Cardiac structure and function in adolescent Sherpa; effect of habitual altitude and developmental stage.

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Abstract

The purpose of this study was to examine ventricular structure and function in Sherpa adolescents to determine whether age-specific differences in oxygen saturation and pulmonary artery systolic pressure (PASP) influence cardiac adaptation to chronic hypoxia early in life. Two-dimensional, Doppler and speckle-tracking echocardiography were performed on adolescent (9-16 years) highland Sherpa (HLS; 3840 m; n=26) and compared with age-matched lowland Sherpa (LLS; 1400 m; n=10) and lowland Caucasian controls (LLC; sea level; n=30). The HLS were subdivided into pre- and post-adolescence; SpO_2 was also recorded. Only HLS exhibited a smaller relative LV EDV; however, both HLS and LLS demonstrated a lower peak LV untwisting velocity in comparison to LLC (92±26 and 100±45 vs. 130±43 °/s, $P<0.05$). Although SpO_2 was similar between groups, PASP was higher in post- vs. pre-adolescent HLS (30±5 vs. 25±5 mmHg, $P<0.05$) which negatively correlated with RV strain rate ($r=0.50$, $P<0.01$). Much like their adult counterparts, HLS and LLS adolescents exhibit slower LV diastolic relaxation despite residing at different altitudes. These findings suggest fundamental differences exist in the diastolic function of Sherpa that are present at an early age and may be retained after migration to lower altitudes. The higher PASP in post-adolescent Sherpa is in contrast to previous reports of lowland children at HA and unlike lowlanders, was not explained by differences in SpO_2; thus, different regulatory mechanisms seem to exist between these two distinct populations.

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New & Noteworthy

Slower diastolic relaxation is evident from an early age in high altitude Sherpa, even in in those who have since migrated to lower altitudes. Furthermore, in direct contrast to lowland children at high altitude, pulmonary pressure is greater in post-adolescent Sherpa; a difference that was not explained by oxygen saturation.

Introduction

High altitude (HA) natives exhibit different left ventricular (LV) diastolic function (12, 33) in comparison to sea level inhabitants that is characterized in *adult* Sherpa by lower early trans-mitral filling, slower LV diastolic relaxation and ultimately a smaller LV end-diastolic volume (EDV). At sea level, this cardiac phenotype is associated with a number of clinical conditions involving hypoxia (e.g. obstructive sleep apnea and chronic obstructive pulmonary disease) (11, 15). Whilst the hypoxemia experienced by HA natives is not pathologic in nature, it is unknown whether hypoxia has a life-long effect on LV diastolic function, or whether differences develop in adulthood subsequent to prolonged hypoxic exposure.

Sherpa residing at HA experience a chronic hypoxemia throughout their lifetime that has a broad effect on the fundamental physiology of HA natives in comparison to life at sea level (26, 32, 35, 42). Interestingly, the severity of this hypoxemia is less during adolescence compared to adulthood (8). The greater oxygen saturation during adolescence has been attributed to developmental changes that occur during infancy and childhood and result in oxygen saturation peaking during adolescence, before a gradual decline with ageing. Accordingly, during adolescence, Sherpa experience a lesser degree of hypoxia-related stress than at any other point throughout their lifetime. It is therefore possible that if the differential LV diastolic function previously observed in Sherpa adults is secondary to hypoxemia, then such differences may be less severe or not present in Sherpa children due to the shorter time of HA exposure and lower degree of hypoxemia. Moreover, if LV diastolic function is modifiable, Sherpa children who have relocated to lower altitudes should exhibit comparable diastolic function to their sea level counterparts.

Vasoconstriction of the pulmonary artery (26) in response to oxygen desaturation is a well-documented response to HA. Above 3000m pulmonary artery pressure is inversely related to oxygen saturation such that the greater the level of desaturation, the higher the pulmonary artery systolic pressure (PASP) (17). This elevation in pulmonary pressure has been suggested to dictate the developmental pattern of ventricular *structure* in children native to high altitude (28); however, little is known regarding the impact on diastolic *function*. Increased pulmonary artery pressure in hypoxia has been shown to negatively impact left ventricular diastolic filling in lowland adults after rapid ascent (<24 hours) to 4559 m (2). The higher arterial oxygen saturation in HA adolescents could therefore reduce the severity of hypoxic pulmonary vasoconstriction

(HPV) thereby improving diastolic function. HPV is, however, known to be higher in pre- vs. post-adolescent lowlanders at high altitude (3), but it is unknown whether this age-related difference is also evident in high altitude natives, and whether there is a subsequent effect on LV diastolic function.

