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Changes in structure and function of the human left ventricle after acclimatization to high altitude

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Summary. To analyse the role of changes in structure and function of the left ventricle in determining cardiac function at rest and during exercise, several two-dimensional and Doppler echocardiographic measurements were performed on 11 healthy subjects immediately before an Himalayan expedition (Nun, 7135 m), during acclimatization (3 weeks) and 14 days after the return. At rest decreases were found in cardiac index (CI) (3.23 $l \cdot min^{-1} \cdot m^{-2}$, SD 0.4 vs 3.82 $l \cdot min^{-1} \cdot m^{-2}$, SD 0.58, $P<0.01$), left ventricular mass (55.3 $g \cdot m^{-2}$, SD 9.4 vs 65.2 $g \cdot m^{-2}$, SD 13.5, $P<0.005$) and left ventricular end-diastolic volume (LVEDV) (53.9 $ml \cdot m^{-2}$, SD 6.9 vs 64.8 $ml \cdot m^{-2}$, SD 9.1, $P<0.001$) after acclimatization; by contrast the coefficient of peak arterial pressure to left ventricular end-systolic volume (PAP/ESV) (7.8, SD 1.6 vs 6.0, SD 1.8, $P<0.005$) and mean wall stress [286 $kdyn \cdot cm^{-2}$, SD 31 vs 250 $kdyn \cdot cm^{-2}$, SD 21 (2.86 $N \cdot cm^{-2}$, SD 0.31 vs 2.50 $N \cdot cm^{-2}$, SD 0.21), $P<0.005$] increased. After return to sea level, low values of CI and mass persisted despite a return to normal of LVEDV and preload. A reduction of PAP/ESV was also observed. At peak exercise, PAP/ESV (8.7, SD 2.4 vs 12.8, SD 2.0, $P<0.0025$), CI (9.8 $l \cdot min^{-1} \cdot m^{-2}$, SD 2.5 vs 11.6 $l \cdot min^{-1} \cdot m^{-2}$, SD 1.6, $P<0.05$) and the ejection fraction (69%, SD 6 vs 76%, SD 4, $P<0.05$) were lower after return to sea level than before departure. The depressed left ventricular performance after prolonged exposure to hypoxia may be related to changes in structure and function including reduction in preload, loss of myocardial mass and depression of inotropic state.

Key words: Cardiac function - Altitude - Stress echocardiography

Introduction

The mechanisms limiting exercise performance after high altitude acclimatization are still controversial (Alexander et al. 1967; Cerretelli 1976; West et al. 1983). Despite the evidence of depressed myocardial function in high altitude residents (Hartley et al. 1967) and in the goat (Tucker et al. 1976), the reduction in stroke volume found in humans has been related to a diminished left ventricular (LV) preload due to a contraction in plasma volume and pulmonary hypertension during high altitude exposure (Fowles and Hultgren 1983). An increased sympathetic nervous activity has been postulated to account for both higher heart rate and enhanced LV contractility at altitude and to explain the constancy of the ejection fraction (EF) and cardiac output (Q_t) (Reeves et al. 1987; Suarez et al. 1987). These results were interpreted as indicating that the performance of normal humans engaged in high altitude mountain-climbing is not limited by LV systolic function. However, a major drawback to the studies conducted in hypobaric chambers is that they only enable the assessment of the effect of hypoxia. Ambient temperature, humidity, nutritional variables and the degree of physical activity are not, however, negligible factors in evaluating the overall effect of high altitude on LV structure and function. Moreover, a morphometric study has shown an important reduction in limb muscle mass after the return of members of the Swiss Lhotse Shar Expedition (Boutellier et al. 1983; Hoppeler et al. 1990).

In our study, we analysed the role of changes in both LV function and structure in determining LV performance at rest and during exercise in normal subjects immediately before an Himalayan expedition, during acclimatization to high altitude (3 weeks) and 14 days after return.

Methods

Eleven healthy subjects, members of an Himalayan expedition (Nun, 7135 m) volunteered for the study (mean age 33.6 year, SD7, range 25-50). Echocardiographic measurements were carried out at rest and during upright cycle-ergometer exercise shortly before leaving for the expedition and 14 days after return. Measurements were also made of LV at rest after 3 weeks of high

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altitude exposure, just before the return to sea level. Before the men left for the expedition and after their return, two-dimensional and Doppler echocardiographic examinations were obtained using a Hewlett-Packard ultrasound system. A SIM 5000 echocardiographic system was used for measurements at high altitude; a 2.5 or 3.5 MHz transducer was employed to visualize the 2D-echocardiogram and pulsed Doppler velocity recordings.

