Alterations in left ventricular function in normal man on exposure to high altitude (3658 m)

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SUMMARY Left ventricular function was estimated by noninvasive methods in 83 normal volunteers at sea level, at an altitude of 3658 m for 10 days, and on return to sea level. Of these subjects, 50 reached high altitude by air in 55 minutes and the rest by road in 6 hours. Controls comprised 56 permanent residents of high altitude and 59 lowlanders resident at high altitudes for 120 to 180 days. Simultaneous recording of electrocardiogram, phonocardiogram, carotid pulse, and first derivative of electrical impedance cardiogram yielded data in respect of pre-ejection period (PEP), left ventricular ejection time (LVET), PEP/LVET ratio, RZ interval, contractility index $\left(\frac{dZ/dt}{RZ}\right)$, stroke index, and cardiac index. A

statistically significant reduction of stroke index, cardiac index, and depression of all indices of left ventricular function was observed from the second day of induction to high altitude despite increased urinary catecholamine excretion. On return to sea level all the values returned to normal by the third day. Permanent residents of high altitude had normal left ventricular function and temporary residents a moderate depression. These findings suggest that left ventricular dysfunction occurs on induction to high altitude.

Accurate delineation of the pathophysiological alterations after subjects have been at high altitudes has interested research workers since the early years of this century (Grollman, 1930; Asmussen and Consolazio, 1941; Hultgren *et al.*, 1964; Menon, 1965; Singh *et al.*, 1965; Banchero *et al.*, 1966; Klausen, 1966; Alexander *et al.*, 1967; Hartley *et al.*, 1967; Hartley, 1971; Roy *et al.*, 1974; Sime *et al.*, 1974; Balasubramanian *et al.*, 1975; Hoon *et al.*, 1977a, b, c). Hostile environmental conditions and limitations of the sample size caused by logistic problems and the traumatic nature of the investigations have been the main deterrents. Wide variations in results have been common. One of the classical examples is the alteration of stroke volume on high altitude induction. Published reports show results ranging from an increase to a distinct decrease (Grollman, 1930; Asmussen and Consolazio, 1941; Klausen, 1966; Vogel *et al.*, 1967; Sime *et al.*, 1974; Vogel *et al.*, 1974; Hoon *et al.*, 1977a). Similarly, controversy continues as to whether or not left ventricular dysfunction occurs at high altitude (Hultgren *et al.*,

1964; Menon, 1965; Vogel *et al.*, 1967; Moret *et al.*, 1972). The answer to this question is of immense practical application in the prevention and management of altitude illnesses.

Moret *et al.* (1972) and Badeer (1973) felt that left ventricular dysfunction did not occur on acute exposure to high altitude. Vogel *et al.* (1967) also felt that left ventricular function was unaltered at high altitude. Kowalsky and Anthony (1972) subjected volunteers to a short term exposure to simulated hypoxia and observed an improvement in myocardial function. They attributed it to increased catecholamine secretion. Alexander *et al.* (1967), however, attributed depression of myocardial function as a dominant aetiological factor in the causation of reduced cardiac output at altitude.

The last decade has witnessed tremendous advances in noninvasive diagnostic methods in cardiac disease, and a large number of reliable techniques to assess left ventricular function have become available. Systolic time intervals are one of the procedures to be so recognised (Weissler *et al.*, 1968, 1969; Aronow, 1970; Kumar and Spodick, 1970; Weissler and Schoenfeld, 1970; Lindquist *et al.*, 1973; Quarry-Pigott *et al.*, 1973; Lewis *et al.*,

1974; Weissler, 1974; Zoneraich, 1974; Lewis, 1975; Chung, 1976; Spodick and Lance, 1976; Weissler, 1976). In an earlier study we estimated systolic time intervals in 20 volunteers exposed to high altitude and reported a significant reduction in left ventricular function (Balasubramanian *et al.*, 1975). The present report covers the investigation of a larger number of measurements in a bigger group and incorporates studies on return to sea level also.

Subjects and methods

SUBJECTS

The subjects consisted of 198 normal healthy male volunteers 20 to 35 years of age. All of them were trained persons and none of them were athletes. All groups were comparable in respect of height, weight, physical training, and dietary habits.