Accordingly, the aims of the current study were to (i) investigate whether the differential diastolic function observed previously in adult Sherpa is present during adolescence at high and low altitude and (ii) assess the age-related differences in HPV and the consequences for LV filling. It was hypothesized that (i) diastolic function in Sherpa adolescents at both high and low altitude would be comparable to lowland controls and (ii) pulmonary artery pressure would be higher in pre-adolescent highland Sherpa compared to their older counterparts.

Methods

Study population

A total of 72 male adolescents volunteered for the study consisting of 42 high-altitude natives originating from the Khumbu Valley of Nepal and 30 Caucasian lowlanders recruited locally in the United Kingdom. Criteria for inclusion in the study were: age between 10-16 years, absence of cardiorespiratory disease and ability to provide written informed consent. The study was approved by the Human Ethics Committee of the University of British Columbia and the Nepal Health Medical Research Council, and conformed with the Declaration of Helsinki. The high altitude native cohort all self-identified to be of Sherpa ethnicity and all participants were divided into three groups depending on their current altitude and ethnicity as defined below. Of the 72 participants, four were omitted from the high altitude group *post-hoc* due to recent travel to lower altitudes and two participants were removed from the lowland Sherpa as they were born at low altitude.

(i) Highland Sherpa (HLS)

Twenty-six high altitude Sherpa (13.1 ± 2.0 years) were studied at Khunde Hospital (3840 m) and recruited via word of mouth. All participants were born in the Khumbu valley above an altitude of 2900 m and currently residing in either Khumjung (3970 m) or Khunde (3840 m). To examine age-related changes in hypoxic pulmonary vasoconstriction, HLS were subdivided into pre and post adolescence groups (10-12 years, n=12 and 14-15 years, n=14, respectively). Maturational stage was assessed by estimating peak height velocity (i.e. the stage at which height changes at the greatest rate) from anthropometric measurements as previously described (24)

(ii) Lowland Sherpa (LLS)

Ten age-matched low altitude Sherpa (11.8 ± 2.3 years) were recruited via their local school in Kathmandu (1400 m). All participants were born at high altitude (Khumbu Valley) but had been residing at low altitude for at least five years. None had visited an elevation above 1400 m in the previous six months.

(iii) Lowland Caucasian (LLC)

Thirty age-matched lowland controls (13.1 ± 1.8 years) were recruited through a local school in the United Kingdom and self-identified as Caucasian ethnicity. None of the lowlanders had previously resided at high altitude. Unlike HLS, the LLC controls were not subdivided into pre- and post-adolescence groups. The purpose of this subdivision was to examine age-related differences in HPV, and because LLC were only assessed at sea level this was not possible.

Experimental Protocol

Stature and body mass were recorded prior to 10 minutes of supine rest. From these data, body mass index (BMI) (5) and body surface area (BSA) were calculated (7). Blood pressure (sphygmomanometer and stethoscope), arterial oxygen saturation (pulse oximetry; Nonin Onyx Oximeter, Plymouth, MN) and heart rate (3-lead ECG; Vivid q, GE Medical Systems, Israel Ltd) were all recorded after the rest period and repeated at the end of a transthoracic echocardiogram.

Transthoracic Echocardiography

A comprehensive left and right ventricular echocardiographic examination was completed by the same sonographer using a commercially available ultrasound system (Vivid q, GE Medical Systems, Israel Ltd). A 1.5-4 MHz phased array transducer was used to collect echocardiographic images in the parasternal long-axis, short-axis and apical four- and two-chamber views with three consecutive cardiac cycles recorded for offline analysis (Echopac, GE Medical, Horton, Norway).

Ventricular Structure

Left ventricular internal diameter and septal and posterior wall thicknesses were assessed from a two-dimensional parasternal long-axis view and used to calculate relative wall thickness and LV mass in accordance with the European Society of Echocardiography guidelines (19). Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were measured from planar tracings of the endocardial border in both the apical four- and two-chamber view using Simpsons biplane method. Right ventricular (RV) end-diastolic area (EDA) and end-systolic area (ESA) were assessed from a modified apical four-chamber. Appropriate visualization to determine areas of the RV was possible in all participants apart from one participant from the LLS group, who was subsequently removed from all RV analysis.

Scaling of Structural Parameters

LV mass was scaled relative to BSA (25) as this is the most appropriate method in a pediatric population (14). Ventricular volumes and areas were allometrically scaled for height through the calculation of a common scaling exponent for the study population, as previously described (6, 33, 40).