For the study at rest, several echocardiographic projections were used, i.e. parasternal long-axis and short-axis views, and apical four-chamber view. Systemic flow velocity was measured by placing a Doppler sample volume at the left ventricular outflow tract just below the aortic valve in the apical long-axis view. After positioning the subject on an upright cycle ergometer, LV visualization from the apical four-chamber view and LV outflow tract Doppler velocity were recorded at rest and during exercise. All subjects underwent a maximal symptom-limited exercise test on the ergometer; exercise began at 30 W, and increased by 30 W every 2 min. Only 9 subjects had adequate echocardiograms for LV measurements during exercise.

Before their departure to the Himalayas, the subjects did not follow any specific training; during the expedition, before the high altitude measurements, they were climbing between 4600 m and 6200 m.

The LV endocardial and epicardial echocardiograms in the apical four-chamber and the parasternal short-axis view in three cycles were digitized at end-diastole (R-wave peak) and at end-systole (time of smallest cavity area) by two independent observers who were not otherwise involved in the study. The averages for each measurement were utilized for calculation.

The LV volume were calculated by an ellipsoid area-length method from the apical four-chamber view (Guaret et al. 1980). The EF was calculated as: EDV-ESV/EDV, where EDV and ESV were LV end-diastolic and end-systolic volumes. The LV myocardial mass was determined by multiplying myocardial volume by the specific mass of cardiac muscle.

The LV mean wall stress (*MWS*), as an index of LV afterload, was calculated as: $MWS = PAP \cdot r_m / th_m$, where *PAP* was the peak arterial systolic pressure measurement during echocardiographic examination by the cuff method and r_m and th_m were the average of end-diastolic and end-systolic LV cavity radius and LV posterior wall thickness, respectively. The MWS represented a good noninvasive indicator of peak left ventricular and end-systolic wall stress as shown by correlations with angiographic data (Quinones et al. 1980). Left ventricular shape is changed significantly by severe LV dilation in chronic cardiac diseases, but scarcely at all by reduction in LV dimensions. Thus, changes in LV shape are not limiting factors in comparing data obtained before and after high altitude acclimatization. In fact, LVEDV became reduced in the course of acclimatization in the subjects of our study (Ford 1976).

The PAP/ESV coefficient was used as an index of myocardial contractility. Theoretically, one would expect PAP/ESV, which is derived from a single point on the pressure-volume loop, not to be as reliable an index of myocardial contractility as the maximal elastance (E_{max}) (Suga and Sagawa 1984). Despite this limitation, several studies have applied this coefficient (which can be derived noninvasively) as a useful index of LV contractility (Nivatpunin et al. 1979).

The LV stroke volume (*SV*) was calculated from Doppler tracing as: $SV = TVI \cdot A$, where *TVI* was LV outflow tract time-velocity integral and *A* was the aortic cross sectional area (Ihlem et al. 1985). The Q_t was derived by multiplying *SV* by heart rate.

The LV diastolic filling was analysed by calculating TVI of the early (E) and late (A) wave of the mitral inflow.

Statistical considerations. The measurements in the text, tables and figures are expressed as mean and SD. Intra- and inter-group differences were tested by paired (two-tailed) and unpaired *t*-tests, considering $P < 0.05$ as significant. The relationship between cardiac index (CI) and PAP/ESV coefficient was assessed by linear regression analysis.

Results

The values at rest of LV left ventricular measurements heart rate, and CI obtained in our subjects before their departure for the expedition, and 3 weeks after high altitude exposure, as well as 14 days after their return to sea level are listed in Table 1. Using the pre-expedition values at rest as controls, we observed that CI, EDV and LV myocardial mass decreased after acclimatization; due to the comparable reductions in LVEDV and mass, the mass to volume coefficient did not change. Myocardial contractility and LV stress increased. A reduction in the *E*-wave TVI was detected in the Doppler tracing. Following return to sea level, measurements at rest disclosed lower CI values. The persistence of a reduced LV mass despite EDV normalization may explain the appearance of lower mass-to-volume coefficients. Of the 11 members, 9 showed a decrease in left ventricular mass greater than 10%, both in the high altitude measurements and in those carried out after their return. A reduction in PAP/ESV was observed, especially when values on the return and at high altitude were compared. Higher values of LV stress persisted after the return. The *E*-wave TVI returned to normal at sea level.