They were studied in the following groups—

Group A: 50 subjects born and brought up at an altitude of less than 1000 m and who had never visited higher altitudes in their life (lowlanders). These volunteers were taken to high altitude by air.

Group B: 33 subjects similar to group A reached high altitude by road in 6 hours.

Group C: 59 subjects were basically lowlanders but had stayed at high altitude continuously for 120 to 180 days preceding the study.

Group D: 56 subjects comparable in respect of height, weight, other anthropometric measurements, and physical training to groups A, B, and C, but who were born and brought up at altitudes above 3500 m. They had never visited altitudes below 1000 m.

STUDY PROCEDURE

The subjects of group A were initially studied at a temperature controlled laboratory ($26 \pm 2^\circ\text{C}$) at 198 m above sea level (henceforth called sea level) to determine baseline data. They were taken to an altitude of 3658 m by a pressurised aircraft in 55 minutes. At that altitude they were housed in a centrally heated hospital kept at $26 \pm 2^\circ\text{C}$ throughout the study. Smoking, alcohol consumption, and drugs were not allowed during the study. Serial estimations were made at 0 to 4 hours, 5 to 8 hours, second, third, fourth, fifth, and tenth day of arrival at high altitude. They were then returned by air to the sea level station, and studies carried out immediately on arrival, and on the second and the third days of return.

The subjects of group B were studied at sea level and reached the altitude of 3658 by road travel in 6 hours. Serial study was conducted at 18 to 20 hours of arrival, on the second, third, fourth, fifth, and tenth days at high altitude. They returned to

sea level by road and studies were carried out on the second and third day of return to sea level. Groups C and D were studied once at high altitude (3658 m).

TECHNIQUES

As the study procedure demanded rapid recording of physiological values repetitively, conventional systolic time intervals, stroke index, and other measures of myocardial function obtained by electrical impedance plethysmography were selected as the data of choice. Simultaneous recording of electrocardiogram, phonocardiogram, and first derivative of thoracic electrical impedance plethysmogram (dZ/dt) were obtained on a direct writing three-channel recorder at a paper speed of 100 mm/s. Carotid pulse, electrocardiogram, and phonocardiogram were similarly recorded.

Technique of recording

All recordings (at sea level and at altitude) were obtained in the supine position in a quiet laboratory kept at $26 \pm 2^\circ\text{C}$. All subjects rested at least 30 minutes before each recording. All data were obtained between 9 am and 11.45 am in the post-absorptive state (except for 0 to 4 hours and 5 to 8 hours recording at altitude of group A. The former was made between 9.30 am and 1.30 pm and the latter from 1.30 pm to 5.30 pm).

Electrical impedance cardiography

Two pairs of silver-coated copper mesh strips bonded at a distance of 5 cm to a neoprene belt were used as the tetrapolar circular lead system. The upper pair of electrodes was applied around the neck (above and below the cricoid cartilage), the lower pair at the level of the xiphisternum and 5 cm distal to it (Fig. 1). Noncorrosive electrolyte cream was used to ensure good skin contact. The electrode sites were marked with indelible ink during the baseline study to ensure application at the same site

Fig. 1 Tetrapolar circular lead system used in electrical impedance cardiography.

Fig. 2 Simultaneous recording of electrocardiogram, first derivative of impedance cardiogram (dZ/dt), and phonocardiogram at a paper speed of 100 mm/s.

during subsequent studies. The patient was connected to a custom built digital impedance plethysmograph by a four core shielded patient cable. The instrument passed a sinusoidal alternating current of 20 kHz 200 μ A RMS across the outer electrodes E_1 and E_4 . The inner pair of electrodes E_2 and E_3 picked up the instantaneous impedance changes caused by the cardiac cycle and fed it into the plethysmograph (Balasubramanian and Hoon, 1975). The signal was processed, amplified, differentiated, and fed into the multichannel recorder to derive the dZ/dt wave form. A calibration signal of 1 ohm/s was recorded before each tracing to calculate the amplitude of dZ/dt wave form. The electrocardiogram was picked up from the outer electrodes E_1 and E_4 and the phonocardiogram by a high fidelity dynamic microphone situated at the best site to record the aortic closure clearly (Fig. 2). All recordings were made at comfortable end expiration to eliminate respiratory artefacts and base-

Fig. 3 Simultaneous recording of electrocardiogram, carotid pulse, and phonocardiogram at a paper speed of 100 mm/s.

line instability. A minimum of 10 complexes were recorded and 5 consecutive complexes were used for data analysis.