Conventional Ventricular Function

LV ejection fraction and stroke volume were calculated from LV EDV and ESV, and cardiac output calculated by multiplying stroke volume by heart rate (19). RV fractional area change (FAC) was calculated as [EDA-ESA/EDA x 100] (29). Transmitral early (E) and late (A) diastolic filling were assessed using pulsed-wave Doppler recordings and the isovolumic relaxation time (IVRT) was measured as previously described (1) using tissue Doppler imaging. The peak systolic right ventricular-right atrial pressure gradient (ΔP_{max}) was determined by continuous-wave Doppler assessment of tricuspid regurgitation using the simplified Bernoulli equation. Right atrial pressure was estimated using collapsibility index of the inferior vena cava and added to ΔP_{max} for the estimation of pulmonary artery systolic pressure (PASP) (4, 30).

Ventricular Mechanics

Three cardiac cycles were exported for speckle-tracking analysis using commercially available software (Echopac, GE Medical, Horten, Norway, version 110.1.1). Right ventricular longitudinal strain and strain rate were assessed from a modified apical four-chamber view using the global RV myocardial method (20). RV strain was successfully assessed in all HLS and LLC, but only 55% of LLS. Left ventricular longitudinal strain and strain rate were measured from an apical four-chamber view, and LV circumferential strain, rotation and their time derivatives were assessed in parasternal short-axis views of the LV base and apex as previously described (33). Short-axis apical data were subtracted from basal data to calculate LV twist, twist velocity and untwist velocity (44). Cubic spline interpolation was completed on frame-by-frame data using custom-made software (2D Strain Analysis Tool, Stuttgart, Germany) in order to time-align data and allow calculation of relative event timings (33, 36). The coefficient of variation of key measurements performed by the sonographer in this study have been published previously (34).

Statistical Analysis

Results are presented as means ± SD. Comparison of high altitude Sherpa, low altitude Sherpa and Caucasian controls were analyzed using a one-way analysis of variance with alpha set *a priori* to 0.05 (IBM SPSS for Windows, V20, Armonk, NY). Relationships were analyzed using linear regression in GraphPad Prism (GraphPad Prism for Windows, Version 5.0.1, San Diego, California, USA) and independent *t*-tests were conducted to determine differences between pre- and post-adolescent HLS.

Results

Clinical, hemodynamic and anthropometric characteristics of the study population

Both HLS and LLS had a lower body mass, height and body surface area than LLC, but all three groups were classified as 'healthy weight' for age-specific BMI (Table 1). Systolic and diastolic blood pressures were slightly higher in HLS compared to LLC (120 ± 12 vs. 107 ± 9 mmHg and 72 ± 9 vs. 66 ± 7, respectively), but there were no differences in heart rate, LV mass, relative wall thickness or LV ejection fraction between groups (Table 1). The PASP was higher in HLS, but only three participants were classified as hypertensive (as defined as a PASP >35 mm Hg).

Left ventricular function

The HLS exhibited a smaller LV EDV compared to LLS (p=0.036) and LLC (p=0.067; Table 1) when normalized for body height. Despite the lower LV EDV, there was no difference in transmitral early to late filling ratio (E/A) between groups. Both HLS and LLS did, however, demonstrate slower diastolic relaxation characterized by lower E', longer IVRT and lower peak untwisting velocity (Table 2, Figure 1). As discussed above, ejection fraction was not different between groups, nor was LV twist, rotation or longitudinal strain.

Right ventricular function

In contrast to the LV, there were no significant differences in RV EDA between groups. RV longitudinal strain and strain rate were lower in HLS compared to LLS (23.3 ± 3.2 vs. 27.1 ± 2.5%, p=0.008 and 1.28 ± 0.23 vs. 1.58 ± 0.25 %/s, p=0.01; n=6 in LLS), with no difference between HLS and LLC.

Age-related changes in HLS

Pre-adolescent Sherpa were estimated to be 0.8 years before and post-adolescent Sherpa 1.9 years post the point at which height changes at the greatest rate (P<0.001).. SpO_2 (90.8 ± 2.9 vs. 91.1 ± 1.9%, P= 0.75) and MAP (90 ± 8 vs. 86 ± 6 mmHg, P= 0.18) did not differ between age groups, nor were there significant differences in LV EDV (scaled for height), transmitral filling ratio, IVRT or untwist velocity. In contrast, PASP was higher in post-adolescent HLS (Figure 2a) and RV strain rate was lower (1.15 ± 0.20 vs. 1.40 ± 0.20, p=0.01). When the age groups were combined, PASP was negatively correlated with RV strain rate (Figure 2b; r=0.496 p<0.01).

