities in lowlanders.

Ventricular Mechanics: Strain, Rotation and Twist

Systolic Mechanics

(i) Left ventricular

For simplicity we report LV twist and not LV torsion, as normalising for LV length did not alter the results. When Sherpa were compared to lowlanders at sea level, the pattern of LV mechanics was similar showing no statistical differences other than a longer time to peak LV systolic longitudinal strain in Sherpa (Figure 1;Table 4). However, at 5050 m basal rotation was greater and apical rotation lower in the Sherpa, but there was no difference in peak twist. This difference in basal and apical rotation between Sherpa and lowlanders at 5050 m can be explained by acute changes in lowlander mechanics following short-term HA exposure. Peak systolic basal rotation was approximately halved and rotation during isovolumic contraction (IVC) doubled after partial acclimatization (Figure 1; Table 4). In contrast to the base, apical; rotation, systolic rotational velocity, circumferential strain and strain rate were all increased (Figure 1; Table 4).

(ii) Right ventricular

In Sherpa, peak RV longitudinal strain was lower and occurred later in the cardiac cycle when compared to lowlanders at sea level ($P<0.05$). Following short-term HA exposure, lowlanders reported a reduction in peak RV longitudinal strain meaning the difference between lowlanders and Sherpa observed at sea level was no longer evident (Table 4; Figure 2).

Diastolic Mechanics

Despite the same peak twist, Sherpa showed a lower peak untwisting velocity than lowlanders at both sea level and 5050 m (Figure 1, see annotation). Relative to peak twist, Sherpa achieved significantly less untwisting during the first 45% of diastole than either of the lowlander conditions (Figure 3). However, when considered relative to the longer IVRT observed in Sherpa, no differences in the percentage of untwist prior to mitral valve opening

were evident. Time to peak LV diastolic strain rate was longer in Sherpa than lowlanders at sea level, but not different at 5050 m. Additionally, time to peak RV diastolic strain rate was longer in Sherpa and lowlanders at 5050 m compared to lowlanders at sea level (Figure 2).

Discussion

The purpose of this study was to assess the impact of chronic hypoxic exposure on cardiac structure and function in HA Sherpa residents through comparison with lowlanders at sea level and after short-term HA exposure. The main findings were: (i) Sherpa have smaller relative left ventricular size compared to lowlanders at sea level yet no difference in the RV/LV area ratio; (ii) Sherpa exhibited slower diastolic relaxation and similar systolic mechanics in comparison to lowlanders at sea level; (iii) in lowlanders, short-term HA exposure resulted in increased PASP, reduced RV strain and SV and a mismatch between right and left ventricular filling; and (iv) acute changes in loading conditions and an increase in PASP lead to a differential response in LV mechanics at the base and apex.

Comparison of Cardiac Structure and Function in Sherpa and Lowlanders

Sherpa are renowned for their superior exercise and mountaineering performance (12). In sea level athletes, higher levels of aerobic fitness normally coincide with a large LV EDV thus enabling a larger SV (24). However, cross-sectional comparison in the present study revealed smaller absolute and relative LV size in Sherpa when compared to lowlanders at sea level. Whilst cross-sectional comparisons cannot establish cause and effect, it is tempting to speculate that the lower RV systolic function observed may result in decreased LV filling and act as a stimulus for structural remodelling and could determine cardiac development in HA natives. This hypothesis is partially supported by findings in pulmonary hypertension patients, where a reduced RV function has been shown to decrease LV filling (27) which ultimately results in ventricular remodelling and a smaller LV (7). It should, however, be noted that despite a decrease in our load-dependent measures of RV systolic function, intrinsic contractility is often preserved in high attitude populations, even in patients with chronic mountain sickness (34). This suggests that the alterations in RV longitudinal function observed previously (21) and in the current study likely reflect altered loading conditions rather than pathological dysfunction.

To generate the required cardiac output with a smaller LV and hence SV, heart rate needs to be higher. In agreement with this, previous authors have shown a greater maximal heart rate in Sherpa compared to lowlanders at HA (25). Therefore, whilst cardiac output may be similar between Sherpa and lowlanders, the way in which it is achieved could differ.

Although we observed a smaller LV EDV in Sherpa compared to lowlanders, Sherpa did not demonstrate a statistically significantly larger RV/LV area ratio (P=0.2). This finding is in contrast to the short-term HA response in lowlanders and also Andean HA natives (21). Although this contradicts our hypothesis, and may be related to limited statistical power, it is also possible that it reflects genetic differences between ethnic groups. Tibetans have been shown to exhibit a lower incidence of RV hypertrophy than other ethnic groups who have migrated to and reside at HA (15). As such, it is possible that Sherpa do not demonstrate the disproportionate increase in RV size seen in other populations.

