

Effects of high altitude hypoxia on left ventricular systolic time intervals in man¹

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Effects of high altitude hypoxia on systolic time intervals were examined in 34 healthy men: 20 sea level residents studied at rest and at the end of 3 minutes steady isometric (handgrip) exercise at sea level and then serially for the first 5 days and on the tenth day, at an altitude of 3658 m, and 14 permanent residents at high altitude studied at high altitude. In the sea level residents there was a significant increase in the pre-ejection period (PEP), abbreviation of the left ventricular ejection time (LVET), both corrected for heart rate, and prolongation of the PEP/LVET ratio at high altitude. The maximum changes were seen on days 2 and 3; these parameters tended to approach sea level control values by the tenth day. The systolic time interval values of high altitude residents were similar to the control values of the sea level residents obtained at sea level but significantly different from the changes in the sea level values seen in the first 4 days at high altitude. It thus appears that while the high altitude residents do not show any left ventricular dysfunction as determined by systolic time intervals, healthy sea level residents when exposed to high altitude hypoxia show a significant depression of the left ventricular function for at least the first 4 days. This might be a contributing factor in the genesis of high altitude pulmonary oedema.

Left ventricular systolic time intervals as indirect indices of myocardial performance have been widely used for the study of ventricular functions in patients with various forms of heart disease including acute myocardial infarction (Moskowitz and Wechsler, 1965; Weissler, Harris, and Schoenfeld, 1968, 1969; Spodick, Dorr, and Calabrese, 1969; Diamant and Killip, 1970; Perloff, Talano, and Ronan, 1971; Weissler and Gerrard, 1971). Effects of circulatory stress-tests such as dynamic and static exercise (Aronow, 1970; Pigott *et al.*, 1971; Siegel *et al.*, 1972; Lindquist, Spangler, and Blount, 1973), pharmacological intervention (Weissler *et al.*, 1965; Weissler and Schoenfeld, 1970; Buyukozturk, Kimbiris, and Segal, 1971), and alteration of preload (Khanna *et al.*, 1973) on the systolic time intervals have also been extensively reported. However, the response of the systolic time intervals to high altitude hypoxia in man has not been well defined. Kowalsky and Anthony (1972) have reported the effects of acute hypobaric hypoxia in 26 normal healthy men at simulated

altitudes of 4572 and 5486 metres for periods of 10 minutes, which they claimed was enough time to allow for a measure of equilibration. This study could hardly be equated to exposure to high altitude hypoxia either for a period of a few days or for a life time. The present study was designed to evaluate the effects of more prolonged exposure to high altitude hypoxia on systolic time intervals in normal healthy sea level residents when suddenly removed to high altitude and compare these observations with those of permanent residents at high altitude.

Subjects and methods

Systolic time intervals estimated in 34 healthy male volunteers form the basis of this clinical report. Twenty of them were plainsmen who were first studied at sea level, then at an altitude of 3658 metres for the first 5 days and on the tenth day after arrival at this altitude. Fourteen permanent residents of high altitude whose forbears had lived there for three generations and who had never been to the plains were also studied on two different occasions at the high altitude. The mean age of the sea level residents was 26.5 years and that of high altitude residents was 27 years. All subjects were scrupulously screened to exclude any disease.

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All measurements were recorded in the morning in a fasting state in a semidarkened room kept at 30°C. The subjects were not allowed to smoke and had ingested no drugs during the entire study. The nature of the procedures had been explained to them beforehand. The blood pressure was measured in the recumbent position. Recordings were made with the subject in a supine position, with the head slightly raised by one pillow, during quiet normal breathing.

Simultaneous tracings of the electrocardiograms, phonocardiograms, and carotid artery pulsations were recorded using a Sanborn four-channel direct writing polygraph at a paper speed of 100 mm/s. The electrocardiogram was obtained from a routine or augmented limb lead wherever the earliest component of the QRS complex was clearly seen. An Electronics for Medicine microphone (A.161) was placed over the praecordium to the left of the sternum in an optimal position for recording the high frequency signals of the first and second heart sounds at a filter range of 40 to 200 Hz. The carotid artery pulsations were recorded using a funnel-shaped pick-up attached to a Statham P23AA manometric pressure transducer by a 20 cm rubber tube with an internal diameter of 3 mm. A minimum of 15 complexes was recorded for measurements from 10 consecutive cardiac cycles.

