Articles in PresS. J Appl Physiol (March 6, 2015). doi:10.1152/japplphysiol.00995.2014

Impaired myocardial function does not explain reduced left ventricular filling and stroke volume at rest or during exercise at high altitude

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Author Contributions

M.S, P.N.A and R.S contributed to the conception and design of the experiment, data analysis, interpretation and the drafting of the manuscript. E.J.S, M.G.H and J.D.C contributed to the data analysis, interpretation and critical review of the manuscript. M.M.T built the custom cycle ergometer. M.M.T, T.A.D and A.B contributed to data collection and analysis, and critically reviewed the manuscript. All authors have approved the final version of the manuscript.

Word Count: 3678

Abstract

Impaired myocardial systolic contraction and diastolic relaxation have been suggested as possible mechanisms contributing to the decreased stroke volume (SV) observed at high altitude (HA). To determine whether intrinsic myocardial performance is a limiting factor in the generation of SV at HA, we assessed left ventricular (LV) systolic and diastolic mechanics and volumes in 10 healthy participants (aged 32 ± 7; mean ± SD) at rest and during exercise at sea level (SL; 344 m) and following 10 days at 5050 m. In contrast to SL, LV end-diastolic volume was ~19% lower at rest (p=0.004) and did not increase during exercise despite a greater untwisting velocity. Furthermore, resting SV was lower at HA (~17%; 60±10 vs. 70±8 ml) despite higher LV twist (43%), apical rotation (115%) and circumferential strain (17%). With exercise at HA, the increase in SV was limited (12 ml *vs.* 22 ml at SL), and LV apical rotation failed to augment. For the first time, we have demonstrated that EDV does not increase upon exercise at high altitude despite enhanced *in vivo* diastolic relaxation. The increase in LV mechanics at rest may represent a mechanism by which SV is defended in the presence of a reduced EDV. However, likely due to the higher LV mechanics at rest, no further increase was observed up to 50% peak power. Consequently, whilst hypoxia does not suppress systolic function *per se*, the capacity to increase SV through greater deformation during submaximal exercise at HA is restricted.

Abstract word count: 245

Key words: Hypoxia; Left ventricular mechanics; stroke volume

Introduction

During initial exposure to hypobaric hypoxia at high altitude (HA), cardiac output for a given absolute workload is increased to compensate for a lower arterial oxygen content before returning to baseline levels with acclimatization (8). However, after 2-5 days of acclimatization, the required cardiac output is generated through a lower stroke volume (SV) and higher heart rate (38). The reduced SV is suggestive of either lower ventricular filling, potentially caused in part by an impaired myocardial relaxation, or impaired ejection secondary to systolic contractile dysfunction. There is however, a paucity of data in humans supporting a direct effect of hypoxia on myocardial function at HA (25, 41).

The suggestion that hypoxia may impair myocardial systolic function during exercise was proposed nearly 50 years ago (3) and has been revisited more recently (27-29). Negative inotropic effects of hypoxia (arterial oxygen tension of 44 mmHg) have been shown in intact animal models (39) and isolated myocardial fibers under severe hypoxia (1% O_2) (33). Exercise training under hypobaric hypoxia is also associated with altered mechanical properties at a cellular level in rodents (9), although chronic hypoxia alone did not decrease myofilament sensitivity to calcium. However, in contrast to animal studies, data in humans indicate that systolic function is maintained or enhanced at HA. For example, Suarez, Alexander and Houston (37) reported the maintenance of systolic function after gradual decompression to a barometric pressure of 282 mmHg, a finding that was subsequently confirmed by numerous investigations during acute and prolonged hypoxic exposure (6, 10, 12, 23, 31). However, of these studies, only Suarez, Alexander and Houston (37) investigated systolic function during light exercise (60 W), where function appeared to be maintained. It is not known whether systolic function is maintained at higher exercise intensities.

It has also been speculated that reduced oxygen availability may impair diastolic relaxation at HA (15, 18) and thus explain the decreased left ventricular (LV) end-diastolic volume (EDV) commonly observed (2, 6, 18). However, despite numerous studies reporting a decrease in plasma volume and

altered transmitral filling patterns (2, 6, 20), myocardial relaxation has only previously been investigated during hypoxia in dogs (15), and no data exist examining LV relaxation during exercise at high altitude. Using sensitive, non-invasive imaging techniques (2D speckle tracking) it is now possible to examine the LV deformation mechanics (strain, twist and untwist velocity) that underpin LV systolic and diastolic function. LV strain and twist have been shown to be sensitive measures of global and regional myocardial function, and reveal sub-clinical dysfunction in patients where ejection fraction is unchanged (16, 22). In addition, diastolic LV untwist velocity correlates well with invasive measures of LV stiffness and provides a temporal link between relaxation and the development of intraventricular pressure gradients (30, 43). Therefore, examination of LV mechanics at HA may determine whether the decreased SV observed at HA is dependent on impaired myocardial relaxation and/or myocardial contractile dysfunction, or confirm previous findings of preserved ventricular function during exercise (37).

We therefore assessed systolic and diastolic ventricular mechanics during incremental exercise at sea level and HA to examine whether impaired myocardial relaxation or systolic dysfunction explains the previously reported reduction in SV at HA. We hypothesized that at HA, (i) ventricular filling would be lower at rest and during exercise and would be accompanied by a reduction in untwist velocity and (ii) systolic mechanics would be impaired during exercise at HA.

Materials and Methods

Participants. 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 to the standards set by the Declaration of Helsinki. Ten Caucasian lowlanders (nine male) aged 32 ± 7 years (mean ± SD), with a height of 176 ± 7 cm and a mass of 80 ± 10 kg, provided informed consent and volunteered to participate in the study. All participants were free from respiratory and cardiovascular disease and were not taking any prescription medications.