Impaired Diastolic Relaxation and Comparable LV Systolic Mechanics in Sherpa compared to Lowlanders at Sea Level

Modification of diastolic function at HA has been widely reported in the literature with a decrease in both LV and RV E/A ratio as the most common finding (8, 21). Researchers have speculated that either changes in intrinsic properties such as calcium handling or ATP availability, or loading conditions modify diastolic function (19-21, 23). In the present study we examined myocardial mechanics to assess the impact of HA exposure on diastolic function. Temporal analysis of our data shows that in Sherpa, peak RV and LV longitudinal systolic strain occurred during early diastole. This is in contrast to lowlanders at sea level where peak longitudinal strain immediately precedes pulmonary and aortic valve closure. Our results support the work of Gibbs (14) who suggested that increased pulmonary pressures at HA impact LV filling by prolonging the systolic ejection time.

While Sherpa achieved less untwisting during early diastole compared to lowlanders at sea level or HA, IVRT was significantly longer and the percentage of untwist preceding mitral valve opening was not different (Figure 3; annotation). Lower untwist during early diastole, as seen in healthy ageing (45), and prolongation of IVRT may reflect a smaller, stiffer LV in Sherpa. In combination, delayed systolic and diastolic longitudinal strain, prolongation of IVRT, and slower untwist velocity suggest altered diastology. Interestingly, despite a longer IVRT in lowlanders at HA, greater untwisting during early diastole was achieved compared to Sherpa. This may represent an acute response to the lower LV filling pressure and greater systolic apical rotational velocity, which over time may act as a stimulus for chronic remodelling.

As shown in Figure 1, lowlanders demonstrate rapid changes in systolic mechanics after ascent to HA. It is known that LV mechanics adjust in response to altered hemodynamics to optimise efficiency and equalize fibre stress across the myocardium (47). The profile of systolic LV mechanics in Sherpa, however, is more comparable to lowlanders at sea level than at HA. As mechanical stress is linearly related to myocardial oxygen demand (6), changes in LV mechanics could represent altered myocardial efficiency. In this context, the heart of lowlanders at HA may be inefficient initially. However, prolonged exposure, as experienced by Sherpa, may result in remodelling of the ventricular wall, normalization of mechanics and improved myocardial efficiency. Moreover, as there are no differences in relative wall thickness between lowlanders and Sherpa, it would appear the Sherpa LV is not exposed to a greater stress than that of lowlanders. Previously we have shown the importance of a mechanical reserve in response to exercise in healthy lowlanders at sea level (41). The 'normalised' systolic mechanics in Sherpa may facilitate this reserve, which is likely absent during acute HA exposure due to higher resting levels of twist, rotation and strain. Whilst systolic mechanics appear to normalise, diastolic mechanics suggest impaired relaxation. However, it is interesting that the higher untwisting velocity observed in lowlanders at 5050 m is not able to facilitate LV filling and increase EDV, suggesting other factors independent of myocardial relaxation reduce LV EDV. Whether the altered diastolic mechanics in Sherpa represent positive long-term adaptation or an inability to remodel is not known, but it appears from our data that systolic function has a greater capacity to adapt to residence at HA.

Ventricular Mismatch: Preserved Right Ventricular End-Diastolic Area and Decreased Left Ventricular Volume after Acute HA Exposure

Short-term HA exposure increased PASP and reduced plasma volume in lowlanders, as has been previously reported (21, 35, 37). However, despite the reduction in plasma volume, there was no change in RV EDA indicating that either RV filling was maintained or, due to a reduced RV SV, the same EDA was achieved with a lower filling pressure (36). There was, however, a reduction in LV EDV, a finding previously thought to be partly related to the lower blood volume observed with short-term HA exposure (8). Our data indicate that the reduction in LV filling may be independent of changes in blood volume and more likely related to the decreased RV SV observed. The reduction in RV SV at HA coincided with a reduction in systolic performance as quantified by RV longitudinal strain and TAPSE. It is

likely that in response to increased PASP, and therefore RV afterload, RV systolic performance is impaired and SV is reduced. This in turn impacts on LV diastolic function resulting in modified LV filling, as evidenced by the change in E/A, and ultimately decreased LV EDV.

