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Heart mechanics at high altitude: 6 days on the top of Europe

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Aims The aim of this study was to analyse the underlying mechanisms of left and right ventricular (LV and RV) functional alterations during several days in high-altitude hypoxia.

Methods and results Resting evaluations of LV and RV function and mechanics were assessed by Speckle Tracking Echocardiography on 11 subjects at sea level (SL_{PRE}), 3 ± 2 h after helicopter transport to high altitude (D0), at day 2 (D2), day 4 (D4) and day 6 (D6) at 4350 m and 5 ± 2 h after return to sea level (SL_{POST}). Subjects experienced acute mountain sickness (AMS) during the first days at 4350 m. LV systolic function, RV systolic and diastolic function, LV and RV strains and LV synchrony were unchanged at high altitude. Peak twist was increased at D0, continued to increase until D6 (SL_{PRE}: 9.0 ± 5.1deg; D6: 13.0 ± 4.0deg, $P < 0.05$), but was normalized at SL_{POST}. Early filling decreased at high altitude with a nadir at D2 (SL_{PRE}: 78 ± 13 cm s^{-1}; D2: 66 ± 11 cm s^{-1}, $P < 0.05$). LV filling pressures index was decreased at high altitude with the minimum value obtained at D2 and remained reduced at SL_{POST}. Untwisting, an important factor of LV filling, was not decreased but was delayed at 4350 m.

Conclusions High-altitude exposure impaired LV diastolic function with the greatest effect observed at D2, concomitantly with the occurrence of AMS. The LV early filling impairments resulted from an increased RV afterload, a decrease in LV filling pressure and a delayed LV untwist. However, the increased LV twist probably acted as a compensatory mechanism to maintain cardiac performance during high-altitude hypoxia.

Keywords hypoxia • echocardiography • ventricle mechanics

Introduction

High altitude-induced hypoxia represents a main physiological stress and is often associated with acute mountain sickness (AMS). The cardiovascular adaptations to hypoxia have been widely assessed and it was well-established that left and right ventricular (LV and RV, respectively) systolic functions were well-preserved whereas the diastolic function of both ventricles was generally impaired.[1] Nevertheless, most of the studies used conventional echocardiographic data[2] that makes unfortunately difficult any conclusion regarding the alterations of regional myocardial function.

Due to the unique arrangement of myofibres, cardiac form and function are intrinsically linked as reflected in the cardiac mechanics underpining ventricular function. During systole, cardiomyocytes contraction induces LV and RV strains and also LV twist, which promotes LV ejection fraction (EF).[3] Systolic twist stores potential energy in elastic components which is released very early in diastole, creating an intraventricular pressure gradient form base to apex that facilitates early filling. The untwisting efficiency can be estimated through the untwisting rate/peak twist ratio (i.e. the untwisting rate for one degree of twist).[4] Strains and twist can be assessed non-invasively using speckle-tracking echocardiography (STE) giving a better report on myocardial regional function and its underlying

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mechanisms. Recent studies reported LV mechanics during high-altitude exposure (>5000 m) after several days of trekking.[5,6] However, trekking implies confounding factors (i.e. physical activity, acclimatization processes), making difficult strong conclusions regarding the specific role of high-altitude hypoxia on myocardial function. To our knowledges, only Dedobbeleer *et al.*[7] recently reported LV strains and torsion adaptation to high altitude using motorized transport, but after 2 days of acclimatization at 3000 m.

The aim of the study was to provide a comprehensive assessment of the impact of high-altitude hypoxia on regional myocardial function of the LV and RV using STE.[8] Whereas many studies explored response to hypoxia after acclimation or during classic mountain acclimation process, the participants involved in our study were transported with a 10-min helicopter flight from sea level to 4350 m. Since AMS occurs generally within the first 6–36 h[9] for visitors spending prolonged time at high altitude, the processes of adaptation of the cardiovascular system occurring during this initial period may well determine the individual's ability to continue to function normally. Thus, we evaluated the time course of the cardiac adaptations during 6 days from the first hours after arrival. We hypothesized that (1) the drop in LV and RV diastolic filling during high-altitude hypoxia is associated with alterations of regional function including alteration in LV relaxation or untwisting efficiency and (2) the efficient heart adaptation to high altitude involves an increase in LV twist acting as a compensatory mechanism counterbalancing the drop in LV diastolic function.

Methods

Study participants

Eleven males (age 28 ± 8 years) were included and examined at the Grenoble University Hospital (altitude: 212 m). Individuals with pulmonary and cardiovascular diseases such as cardiopathy, arteriopathy and arterial hypertension were excluded. Subjects were usual recreational climbers with no history of high-altitude pulmonary edema during previous high-altitude ascents and were not acclimatized to high altitude. All participants provided written informed consent and the study was approved by the local institutional Ethics Committee and performed according to the Declaration of Helsinki (registration number: RCB2011-A00071-40, ClinicalTrials.gov ID: NCT01565603).

Research design

All participants underwent helicopter transport to be dropped 10 min later at 4350 m (*Vallot scientific hut*, Mont Blanc, Chamonix, France). They stayed 6 days without further ascent and received no treatment to prevent/treat AMS. All investigations were conducted at sea level (SL_{PRE}), 3 ± 2 h after arrival at altitude (D0), day 2 (D2), day 4 (D4) and day 6 (D6) at 4350 m and 5 ± 2 h after return to sea level (SL_{POST}).

Clinical examination

Clinical examination included measurements of systolic and diastolic blood pressure (BP) (Dinamap, GE Medical Systems Inc., Milwaukee, WI) in supine position after 10 min of rest. Arterial oxygen saturation (SpO_2) was measured using finger-pulse oximetry (Biox 3740 Pulse Oximeter, Ohmeda, Louisville, CO) after finger warming and signal stabilization (room temperature: 15–20 °C). Subjects were also asked to complete self-reported questionnaires at SL_{PRE}, D2, D4 and D6 for AMS evaluation according to the Lake Louise Score (LLS, five items).[10] The presence of AMS was defined as LLS > 3.