Another set of recordings comprising electrocardiogram, phonocardiogram, and carotid pulse using a crystal transducer (APT 102) was similarly obtained (Fig. 3).

The following were calculated (Fig. 4).

(a) *Heart rate*: obtained from the RR interval.

(b) *Electromechanical systole (QS_2)*: the duration in milliseconds from the earliest point of QRS complex to the first high frequency component of aortic closure.

(c) *Left ventricular ejection time (LVET)*: the duration in milliseconds from the onset of the carotid wave form to the nadir of the dicrotic notch.

(d) *Pre-ejection period (PEP)*: obtained by deducting LVET from QS_2 .

(e) *PEP/LVET ratio*.

(f) *RZ interval*: the duration in milliseconds from the peak of the R wave of the electrocardiogram to the peak of the dZ/dt wave form.

(g) *Contractility index*: obtained by the formula $(dZ/dt)_{\min}/RZ:(dZ/dt)_{\min}$ being the amplitude of the wave form in ohms/s.

The values were corrected for the heart rate by using the following regression equations (Lindquist, *et al.*, 1973)

$$VET\ I = 1.42\ HR + \text{observed value}$$

$$PEP\ I = 0.44\ HR + \text{observed value}$$

$$RZ\ I = 0.76\ HR + \text{observed value}$$

(HR = heart rate, I denotes index corrected for HR)

PEP/LVET and $\frac{dZ/dt}{RZ}$ were obtained from the un-

corrected values.

(h) *Stroke Volume (SV)*: calculated by the formula

Fig. 4 Simultaneous recording of electrocardiogram, phonocardiogram, dZ/dt , and carotid pulse to show the parameters calculated. The amplitude of the dZ/dt waveform is calculated from the peak of the dZ/dt to the zero reference line. The contractility index is obtained by dividing the dZ/dt amplitude in ohms/s by the RZ interval in seconds.

$SV = p \times \left(\frac{L}{Z_0} \right)^2 \times VET \times (dZ/dt) \text{ min}$, p = resistivity constant of blood (150 at 37°C) (Hill and Lowe, 1973), L = mean distance in cm between the inner electrodes, Z_0 = mean transthoracic electrical impedance in ohms, VET = ventricular ejection time in seconds measured from the onset of the dZ/dt wave form to 'X' point, a clear dip synchronous with aortic closure (Fig. 4). $(dZ/dt) \text{ min}$ = amplitude of the dZ/dt wave form in ohms/s.

Stroke index was calculated by standard nomograms. Cardiac index was obtained by multiplying stroke index by heart rate. 24 hour urinary catecholamine excretion was estimated in all subjects at sea level and on days 1, 2, 4, and 10 at high altitude. Studies were done on days 1 and 4 of return to sea level (Hoon *et al.*, 1976, 1977b).

All recordings were obtained by the same recorder and impedance plethysmograph at a constant calibration of 15 mm/ohm per s. All values were calculated by the same group of observers to eliminate variations. The data were fed into an ICL 1904 computer and the results analysed by standard statistical methods of analysis of variance, and Student's *t* test.

Results

HEART RATE (Tables 1 and 2)

The resting heart rate of group A at sea level was 64.4/min. On induction to high altitude no significant alteration was noticed until the second day, but a steady increase occurred which later reached 77.2/min on the fifth day. On return to sea level normal rates were noted by the third day. Group B had a resting heart rate of 63.2/min at sea level. At 18 to 20 hours of induction to high altitude it increased to 86.7/min. The peak value of 92.3 was observed on the second day. Returning to sea level

resulted in a return to normal by the third day. Group C had a mean heart rate of 69.1/min and group D 56.2/min.