Experimental Design and Protocol. The experimental design required two periods of data collection, each consisting of two separate laboratory visits separated by 24 hours. Within each period, the first visit was to determine peak power, while the second was to assess cardiac function at rest and during exercise. For the determination of peak power, participants performed an incremental exercise test to volitional fatigue on a purpose built, portable supine ergometer close to sea level (SL; Kelowna, Canada; 344 m) and 10 days after arrival at the Ev-K2-CNR Pyramid Laboratory (Lobuche, Nepal; 5050 m). During the incremental test, power output was increased in a stepwise fashion by 50 W every two minutes until fatigue. Participants were asked to maintain a steady cadence and resistance was adjusted by a test administrator. The maximum workload achieved was recorded in order to calculate relative workloads for the graded exercise test. The following day, venous blood samples were taken in the supine position to assess total hemoglobin concentration (HemoCue®, Ängelholm, Sweden) and hematocrit (Micro Hematocrit Reader). Altitude-mediated reductions in plasma volume were then estimated from hemoglobin and hematocrit (11) assuming erythropoiesis to have had only minor effects on hemoglobin content after 10 days at HA (32).

Following blood sampling, a brief echocardiographic examination was completed in the left lateral decubitus position. Participants were then asked to complete a discontinuous, graded exercise challenge at 10, 30 and 50% of the peak power achieved during the preceding maximal test at the corresponding altitude. Exercise bouts lasted four minutes and were separated by four minutes of

rest. Echocardiographic image acquisition was completed during the final two minutes of exercise. During echocardiography, measurements were made of blood pressure using a manual sphygmomanometer, arterial oxygen saturation (SpO_2) from finger pulse oximetry (Nonin Onyx Oximeter, Plymouth, MN) and heart rate from a 3-lead ECG (Vivid q, GE Medical Systems, Israel Ltd) at the beginning and end of the two-minute imaging protocol and averaged.

This study was conducted as part of a large-scale high altitude research expedition. Due to the nature of high altitude research, participants recruited for this study also took part in a number of other investigations (1). Therefore, particular attention was paid to the timing and management of experiments to ensure there was no potential for confounding results. In addition, some of the resting cardiac data from a selection of our participants (n=9) has already been published (34). However, these data were only used to compare resting LV function with highland natives.

Transthoracic Echocardiography. Echocardiographic images were obtained by the same highly trained sonographer using a commercially available ultrasound system (Vivid q, GE Medical Systems, Israel Ltd) with a 1.5-4 MHz phased array transducer. Parasternal short-axis and apical four chamber views were recorded and three consecutive cardiac cycles were stored for analysis offline (Echopac, GE Medical, Horton, Norway). Left ventricular end-systolic volume (ESV) and end-diastolic volume (EDV) were calculated from planar tracings of the LV endocardial border in the apical four-chamber view in accordance with the European Society of Cardiology (24). Left ventricular stroke volume and ejection fraction were then calculated. Pulmonary artery systolic pressure was quantified as the maximum systolic pressure gradient across the tricuspid valve (ΔP_{max}) (4). Peak systolic regurgitation jet velocity (V) was measured using continuous wave Doppler and the peak systolic right ventricle (RV) to right atrium (RA) pressure gradient was calculated using the simplified Bernoulli equation ($4V^2$). Due to the difficult and time consuming nature of this measurement during exercise, it was only attempted at 50% peak power and accurately obtained in 60% of the participants.

Left ventricular circumferential strain, rotation and their respective deformation rates 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 (40) and obtained by moving the transducer one-two inter-costal spaces caudally from the basal position to align with the apical short-axis. Left ventricular longitudinal strain and strain rate were analyzed from an apical four chamber view. Image analysis was performed offline using 2D speckle tracking to assess global rotation, rotational velocity, strain and strain rate. Apical frame-by-frame data were subtracted from basal data to calculate LV twist and untwist (Echopac, GE Medical, Horten, Norway, version 110.1.1). Peak untwist velocity was identified as the highest point of the first peak in diastole. In order to time-align and adjust for inter-individual variability of heart rate, frame-by-frame data were exported to custom-made software that completed cubic spline interpolation to produce 600 data points for both the systolic and diastolic periods as previously described (34, 35). Intra-observer coefficient of variation of the sonographer in the present study for twist, systolic twist velocity and untwisting velocity are 8.1%, 7.8% and 11%, respectively.

Statistics. Results are presented as means ± SD. Differences between conditions and exercise intensities were analyzed using repeated measures two-way ANOVA, with altitude and exercise intensity as within-subject factors (IBM SPSS for Windows, V20, Armonk, NY). When *F* was significant, pair-wise comparisons were carried out *post hoc* using paired-samples *t*-test with Bonferroni correction. Relationships were determined using non-linear regression analysis (GraphPad Prism for Windows, Version 5.0.1, Dan Diego, California, USA) with alpha set *a priori* to 0.05.

Results

Maximal incremental exercise test

Exposure to HA reduced maximal aerobic power output by 44%. At exhaustion, SpO_2 was 96 ± 3% and 72 ± 4% at sea level and HA, respectively.

Systemic and pulmonary response to incremental exercise

Plasma volume decreased by 18% with HA exposure ($P<0.05$). Resting mean arterial pressure (MAP) was higher at HA but increased to a lesser extent with incremental exercise (Figure 1; interaction $P<0.05$). After ascent to 5050 m, resting pulmonary artery systolic pressure increased from 16.0 ± 1.1 to 28.9 ± 6.4 mmHg ($P<0.05$) compared to sea level and remained elevated during exercise (Figure 2). From rest to 50% peak power, ΔP_{max} increased by 49% and 50% at sea level and HA, respectively (Figure 2).