Isometric hand-grip exercise was given by means of a balloon dynamometer. The subject was required to grip at 30 per cent of his maximum voluntary contraction for a duration of 3 minutes. The hand balloon dynamometer was held at arm's length and the arm supported on a rest. Recordings were then repeated at the end of 3 minutes while the patient was still performing the handgrip. Care was taken to ensure that the subject was breathing normally during the recording (Flessas, Kumar, and Spodick, 1970). All studies both at sea level and high altitude were conducted under identical conditions by the same observers using the same equipment. Using 10 consecutive complexes the following time intervals were measured.

- 1) *Total electromechanical systole* (QS_2). The interval from the onset of ventricular depolarization to the first high frequency vibration of the aortic component of the second sound;
- 2) QS_1 from the earliest component of the QRS complex to the first high frequency vibration of the first heart sound;
- 3) *Left ventricular ejection time* (LVET) measured from the onset of rapid upstroke of the carotid pulse to the nadir of the dicrotic notch.
- 4) *Pre-ejection period* (PEP) from the onset of electrical activity to the beginning of left ventricular ejection was calculated by the equation

$$PEP = QS_2 - LVET$$

The averages of each of the above measurements from the 10 consecutive cardiac cycles were calculated.

Indices correcting the data for heart rate were calculated using the regression equations suggested by

Lindquist *et al.* (1973) for resting and isometric exercise:

Resting

| | |
|--------------------------|--------------------|
| PEP Index (PEPI) | = PEP + 0.44 HR |
| QS_1 Index (QS_1I) | = QS_1 + 0.43 HR |
| QS_2 Index (QS_2I) | = QS_2 + 1.85 HR |
| LVET Index (LVETI) | = LVET + 1.42 HR |

After isometric exercise

| | |
|----------|--------------------|
| PEP I | = PEP + 0.60 HR |
| QS_1 I | = QS_1 + 0.17 HR |
| QS_2 I | = QS_2 + 1.75 HR |
| LVET I | = LVET + 1.15 HR |

The PEP/LVET ratio was calculated from the appropriate values uncorrected for heart rate.

Significance of difference was evaluated using the paired 't' test.

Results

Heart rate

Response of the mean heart rate, at rest and after isometric hand grip exercise, of the 20 healthy sea level residents to high altitude is shown in Fig. 1. The maximal increase is seen on the first two days after arrival at the altitude; heart rates are significantly higher ($P < 0.001$) than the sea level values as well as from those of the permanent residents of high altitude.

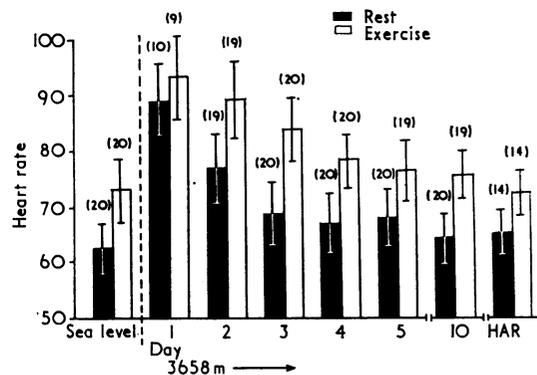


FIG. 1 The response of the heart rate (resting and exercise) of 20 healthy sea level residents when exposed to 3658 m from day 1 to 5 and on day 10. The last two columns represent the resting and exercise heart rate of 14 permanent residents at high altitude. The values are shown here as means with standard deviations. The number in parentheses at the top of each bar represents the number of subjects studied. Data in Fig. 2, 3, and 4 are also presented in similar pattern.

TABLE Mean values and standard deviation of QS_1 , QS_2 , and QS_2I in ms in sea level residents at sea level and at high altitude with values for high-altitude residents for comparison

| | QS_1 | | QS_2 | | QS_2I | |
|-------------------------|--------|----------|--------|----------|---------|----------|
| | Basal | Exercise | Basal | Exercise | Basal | Exercise |
| Sea level | 51 | 52 | 385 | 387 | 500 | 515 |
| SD | 7.4 | 9.6 | 33.2 | 20.4 | 29.3 | 15.6 |
| Day 1 | 45 | 50 | 331 | 329 | 489 | 493 |
| SD | 11.4 | 19.9 | 24.7 | 22.9 | 14.7 | 15.5 |
| Day 2 | 47 | 46 | 352 | 352 | 494 | 509 |
| SD | 11.0 | 14.8 | 36.0 | 30.4 | 33.5 | 20.7 |
| Day 3 | 47 | 50 | 368 | 366 | 495 | 513 |
| SD | 8.9 | 12.7 | 40.3 | 30.7 | 32.0 | 15.7 |
| Day 4 | 50 | 53 | 375 | 371 | 498 | 507 |
| SD | 12.5 | 14.2 | 37.6 | 27.5 | 30.3 | 20.4 |
| Day 5 | 50 | 51 | 366 | 364 | 491 | 500 |
| SD | 7.5 | 11.8 | 31.7 | 24.6 | 27.2 | 15.4 |
| Day 10 | 50 | 50 | 377 | 373 | 497 | 505 |
| SD | 9.6 | 19.9 | 30.1 | 18.7 | 25.9 | 14.2 |
| High altitude residents | 45 | 47 | 393.3 | 392.3 | 513.4 | 520.5 |
| SD | 8.8 | 12.1 | 23.7 | 24.9 | 19.1 | 21.7 |