LEFT VENTRICULAR EJECTION TIME

Subjects of group A had a basal LVET index of 378 ms at sea level. There was no significant change in this value until the second day at altitude when it dropped to 363 ms. Thereafter a steady decline continued until the tenth day at high altitude when 348 ms was recorded. A return to normal occurred on the third day of return to sea level (368 ms). Group B had a LVET index of 381 ms at sea level. Reduction to 359 ms was noticed on the first day, which persisted until the fifth day. On the tenth day a further reduction to 350 ms was observed. By the third day of return to sea level the values had increased to 373 ms. Group C had LVET I values of 369 ms and group D 375 ms, respectively.

PRE-EJECTION PERIOD

The sea level control values of PEP-I of group A was 123 ms. The second day recording at altitude yielded a value of 126 which gradually increased to 136 ms on the fifth day. Reversion to a level of 123 ms was observed on the third day of return to sea level. Group B had sea level control values of 127 ms which increased to 133 ms on the first day and reached a peak of 144 ms on the tenth day. A mean value of 133 ms was obtained by the third day of return to sea level. Group C had values of 126 ms and group D 116 ms.

PEP/LVET RATIO ($\times 1000$)

The mean PEP/LVET ratio of group A at sea level was 337. This started to increase on arrival at high altitude and reached the maximum of 415 on the tenth day. A return to normal to 342 occurred by the third day of return to sea level. The individual

Table 1 Serial changes in measures of myocardial function in subjects inducted to 3658 m by air

Time of study	Heart rate/ min	P*	PEP	P*	LVET	P	PEP/LVET	P	PEP/LVET > 400	RZ interval	P	dZ/dt RZ	P
Sea level	64.4 (1.3)	—	123	—	378 (1.8)	—	337 (4)	—	Nil	149 (1.3)	—	17.4 (0.5)	—
High altitude induction (55 min by air)													
Day 1													
0-4h	66.9 (3.2)	NS	124	NS (1.1)	370 (2.0)	NS	345 (4)	NS	1	150 (1.4)	NS	15.9 (0.3)	< 0.01
5-8h	67.0 (1.4)	NS	125	NS (1.2)	369 (1.8)	NS	352 (5)	NS	3	149 (1.4)	NS	13.4 (0.5)	< 0.001
Day 2 (25-28h)	71.5 (1.8)	< 0.01	126	NS (1.2)	363 (1.8)	NS	365 (4)	< 0.001	8	156 (1.5)	NS	12.7 (0.5)	< 0.001
Day 3 (49-52h)	73.8 (1.9)	< 0.001	128	NS (1.2)	357 (1.5)	< 0.01	384 (6)	< 0.001	15	157 (1.6)	< 0.01	12.2 (0.4)	< 0.001
Day 4 (73-76h)	74.6 (2.0)	< 0.001	129	< 0.01 (1.4)	356 (1.9)	< 0.01	386 (6)	< 0.001	20	157 (1.7)	< 0.01	14.6 (0.4)	< 0.001
Day 5 (97-100h)	77.2 (2.1)	< 0.001	136	< 0.001 (1.3)	354 (2.0)	< 0.01	405 (1)	< 0.001	31	161 (1.8)	< 0.01	14.5 (0.4)	< 0.001
Day 10 (217-220h)	74.8 (1.9)	< 0.001	133	< 0.001 (1.2)	348 (2.0)	< 0.001	415 (7)	< 0.001	28	162 (1.8)	< 0.01	15.2 (0.4)	< 0.001
Return to sea level (55 min by air)													
Day 1 (3-7h)	80.3 (1.8)	< 0.001	128	NS (1.3)	354 (1.8)	< 0.001	392 (7)	< 0.001	19	162 (2.1)	< 0.01	16.6 (0.4)	NS
Day 2 (25-28h)	67.5 (1.4)	NS	124	NS (1.2)	366 (1.6)	NS	347 (4)	NS	Nil	153 (1.4)	NS	17.5 (0.4)	NS
Day 3 (49-52h)	65.3 (1.4)	NS	123	NS (1.1)	368 (1.6)	NS	342 (4)	NS	Nil	152 (1.4)	NS	17.9 (0.4)	NS
TRHA (group C)	69.1		126		369		359		6	160		12.8	
			(1.2)		(1.7)		(5)			(1.6)		(0.2)	
PRHA (group D)	56.2		116		375		321		Nil	150		19.3	
			(1.2)		(1.6)		(5)			(1.7)		(0.2)	

*Statistical levels as compared with sea level values. Figures in parentheses indicate standard error of mean. PRHA, Permanent residents of high altitude; TRHA, temporary residents of high altitude.