Echocardiographic image acquisition

Images were obtained by a fully trained operator (GW) in the left lateral decubitus position using a commercially available system (Vivid Q, GE Healthcare, Horten, Norway) according to the recommendations.[11,12] Two-dimensional greyscale harmonic images were obtained at 65–90 frames per second and colour tissue velocity at 120–140 frames per second. Images were saved digitally for subsequent off-line analysis (EchoPac 6.0, GE Healthcare, Horten, Norway).

Two-dimensional and tissue Doppler echocardiography

Standard parameters were assessed according to the recommendations.[11,12] Tissue Doppler imaging (TDI) measures of LV myocardial systolic (S_m), early diastolic (E_m), and atrial (A_m) velocities were assessed at the mitral annulus level (mean of septal, lateral, inferior and anterior walls). We assessed wall velocities (S'_{RV}, E'_{RV} and A'_{RV}) at the tricuspid annulus level on the free-wall. LV E wave/$E'_{lateral}$ ratio was used as an index LV filling pressure.[13] Systolic tricuspid regurgitation (TR) gradient, a surrogate of systolic pulmonary artery pressure (systolic PAP), was calculated with the modified Bernouilli equation $TR = 4 \times V_{max}$.[2]

Speckle tracking echocardiography

STE analysis was conducted as previously described.[14] RV longitudinal strains were assessed on the free wall (three segments), from an apical 4-chamber view. LV global longitudinal strain (GLS) was assessed from apical 2-, 3- and 4-chamber views. LV circumferential strain (CS), rotations and twist were obtained from short-axis views according to specific recommendations.[15] Strain data were processed with a specific toolbox (Scilab 4.1, Consortium Scilab, INRIA-ENPC, Paris, France).[14,16] Longitudinal strain rate in early diastole (SrLd) was used as an index of LV relaxation.[17] The good intra-observer reproducibility of strain analysis (<8% for strains and rotations) has been reported in our laboratory.[14] The percentage of untwist during isovolumic relaxation time ($\%UT_{IVRT}$) was calculated as follows: $\%UT_{IVRT}$ = (twist at aortic valve closure–twist at the end of IVRT)/twist at aortic valve closure × 100. The untwisting rate/peak twist ratio was calculated as peak untwisting velocity normalized for peak twist. The twist-to-shortening ratio (TSR), an index of subendocardial dysfunction,[18] was calculated as peak twist divided by CS averaged from the basal and apical levels. The longitudinal strain delay index (LSDI) was used to analyse LV mechanical synchrony.[19] LSDI represents the sum of the wasted energy due to LV dyssynchrony across the 18 myocardial segments of the LV longitudinal strains from apical 2-, 3- and 4-chamber views.

Statistical analysis

Data are expressed as mean ± SD. Analysis of the statistical significance of temporal changes from SL_{PRE} to D6 was performed using one-way analysis of variance for repeated measurements (StatView SE program, SAS Institute, Cary, NC). When a significant main effect was found, *post hoc* analysis was performed with Bonferroni test for multiple comparisons, with sea level taken as the reference time. To analyse differences at sea level from before to after altitude exposure, SL_{PRE} and SL_{POST} were compared with paired *T*-test. Correlations were performed using pooled data from SL_{PRE} and the four evaluations at altitude using linear regression and Pearson's coefficient. Statistical significance was declared when $P < 0.05$.

Table 1 Subjects clinical characteristics at sea level (SL_{PRE}), after arrival (D0), on day 2 (D2), day 4 (D4), day 6 (D6) at high altitude and after return to sea level (SL_{POST})

	SL_{PRE}	D0	D2	D4	D6	ANOVA *P* value	SL_{POST}	vs. SL_{PRE} *P* value
SpO_2 (%)	97.9 ± 0.9	79.9 ± 3.3*	82.7 ± 3.0*†	84.5 ± 4.0*†	87.6 ± 2.2*†‡§	*<0.001*	97.8 ± 0.6	*1.00*
Systolic BP (mmHg)	120 ± 8	126 ± 10*	128 ± 8*	132 ± 8*†	135 ± 6*†‡	*<0.001*	119 ± 7	*0.61*
Diastolic BP (mmHg)	66 ± 9	65 ± 8	68 ± 11	72 ± 9	72 ± 10	*0.17*	70 ± 7	*0.15*
Mean BP (mmHg)	104 ± 6	107 ± 7	109 ± 7	114 ± 8*†	116 ± 7*†‡	*<0.001*	106 ± 7	*0.51*
Lake Louise Score (pts)	0.7 ± 0.8	–	3.5 ± 2.8*	2.5 ± 2.2*	1.1 ± 1.0‡§	*<0.001*	/	/

Significant differences: *$P < 0.05$ vs. SL_{PRE}; †$P < 0.05$ vs. D0; ‡$P < 0.05$ vs. D2; §$P < 0.05$ vs. D4.
SpO_2, arterial pulse oxygen saturation; BP, blood pressure.

Results

Clinical characteristics of the subjects

At D0, SpO_2 was reduced compared to SL_{PRE}, then progressively increased from D0 to D6 (*Table 1*). Systolic and mean BP progressively increased at 4350 m. At SL_{POST}, SpO_2 and BP were similar to baseline data. LLS was increased at D2 and D4 compared to SL_{PRE} and returned closed to SL_{PRE} values at D6.