Differential Response in LV Basal and Apical Mechanics in Lowlanders following ascent to 5050 m

Following ascent to HA, lowlanders demonstrated a reduction in peak LV basal systolic rotation and an increase in LV apical circumferential strain and rotation. It is likely that the reduction in LV EDV, increase in PASP and subsequent changes in LV geometry, as indicated by an increased LV eccentricity index, play a significant role in the differential response of the base and apex. Increased PASP and altered LV geometry have been shown to lower peak LV basal rotation in pulmonary hypertension (10) while a reduction in LV preload has been associated with increased apical rotation (13, 18). In addition to the decrease in peak LV basal systolic rotation, basal rotation during IVC was elevated in lowlanders at HA as previously described where PASP is increased or LV preload reduced (10, 48). The increase in rotation during IVC alters the starting position of clockwise systolic basal rotation. However, the net change in rotation between peak IVC and peak systole remains relatively constant at sea level and HA, with no change in circumferential deformation. As this modification of basal rotation was not evident in Sherpa, who exhibited a similar PASP, it seems more likely that the decrease in basal rotation was due to decreased LV filling rather than significant LV-RV interaction.

In contrast to basal mechanics, and in agreement with our hypothesis, systolic apical rotation and circumferential strain were significantly increased at HA compared to sea level. This is likely related to the decreased LV EDV and increased sympathetic drive previously reported at HA (17). Although the importance and functional significance of changes in apical mechanics is yet to be determined, such changes likely signify enhanced systolic function at HA. For example, increased apical rotation and deformation could help to maintain ejection fraction and prevent further decline in stroke volume in the presence of decreased LV filling.

Limitations and Future Directions

We acknowledge the limitations associated with small, cross-sectional studies however due to logistical difficulties and expense associated with work of this nature, large longitudinal studies are less practicable. Due to the anatomy of the heart, imaging of the right ventricle with ultrasound is not ideal, however, the guidelines published by the American Society of Echocardiography were followed (38) and magnetic resonance imaging was not available. Whilst all participants were physically active and matched for age, we were unable to quantify physical activity patterns and therefore cannot rule out the influence of training status. Lastly, we acknowledge the confounding nature of drawing comparisons between two diverse ethnic groups, it is possible that Sherpa may exhibit different cardiac phenotypes irrespective of HA exposure. However, in order to address our primary research question it was not possible to avoid the comparison of different ethnic groups. Future research should attempt to investigate the combined influence of chronic altitude exposure and healthy aging, the reversible nature of long-term cardiac adaptation to HA and the consequences for exercise capacity in Sherpa.

Conclusions

Life-long HA exposure resulted in structural and functional remodelling of the Sherpa heart. Altered biventricular loading conditions are likely the cause for the physiological adaptation observed. Despite a higher RV afterload, there was no evidence of disproportionate RV structural enlargement in Sherpa, which may be a consequence of environmental or genetic adaptation. Normalization of LV systolic mechanics in Sherpa but slower diastolic relaxation indicates differential functional remodelling that has not been observed previously in HA populations and its functional relevance remains to be confirmed. Lowlanders also demonstrated increased RV afterload and consequently altered RV function, which may impair LV filling. Decreased LV filling is accompanied by an increase in apical systolic mechanics likely helping to prevent a further decline in SV. Persistent under filling of the LV and elevated apical mechanics may restrict cardiac reserve during exercise and be the precursor to the chronic LV structural and functional remodelling observed in well-adapted Sherpa population.

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Competing Interests

No conflicts of interest are declared by the authors.

Figure Legends

Figure 1- Temporal representation of twist, basal and apical rotation and their respective velocities in lowlanders at sea level and 5050 m and Sherpa at 5050 m. Annotations indicate key findings. For clarity, statistical differences have not been identified. Please refer to Table 3. RV, right ventricle; LV, left ventricle; AVC, aortic valve closure.

Figure 2- Temporal representation of RV and LV strain and strain rate in lowlanders at sea level and 5050 m and Sherpa at 5050 m. Annotations indicate key findings. For clarity, statistical differences have not been identified. Please refer to Table 3. RV, right ventricle; LV, left ventricle; AVC, aortic valve closure; PVC, pulmonary valve closure.

Figure 3. Panel A illustrates the slower untwisting in Sherpa expressed relative to peak systolic twist up to 50% diastole. Sherpa isovolumic relaxation time (IVRT) is double that of lowlanders at sea level when expressed as a % of diastole. Vertical lines indicate mitral valve opening for each condition and horizontal lines indicate the percentage of untwist preceding mitral valve opening. Panel B shows % untwist in three conditions against % IVRT. No statistical differences were observed when untwisting was normalised for IVRT duration. Data presented are mean ± SEM; * $p<0.05$ vs. lowlander sea level; † $p< 0.05$ vs. 5050m lowlander. AVC, aortic valve closure; MVO, mitral valve opening; SL, sea level.

Tables

Table 1. Anthropometric and cardiovascular measurements in lowlanders at sea level and 5050 m and Sherpa at 5050 m.