PEP/LVET = actual values $\times$ 1000. PEP, LVET, RZ are in milliseconds corrected for heart rate. PEP/LVET, and $\frac{dZ}{dt}$ RZ are from uncorrected values.

values were scanned to note the number of individuals showing a PEP/LVET ratio of over 400 on the days of study. At sea level no subject had a PEP/LVET ratio of more than 400. Up to 4 hours of stay at high altitude only one subject had a ratio more than 400. At 5 to 8 hours 3 subjects, on the second day 8 subjects, on the third day 15 subjects, on the fourth day 20, on the fifth day 31, and on the tenth day 28 subjects had values in excess of 400. Immediately on return to sea level, 19 continued to show abnormal figures on the first day. On the second and third day of return none of the subjects had abnormal values.

The mean sea level control value of group B was 325. This rose to 374 on arrival at altitude and gradually rose to 434 on the tenth day. On the third day of return to sea level the values had dropped to

350. At sea level no subject had a ratio exceeding 400. On the first day at altitude 7 subjects, on the second day 5 subjects, on the third day 13, the fourth day 14, the fifth day 16, and on the tenth day 23 subjects showed values above 400. On the second day of return to sea level 10 subjects continued to show abnormal values and on the third day none had abnormal values. The mean PEP/LVET ratio of group C was 359 and that of group D 321.

The QS₂ interval corrected for heart rate did not show significant changes in both the groups.

RZ INTERVAL

In group A, the control RZ interval index was 149 ms. This began to increase by the second day of arrival at altitude and reached a peak of 162 ms on the tenth day. On the third day of return to sea level

Table 2 Serial changes in levels of myocardial function in subjects inducted to 3658 m by road

Time of study	Heart rate	P	PEP	P	LVET	P	PEP/LVET	P	PEP/LVET > 400	RZ interval	P	dZ/dt RZ	P
Sea level	63.2 (1.7)	—	127 (1.7)	—	381 (1.6)	—	325 (6)	—	Nil	159 (1.7)	—	17.9 (0.6)	—
<i>High altitude (3658 m by road in 6 h)</i>													
Day 1 (18-20h)	86.7 (3.1)	< 0.001	133 (1.5)	NS	359 (2.1)	< 0.01	374 (7)	< 0.001	7	168 (2.3)	< 0.01	14.9 (0.8)	< 0.001
Day 2 (42-44h)	92.3 (3.2)	< 0.001	140 (1.7)	< 0.01	363 (1.9)	< 0.01	374 (9)	< 0.001	5	170 (3.1)	< 0.01	14.7 (0.7)	< 0.001
Day 3 (66-68h)	90.7 (3.2)	< 0.001	139 (2.0)	< 0.01	358 (2.1)	< 0.01	396 (9)	< 0.001	13	171 (2.4)	< 0.01	13.0	< 0.001
Day 4 (90-92h)	80.8 (2.3)	< 0.001	142 (2.2)	< 0.001	365 (1.9)	< 0.01	394 (9)	< 0.001	14	173 (2.8)	< 0.001	12.6 (0.7)	< 0.001
Day 5 (114-116h)	84.4 (2.7)	< 0.001	143 (1.6)	< 0.001	360 (2.1)	< 0.01	406 (8)	< 0.001	16	176 (2.8)	< 0.001	13.0 (0.6)	< 0.001
Day 10 (235-237h)	87.9 (2.4)	< 0.001	144 (1.7)	< 0.001	350 (1.6)	< 0.001	434 (8)	< 0.001	23	179 (2.8)	< 0.001	13.6 (0.6)	< 0.001
<i>Return to sea level (by road in 6 h)</i>													
Day 2 (25-27h)	62.9 (1.5)	NS	142 (1.4)	< 0.001	366 (1.6)	< 0.01	393 (6)	< 0.001	10	165 (1.7)	< 0.01	15.5 (0.6)	< 0.01
Day 3 (49-51h)	63.0 (1.3)	NS	133 (1.7)	NS	373 (1.6)	NS	350 (7)	NS	Nil	157 (2.3)	NS	17.0 (0.6)	NS

Abbreviations as in Table 1.

the interval index was normal. Group B had control levels of 159 ms at sea level. This gradually increased to 179 ms on the tenth day at altitude and completely normal values occurred on the third day of return. Group C had values of 160 ms and group D 150 ms.