Discussion

For the first time this study examined cardiovascular structure and function in adolescent Sherpa. There were three novel findings. (i) In comparison to lowland controls, adolescent Sherpa residing at high altitude demonstrate a smaller LV EDV that is accompanied by slower LV diastolic relaxation. (ii) Slower diastolic relaxation was also evident in age-matched Sherpa residing at low altitude. Lastly, (iii) post-adolescent Sherpa exhibit a higher pulmonary artery pressure that was associated with a lower RV longitudinal function in comparison to their pre-adolescent counterparts.

LV diastolic function

The smaller LV EDV relative to body size is in agreement with recent reports of LV structure in adult Sherpa and historical evidence in Andeans (31, 33). The smaller ventricular volumes were accompanied by a slower LV relaxation compared to lowland controls, as assessed by lower early myocardial velocity, longer IVRT and slower untwisting velocity. At sea level, rapid untwisting is associated with positive diastolic function, and is known to be reduced in systemic hypertension (37), pathologic LV hypertrophy (38) and to decline with healthy ageing (41). The rapid relaxation resulting from the release of potential energy generated during systole facilitates LV pressure decay and aids passive transmitral filling (27, 41). The absence of rapid untwisting leads to less efficient filling of the LV and ultimately elevated atrial pressure (10, 13). Data in the present study suggest this alteration to diastolic function is a life-long feature of high altitude natives, but the underlying cause and long-term consequences are yet to be determined. Perhaps most surprising is the presence of decreased untwisting velocity in LLS residing at 1400 m despite maintained oxygen saturation (96%). Recently, Dedobbeleer and coworkers (12) reported slower LV untwisting in high altitude Andeans ruling out the possibility that this feature of diastolic function is unique to Sherpa. The lower untwist velocity may be partially explained by arterio-ventricular coupling, as HLS exhibited higher systolic and diastolic blood pressure compared to LLC. Previously, high-normal blood pressure has been shown to result in lower untwist velocity (37). However, intriguingly LLS presented with slower untwisting velocity despite comparable blood pressure to LLC. This would suggest than an alternative mechanism other than systemic blood pressure is responsible for the slower diastolic relaxation observed.

As a potential explanation, we speculate that the slower LV relaxation observed in both adult and adolescent highlanders may be a consequence of high altitude exposure early in fetal development or life, which is retained even after migration to lower altitudes. A potential mechanism is discussed in the following section.

Slower diastolic relaxation in Sherpa; potential role of titin

Hypoxic exposure during critical stages of development has the potential to result in permanent physiological differences, and has therefore led to the development of a concept termed 'programming' (16, 21). For example, chronic hypoxemia *in utero* has a profound effect on the relaxation of the peripheral vasculature in the offspring during adulthood (16, 39). Whether such differences exist in cardiac relaxation is yet to be established. In the mammalian heart, energy generated during contraction is stored within the extracelluar collagen matrix (43) and in a large protein called titin, which forms a dynamic intrasarcomeric filament that acts as a 'spring' within the cardiomyocyte (18). Titin is therefore actively involved in the rapid relaxation of the ventricle during early diastole (27), and its gene activation is regulated exclusively by hypoxic-inducible factors (HIF) during embryogenesis.. Therefore, HIF1α provides a possible mechanistic basis for oxygen signaling and the regulation of key components of myofibrillogenesis *in utero*. In comparison with adults, at this stage of development titin is expressed as a more compliant isoform of the protein termed 'fetal titin' (N2BA). N2BA develops a lower passive tension than the adult N2B isoform, and the higher compliance results in a slower relaxation of the ventricle. In the first week of life, there is a gradual shift from the N2BA isoform towards the stiffer adult N2B isoform (18). This change coincides with an increase in the early transmitral blood flow velocity that is likely a consequence of faster LV relaxation and recoil (18, 45). Considering the integral role titin plays in the restoring forces of the myocardium and its control via HIF pathways, it is tempting to speculate that modification to this molecular spring may play a role in the slower relaxation observed in the current study through cardiac 'programming'. Divergent postnatal development of RV-LV structure and geometry has already been observed between high altitude Andeans and lowland controls (28), and changes in molecular components likely underpin gross structural changes.

We have confirmed the presence of slower diastolic relaxation in adolescent Sherpa in comparison to their lowland counterparts. The consequences later in life are, however,

currently unknown and require further attention to determine whether difference sin LV diastolic function become more apparent with ageing. A greater understanding of the unusual vascular phenotype previously reported in this unique adult population (9) is also required. In contrast to adults, the slower early diastolic untwisting does not appear to affect the ratio of early to atrial transmitral filling, as both were preserved in HLS and LLS. In this context, a lower untwisting velocity despite the absence of disease and traditional cardiovascular risk factors is intriguing, but further work is required to establish the long-term cardiovascular consequences in older generations.