	Altitude (m)				
	SL	5050		Sherpa 5050 m	
Mass (kg)	82 ± 10	78 ± 10		68 ± 10	*†
SaO2 (%)	98 ± 2	82 ± 3	*	83 ± 3	*
Systolic BP (mm Hg)	113 ± 8	127 ± 6	*	120 ± 10	
Diastolic BP (mm Hg)	59 ± 5	79 ± 6	*	79 ± 8	*
MAP (mm Hg)	77 ± 4	93 ± 8	*	89 ± 9	*
Heart Rate (bpm)	54 ± 6	61 ± 16		76 ± 14	*†
PASP (mmHg)	19.7 ± 3.0	28.1 ± 4.7	*	28.8 ± 4.8	*

Data presented are mean ± SD; * $p<0.05$ vs. sea level; † $p< 0.05$ vs. 5050m lowlander. SaO2, oxygen saturation; MAP, Mean Arterial Pressure; BP, Blood Pressure; bpm, beats/min; PASP, pulmonary artery systolic pressure.

608 **Table 2. Absolute and relative ventricular structural parameters in lowlanders at sea**
609 **level and 5050 m and Sherpa at 5050 m.**

	Altitude (m)				
	SL	5050 m		Sherpa 5050 m	
Absolute LV Structural Parameters					
IVSd (cm)	1.21 ± 0.08	1.19 ± 0.14		1.00 ± 0.20	*†
LVIDd (cm)	4.74 ± 0.30	4.57 ± 0.26	*	4.15 ± 0.24	*†
LVPWd (cm)	1.18 ± 0.11	1.10 ± 0.11		1.02 ± 0.09	*
LV Mass (g)	211 ± 22	190 ± 29	*	139 ± 31	*†
EDV (ml)	129 ± 15	107 ± 16	*	82 ± 13	*†
ESV (ml)	54 ± 8	44 ± 8	*	33 ± 7	*†
SV (ml)	75 ± 8	63 ± 10	*	49 ± 8	*†
Q̇ (l/min)	4.0 ± 0.6	3.9 ± 0.7		3.5 ± 0.7	
Ejection Fraction (%)	55 ± 3	58 ± 5		57 ± 4	
LV Eccentricity Index (Systole)	1.03 ± 0.06	1.08 ± 0.06	*	1.08 ± 0.08	*
LV Eccentricity Index (Diastole)	1.06 ± 0.05	1.13 ± 0.09	*	1.13 ± 0.09	*
Relative Wall Thickness	0.51 ± 0.06	0.50 ± 0.05		0.49 ± 0.04	
Relative LV Structural Parameters					
IVSd/ Height ($mm/m^{0.83}$)	7.55 ± 0.58	7.41 ± 0.92		6.50 ± 1.32	*
LVIDd/ Height ($mm/m^{1.21}$)	23.71 ± 1.77	22.81 ± 1.52	*	21.90 ± 1.24	*
LVPWd/ Height ($mm/m^{1.11}$)	6.25 ± 0.70	5.84 ± 0.71		5.67 ± 0.43	*
LV Mass/ Height ($g/m^{3.27}$)	33.27 ± 5.70	29.61 ± 6.33	*	24.83 ± 5.62	*
EDV/ Height ($ml/m^{3.79}$)	14.87 ± 2.67	12.41 ± 2.81	*	11.10 ± 1.79	*
ESV/ Height ($ml/m^{1.51}$)	22.90 ± 3.42	18.54 ± 3.60	*	14.94 ± 2.85	*†
SV/ Height ($ml/m^{3.68}$)	9.17 ± 1.65	7.79 ± 1.92	*	6.96 ± 1.13	*
Q̇/ Height ($l/min/m^{2.95}$)	0.74 ± 0.11	0.72 ± 0.10		0.74 ± 0.11	
Absolute RV Structural Parameters					
EDA (cm^3)	23.3 ± 3.6	23.6 ± 3.1		19.0 ± 2.5	*†
ESA (cm^3)	13.9 ± 2.5	14.8 ± 3.2		11.7 ± 1.9	*†
SV (ml)	77 ± 13	63 ± 16	*	50 ± 10	*†
Relative RV Structural Parameters					
EDA ($cm^3/m^{1.05}$)	12.80 ± 2.30	12.96 ± 2.04		10.92 ± 1.41	*†
ESA ($cm^3/m^{0.79}$)	8.88 ± 1.74	9.45 ± 2.11		7.72 ± 1.26	†
SV ($ml/m^{3.31}$)	11.52 ± 1.90	9.51 ± 2.46	*	8.85 ± 2.05	*
RV-LV Proportional Measurements					
RV-LV Basal Diameter Ratio	1.05 ± 0.20	0.97 ± 0.12		1.11 ± 0.13	†
RV-LV Area Ratio	0.67 ± 0.10	0.75 ± 0.07	*	0.72 ± 0.10	

610

611 Data presented are mean ± SD; * $p<0.05$ vs. sea level; † $p< 0.05$ vs. 5050m lowlander. IVSd,
612 interventricular septum diameter diastole; LVIDd, left ventricular internal diameter diastole;
613 LVPWd, left ventricular posterior wall diastole; EDV, end-diastolic volume; ESV, end-
614 systolic volume; SV, stroke volume; Q□, cardiac output; EDA, end-diastolic area; ESA, end-
615 systolic area.