Electromechanical time intervals

It is apparent from the Table that QS_1 , QS_2 (and also corrected for heart rate QS_2I) time intervals of sea level residents do not change appreciably at high altitude and are similar to those of high altitude residents.

Pre-ejection period index (PEPI) (Fig. 2)

Maximum prolongation of pre-ejection period index values, both resting and after static exercise, are seen on day 2 and 3 after arrival at the altitude; the resting values change from 115 to 130 ms and the exercise values from 137 to 154 and 158 ms ($P < 0.001$). The values tended to approach sea level value by the tenth day. The pre-ejection period index values of the high altitude residents are similar to those of the sea level residents at sea level, but significantly different from those of sea level residents obtained at high altitude on the second and third days ($P < 0.005$ and < 0.001).

Left ventricular ejection time index (LVETI) (Fig. 3)

Both the resting and exercise left ventricular ejection time index values are significantly shortened on all the days at the high altitude ($P < 0.001$). The resting and exercise sea level values of 395 and 379 ms decrease to 368 and 348 ms on day 1. Thereafter the values steadily increase up to the tenth day but are significantly lower than those obtained at sea level as well as those of the high altitude residents ($P < 0.001$).

PEP/LVET ratio (Fig. 4)

The resting PEP/LVET ratio shows maximum increase on day 2 (from 0.287 to 0.370) and on day 3 (to 0.362) after which the values progressively decrease to 0.318 on the tenth day, which is still significantly increased ($P < 0.005$). The exercise value similarly shows a maximum increase on day 2 (from 0.315 to 0.403) and on day 3 (to 0.418), after

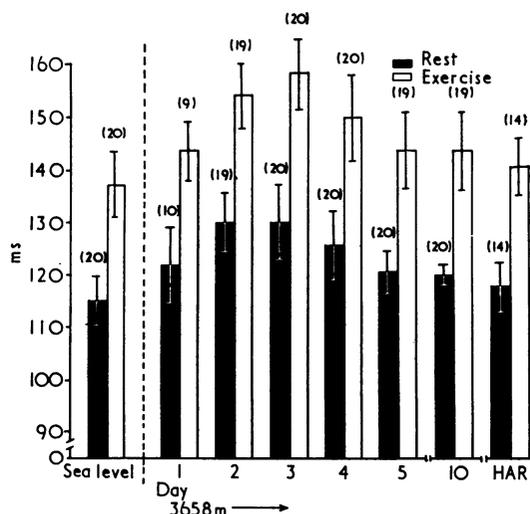


FIG. 2 Mean and standard deviation values of pre-ejection period index (PEPI) of the same 20 healthy sea level residents and 14 high altitude residents.

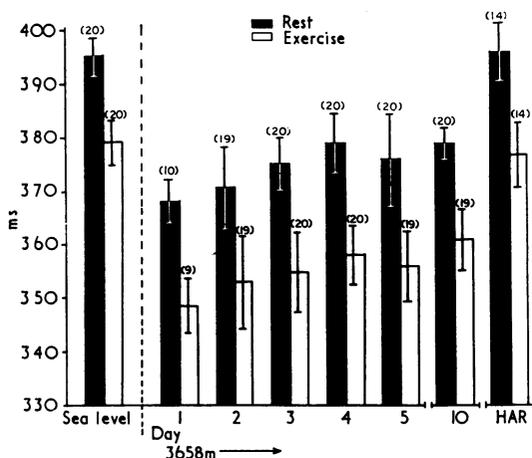


FIG. 3 Left ventricular ejection time index (LVETI) values of the same group of 20 healthy sea level residents and 14 high altitude residents.