Age-related changes in hypoxic pulmonary vasoconstriction

In addition to changes in LV relaxation, HPV has also previously been implicated in diastolic dysfunction secondary to the hypoxemia. It has been proposed that greater RV afterload leading to lower RV ejection and consequently under filling of the LV could explain the modified LV filling observed (2). In the current study, the primary differences between HLS and LLS in this regard were the absence of HPV, higher RV longitudinal systolic function and larger LV EDV in LLS. Therefore, as previously suggested, HPV may increase RV afterload, decrease RV function and lower LV filling in high altitude natives, and we propose this effect may be present at an early stage of life.

Previously, the hypoxia-mediated increase in PASP has been shown to be nearly two-fold higher in younger (6-9 years) versus older (14-16 years) lowland adolescents after ascent to 3450 m (3). The authors speculated this differential response maybe due to to higher sympathetic activity in the younger population, as determined by heart rate variability. The higher sympathetic activity was assumed to have had a direct effect on HPV thus elevating PASP. This was an important finding as increased PASP is related to high altitude pulmonary edema and chronic mountain sickness (22, 23), and could render younger children more susceptible to these illnesses. In addition to the negative correlation between pulmonary artery pressure and age ($r=-0.33$; $P<0.001$), the authors also reported arterial oxygen saturation to be inversely related to pulmonary artery pressure ($r= -0.32$; $p<0.001$). The age-related differences in pulmonary artery pressure may therefore not be a direct effect of sympathetic activity as suggested by the authors, and be a consequence of greater desaturation in the younger children instead. The pulmonary pressure response we present in HLS is in direct contrast with the previous findings in lowlanders. In HLS, PASP was *greater* in pre- verses post-adolescents. The RV longitudinal strain rate was also lower in post-adolescents, a difference that was related

to the higher PASP suggesting an impact on fundamental RV systolic function. There was, however, no difference in oxygen saturation or MAP between groups, leading us to speculate that unlike lowlanders, the difference was not related to greater levels of oxygen desaturation or a systemic effect on the vasculature. In summary, it would appear age-related differences in HPV are not the same in lowlanders during short-term exposure and life-long residents of high altitude, nor are they controlled via the same mechanism.

Limitations and future directions

Comparison between different ethnicities is an ever-present issue with high altitude research. We attempted to control for this by recruiting Sherpa from lower altitudes. As Kathmandu is not traditionally inhabited by Sherpa, it was difficult to recruit large numbers in the LLS group. As stated in the discussion, the HPV response to high altitude varies greatly between individuals. Therefore, caution must be exerted when drawing conclusions from comparisons of relatively low numbers. Future research should aim to investigate the effects of chronic hypoxemia on myocardial development at a molecular level, and establish the consequences of impaired diastolic relaxation with ageing in Sherpa. In addition, attention should also be played to the role autonomic control in relation to the pulmonary vascular responses and ventricular function.

Conclusions

In conclusion, this study demonstrated that slower diastolic relaxation is present during adolescence in Sherpa, irrespective of high or low altitude residence. Such differences in diastolic function may be a consequence of hypoxic exposure *in utero* or early in life that has resulted in permanent fundamental changes in cardiac physiology. In contrast to previous reports of lowland children during short-term high altitude exposure, post-adolescent Sherpa demonstrate greater pulmonary artery pressure compared to their pre-adolescent counterparts. This highlights the importance of ethnicity and duration of exposure when considering the cardiovascular responses to hypoxia in a pediatric population. Collectively these findings further our understanding of the effects of chronic hypoxemia on cardiac structure and function. Such knowledge is applicable to an increasing population of high altitude dwellers (>140 million people) and to a myriad of clinical conditions involving hypoxemia.

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Competing Interests

No conflicts of interest are declared by the authors.

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555 Table 1. Clinical and hemodynamic characteristics of HLS, LLS and LLC.