Cardiac output was the same at rest between conditions but increased to a greater extent at sea level, such that there was a 25% difference at 50% peak power ($P<0.01$; Table 1). The higher cardiac output at sea level was driven by a larger SV, as heart rate was not different between conditions. The higher SV at sea level reflected a significantly larger EDV and ESV with a lower ejection fraction; however, by 50% peak power, previous differences in ejection fraction between sea level and HA were no longer present. With the onset of exercise, EDV increased at sea level but not at HA (Figure 1 and Table 1).

Left ventricular diastolic mechanics

Left ventricular untwist velocity and apical diastolic rotational velocity both increased with incremental exercise and were significantly higher at HA compared to sea level (Table 2; Figure 3). There was, however, no significant interaction between conditions (exercise intensity *vs.* altitude) and basal rotational velocity was not different at HA. In addition to changes in untwist velocity, the slope of the relationship between systolic and diastolic untwisting was altered, in that untwisting velocity was higher at HA for a given systolic twist velocity (Figure 3).

Left ventricular systolic mechanics

LV twist was higher at HA compared to sea level driven by an increase in apical rotation with no significant effect of altitude on basal rotation. There was, however, no difference in peak twist and apical rotation at 50% peak power between sea level and HA,. Therefore, apical rotation did not augment with exercise at HA (Table 2 and Figure 4a). Higher LV twist and apical rotation were also accompanied by greater velocities at HA. In contrast to changes in apical rotation, apical circumferential strain and strain rate increased with submaximal incremental exercise in *both* conditions. However, higher resting strain and strain rate at HA meant the magnitude of increase during exercise was smaller than at sea level (interaction $P<0.01$; Table 2), mirroring the response in rotational mechanics. Although longitudinal strain and strain rate increased with exercise intensity, and strain rate was higher at HA, the profiles were not different between sea level and HA.

Relations between left ventricular volumes and mechanics

The close relation between twist and apical rotation with SV during incremental exercise at sea level was not evident at HA (Figure 4b). Elevated resting systolic mechanics resulted in a rightward shift of the relation between SV with twist and apical rotation. Higher resting apical rotation (115%) meant there was no increase during incremental exercise and SV only increased by 20% at HA compared to a 31% increase at sea level.

Discussion

The primary aim of this study was to determine whether ten days of exposure to hypobaric hypoxia impairs LV contractile function and/or diastolic relaxation during incremental exercise. There were three novel findings (1) in contrast to sea level, LV EDV does not increase from rest to exercise at HA; (2) despite the lack of increase in EDV, diastolic untwisting was enhanced at HA and the coupling of systolic-diastolic twist velocity was preserved, and; (3) in contrast to our hypothesis, despite lower arterial oxygenation, ejection fraction was higher at HA and coincided with greater twist, rotation and strain. Thus, decreased SV observed during submaximal exercise at HA is not explained by impaired systolic contractile function or myocardial relaxation *per se*, and is more likely explained by a decreased ventricular filling pressure.

Decreased left ventricular filling and enhanced myocardial relaxation at 5050 m

The increase in SV observed during submaximal incremental exercise at sea level is partly the result of an increase in EDV (Sundstedt, Hedberg et al. 2004). However, at HA EDV did not increase with exercise which is indicative of a limitation to ventricular filling, to which three possible mechanisms have been proposed; (i) impaired myocardial relaxation (15, 18), (ii) lower ventricular preload secondary to decreased blood volume (6), and (iii) higher pulmonary artery pressure limiting right ventricular systolic performance (26).

In contrast to the proposed impairment of myocardial relaxation, we found LV diastolic untwisting velocity to be significantly enhanced at HA during both rest and exercise despite lower absolute exercise intensities and the same heart rate. In addition, the close relation between systolic twist velocity and diastolic untwist velocity was altered such that untwist velocity was greater for a given systolic velocity (Figure 3). Combined, these data indicate that myocardial relaxation and the coupling with systolic twist normally expected are preserved or even enhanced during short-term exposure to HA. Whilst speculative, It would appear the myocyte components responsible for the restoring forces in the myocardial fibers appear to be unaffected by moderate-severe levels of

arterial deoxygenation and subsequent changes in cardiac metabolism (18). In addition to the impact at HA, this could have relevance for a myriad of clinical conditions where transient arterial hypoxemia is present, such as an acute exacerbation of chronic obstructive lung disease.

The reduction in SV observed at rest and during sub-maximal exercise at HA has also previously been attributed to a decrease in PV (6, 20). However, when lowlanders were made hypervolemic through the infusion of 1 liter of 6% dextran after nine weeks of residence at 5260 m, SV remained the same and HR increased to compensate for the hemodilution (7). In addition, from studies performed by Calbet, Radegran, Boushel, Sondergaard, Saltin and Wagner (7) and Robach, Dechaux, Jarrot, Vaysse, Schneider, Mason, Herry, Gardette and Richalet (32), only the latter found PV expansion to increase VO_2 peak at HA. Neither study reported LV EDV and importantly, both employed upright cycle ergometry as opposed to the supine modality used in the present investigation. During exercise on the supine ergometer developed for this study, the torso was in a horizontal position with a slight elevation (~25 cm) of both feet when the pedals were in the neutral position. This elevation, which was consistent in both trials, would have likely aided venous return and could negate the effect of a decreased blood volume at HA by transiently increasing central blood volume. Elevation of the feet combined with increased muscle pump activity would normally be expected to increase EDV, as was evident at sea level in the present study. However, as both EDV and SV were lower at rest and during exercise at HA, it would appear an alternative mechanism other than blood volume *per se* was the limiting factor in LV EDV.