RV diastolic and systolic function

Systolic PAP, RV gradient and pulmonary vascular resistance (PVR) were increased at D0, then decreased from D2 to D6 and remained higher than SL_{PRE} at SL_{POST}. All parameters of RV morphological parameters systolic function and free wall longitudinal strains were unaltered at high altitude (*Table 2*). Tricuspid E/A was decreased during the 6 days at 4350 m and returned to baseline values at SL_{POST}. Tricuspid A wave was increased at D0 and was normalized at D2 whereas tricuspid E wave was decreased at high altitude but did not reach statistical significance.

LV diastolic function

LV end-diastolic diameter (EDD) was decreased at D2 and D4 compared to SL_{PRE} (*Figure 1*). Peak E decreased at 4350 m but only from D2. Peak A and Am increased from SL_{PRE} to D0 and then decreased from D0 to D6, but still remaining higher than SL_{PRE}. Em and SrLd were unaffected at high altitude (*Table 3*). Left atrial EDD was unaltered at high altitude. The filling pressure index was decreased at high altitude with the minimum value obtained at D2. We observed a relationship between filling pressure index and both peak E ($r = 0.72$, $P < 0.001$) and LV EDD ($r = 0.37$, $P < 0.01$). We observed a negative correlation between peak E and PVR ($r = 0.46$, $P < 0.001$). Peak untwisting rate was greater at high altitude compared to SL_{PRE} and we observed a relationship between peak untwisting rate and peak twist ($r = 0.67$, $P < 0.001$). Peak untwisting rate was delayed at high altitude (time-to-peak (TTP) SL_{PRE} vs. TTP D2, respectively: 119 ± 6% vs. 130 ± 9%, $P < 0.05$) and was normalized at SL_{POST} (*Figure 2*). $\%UT_{IVRT}$ was decreased from D0 to D6, but returned to normal values at SL_{post}.

LV systolic function

LV EF and stroke volume (SV) were unchanged at 4350 m (*Figure 3*). Heart rate (HR) and cardiac output (CO) were increased at D0 and then remained higher than SL_{PRE} even after return to sea level. At high altitude, GLS, apical CS and basal CS were unchanged (*Table 4*). Peak twist was increased at D0 and tended to become even greater from D0 to D6. These changes were due to an increase in apical rotation, since basal rotation did not change. TTP twist was unaltered at 4350 m. TSR was greater at D0 compared to SL_{PRE}, remained stable from D0 to D6 and returned to SL_{PRE} values at SL_{POST}. We observed a relationship between twist and SV ($r = 0.44$, $P < 0.001$) and between SpO_2 and TSR ($r = 0.33$, $P < 0.05$). LSDI was unchanged at high altitude and at SL_{POST} compared to SL_{PRE}.

Discussion

To our knowledge, this is the first study to follow-up the effect of high-altitude hypoxia on heart function and mechanics during a 6-day period and immediately after return to sea level in healthy young adults. Using helicopter transport to avoid any confounding effect, we demonstrated that prolonged altitude exposure (1) induced a transient LV diastolic dysfunction associated with both a decrease in LV filling pressure and a delayed LV untwisting, (2) did not affect the parameters of systolic function of both the RV and LV, and (3) was associated with a progressive increase in LV twist from sea level to D6.

Mechanisms underlying LV diastolic function perturbations

It was well-described that, during the first hours in hypoxia, abnormal LV filling pattern results only from an increase in left atrial contraction,[20] whereas after several days of high-altitude trekking[6] or in a hypobaric chamber (e.g. Operation Everest III[2]), it results also from an additional decrease in early filling. A recent study also reported a decrease in early filling and an increase in atrial filling after 4-day ascent to 4350 m by motorized transport.[7] In our study, after an initial increase in atrial component after arrival at 4350 m (D0), LV early filling, LV filling pressure index and LVEDD progressively decreased and were all at their lowest values at D2 and then plateaued until D6, suggesting a transient impairment in LV diastolic function during sustained hypoxic exposure. Interestingly, the lowest values of LV diastolic function at D2 were concomitant with the most severe LLS, suggesting that diastolic function impairment and symptoms of AMS shared common underlying mechanisms.

Whereas the initial increase in atrial filling might be related to the tachycardia induced by an activation of the sympathetic nervous

Table 2 Right ventricular function and mechanics at sea level (SL_{PRE}), after arrival (D0), on day 2 (D2), day 4 (D4), day 6 (D6) at high altitude and after return to sea level (SL_{POST})