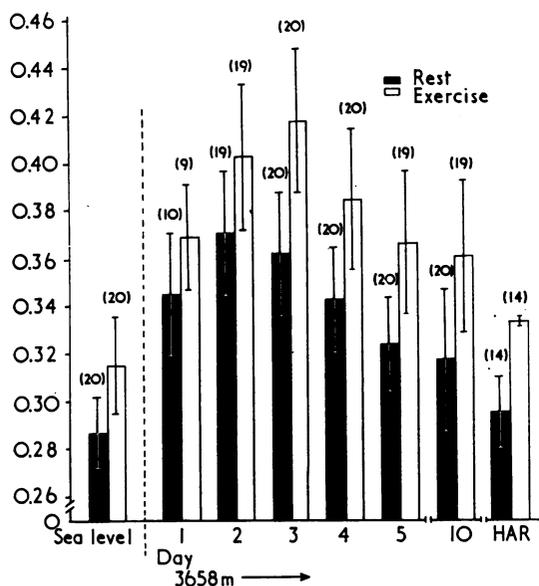


FIG. 4 The PEP/LVET ratio in the same subjects.

which the values progressively decrease, though the tenth day value of 0.361 is still significantly higher ($P < 0.001$). The mean PEP/LVET ratios of 0.296 at rest and 0.334 with exercise of the high altitude residents are not different from those obtained in the sea level residents at sea level, but are significantly lower than the values in the latter obtained on days 1, 2, and 3 at high altitude ($P < 0.001$).

Discussion

From the data presented, it appears that healthy residents at sea level when exposed to high altitude hypoxia show evidence of left ventricular dysfunction as indicated by the systolic time intervals. There was prolongation of the pre-ejection period index (PEPI), abbreviation of the left ventricular ejection time index (LVETI), and an increase of the PEP/LVET ratio. The maximum changes in the systolic time intervals were observed on the second and third day after arrival at the altitude. These changes were greater with isometric exercise.

As patients with heart failure show similar changes in systolic time intervals (Weissler *et al.*, 1968), it is reasonable to assume that there is definite dysfunction of the left ventricle in normal healthy sea level residents when suddenly exposed to high altitude hypoxia. The present findings are, however, not comparable to the observations of Kowalsky and Anthony (1972) who found that the PEPI shortened, LVETI increased, and PEP/LVET ratio decreased when exposed to hypobaric hypoxia. This difference could perhaps be explained by the fact that when a person is exposed for a short period of 10 minutes in a hypobaric chamber, there is excessive sympathetic activity which overshadows the effects of the hypoxia.

On the other hand, in the present study, as the 20 healthy residents of sea level acted as their own controls and as there were subsequent serial observations at high altitude, both at rest and with static exercise, the validity of the findings and the significance of the changes seen in systolic time intervals appear reliable.

It is also of interest to note that in half of the subjects the resting PEP/LVET ratio and in two-thirds of them the exercise PEP/LVET ratio remained significantly increased even on the tenth day. Perhaps of greater interest is the finding that the maximum increase in the PEPI, decrease in the LVETI, and increase of PEP/LVET ratio were seen on the second and third day after arrival at high altitude (especially with exercise), a vulnerable period when the maximum incidence of high altitude pulmonary oedema is also seen (Singh *et al.*, 1965).

Physiological studies (Fred *et al.*, 1962; Hultgren *et al.*, 1964; Penalzoza and Sime, 1969; Roy *et al.*, 1969; Bhatia *et al.*, 1972) have shown that these patients hyperventilate washing away the CO_2 , have unsaturated arterial blood, have widened alveolar-arterial O_2 gradients, have low cardiac outputs and increased pulmonary arterial pressures but normal pulmonary artery wedge, left atrial mean, and left ventricular filling pressures. Specific

tests for left ventricular function like left ventricular dp/dt or V max were not employed in these studies. However, the brachial artery mean resting dp/dt value of 1030 ± 243 mmHg (136.9 ± 32.3 kPa) and 1227 ± 129 mmHg (163.2 ± 17.2 kPa) with mild supine leg-raising exercise obtained in 18 healthy soldiers at sea level increased to 1308 ± 329 mmHg (173.9 ± 43.8 kPa) (resting) and 1507 ± 27 mmHg (200.4 ± 3.6 kPa) (exercise) at 3658 m which led us to assume that the left ventricular function remained normal at high altitude (Roy, 1973).

The present observations, however, show definite evidence of left ventricular dysfunction as judged by systolic time intervals. It is suggested that this might be another contributory factor in the hitherto unexplained genesis of high altitude pulmonary oedema.

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