Pulmonary artery pressure was higher at rest and 50% peak power at HA compared to sea level. This is to be expected, as hypoxia is known to induce pulmonary vasoconstriction (HPV) almost immediately upon exposure (25). In response to HPV, we have previously shown RV longitudinal systolic function and SV to be decreased at HA with no change in RV end-diastolic area (34). Collectively, these findings indicate that increased pulmonary artery pressure likely reduces RV SV which would in turn affect LV filling. This is supported by investigations that pharmacologically

reversed HPV and demonstrated an increased VO_2 peak (13, 19, 26). Further work is required to establish causality between HPV and decreased LV EDV during exercise, especially during exercise in an upright posture.

Higher ejection fraction and greater twist, apical rotation and strain during submaximal exercise at 5050 m.

Very limited data exist on detailed LV function during exercise at HA, which has led to speculation that hypoxia may directly impair contractile function. Similar to Suarez, Alexander and Houston (37), we observed a higher ejection fraction at rest and during incremental exercise at HA. However, ejection fraction alone does not solely reflect systolic function due to its dependency on diastolic filling, and more sensitive measures can assess the underlying function (21). The higher ejection fraction in the current study was coupled with higher LV twist, apical rotation and their respective velocities, indicating a short-term response to HA exposure in LV function in order to maximize SV when EDV is reduced. In experimental models, myocardial ischemia lowers LV twist and strain, a change that is considered to reflect impaired function (5, 43). However, the increased LV systolic mechanics evident in the present study indicate that moderate-severe hypoxemia (SpO_2 72%) in healthy individuals does not impair systolic performance. The increase in mechanics is likely mediated through a combination of decreased LV preload and increased sympathetic nerve activity, as both stimuli are known to increase LV mechanical parameters such as apical rotation (14, 17). An increase in LV twist has also been reported during acute (30 minutes) normobaric hypoxia (10). However, unlike acute normobaric hypoxia where LV twist is higher due to systemic vasodilation, we report a concomitant increase in MAP. Under these hemodynamic conditions, one would expect LV twist to decrease (42), indicating that different regulatory mechanisms may exist for LV twist between acute and chronic hypoxic exposure.

Modified interaction between left ventricular mechanics and volumes at 5050 m.

Previously, the maintenance or increase in ejection fraction at HA has been reported as 'enhanced' systolic function (37). Whilst this indicates that the LV has the capacity to respond to the acute challenge, particularly at rest, it does not necessarily indicate an exclusively positive outcome due to the load-dependency of ejection fraction discussed above. The higher twist, apical rotation and strain at HA likely meant that cardiac mechanics were closer to the 'ceiling' previously reported during incremental exercise (36). Consequently, apical rotation at HA did not increase with increasing exercise intensity, and the rise in SV during incremental exercise was much smaller. Therefore, higher resting systolic mechanics reduce the functional reserve normally available during incremental exercise. Figure 4b illustrates this, where from rest to 50% peak power twist increases by 82% at sea level but only 23% at HA, with no significant change in apical rotation. Moreover, the increase in SV was 15% greater at SL than at HA. It is worth noting that apical rotational velocity was still able to increase beyond the limit to apical rotation, suggesting the sympathetically-mediated response to exercise was still evident. Therefore, whilst maximum deformation was achieved, the rate of deformation could still be augmented as heart rate increased. As mentioned above, EDV is the major determinant of SV during exercise, and it would appear that at HA impaired ventricular filling alters the relation between twist and SV normally observed at sea level. The shortening of the LV functional reserve at HA appears to limit the increase in SV during exercise. As such, these changes could ultimately negatively impact exercise capacity, especially at higher intensities.

Limitations and future directions

The current study only reports data up to 50% maximal exercise due to limitations in echocardiographic image acquisition at higher exercise intensities in a field research setting. To obtain optimal images of the LV, participants were required to perform an end-expiration breath hold during image capture. During higher intensity exercise at 5050 m this became extremely difficult for the participants and meant image acquisition was not possible. Imaging of the RV was

also attempted, but due to poor acoustic windows reliable imaging was not possible in our participants. The authors acknowledge that the assessment of LV volumes through single plane is not the gold standard. However, this method was chosen due to the shorter time required for single image acquisition. Future work should aim to determine the relative contribution of higher pulmonary pressures and decreased blood volume on LV EDV during exercise and the consequences for systolic function by lowering pulmonary pressure and normalizing blood volume, respectively. Additionally, future work examining the heart at HA should also incorporate an assessment of right ventricular function and the potential for region-specific LV-RV interaction during exercise.

Conclusions

At HA, LV filling is impaired during incremental submaximal exercise despite enhanced myocardial diastolic mechanics. The resultant decrease in EDV and its lack of increase with exercise requires a higher ejection fraction mediated through greater twist, rotation and strain. Higher resting mechanics and lower EDV result in a smaller mechanical and functional reserve available during incremental exercise at HA. Combined, this means the lower SV observed at HA is not due to impairment of myocardial relaxation or hypoxic systolic dysfunction *per se*, rather the inability to increase EDV, which is most likely due to higher pulmonary artery pressure.

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Acknowledgements

This study was carried out within the framework of the Ev-K2-CNR Project in collaboration with the Nepal Academy of Science and Technology as foreseen by the Memorandum of Understanding between Nepal and Italy, and thanks to contributions from the Italian National Research Council. This study was supported in part by the Natural Sciences and Engineering Research Council of Canada and a Canada Research Chair to PNA. The authors are grateful to the other members of this international research expedition for assistance with the organization of this project.

Competing Interests

No conflicts of interest are declared by the authors.

453 Tables

454 **Table 1.** Cardiovascular responses to incremental exercise at sea level and 5050 m.