	SL_{PRE}	D0	D2	D4	D6	ANOVA *P* value	SL_{POST}	vs. SL_{PRE} *P* value
Conventional and Doppler data								
Systolic PAP (mmHg)	19 ± 4	34 ± 8*	35 ± 6*	32 ± 3*	29 ± 4*†‡	*<0.001*	24 ± 5*	*0.04*
RV gradient (mmHg)	14 ± 2	22 ± 5*	23 ± 4*	21 ± 2*	19 ± 3*†‡	*<0.001*	19 ± 5*	*0.04*
PVR (mmHg min^{-1} l^{-1})	1.2 ± 0.7	3.1 ± 1.2*	3.6 ± 1.3*	3.0 ± 0.9*	2.5 ± 0.7*‡	*<0.001*	1.8 ± 0.6*	*0.01*
RV end-diastolic area (cm^2)	19.6 ± 2.9	19.3 ± 1.9	19.5 ± 2.6	18.7 ± 2.8	18.1 ± 2.9	*0.36*	17.8 ± 2.1	*0.14*
RV end-systolic area (cm^2)	11.0 ± 1.8	11.6 ± 1.5	11.6 ± 1.9	11.2 ± 1.0	10.3 ± 1.8	*0.18*	10.6 ± 1.6	*0.63*
RV FAC (%)	44 ± 4	39 ± 8	41 ± 5	40 ± 7	43 ± 4	*0.06*	42 ± 9	*0.79*
TAPSE (cm)	2.49 ± 0.33	2.46 ± 0.33	2.28 ± 0.20	2.36 ± 0.23	2.29 ± 0.19	*0.13*	2.31 ± 0.35	*0.16*
Tricuspid E wave (cm s^{-1})	59 ± 11	54 ± 9	51 ± 8	52 ± 8	53 ± 8	*0.12*	54 ± 6	*0.20*
Tricuspid A wave (cm s^{-1})	32 ± 7	39 ± 6*	34 ± 4†	35 ± 8†	34 ± 7†	*0.02*	31 ± 4	*0.68*
Tricuspid E/A	1.87 ± 0.30	1.41 ± 0.29*	1.53 ± 0.24*	1.51 ± 0.25*	1.58 ± 0.34*	*0.0003*	1.75 ± 0.26	*0.26*
Tissue Doppler imaging								
E'_{RV} (cm s^{-1})	14.6 ± 3.8	16.5 ± 4.2*	14.5 ± 3.3†	13.6 ± 2.9†	13.7 ± 3.0†	*0.005*	16.3 ± 3.4	*0.22*
A'_{RV} (cm s^{-1})	9.6 ± 2.3	12.3 ± 3.1*	11.3 ± 3.1*	10.9 ± 2.1	10.5 ± 2.7†	*0.03*	8.4 ± 2.7	*0.28*
S'_{RV} (cm s^{-1})	14.3 ± 1.9	14.6 ± 1.6	14.3 ± 1.8	14.7 ± 2.3	14.5 ± 2.1	*0.96*	13.3 ± 2.1	*0.27*
STE-derived parameters								
Free wall longitudinal strain (%)	-22.3 ± 9.2	-26.1 ± 5.1	-25.1 ± 5.2	-22.3 ± 6.1	-25.6 ± 3.5	*0.25*	-24.2 ± 5.8	*0.39*

Significant differences: *$P < 0.05$ vs. SL_{PRE}; †$P < 0.05$ vs. D0.
RV, right ventricle; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; FAC, fractional area change, TAPSE, tricuspid annular plane systolic excursion; STE, speckle tracking echocardiography.

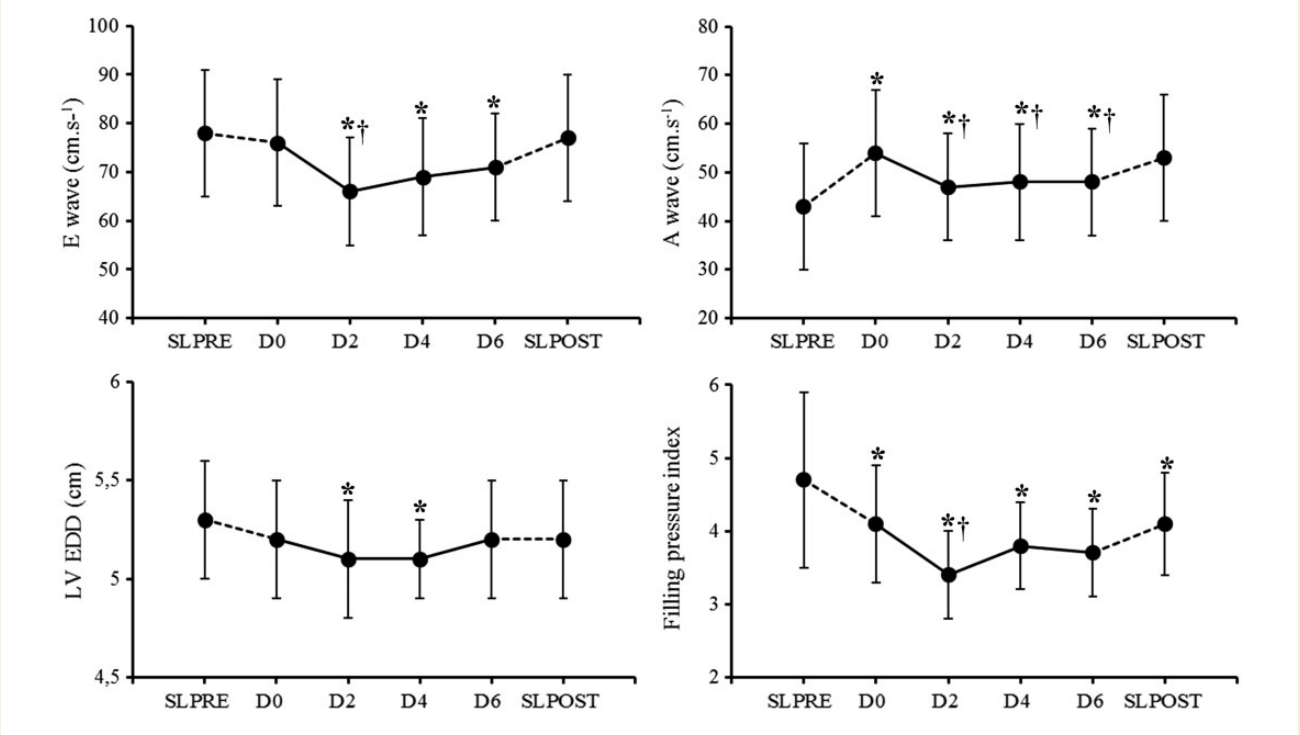

Figure 1 Kinetic of LV global diastolic function at sea level (SL_{PRE}), after arrival (D0), on day 2 (D2), day 4 (D4), day 6 (D6) at high altitude and after return to sea level (SL_{POST}). LV EDD, left ventricular end-diastolic diameter. Significant differences: *$P < 0.05$ vs. SL_{PRE}; †$P < 0.05$ vs. D0.