Peak work load during maximal exercise on the return had not changed compared to the pre-expedition control (227 W, SD 50 vs 237 W, SD 48; *P*, NS).

Compared to pre-expedition exercise values, LV myocardial contractility, CI, and EF decreased at high workloads and at peak exercise after return to sea level. No significant changes in EDV were demonstrated. Heart rate reached the same value at peak exercise, but showed a decrease at the initial workload in the post-expedition exercise tests (Table 2).

A linear correlation between PAP/ESV and CI at peak exercise was demonstrated, when considering pre- and post-expedition values together (Fig. 1).

Discussion

During the ascent to high altitude by normal men, the reduction in SV has generally been related to right ventricular systolic hypertension and reduced preload due to plasma volume contraction (Alexander et al. 1967; Cerretelli 1976; Fowles and Hultgren 1983; West et al. 1983; Surks et al. 1966). Hypobaric chamber studies (Reeves et al. 1987; Suarez et al. 1987) showed that LV systolic function was maintained or somewhat enhanced in association with augmented sympathetic activity. It was suggested that depressed cardiac function was not responsible for the observed reduction in exercise capacity at high altitude (Reeves et al. 1987; Suarez et al. 1987); on the other hand, increased circulating catecholamine levels (Cunningham et al. 1965; Watanabe 1983) may account for both higher heart rate and enhanced myocardial contractility at simulated altitude. High altitude simulation in a hypobaric chamber is designed to study the effects of chronic hypoxia on LV performance under controlled conditions of temperature, humidity, activity and nutrition. Our study was conducted under natural

Table 1. Resting left ventricular measurements, heart rate and cardiac index before departure, at high altitude (Nun) and after return to sea level

		Before		Nun		After	
		mean	SD	mean	SD	mean	SD
Cardiac index	($l \cdot min^{-1} \cdot m^{-2}$)	3.82	0.58	3.23	0.4*	3.4	0.54*
LVEDV	(ml)	114.6	24.8	91.4	18.4***	104.9	20.0
LVEDVI	($ml \cdot m^{-2}$)	64.8	9.1	53.9	6.9***	60.6	7.6
EF	(%)	66	6.5	65.8	4.7	60.6	7.4*
Mass	(g)	117.0	35.2	97.5	22.6**	89.8	26.6***
Mass index	($g \cdot m^{-2}$)	65.2	13.5	55.3	9.4**	51.5	11.4***
PAP/ESV	($mm \cdot ml^{-1}$)	6.0	1.8	7.8	1.6**	4.8	1.6* °°°
m/V	($g \cdot ml^{-1}$)	1.0	0.15	1.0	0.09	0.83	0.11***
f_c	($beats \cdot min^{-1}$)	62	13.5	67	11.2	62	13
BP_S	(mmHg)	122	7	134	12**	114	10.5
	(kPa)	(16.3	0.93)	(17.9	1.60)	(15.2	1.40)
BP_D	(mmHg)	76	7	90	6.6***	77	6
	(kPa)	(10.1	0.93)	(12.0	0.88)	(10.3	0.80)
MWS	($kdyn \cdot m^{-2}$)	250	21	286	31**	284	25**
	($N \cdot m^{-2}$)	(2.50	0.21)	(2.86	0.31)	(2.84	0.25)
A		4.2	1	4.8	1.1	4.6	1.4
E		12.6	2.6	10.1	2.2*	11.9	2.8

Statistical significance: in comparison with pre-expedition control values (before) * $P<0.01$, ** $P<0.005$, *** $P<0.001$; comparison between the values recorded at high altitude (Nun) and after return °°° $P<0.001$; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; EF, ejection fraction; PAP/ESV, peak arterial pressure to end-systolic volume coefficient; *m/V*, mass to volume coefficient; f_c, heart rate; BP_S, systolic blood pressure; BP_D, diastolic blood pressure; MWS, mean wall stress; E, early filling time-velocity integral; A, late filling time-velocity integral

Table 2. Pre- and post-expedition exercise values of heart rate, cardiac index, left ventricular end-diastolic volume, ejection fraction and peak arterial pressure to end-systolic volume coefficient

		Load											
		One-third				Two-thirds				Peak			
		B		R		B		R		B		R	
		mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
PAP/ESV	($mm \cdot ml^{-1}$)	7.8	2.0	7.0	2.7	12.0	3.4	8.2	2.4***	12.8	2.0	8.7	2.4****
CI	($l \cdot min^{-1} \cdot m^{-2}$)	6.9	1.2	6.3	1.3	9.6	1.2	8.8	1.1*	11.6	1.6	9.8	2.5*
LVEDV	($ml \cdot m^{-2}$)	63.4	14.3	70.4	9.6*	66.8	15	74.2	7.8	70.4	17.6	74.6	10.4
f_c	($beats \cdot min^{-1}$)	114	22	106	15*	141	19	136	21	174	20	175	17
EF	(%)	67	7	69	9	75	5	72	6	76	4	69	6*