		Workload (%peak power output)								
		Rest	**10%**		**30%**		**50%**		***Ex Intensity***	***SL vs. HA***	***Interaction***
MAP (mm Hg)	*SL*	76 ± 6	88 ± 9	*	94 ± 7	*†	104 ± 8	*†‡	P<0.001	P<0.001	P<0.001
	HA	94 ± 4	100 ± 5	*	103 ± 6	*	110 ± 5	*†‡			
SpO_2 (%)	*SL*	98 ± 2	98 ± 2		97 ± 2		96 ± 3		P<0.001	P<0.001	P<0.01
	HA	81 ± 3	79 ± 2		74 ± 6		72 ± 6				
Heart Rate (bpm)	*SL*	54 ± 6	75 ± 12	*	95 ± 13	*†	115 ± 12	*†‡	P<0.001	*NS*	P<0.01
	HA	64 ± 17	76 ± 19	*	96 ± 17	*†	111 ± 17	*†‡			
EDV (ml)	*SL*	128 ± 18	139 ± 19	*	144 ± 30		140 ± 24	*	P<0.01	P<0.001	P<0.05
	HA	104 ± 18	104 ± 16		102 ± 15		106 ± 16				
ESV (ml)	*SL*	58 ± 11	60 ± 11		56 ± 13		48 ± 9	*†	P<0.001	P<0.001	P<0.05
	HA	44 ± 11	37 ± 6		33 ± 6	*	33 ± 7	*			
SV (ml)	*SL*	70 ± 8	79 ± 10	*	88 ± 18	*	92 ± 18	*†	P<0.001	P<0.01	P<0.05
	HA	60 ± 10	67 ± 11		69 ± 10	*	72 ± 11	*			
$\dot{Q}$ (l/min)	*SL*	3.8 ± 0.5	5.8 ± 1.3	*	8.4 ± 1.7	*†	10.6 ± 2.3	*†‡	P<0.01	P<0.01	P<0.001
	HA	3.8 ± 0.7	5.0 ± 1.0	*	6.5 ± 0.6	*†	7.9 ± 1.3	*†‡			
Ejection Fraction (%)	*SL*	55 ± 3	57 ± 3		61 ± 3		66 ± 4		P<0.001	P<0.001	*NS*
	HA	58 ± 5	64 ± 3		68 ± 3		69 ± 3				

455

456 Data are mean ± SD. SL, sea level; HA, high altitude; MAP, mean arterial pressure; SpO_2, arterial
457 oxygen saturation; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; $\dot{Q}$,
458 cardiac output. *P <0.05 *vs.* rest. † P <0.05 *vs.* 10%. ‡ P <0.05 *vs.* 30%. *NS*, not significant.

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Table 2. Peak LV twist, basal, apical and longitudinal mechanics at rest and during incremental exercise at sea level and 5050 m.

		Workload (%peak power output)						
		Rest	10%	30%	50%	*Ex Intensity*	*SL vs. HA*	*Interaction*
LV Twist Parameters								
Twist (°)	*SL*	13.2 ± 2.5	15.0 ± 4.1	19.1 ± 4.9	24.0 ± 6.5	P<0.01	P<0.05	*NS*
	HA	18.9 ± 6.2	19.9 ± 5.9	24.4 ± 6.0	23.2 ± 4.6			
Systolic Twist Velocity (° s^{-1})	*SL*	85 ± 24	92 ± 34	140 ± 35	209 ± 56	P<0.001	P<0.05	*NS*
	HA	129 ± 51	144 ± 54	171 ± 44	220 ± 47			
Untwisting Velocity (° s^{-1})	*SL*	122 ± 28	111 ± 44	172 ± 63	238 ± 76	P<0.001	P<0.001	*NS*
	HA	159 ± 38	178 ± 44	238 ± 76	308 ± 82			
LV Basal Parameters								
Basal Rotation (°)	*SL*	6.2 ± 1.9	5.6 ± 2.7	8.2 ± 3.0	8.5 ± 3.1	P<0.001	*NS*	*NS*
	HA	3.3 ± 2.2	5.3 ± 3.1	6.3 ± 1.9	8.0 ± 2.8			
Basal Rotational Velocity (° s^{-1})	*SL*	63 ± 22	60 ± 19	98 ± 28	132 ± 38	P<0.001	*NS*	*NS*
	HA	68 ± 25	80 ± 25	95 ± 28	138 ± 35			
Basal Circumferential Strain (%)	*SL*	18.2 ± 2.8	15.8 ± 2.5	16.5 ± 5.4	15.9 ± 5.7	*NS*	P<0.01	*NS*
	HA	19.5 ± 3.5	17.4 ± 4.4	20.5 ± 4.4	20.3 ± 3.1			
Basal Circumferential Strain Rate (s^{-1})	*SL*	1.12 ± 0.13	0.97 ± 0.19	1.22 ± 0.22	1.43 ± 0.19	P<0.001	P<0.05	*NS*
	HA	1.25 ± 0.28	1.18 ± 0.28	1.58 ± 0.38	1.76 ± 0.35			
LV Apical Parameters								
Apical Rotation (°)	*SL*	7.4 ± 2.5	10.2 ± 2.5	11.6 ± 3.5	17.0 ± 5.4 *†	P<0.01	P<0.001	P<0.01
	HA	15.9 ± 4.7	14.7 ± 4.7	18.6 ± 5.7	16.2 ± 3.2			
Apical Rotational Velocity (° s^{-1})	*SL*	52 ± 25	69 ± 22	97 ± 25	189 ± 57	P<0.001	P<0.01	*NS*
	HA	103 ± 38	110 ± 35	143 ± 57	210 ± 51			
Apical Circumferential Strain (%)	*SL*	25.1 ± 4.7	24.1 ± 4.7	29.8 ± 7.0 †	31.4 ± 7.3	P<0.001	P<0.001	P<0.01
	HA	29.4 ± 6.0	33.6 ± 5.1	39.1 ± 4.4 *†	31.8 ± 5.1			
Apical Circumferential Strain Rate (s^{-1})	*SL*	1.40 ± 0.28	1.37 ± 0.28	1.90 ± 0.47 *†	2.70 ± 0.73	P<0.001	P<0.001	P<0.01
	HA	2.12 ± 0.70	2.40 ± 0.89	3.06 ± 0.54 *†	3.04 ± 0.51			
LV Longitudinal Parameters								
Longitudinal Strain (%)	*SL*	19.3 ± 2.5	20.2 ± 2.2	22.2 ± 2.2	23.5 ± 1.6	P<0.001	*NS*	*NS*
	HA	18.6 ± 2.2	21.2 ± 2.2	22.5 ± 2.2	23.2 ± 2.8			
Longitudinal Strain Rate (s^{-1})	*SL*	0.97 ± 0.16	1.07 ± 0.16	1.31 ± 0.19	1.66 ± 0.19	P<0.001	P<0.05	NS
	HA	1.05 ± 0.16	1.24 ± 0.19	1.53 ± 0.19	1.81 ± 0.28			