Table 3 Left ventricular diastolic function at sea level (SL_{PRE}), after arrival (D0), on day 2 (D2), day 4 (D4), day 6 (D6) at high altitude and after return to sea level (SL_{POST})

	SL_{PRE}	D0	D2	D4	D6	ANOVA *P* value	SL_{POST}	vs. SL_{PRE} *P* value
Conventional and Doppler data								
Left atrial end-diastolic diameter (cm)	2.7 ± 0.3	2.6 ± 0.3	2.7 ± 0.2	2.8 ± 0.3	2.8 ± 0.3	*0.38*	2.7 ± 0.4	*0.98*
Mitral E/A ratio	1.86 ± 0.43	1.43 ± 0.33*	1.38 ± 0.16*	1.46 ± 0.29*	1.51 ± 0.38*	*<0.001*	1.72 ± 0.54	*0.49*
IVRT (ms)	57 ± 17	57 ± 17	59 ± 19	55 ± 20	50 ± 12	*0.71*	63 ± 9*	*<0.001*
IVRT (% of systolic duration)	116 ± 5	118 ± 5	119 ± 6	117 ± 5	116 ± 4	*0.57*	119 ± 3	*0.09*
Tissue Doppler imaging								
E_m (cm s^{-1})	14.5 ± 1.8	16.3 ± 1.8	16.3 ± 1.6	15.8 ± 2.5	15.9 ± 1.9	*0.10*	16.3 ± 1.8*	*0.02*
A_m (cm s^{-1})	7.4 ± 1.2	10.1 ± 1.9*	9.1 ± 2.4*†	8.4 ± 1.7*†	8.4 ± 1.9*†	*<0.001*	8.3 ± 1.8*	*0.04*
STE-derived parameters								
Diastolic longitudinal strain rate (s^{-1})	1.3 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.3	*0.60*	1.4 ± 0.2	*0.38*
Untwisting rate/peak twist ratio (s^{-1})	-11.7 ± 6.6	-12.3 ± 5.1	-11.3 ± 3.2	-10.2 ± 4.5	-8.3 ± 2.4	*0.15*	-9.1 ± 4.5	*0.11*

Significant differences: *$P < 0.05$ vs. SL_{PRE}; †$P < 0.05$ vs. D0.
IVRT, isovolumic relaxation time; STE, speckle tracking echocardiography.

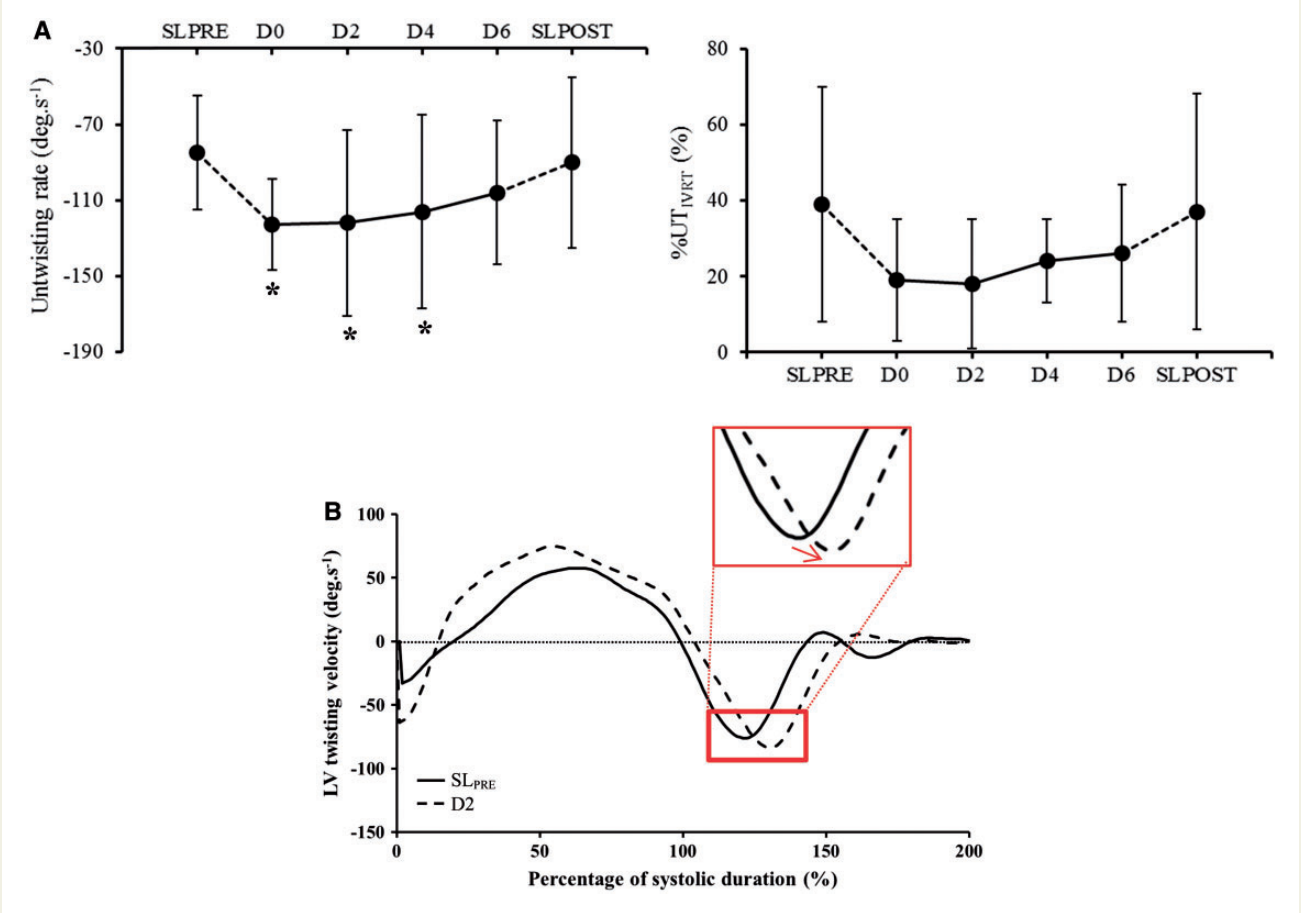

Figure 2 (*A*) Kinetic of LV untwisting parameters at sea level (SL_{PRE}), after arrival (D0), on day 2 (D2), day 4 (D4), day 6 (D6) at high altitude and after return to sea level (SL_{POST}). (*B*) LV twisting velocity during the cardiac cycle at SL_{PRE} and D2. Significant differences: *$P < 0.05$ vs. SL_{PRE}.