Table 3. Left and right ventricular function from Doppler, tissue Doppler and M mode echocardiography.

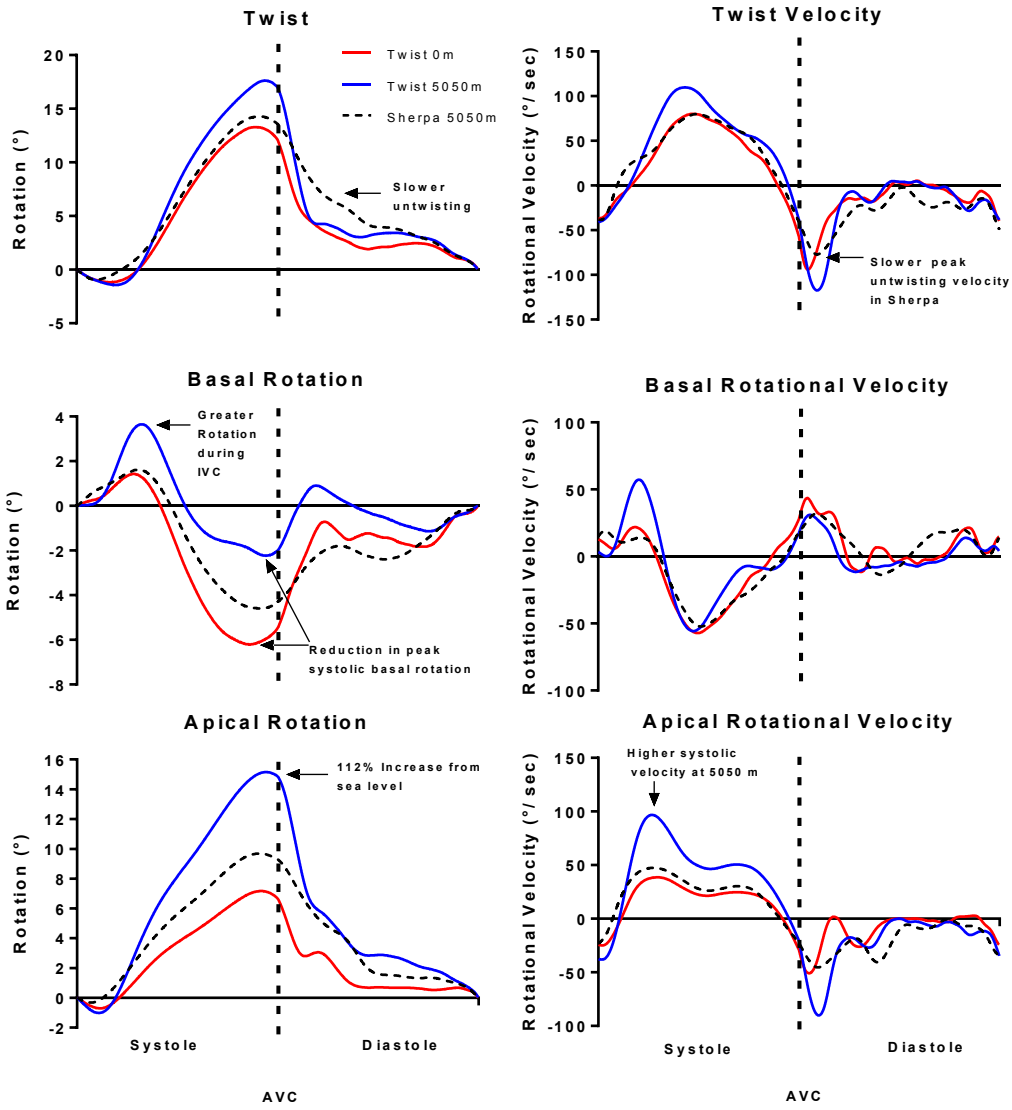
	Altitude (m)				
	SL	5050 m		Sherpa 5050 m	
Doppler and Tissue Doppler Parameters					
Transmitral E Velocity	0.90 ± 0.14	0.77 ± 0.14	*	0.76 ± 0.20	*
Transmitral A Velocity	0.44 ± 0.08	0.47 ± 0.08		0.53 ± 0.09	*
E/A Ratio	2.05 ± 0.31	1.65 ± 0.22	*	1.47 ± 0.48	*
Septal S'	0.09 ± 0.01	0.09 ± 0.02		0.08 ± 0.01	
Septal E'	0.14 ± 0.01	0.11 ± 0.01		0.11 ± 0.03	*
Septal A'	0.08 ± 0.02	0.09 ± 0.02		0.08 ± 0.01	
Septal E'/A' Ratio	1.68 ± 0.27	1.27 ± 0.36	*	1.39 ± 0.48	
RV S'	0.14 ± 0.02	0.14 ± 0.03		0.13 ± 0.01	
RV E'	0.16 ± 0.02	0.15 ± 0.03		0.15 ± 0.05	
RV A'	0.12 ± .0.3	0.12 ± 0.02		0.11 ± 0.04	
LV IVRT (ms)	55 ± 9	69 ± 14	*	68 ± 11	*
LV IVRT as Percentage of Diastole (%)	8 ± 1	11 ± 2	*	16 ± 4	*†
RV IVRT (ms)	41 ± 11	78 ± 14	*	64 ± 20	*
TAPSE	2.9 ± 0.3	2.3 ± 0.3	*	2.2 ± 0.4	*