Data are mean ± SD. SL, sea level; HA, high altitude. **P* <0.05 *vs.* rest. † *P* <0.05 *vs.* 10%. ‡ *P* <0.05 *vs.* 30%. *NS*, not significant. Untwisting velocity; peak during early diastole.

Figures and Legends

Figure 1. Left ventricular volumes and systemic cardiovascular responses to incremental exercise at sea level (SL) and high attitude (HA). Cardiac output was the same at rest but increased to a greater extent at sea level achieved through a greater stroke volume (SV). End-diastolic volume (EDV) was lower at HA and did not increase with exercise, meaning a greater ejection fraction was required at HA**.** MAP, mean arterial pressure; SpO_2, arterial oxygen saturation; ESV, end-systolic volume. Filled circles represent sea level and open squares the high altitude. Data are mean ± SEM. For P value of ANOVA and *post hoc* analysis of exercise intensities please refer to Table 1. §*P*<0.05 *vs.* Sea level and #*P*<0.01 *vs.* Sea level where interaction P<0.05.

Figure 2. Individual response of pulmonary artery systolic pressure at rest and 50% peak power at sea level and 5050 m. Pulmonary artery systolic pressure increased from rest to exercise in both conditions and was higher in both HA conditions compared to sea level. *P<0.05 SL vs. HA and # P<0.05 rest vs. 50% exercise; n=6.

Figure 3. Diastolic relaxation at sea level (SL) and high attitude (HA). Panels A and B display peak velocity and apical diastolic rotational velocity, respectively, during incremental exercise at sea level and high altitude. Peak untwisting velocity was higher at HA until 50% peak power, which was driven by an increase in apical diastolic rotational velocity. Panel C indicates that the strong relationship between systolic and diastolic twisting and untwisting velocities remained after acclimatization, although there was a greater untwisting velocity for a given systolic twist velocity at HA. As there was no significant increase in twist exercise intensity at HA, the relationship between untwist velocity and twist was altered (D). This suggests untwist velocity is able to increase beyond the limitation to twist to achieve total untwist at higher heart rates. Data are mean ± SEM. *P<0.05 main effect (seal level *vs.* high altitude).

Figure 4. Peak twist, apical rotation and their relationship with stroke volume during incremental exercise at sea level (SL) and high attitude (HA). Panel A; twist and apical rotation were higher at rest and during sub-maximal exercise at HA, but there was no increase in apical rotation at HA. A combination of higher resting mechanics and absence of change with exercise meant a rightward shift in the exponential relationship between twist and apical rotation with stroke volume after HA exposure. Resting apical rotation at HA was equivalent to 50% peak power at sea level, suggesting the mechanical reserve had been fully utilized at rest in the hypoxic condition. Filled circles (A) and blue line (B) represent the sea level and open squares (A) and red line (B) the high altitude exercise conditions, respectively. Data are mean ± SEM. *P<0.05 main effect (sea level vs. high altitude; §*P*<0.05 *vs.* sea level and #*P*<0.01 *vs.* sea level where interaction effect P<0.05; for P value of ANOVA and *post hoc* analysis of exercise intensities please refer to Table 2.

Figure 1:

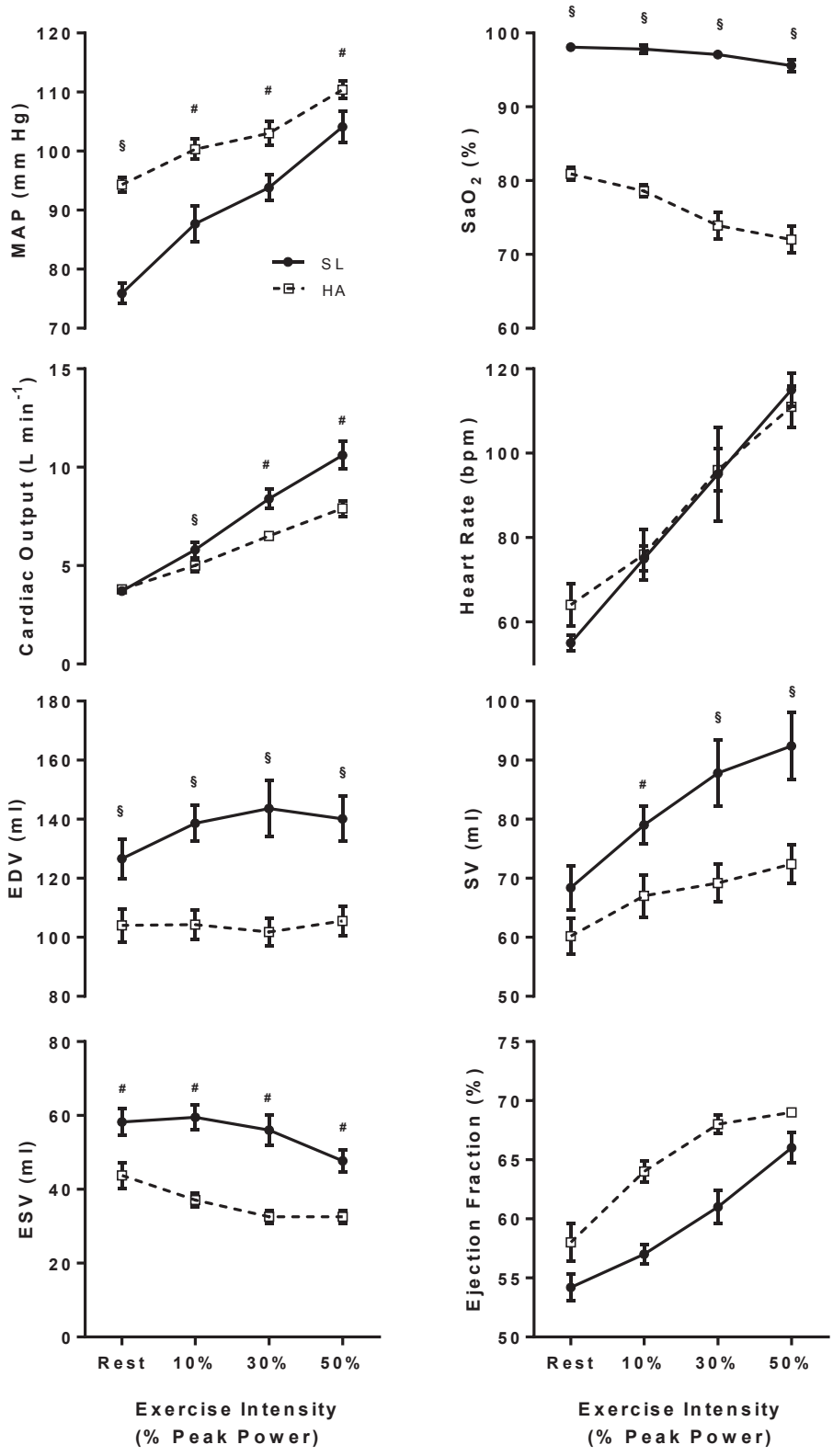

MAP (mm Hg)
SL
HA
SaO2 (%)
Cardiac Output (L min-1)
Heart Rate (bpm)
EDV (ml)
SV (ml)
ESV (ml)
Ejection Fraction (%)
Rest
10%
30%
50%
Exercise Intensity
(% Peak Power)

Figure 2:

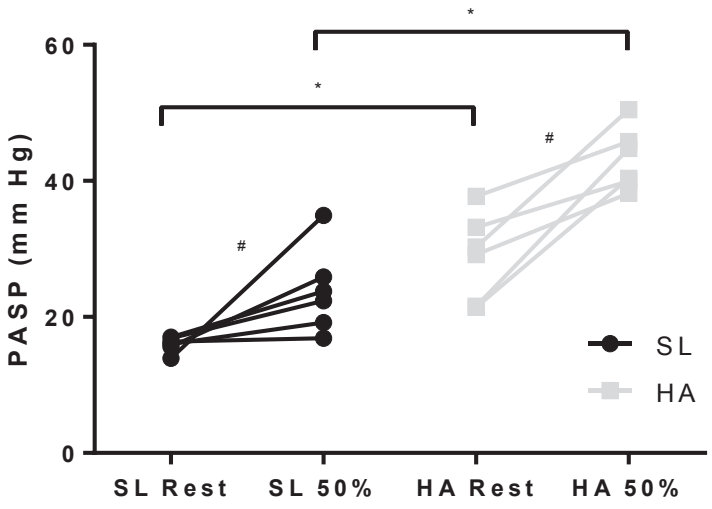


Figure 3:

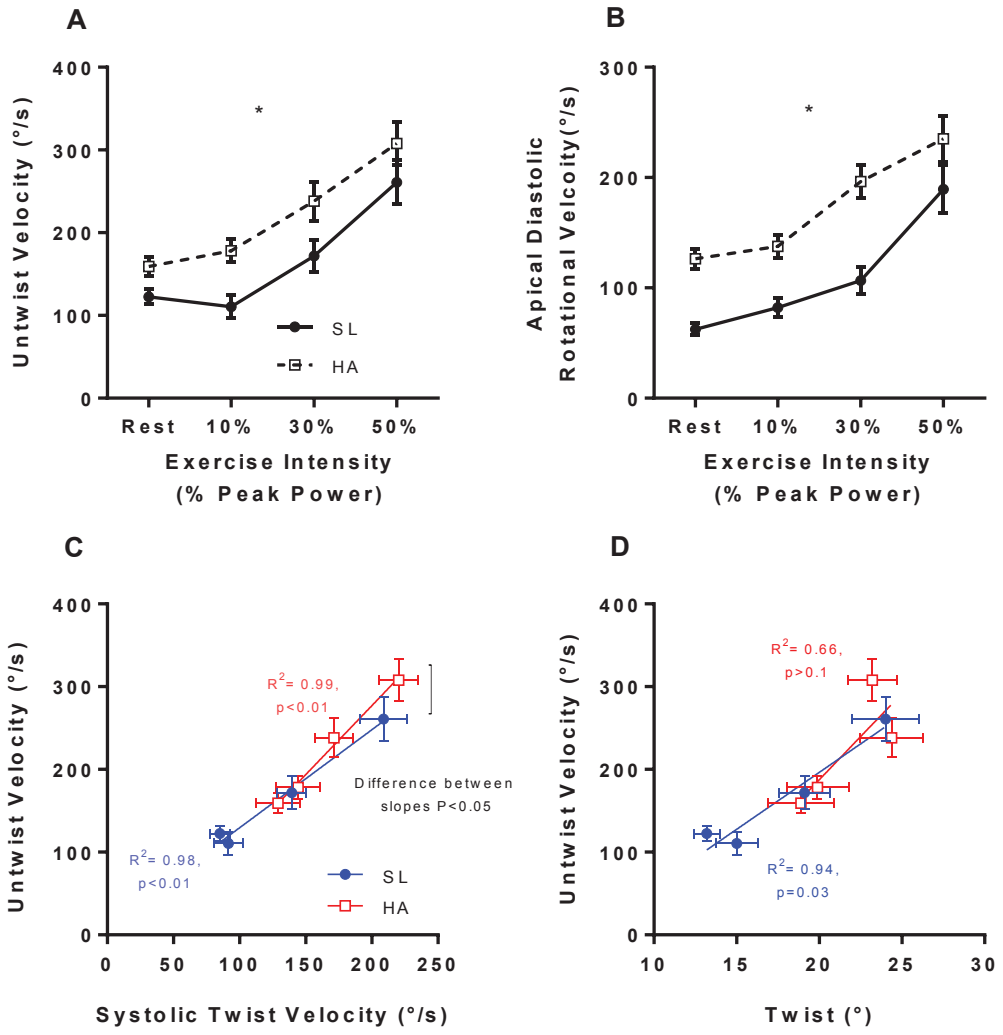
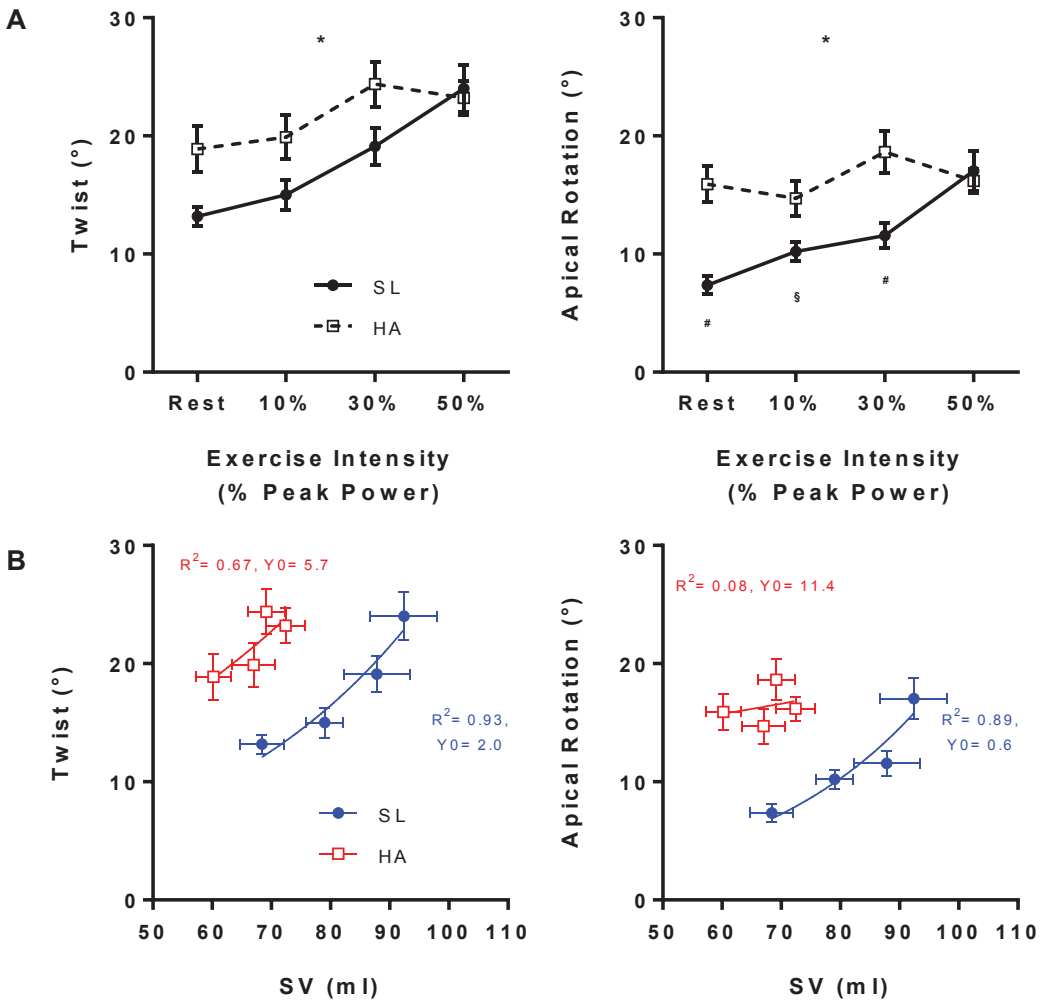

A
Untwist Velocity (°/s)
400
300
200
100
0
*
SL
HA
Rest
10%
30%
50%
Exercise Intensity
(% Peak Power)
B
Apical Diastolic
Rotational Velcoity(°/s)
300
200
100
0
*
Rest
10%
30%
50%
Exercise Intensity
(% Peak Power)
C
Untwist Velocity (°/s)
400
300
200
100
0
R2= 0.99,
p<0.01
Difference between
slopes P<0.05
R2= 0.98,
p<0.01
SL
HA
0
50
100
150
200
250
Systolic Twist Velocity (°/s)
D
Untwist Velocity (°/s)
400
300
200
100
0
R2= 0.66,
p>0.1
R2= 0.94,
p=0.03
10
15
20
25
30
Twist (°)

Figure 4:


A
Twist (°)
Apical Rotation (°)
30
20
10
0
*
§
#
SL
HA
Rest
10%
30%
50%
Exercise Intensity
(% Peak Power)
B
R2= 0.67, Y0= 5.7
R2= 0.93,
Y0= 2.0
R2= 0.08, Y0= 11.4
R2= 0.89,
Y0= 0.6
50
60
70
80
90
100
110
SV (ml)