Values measured at one-third and two-thirds of maximum load and at the peak of exercise. Statistical significance: * $P<0.05$, ** $P<0.025$, *** $P<0.01$, **** $P<0.0025$; B, before expedition; R, after return; PAP/ESV, peak arterial pressure to end-systolic volume coefficient; CI, cardiac index; LVEDV, left ventricular end-diastolic volume; f_c, heart rate; EF, ejection fraction

environmental conditions, in 11 healthy participants of the Nun Himalayan Expedition (7135 m), and confirmed some haemodynamic changes and LV adaptive mechanisms. At high altitudes, a reduced CI was associated with a reduction in EDV and *E*-wave TVI of the mitral inflow, indicating a diminished preload. After acclimatization, LV mass decreased concomitantly with EDV. Thus, a normal mass to volume coefficient was maintained. The importance of structural LV changes (in terms of loss in myocardial mass) clearly appeared after the return to normal of the LV preload, and disappearance or attenuation of adrenergic activation following return to sea level. The persistence of a reduced LV mass, despite the LV dimension becoming normal, produced a condition of high LV MWS at any systolic pressure at rest and during exercise. Moreover, the disappearance of adrenergic activation unmasked a depressed LV myocardial contractile level.

These LV changes, which were due to prolonged exposure to hypoxia and persisted for 14 days after return to sea level, were the main factors determining the reduction in CI, EF, and myocardial contractility at peak exercise (Table 2). The peak exercise CI to PAP/ESV relationship (Fig. 1) shows that the depressed myocardial performance was an important cause of the reduced capacity to improve CI during exercise. The loss of myocardial performance may explain both the reduced basal contractile level which was detected after return, and the reduced increase in myocardial contractility during exercise. Moreover, the net loss of myocardial mass, which

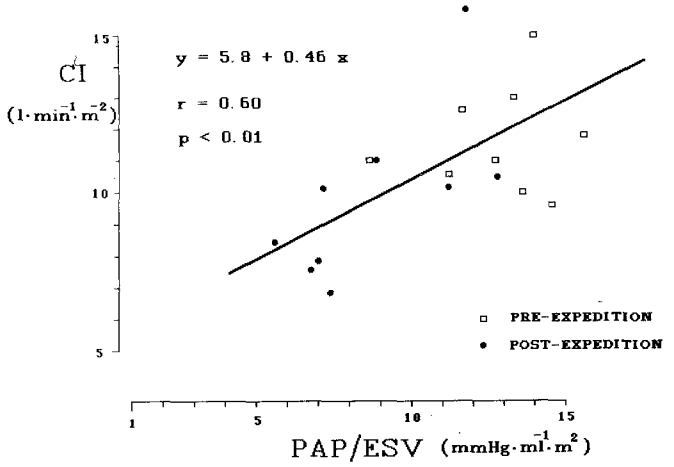

Fig. 1. Correlation between peak arterial pressure to end-systolic volume coefficient (*PAP/ESV*) and cardiac index (*CI*), considering pre- and post-expedition exercise values together

led to a higher level of LV afterload, may have further decreased the CI at any contractile level (Table 2). In our study we assessed myocardial contractility as a PAP/ESV coefficient. This has been proposed as a simplified estimate of the slope of the linear pressure-volume relationship. This is a controversial simplification obtained from the analysis of a single beat. The critical assumption is that the volume of the unloaded ventricle at the end of systole is exactly zero. This coefficient is generally independent of preload but is clearly affected by LV afterload (Starling et al. 1989): it increases by interventions which increase LV afterload. However, it is probably safe to say that, if afterload is high and the coefficient is low despite the increased afterload, the contractile function is depressed (Carabello 1989). From practical concept it is possible to suggest that myocardial contractility was depressed after the return to sea level because the PAP/ESV coefficient was lower, while LV stress (afterload) was higher, than before departure.

These myocardial structural changes may have occurred in parallel with the reduction in limb muscle mass observed after a prolonged period spent at high altitude (Boutellier et al. 1983; Hoppeler et al. 1990).