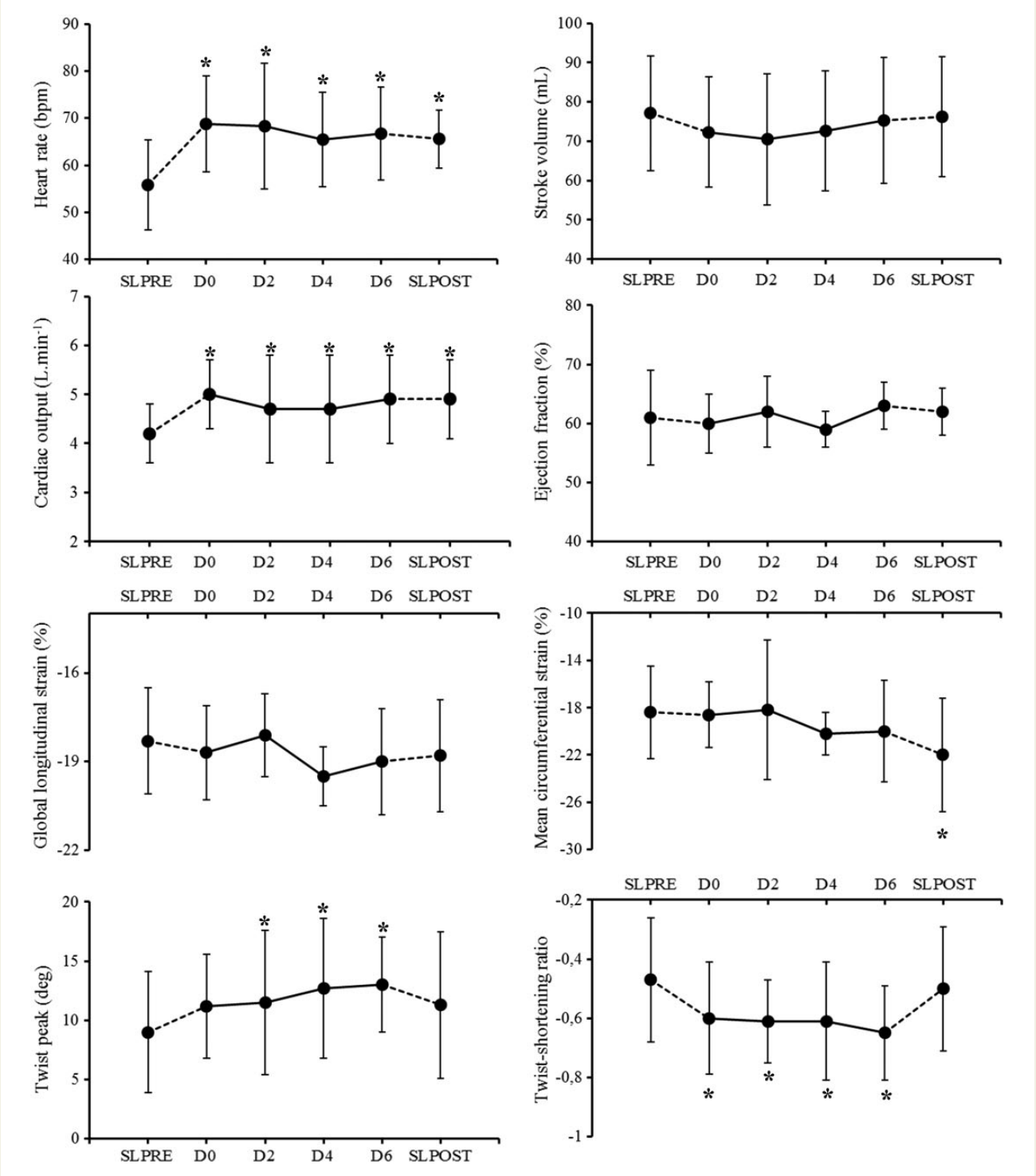

Figure 3 Kinetic of LV global systolic function and LV mechanics at sea level (SL_{PRE}), after arrival (D0), on day 2 (D2), day 4 (D4), day 6 (D6) at high altitude and after return to sea level (SL_{POST}). Significant differences: *$P < 0.05$ vs. SL_{PRE}.

system (SNS),[21] the drop in LV early filling at D2 remained under debate. In our study, LV intrinsic relaxation seemed unaffected by hypoxia since SrLd and E_m remained unchanged from D0 to D6. In contrast, LV filling pressures (estimated via the E/E_m ratio) were lower and significantly correlated with the drop in LV EDD ($P < 0.01$, $r = 0.37$). The well-described hypovolemia-induced decrease in preload and sympathetic hyperactivity at high altitude[1,7] probably played a major role in these alterations. Moreover, it is likely that the increased PVR, and therefore RV afterload, directly impacted LV diastolic function resulting in modified LV filling. It has been well-

Table 4 **Left ventricular systolic function at sea level (SL_{PRE}), after arrival (D0), on day 2 (D2), day 4 (D4), day 6 (D6) at high altitude and after return to sea level (SL_{POST})**