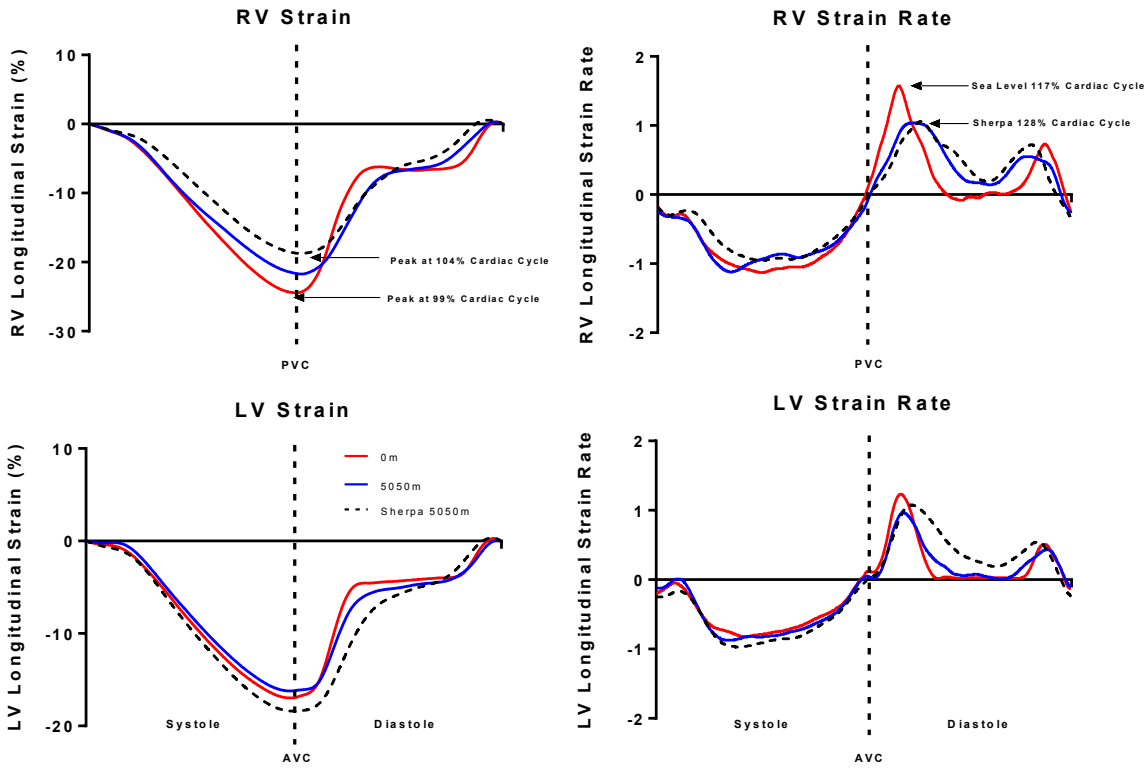
Data presented are mean ± SD; * $p<0.05$ vs. sea level; † $p< 0.05$ vs. 5050m lowlander. E, early; A, late; S', peak systolic tissue velocity; E', peak early diastolic tissue velocity; A', late diastolic tissue velocity; IVRT, isovolumic relaxation time; TAPSE, tricuspid annular plane systolic excursion.