	HLS	LLS	LLC	*p value*
Clincal and Haemodynamic Characteristics				
Age (years)	13 ± 2	12 ± 2	13 ± 2	0.08
SpO2 (%)	91 ± 2	96 ± 1 *	98 ± 1 *†	<0.001
Mass (kg)	40.6 ± 11.4	40.1 ± 10.1	51.4 ± 11.1 *†	<0.001
Height (cm)	149.0 ± 16.7	145.5 ± 14.2	161.1 ± 12.5 *†	0.001
BSA (m^2)	1.29 ± 0.25	1.20 ± 0.20	1.51 ± 0.22 *†	<0.001
BMI (kg/m^2)	17.9 ± 2.1	18.1 ± 2.3	19.7 ± 2.5 *	0.013
Systolic BP (mm Hg)	120 ± 12	111 ± 15	107 ± 9 *	<0.001
Diastolic BP (mm Hg)	72 ± 9	62 ± 8 *	66 ± 7 *	0.003
Total Peripheral Resistence (mm Hg L min^{-1})	36 ± 12	25 ± 6 *	27 ± 5 *	<0.001
PASP (mm Hg)	27.4 ± 5.7	19.7 ± 3.4 *	19.3 ± 3.2 *	<0.001
Cardiac Parameters				
LV Mass (g/m^2)	63 ± 16	65 ± 13	68 ± 12	0.35
Relative Wall Thickness	0.40 ± 0.70	0.41 ± 0.08	0.37 ± 0.06	0.11
Heart Rate (bpm)	69 ± 15	80 ± 16	77 ± 13	0.015
Cardiac Output/ Height ($l/min/cm^{2.01}$)	1.10 ± 0.24	1.52 ± 0.23 *	1.43 ± 0.49 *	<0.001
Stroke Volume ($ml/cm^{2.48}$)	13.7 ± 2.6	15.5 ± 2.8	14.9 ± 2.1	0.06
LV EDV ($ml/cm^{2.43}$)	23.5 ± 5.0	26.3 ± 4.5 *	26.0 ± 3.3	0.042
LV ESV ($ml/cm^{2.33}$)	10.0 ± 2.2	10.9 ± 2.0	11.3 ± 1.6 *	0.04
RV EDA ($ml/cm^{1.61}$)	7.21 ± 1.06	7.43 ± 1.57	7.58 ± 1.00	0.488
RV ESA ($ml/cm^{1.64}$)	3.96 ± 0.78	3.90 ± 0.98	4.24 ± 0.85	0.285
LV Ejection Fraction (%)	59 ± 3	60 ± 3	59 ± 3	0.53
RV Fractional Area Change[a] (%)	56 ± 5	52 ± 5	57 ± 6	0.107

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557 SpO_2, oxygen saturation; BSA, body surface area; BMI, body mass index; BP, blood
558 pressure; PASP, pulmonary artery systolic pressure; LV, left ventricle; EDV, end-diastolic
559 volume; ESV, end-systolic volume; EDA, end-diastolic area; ESA, end-systolic area. * $p <$
560 0.05 vs. HLS and † $p < 0.05$ vs. LLS. [a] Data available on six LLS.

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564 Table 2. Left ventricular systolic and diastolic function in HLS, LLS and LLC.

	HLS	LLS	LLC		*p value*
Systolic Parameters					
Twist (°)	15.2 ± 5	14.1 ± 4.6	14.2 ± 5.0		0.72
Systolic Twist Velocity (°/s)	104 ± 34	101 ± 30	98 ± 30		0.71
Basal Rotation (°)	5.6 ± 3.4	7.4 ± 3.2	7.1 ± 3.1		0.31
Basal Rotational Velocity (°/s)	62 ± 24	67 ± 23	81 ± 21	*	0.009
Basal Circumferential Strain (%)	17.7 ± 3.0	18.2 ± 4.5	20.9 ± 1.9	*†	<0.001
Basal Circumferential Strain Rate (%/s)	1.06 ± 0.16	1.25 ± 0.27	1.28 ± 1.55	*	<0.001
Apical Rotation (°)	10.3 ± 3.9	7.5 ± 3.5	8.5 ± 3.8		0.087
Apical Rotational Velocity (%/s)	56 ± 16	50 ± 22	68 ± 32		0.095
Apical Circumferential Strain (%)	22.2 ± 4.9	22.7 ± 4.7	25.7 ± 3.2	*	0.006
Apical Circumferential Strain Rate (%/s)	1.49 ± 0.35	1.63 ± 0.25	1.67 ± 0.29		0.091
Longitudinal Strain (%)	20.2 ± 2.0	19.4 ± 2.5	18.9 ± 2.1		0.086
Longitudinal Strain Rate (%/s)	1.10 ± 0.16	1.15 ± 0.10	1.10 ± 0.14		0.652
Diastolic Parameters					
Transmitral E (cm/s)	0.99 ± 0.10	1.03 ± 0.18	0.97 ± 0.14		0.486
Transmitral A (cm/s)	0.46 ± 0.09	0.50 ± 0.11	0.50 ± 0.10		0.245
Transmitral E/A	2.21 ± 0.46	2.15 ± 0.58	2.00 ± 0.55		0.315
E' (cm/s)	0.12 ± 0.03	0.12 ± 0.01	0.15 ± 0.02	*†	<0.001
A' (cm/s)	0.06 ± 0.01	0.07 ± 0.01	0.07 ± 0.02		0.087
E'/A'	2.00 ± 0.74	1.78 ± 0.43	2.20 ± 0.61		0.176
IVRT (ms)	65 ± 11	61 ± 8	52 ± 10	*†	<0.001
Untwist Velcoity (°/s)	92 ± 27	99 ± 48	130 ± 43	*	0.001
Basal Diastolic Rotational Velocity (°/s)	43 ± 21	58 ± 19	66 ± 23	*	0.001
Basal Diastolic Circumferential Strain Rate (%/s)	1.72 ± 0.31	1.74 ± 0.39	2.07 ± 0.40	*†	0.001
Apical Diastolic Rotational Velocity (°/s)	69 ± 26	56 ± 37	77 ± 32		0.134
Apical Diastolic Circumferential Strain Rate (%/s)	1.94 ± 0.61	2.25 ± 0.67	2.74 ± 0.63	*	<0.001
Longitudinal Diastolic Strain Rate (%/s)	2.07 ± 0.37	1.95 ± 0.24	1.96 ± 0.23		0.348