CONTRACTILITY INDEX

The control value of 17.4 of group A showed a reduction to 12.2 on the third day. This was followed by a gradual improvement till the tenth day when a value of 15.2 was noted. Normal figures occurred on the third day of return to sea level. Group B had control levels of 17.9 which declined to 12.6 on the fourth day. A subsequent improvement occurred till the tenth day when a value of 13.6 was obtained. Normal values obtained by the third day of return to sea level. Group C had a value of 12.8 and group D 19.3 at high altitude. The values, along with levels of statistical significance, are expressed in Tables 1 and 2.

STROKE INDEX (Table 3)

The stroke index of group A was 46.2 ml/m² at sea level. It showed a gradual and sustained reduction to 29.8 ml/m² on the tenth day. The values were normal on the second day of return. The stroke index of group B was 48.8 ml/m² and it showed a

reduction to 28.9 ml/m² on the tenth day of stay at high altitude. Normal values were obtained on the second day of return to sea level. Group C had values of 31.5 ml/m² and group D 49.7 ml/m².

CARDIAC INDEX

The cardiac index of group A was 2.94 l/min per m² at sea level and it came down to 2.47 l/min per m² on the tenth day at high altitude. Normal values were reached immediately on return.

Group B had values of 3.09 l/min per m² which came down to 2.49 l/min per m² on the tenth day at high altitude. Normal values were reached on the second day of return to sea level.

URINARY CATECHOLAMINE EXCRETION

The levels of urinary catecholamine excretion in 24 hours are shown in Table 4. Group A showed a significant increase in the values, reaching a peak on the tenth day. Group B showed a mild and statistically insignificant increase in 24 hours' catecholamine excretion.

Discussion

Accurate assessment of myocardial function at high altitude has been difficult for many reasons. Hostile environment, rough terrain, and lack of

Table 3 Serial changes in stroke index and cardiac index of subjects inducted to 3658 m by air and road

Time of study	Group A				Group B			
	Stroke index (ml/m ²)	P	Cardiac index (l/min per m ²)	P	Stroke index (ml/m ²)	P	Cardiac index (l/min per m ²)	P
Sea level	46.2 (1.3)	—	2.94 (0.10)	—	48.8 (2.2)	—	3.09 (0.14)	—
<i>High altitude induction</i>								
Day 1								
0-4h	37.4 (1.4)	< 0.001	2.36 (0.10)	< 0.001	—	—	—	—
5-8h	36.5 (1.2)	< 0.001	2.39 (0.04)	< 0.001	—	—	—	—
18-20h	—	—	—	—	35.7 (2.0)	< 0.001	2.94 (0.10)	NS
Day 2	32.0 (1.0)	< 0.001	2.23 (0.07)	< 0.001	35.1 (1.8)	< 0.001	3.08 (0.12)	NS
Day 3	31.1 (1.2)	< 0.001	2.21 (0.08)	< 0.001	30.5 (1.8)	< 0.001	2.64 (0.11)	< 0.001
Day 4	33.6 (1.2)	< 0.001	2.50 (0.07)	< 0.001	33.0 (1.9)	< 0.001	2.68 (0.11)	< 0.001
Day 5	35.0 (1.3)	< 0.001	2.60 (0.07)	< 0.001	33.2 (1.8)	< 0.001	2.70 (0.09)	< 0.001
Day 10	29.8 (0.9)	< 0.001	2.47 (0.06)	< 0.001	28.9 (1.3)	< 0.001	2.49 (0.09)	< 0.001
<i>Return to sea level</i>								
Day 1	37.5 (1.2)	< 0.001	3.05 (0.08)	NS	—	—	—	—
Day 2	45.8 (1.3)	NS	3.00 (0.12)	NS	50.0 (1.7)	NS	3.13 (0.09)	NS
Day 3	48.6 (1.0)	NS	3.02 (0.11)	NS	52.2 (1.7)	NS	3.18 (0.11)	NS

The actual hours during which the data were obtained for groups A and B at high altitude for days 2 to 10 have been given in detail in Tables 1 and 2.