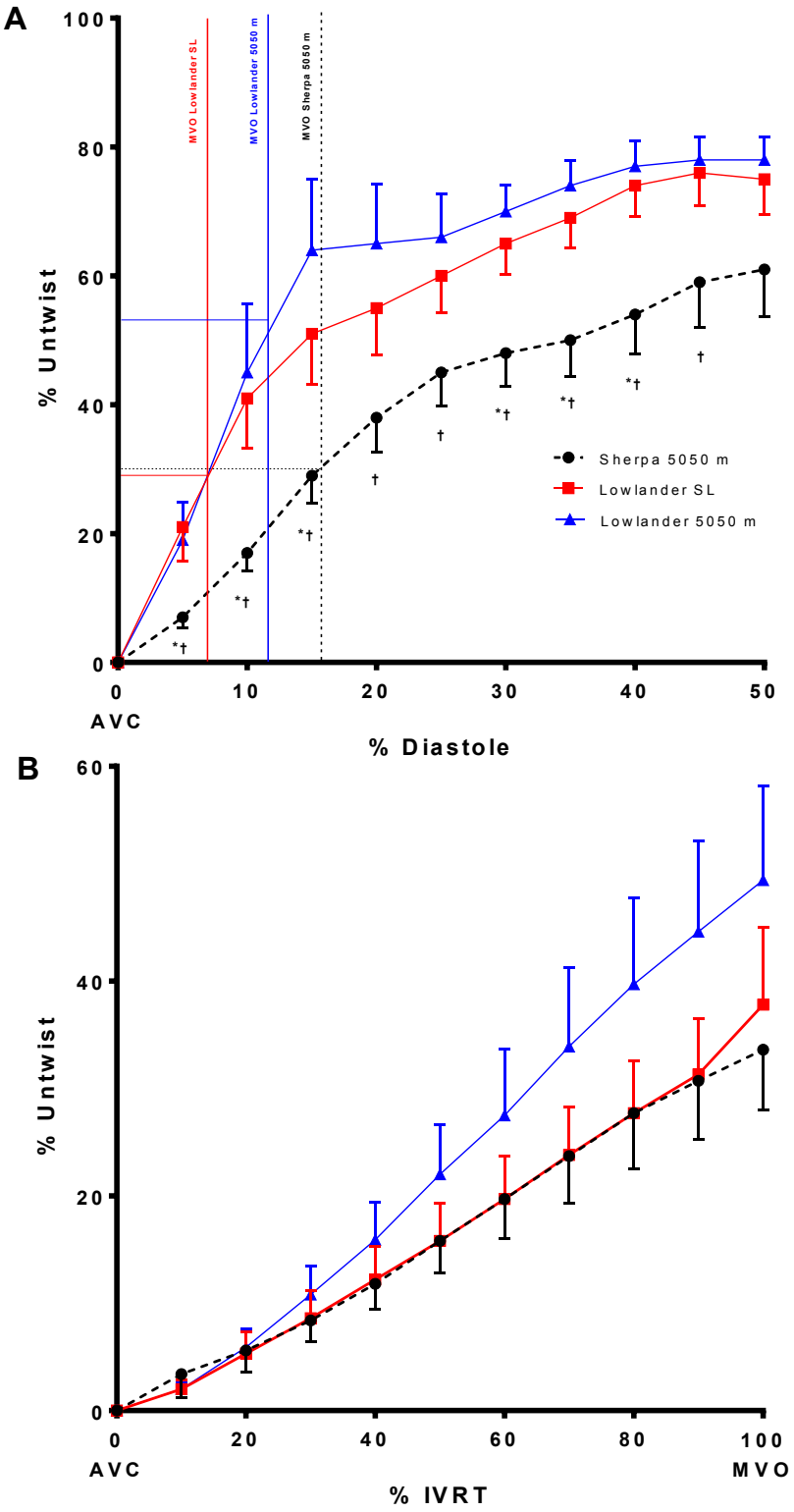
Table 4. Myocardial Mechanics in Lowlanders at sea level and 5050 m and Sherpa at 5050 m.