An hypoxia-related blunted response of β-adrenergic myocardial receptors has been found in humans (Richalet et al. 1988). This particular mechanism, together with the net loss of contractile elements due to reduction in myocardial mass, could have accounted for the depressed contractility detected after return, both at rest and at peak exercise. The late chronotropic response during exercise in these subjects on return could also have been related to the blunted response of β-receptors, due to the prolonged exposure to high catecholamine concentration during high altitude acclimatization.

In conclusion, the reduction in CI at high altitudes may have been related to complex pathophysiological mechanisms including reduction in preload, loss of myocardial mass, and depressed contractility. An excessive LV afterload and an inadequate contractile recruitment may have caused the reduction in LV pump performance during exercise after return. A β-adrenergic activation and optimization of peripheral gas exchange would represent the adaptative mechanisms to depressed LV performance at high altitude.

References

Alexander JK, Hartley LH, Modelski M (1967) Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude. J Appl Physiol 23:849–858

Boutellier U, Howald H, Di Prampero PE (1983) Human muscle adaptations to chronic hypoxia. Hypoxia, exercise and altitude. Prog Clin Biol Res 136:273–281

Carabello BA (1989) Ratio of end-systolic stress to end-systolic volume: is it a useful clinical tool? J Am Coll Cardiol 14:496–498

Cerretelli P (1976) Limiting factors to oxygen transport on Mt. Everest. J Appl Physiol 40:658–667

Cunningham WL, Becker EJ, Kreuzer F (1965) Catecholamines in plasma and urine at high altitude. J Appl Physiol 20:607–610

Ford LE (1976) Heart size. Circ Res 39:297–307

Fowles RE, Hultgren HN (1983) Left ventricular function at high altitude examined by systolic time intervals and M-mode echocardiography. Am J Cardiol 52:862–866

Guaret P, Meerbaurer S, Wyatt HL, Uchiyama T, Lang TW, Corday E (1980) Two dimensional echocardiographic quantitation of left ventricular volumes and ejection fraction. Circulation 62:1308–1319

Hartley LH, Alexander JK, Modelski M, Grover RF (1967) Subnormal cardiac output at rest and during exercise in residents at 3100 m altitude. J Appl Physiol 23:839–848

Hoppeler H, Kleinert E, Schlegel C, Claassen H, Howald H, Kayar SR, Cerretelli P (1990) Morphological adaptations of human skeletal muscle to chronic hypoxia. Int J Sports Med 11 [Suppl 1]:S3–S9

Ihlem H, Myhre E, Pamlie J, Forfang K, Larsen S (1985) Changes in left ventricular stroke volume measured by Doppler echocardiography. Br Heart J 54:378–383

Nivatpunin T, Katz S, Scheurer Y (1979) Peak left ventricular systolic pressure/end-systolic volume ratio: a sensitive detector of left ventricular disease. Am J Cardiol 43:969–974

Quinones MA, Makotoff DM, Nouri S, Winters WL, Miller RR (1980) Non invasive quantitation of left ventricular wall stress. Validation of method and application to assessment of chronic pressure overload. Am J Cardiol 45:782–790

Reeves JT, Groves BM, Sutton JR (1987) Operation Everest II: preservation of cardiac function at extreme altitude. J Appl Physiol 63:531–539

Richalet JP, Larmignat P, Rathat C, Bond P, Lhoste F (1988) Decrease cardiac response to isoproterenol infusion in acute and chronic hypoxia. J Appl Physiol 65:1957–1961

Starling MR, Montgomery DG, Walsh RA (1989) Load dependence of the single beat maximal pressure (stress)/volume ratios in humans. J Am Coll Cardiol 14:345–353

Suarez J, Alexander JK, Houston CS (1987) Enhanced left ventricular systolic performance at high altitude during Operation Everest II. Am J Cardiol 60:137–142

Suga H, Sagawa K (1984) Instantaneous pressure-volume relationships and their ratio in the excised supported canine LV. Circ Res 35:117–126

Surks MI, Chinn KSK, Meatoush LO (1966) Alteration in body composition in man after acute exposure to high altitude. J Appl Physiol 21:1741–1746

Tucker CE, Jones WE, Berry MA (1976) Depressed myocardial function in the goat at high altitude. J Appl Physiol 41:356–361

Watanabe AM (1983) Recent advances in knowledge about Beta-adrenergic receptors: applications to clinical cardiology. J Am Coll Cardiol 1:82–89

West JB, Bayer SJ, Graber DJ (1983) Maximal exercise at extreme altitude on Mount Everest. J Appl Physiol 55:688–698