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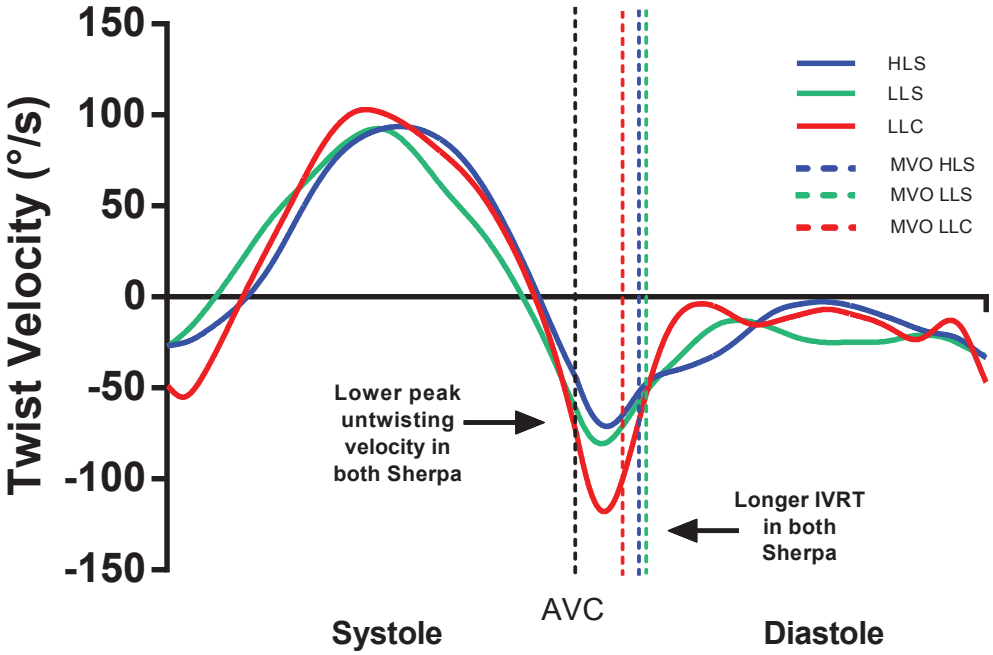
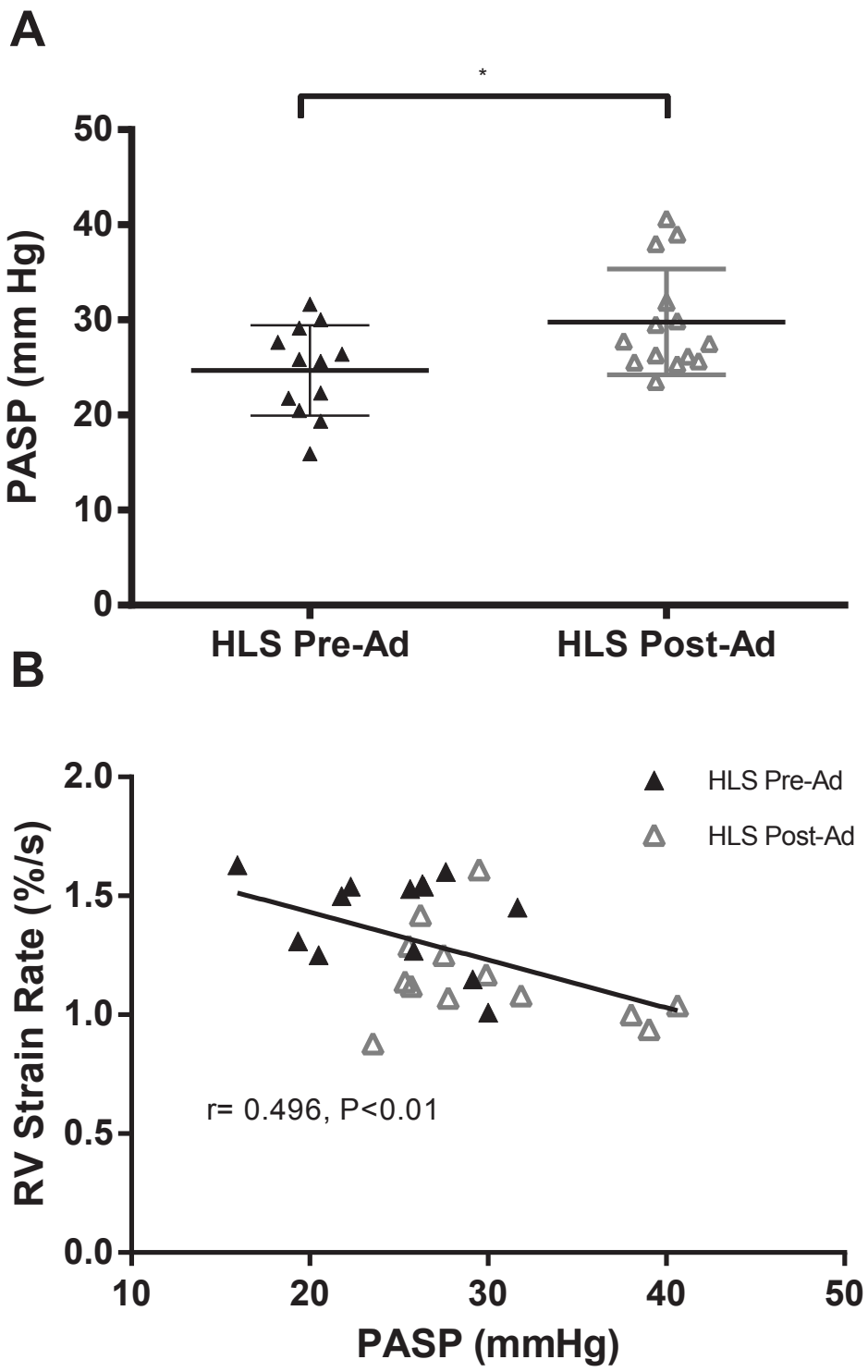
566 E, early; A, atrial; E', early velocity; A', atrial velocity; IVRT, isvolumic relaxation time. * p
567 < 0.05 vs. HLS and † p < 0.05 vs. LLS.