	SL_{PRE}	D0	D2	D4	D6	ANOVA *P* value	SL_{POST}	vs. SL_{PRE} *P* value
Conventional data								
Left ventricular end-systolic diameter (cm)	3.3 ± 0.3	3.1 ± 0.2*	3.0 ± 0.3*	3.1 ± 0.4*	3.1 ± 0.3*	*0.01*	3.2 ± 0.4	*0.57*
Systemic vascular resistance (A.U.)	25.1 ± 2.7	22.2 ± 3.0	24.4 ± 6.1	25.8 ± 5.9	24.1 ± 4.6	*0.21*	22.1 ± 4.4*	*0.04*
Tissue Doppler imaging								
S_m (cm s^{-1})	10.8 ± 1.7	13.1 ± 2.5*	12.3 ± 2.7*	12.8 ± 1.3*	12.6 ± 1.3*	*0.006*	12.0 ± 2.0	*0.20*
STE-derived parameters								
Apical circumferential strain (%)	-20.1 ± 5.4	-21.1 ± 4.0	-20.6 ± 8.2	-23.0 ± 7.0	-23.4 ± 5.6	*0.27*	-26.1 ± 7.3*	*<0.001*
Basal circumferential strain (%)	-16.6 ± 3.6	-16.0 ± 2.7	-15.9 ± 5.0	-17.4 ± 3.7	-16.7 ± 4.2	*0.66*	-17.8 ± 3.3	*0.14*
Apical rotation (deg)	6.2 ± 4.1	7.9 ± 5.0	8.5 ± 4.7*	8.9 ± 4.2*	9.7 ± 4.2*	*0.01*	9.1 ± 5.2*	*0.008*
Basal rotation (deg)	-4.0 ± 1.7	-4.2 ± 2.0	-3.9 ± 2.0	-4.9 ± 1.7	-3.9 ± 2.0	*0.60*	-3.0 ± 1.9	*0.17*
Longitudinal strain delay index (%)	-19.4 ± 8.4	-22.8 ± 16.1	-16.0 ± 5.7	-11.4 ± 6.0	-13.0 ± 7.2	*0.09*	-11.6 ± 4.1	*0.11*

Significant differences: *$P < 0.05$ vs. SL_{PRE}.
STE, speckle tracking echocardiography.

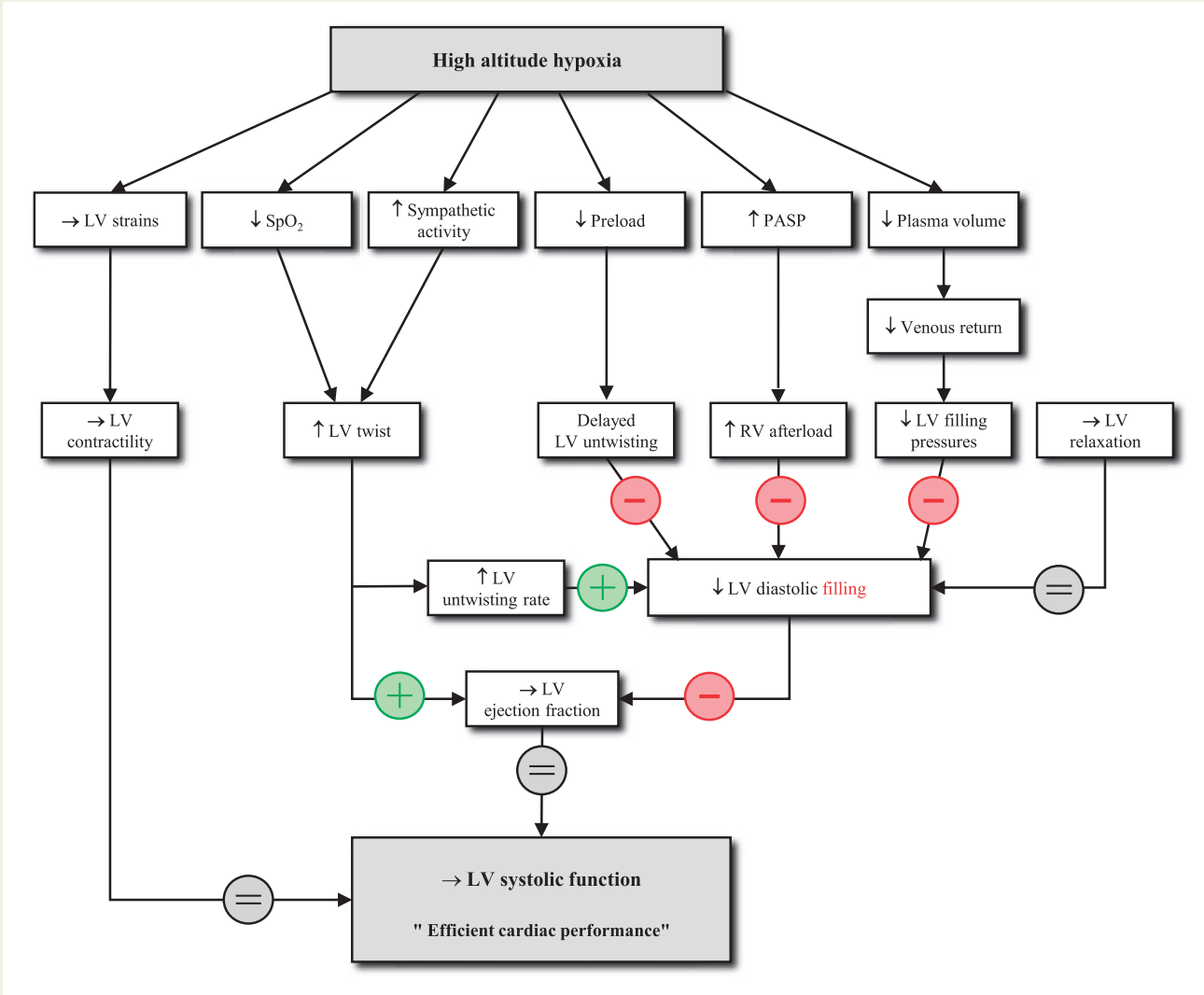

Figure 4 Proposed mechanisms maintaining an efficient cardiac performance in response to high-altitude hypoxia. LV, left ventricular; SpO_2, arterial oxygen saturation; PASP, pulmonary artery systolic pressure; RV, right ventricular.