Table 4 24 hour urinary catecholamine excretion in groups A and B

Time of study	Air inductees* group A		P	Road inductees* group B		P
Sea level	46.0 (2.5)		—	50.5 (2.4)		—
<i>High altitude induction</i>						
Day 1	54.7 (4.3)		NS	55.6 (3.0)		NS
Day 2	64.4 (6.2)		< 0.01	56.2 (1.1)		NS
Day 4	59.7 (5.3)		NS	50.0 (1.2)		NS
Day 10	90.7 (9.9)		< 0.001	55.0 (3.3)		NS
<i>Return to sea level</i>						
Day 1	53.6 (4.2)		NS	50.5 (2.0)		NS
Day 4	49.1 (2.5)		NS	53.1 (1.6)		NS

*µg/24 h.

adequate laboratory facilities have been the main deterrents. The traumatic techniques of assessing left ventricular function limited the sample size because of ethical and logistical reasons. Attempts at stimulating hypoxia in a chamber yielded conflicting results because of the short duration of exposure and other physiological responses. The

availability of simple, rapid, reliable, and reproducible noninvasive procedures stimulated interest in assessment of myocardial function in various situations. In our pilot study alterations in systolic time intervals suggested left ventricular dysfunction on exposure to high altitude (Balasubramanian *et al.*, 1975).

In the current study, the subjects were exposed to high altitude by air and road. The recordings were made more frequently to delineate the immediate and late effects of hypoxia. Two additional control groups of highlanders and lowlanders were included. Studies on return to sea level were incorporated to distinguish the pattern of reversion to normal. Electrical impedance cardiography and systolic time intervals were chosen as the methods of choice. They yielded maximal information regarding left ventricular function and stroke index. The daily recordings could be completed within 4 hours eliminating diurnal variations.

The impedance plethysmogram picked up body potentials through inexpensive, reusable, cutaneous electrodes. It yielded two additional parameters of

myocardial function, that is RZ interval and $\frac{dZ/dt}{RZ}$

index. In addition, data could be simultaneously obtained noninvasively in respect of stroke index, cardiac index, and thoracic extravascular fluid volume (Kubicek *et al.*, 1966; Geddes and Baker, 1968; Siegel *et al.*, 1970; Lababidi *et al.*, 1970; Hill and Lowe, 1973; Luepker *et al.*, 1973; Balasubramanian and Hoon, 1976; Hill and Merrifield, 1976).

This study was planned to delineate the effect of high altitude hypoxia in isolation on myocardial performance, excluding other influences such as cold and physical activity. We could accumulate data regarding the myocardial function at 0 to 4 hours, 5 to 8 hours, 18 to 20 hours, 25 to 28 hours, 2, 3, 4, 5, and 10 days of stay at an altitude of 3658 m. The subjects were studied under carefully controlled conditions of temperature, physical activity, and other requisites for comparable data. Two control groups of temporary and permanent residents at high altitude were also studied under identical conditions. Scrupulous care was taken to avoid smoking, consumption of alcohol, drug ingestion, exposure to cold, and physical exertion during the entire study. No other simultaneous invasive study was conducted in these subjects, thus avoiding the possibility of sympathetic stimulation caused by these procedures. Simultaneous estimation of urinary catecholamine excretion ensured quantification of compensatory sympathetic overactivity which occurred as a result of high altitude hypoxia.

Alterations of pre-ejection period, left ventricular ejection time, PEP/LVET ratio, RZ interval, and contractility index clearly indicated depression of myocardial function. A predictable and reproducible pattern was observed in all of them. No significant changes were discernible in these values at 0 to 4 hours and 5 to 8 hours after arrival at altitude. The

earliest alterations occurred at 18 hours. There was gradual but sustained deterioration as the days progressed, reaching a maximum on the tenth day of stay. The only value which showed a consistent

improvement after the fourth day was the $\frac{dZ/dt}{RZ}$

index. Reversion to normal did not occur immediately on return to sea level but took 48 to 72 hours.