Figure 1. Mean twist and untwist velocity curves for HLS, LLS and LLC over the entire cardiac cycle. Despite comparable systolic twist velocity, diastolic untwisting was slower in both Sherpa groups, and the isovolumic relaxation time prolonged. AVC= aortic valve closure; MVO= mitral valve opening. Please note, statistical differences are presented in Table 2.

Figure 2. Individual pulmonary artery systolic pressure data plots and subsequent relationship with right ventricular function in pre- and post-adolescent highland Sherpa. PASP was higher in the post-adolescent group compared to pre**-adolescents and** PASP was negatively correlated with RV longitudinal strain rate. PASP= pulmonary artery systolic pressure; Pre-Ad, pre-adolescent; Post-Ad, post-adolescent. * p=0.02.


150
100
50
0
-50
-100
-150
Twist Velocity (°/s)
HLS
LLS
LLC
MVO HLS
MVO LLS
MVO LLC
Lower peak untwisting velocity in both Sherpa
Longer IVRT in both Sherpa
AVC
Systole
Diastole


A
*
50
40
30
20
10
0
PASP (mm Hg)
HLS Pre-Ad
HLS Post-Ad
B
2.0
1.5
1.0
0.5
0.0
RV Strain Rate (%/s)
HLS Pre-Ad
HLS Post-Ad
r= 0.496, P<0.01
10
20
30
40
50
PASP (mmHg)