	Altitude (m)					
	SL	5050		Sherpa 5050 m		
Left Ventricular Twist Parameters						
Twist (°)	13.6 ± 2.6	18.1 ± 5.6		15.0 ± 5.6		
Systolic Twist Velocity (°/s)	88 ± 24	125 ± 48		93 ± 25		
Untwisting Velocity (°/s)	-123 ± 30	-153 ± 38		-93 ± 31	†*	
Left Ventricular Basal Parameters						
Basal IVC Rotation (°)	1.6 ± 1.3	3.9 ± 1.9	*	1.9 ± 1.0	†	
Basal Rotation (°)	-6.7 ± 1.3	-2.9 ± 1.9	*	-5.2 ± 2.4	†	
Basal Systolic Rotational Velocity (°/s)	-63 ± 22	-67 ± 28		-55 ± 25		
Basal Diastolic Rotational Velocity (°/s)	63 ± 27	51 ± 24		53 ± 26		
Basal Circumferential Strain (%)	17.8 ± 2.5	18.9 ± 3		17.8 ± 2.5		
Basal Circumferential Strain Rate (%/s)	1.1 ± 0.1	1.2 ± 0.3		1.1 ± 0.2		
Left Ventricular Apical Parameters						
Apical Rotation (°)	7.3 ± 2.2	15.5 ± 4.8	*	10.5 ± 4.3	†	
Apical Systolic Rotational Velocity (°/s)	46 ± 13	101 ± 40	*	66 ± 20	†*	
Apical Diastolic Rotational Velocity (°/s)	-60 ± 18	-125 ± 30	*	-69 ± 18	†	
Apical Circumferential Strain (%)	25.0 ± 4.9	29.2 ± 6.4	*	23.8 ± 3.8		
Apical Circumferential Strain Rate (%/s)	1.4 ± 0.3	2.1 ± 0.7	*	1.60 ± 0.3		
Left Ventricular Longitudinal Parameters						
Longitudinal Strain Peak (%)	19.1 ± 2.7	18.4 ± 2.1		18.5 ± 1.1		
Longitudinal Strain Time to Peak (%)	98 ± 2	103 ± 5	*	102 ± 4	*	
Longitudinal Strain Rate Peak (%/s)	1.0 ± 0.2	1.0 ± 0.2		1.0 ± 0.1		
Longitudinal Strain Rate Time to Peak (%)	43 ± 10	42 ± 10		42 ± 9		
Longitudinal Diastolic Strain Rate Peak (%)	1.5 ± 3	1.2 ± 0.2		1.4 ± 0.3		
Longitudinal Diastolic Strain Rate Time to Peak (%)	118 ± 2	122 ± 7		128 ± 9	*	
Right Ventricular Longitudinal Parameters						
Longitudinal Strain Peak (%)	24.7 ± 3.2	21.8 ± 2.7	*	18.9 ± 2.5	†*	
Longitudinal Strain Time to Peak (%)	99 ± 3	103 ± 3		104 ± 5	*	
Longitudinal Systolic Strain Rate Peak (%/s)	1.2 ± 0.2	1.2 ± 0.2		1.1 ± 0.1		
Longitudinal Systolic Strain Rate Time to Peak (%)	53 ± 16	40 ± 8	*	41 ± 18	*	
Longitudinal Diastolic Strain Rate Peak (%)	1.7 ± 0.4	1.3 ± 0.2		1.5 ± 0.3		
Longitudinal Diastolic Strain Rate Time to Peak (%)	117 ± 2	123 ±7	*	128 ± 8	*	

Data presented are mean ± SD; * $p<0.05$ vs. sea level; † $p< 0.05$ vs. 5050m lowlander. Time to peak is expressed as a percentage with 0-100% for systole and 101-200% representing diastole.


Twist
Twist 0m
Twist 5050m
Sherpa 5050m
Rotation (°)
Slower untwisting
Twist Velocity
Rotational Velocity (°/ sec)
Slower peak untwisting velocity in Sherpa
Basal Rotation
Greater Rotation during IVC
Reduction in peak systolic basal rotation
Basal Rotational Velocity
Apical Rotation
112% Increase from sea level
Apical Rotational Velocity
Higher systolic velocity at 5050 m
Systole
Diastole
AVC


RV Strain
RV Longitudinal Strain (%)
10
0
-10
-20
-30
Peak at 104% Cardiac Cycle
Peak at 99% Cardiac Cycle
PVC
RV Strain Rate
RV Longitudinal Strain Rate
2
1
0
-1
-2
Sea Level 117% Cardiac Cycle
Sherpa 128% Cardiac Cycle
PVC
LV Strain
LV Longitudinal Strain (%)
10
0
-10
-20
0m
5050m
Sherpa 5050m
Systole
Diastole
AVC
LV Strain Rate
LV Longitudinal Strain Rate
2
1
0
-1
-2
Systole
Diastole
AVC


A
100
80
60
40
20
0
% Untwist
MVO Lowlander SL
MVO Lowlander 5050 m
MVO Sherpa 5050 m
Sherpa 5050 m
Lowlander SL
Lowlander 5050 m
0
10
20
30
40
50
AVC
% Diastole
B
60
40
20
0
% Untwist
0
20
40
60
80
100
AVC
MVO
% IVRT