The findings of our current study, though essentially similar to our initial report, differ in a few aspects. During the last expedition we studied 20 subjects serially on high altitude exposure and found that maximal changes were seen until the fourth day, with a tendency for the mean values to improve by the tenth day even though tenth day values were still abnormal (Balasubramanian *et al.*, 1975). During the present study we found that all values

except $\frac{dZ/dt}{RZ}$ continued to deteriorate gradually till

the tenth day. The 56 permanent residents of high altitude (group D) had completely normal myocardial function. On the other hand, the lowlanders temporarily resident at altitude (group C) showed only a mild impairment of these indices compared with the highlanders, thus suggesting a fair degree of return to normal as a result of acclimatisation.

The exact genesis of the alterations of these systolic time intervals at high altitude is still a matter of conjecture. Some authors have reported lengthening of PEP, diminution of LVET, and increase in the PEP/LVET ratio in patients with diminished left ventricular performance (Weissler *et al.*, 1968, 1969; Lewis, 1975). The PEP/LVET ratio was found to be closely correlated to the ejection fraction by a number of workers (Weissler *et al.*, 1969; Garrard *et al.*, 1970). Ahmed and co-workers (1972) showed significant correlation between the PEP/LVET and the ejection fraction, contractile element velocity at peak isometric stress, and the Frank-Levison contractility index in patients with left ventricular myocardial disease. On the other hand, when valvular heart disease or intra-cardial shunts were present no such correlation could be found. As our subjects were entirely normal and had distinct alterations in PEP/LVET ratio, it is reasonable to conclude that primary depression of the left ventricular function caused by high altitude hypoxia may be an important contributing factor.

The importance of alterations in preload in the genesis of these changes requires clarification. Boudoulas *et al.* (1971) reported deterioration of PEP/LVET in patients with congestive heart

failure after diuresis. This was attributed to a diminished filling pressure for a noncompliant left ventricle. It is unlikely that this mechanism plays a dominant role in the causation of these alterations. The main changes that occur in high altitude are a shift of the blood volume more centrally. Some authors have reported a reduction in urine output at high altitude (Singh *et al.*, 1969). Wood and Roy (1970) showed a decrease in peripheral blood flow using a venous occlusion plethysmograph. The possibility of a reduced preload occurring at high altitude causing these changes in systolic time intervals, therefore, appears unlikely.

In group A the alterations in left ventricular function were observed despite an increase in urinary catecholamine excretion levels. In group B, where the catecholamine excretion was not increased, the extent of changes particularly the PEP/LVET ratio was more pronounced. The distinct chronological correlation between the reduction in stroke index with depression of the levels of myocardial contractility was striking, suggesting left ventricular dysfunction as the prime cause for the reduced stroke and cardiac indices.

The practical implications and applications of this study are obvious. Distinct alterations of all indices of myocardial function have been observed in young, normal, well-trained subjects exposed to high altitude for the first time. The changes are likely to be much more obvious in older subjects and in those returning to sea level. Most of the workers had hitherto not seriously considered left ventricular dysfunction as one of the possible factors in the aetiology of high altitude illnesses. Attempts were made to explain and attribute the changes solely to local changes in the pulmonary vessels, with no contributing part of the left ventricle (Viswanathan *et al.*, 1969). Attempts at prophylaxis of high altitude illnesses were also naturally aimed at correcting these factors rather than improving left ventricular performance (Singh *et al.*, 1969). The results of our study suggest that left ventricular dysfunction occurs on high altitude exposure and cannot be ignored as one of the causes of high altitude illnesses. Attempts to improve myocardial performance by specific inotropic agents may be a suitable avenue for at least a partial prophylaxis against these groups of illnesses.

It should, however, be conceded that left ventricular dysfunction may not be the sole or dominant cause for the pathophysiological alterations at altitude. At best, it can only be postulated that it might play a role in the genesis of these changes, the pathogenesis of which is as yet undefined. They are most probably caused by an accumulation of a multitude of adverse reactions occurring in the

human cardiorespiratory system on exposure to high altitude.

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