demonstrated that LV untwisting represented another important factor of early filling by creating an intraventricular pressure gradient.[22] Our data indicated that peak untwisting rate was higher from D0 to D4. This result is in accordance with the observations of Dedobbeleer *et al.*[7] after 4 days at high altitude. However, in the present study, the untwisting rate/peak twist ratio remained unchanged compared to sea level, meaning that the increase in LV untwisting rate was mainly due to the higher LV twist. A better untwisting efficiency and elastic recoil remain therefore controversial. Of note, LV untwist must be also as early as possible to be efficient. In healthy young subjects, LV untwisting is the first mechanical event in diastole, ~40% occurring during IVRT.[4] Despite alterations did not reach statistical difference, $\%UT_{IVRT}$ progressively decreased, indicating that LV untwisting was delayed with high-altitude hypoxia. Delayed LV untwisting has already been reported in various diseases[23] and can be used to diagnose patients with diastolic dysfunction.[24] Hodt *et al.*[25] recently described a delayed LV untwisting after 4 min of preload reduction induced by low body negative pressure. A decreased preload could thus explain the delayed untwist observed at high altitude.

High-altitude exposure is associated with an efficient cardiac performance

Many studies using hypoxic chamber[26] or exposure to high altitude during trekking[27] indicated that indexes of global systolic function (i.e. EF and SV) were unaffected by acute or prolonged hypoxia. In the present study, despite significant arterial oxygen desaturation, increased systolic PAP and symptoms of AMS at D2, we confirmed a well maintained cardiac performance during 6 days at high altitude. The increased CO was driven by a higher HR (*Figure 2*) probably related to an activation of the SNS.[28]

Ventricular regional mechanics can reveal sub-clinical dysfunction in patients with unchanged EF.[23] Interestingly, from D0 to D6, LV GLS and CS and RV longitudinal strain remained also unchanged. Similar results were obtained regionally (i.e. at apical or basal levels, data not presented). During a trek, Stembridge *et al.*[29] reported a decreased RV free wall longitudinal strains. Recent studies have concluded that the RV is more affected by exercise than LV because of a greater hemodynamic load and wall stress imposed on the RV during intense exercise.[30] Thus, the discrepancies between the normal RV function observed in our study and the RV dysfunction reported after trekking[29] may be explained by physical activity as encountered in trekking session.

The progressive increase in LV twist: a compensatory mechanism to maintain LV systolic function?

An important finding of our study was the progressive increase of LV peak twist from the arrival at 4350 m to D6. Interestingly, LV peak twist returned to baseline level immediately after descent to sea level, further supporting that these alterations were driven by high-altitude hypoxia. Recently, Stembridge *et al.*[5] and Osculati *et al.*[6] also described an increased LV twist after several days of trekking at high altitude, but trekking implied exercise stress, dehydration, diet, that precluded any definitive conclusions regarding the specific effects of hypoxia.

Several underlying mechanisms may explain the progressive increase in LV twist with high-altitude hypoxia. High-altitude exposure is associated with an increased catecholamine concentration,[31] an activation of the SNS[28] and a decreased preload.[5] The increase in LV twist was likely mediated by a combination of these stimuli, as they are known to increase apical rotation.[32–34] Another mechanism that could have increased LV twist is a decrease of subendocardial fibres contractility. LV twist is mainly driven by the contraction of the subepicardial fibres, due to their higher lever arm, the subendocardial layers acting only as a brake of LV twist. When subendocardial function is impaired, LV twist increases.[16] Recent findings brought evidences that subendocardial fibres were more affected by hypoxia than subepicardial ones.[6] In our study, the TSR, a marker of subendocardial dysfunction[18] was increased with high-altitude hypoxia. Moreover, the significant relationship between SpO_2 and TSR underlined a potential link between the subendocardial dysfunction and the severity of hypoxia.

LV twist is a primary component of normal systolic function because for a similar myocardial contractility, it enhances the blood ejection.[3] As previously suggested,[5] an increased LV twist helps to preserve global LV EF despite the presence of subendocardial dysfunction. During severe hypoxia, it could be proposed as a compensatory mechanism to maintain EF despite the decrease in LV filling. Of note, this greater LV twist at rest may impact its ability to increase during effort (i.e. twist reserve), that could be one potential mechanism responsible for the lower increase in SV during submaximal exercise at high altitude.[5] *Figure 4* summarizes the potential mechanisms responsible for the efficient LV performance observed at high altitude, including the new findings observed in our study.

Conclusion

Based on an original approach using helicopter flight to transport the subjects near the "top of Europe" to avoid the confounding effects of exercise or acclimatization process, using cutting-edge echocardiographic tools during 6 days at 4350 m, this study provides new insights into the underlying mechanisms alteration in LV and RV function. The strength of this article was to provide novel data regarding the adaptation of regional ventricular function and mechanics, and especially LV twist, to high altitude. We confirmed the good tolerance of the heart to high-altitude hypoxia. However, the clinical relevance of the present findings need to be confirmed in non-recreational climbers and in patients with previous cardiovascular conditions.

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