Effect of Digoxin and Diuretics on High Altitude Left Ventricular Dysfunction


SUMMARY Systolic time intervals, stroke volume, cardiac output and \( \frac{dZ}{dt} / RZ \) index were serially estimated in 51 normal healthy volunteers at sea level, for ten days after air induction to 3658 m altitude and on return to sea level. The subjects were divided into three groups and were administered a diuretic, beta methyl digoxin and placebo in a double blind protocol. The group on placebo showed an increase in heart rate, reduction in stroke index and cardiac index during high altitude exposure with normalization on return to sea level. A deterioration in left ventricular function as manifested by prolongation of pre-ejection period, increase in PEP/LVET ratio, reduction in \( \frac{dZ}{dt} / RZ \) index and left ventricular ejection time was also noted at high altitude. The subjects on digoxin maintained normal stroke/cardiac index and did not show any significant change in the parameters of myocardial function. The diuretic group showed more deterioration in the parameters than the placebo group. No significant side effects were noted. Left ventricular dysfunction and reduction of stroke index at high altitudes may be causally related; digoxin administration may prevent them from occurring.

THE EFFECT OF HIGH ALTITUDE HYPOXIA on human cardiorespiratory dynamics has been the subject of intense research and a number of communications for the last two decades.1-10 Some of these reports, though restricted to a small sample size due to the hostile terrain, logistic problems and invasive nature of investigations, were of immense value in clarifying the genesis of high altitude illnesses.1, 2, 6-7, 9 Simultaneously, clinical studies in a large number of patients generated further interest in these problems.3, 4, 8 Emergence of noninvasive methods as reliable indicators of alterations in cardiovascular function prompted us to use such methodology serially in a large sample size to study responses to high altitude exposure. Using systolic time intervals and electrical impedance plethysmography, we detected alterations in pulmonary extravascular water volume, stroke volume, cardiac output and left ventricular function in normal volunteers inducted to 3658 m.11-16

Having established that a definite reduction in left ventricular function, stroke volume and cardiac output occurs on acute exposure to high altitude, we planned and conducted a carefully controlled study in which drugs with a possible prophylactic potential were used and their effects on the parameters of myocardial function studied in detail.

Materials and Methods

Subjects

Fifty-one normal healthy male volunteers between 21 and 35 years of age were chosen as the subjects for the study. They were born and brought up at altitudes less than 1000 m and had never visited higher altitudes. They were similar in dietary habits, physical training and anthropometric measurements. They were divided into three groups of 17 each by table of random numbers and assigned to one of the drug groups by a double blind protocol. Once assigned, they continued to take the same drug throughout the entire study period, at fixed constant time intervals.

Drugs

The following drugs were used during the trial: 1) betamethyl digoxin, 0.1 mg tablets (Lanitop); 2) aldactone (a combination of 25 mg of spironolactone-A and 25 mg of hydroflumethiazide); 3) placebo.

The drugs were coded and the codes sealed until after the final analysis of data. All subjects received a fixed dose regime of 1 tablet thrice daily (before breakfast, lunch and dinner). The worker in charge of drug administration did not participate in data collection or analysis.

Study Protocol

The study protocol comprised serial estimation of systolic time intervals, stroke volume and cardiac output. The first study was performed at 198 m above sea level (henceforth called sea level) under basal conditions. The subjects then were administered the drugs for five days and the studies repeated on the fifth day of drug therapy to arrive at a second data base with drugs at sea level. The drugs were then withdrawn and the studies repeated after two days of withdrawal. They were again restarted 48 hours before induction to high altitude. The subjects were transported to 3658 m by a pressurized aircraft in 75 minutes while under drug treatment. Serial studies of systolic time intervals and impedance plethysmography were carried out at 1, 2, 3, 4, 5 and 10 days at high altitude. They were then returned to sea level by air in 75 minutes while under drugs and the studies repeated on days 1 and 3 and after withdrawal of drugs for five days. All recordings were obtained in the post absorptive state between 9 a.m. and 12:30 p.m. in the supine posture under basal conditions.

Technique

The methods chosen for serial estimation of myocardial function were mechanocardiography and electrical impedance plethysmography. The carotid pulse was obtained by a crystal transducer, the phonocardiogram with a dynamic microphone at a site where the earliest component of the second sound was well recorded and ECG by standard leads. The impedance cardiogram was obtained by I for M, Minnesota impedance cardiograph model 404. One set of silver plated copper mesh reusable electrodes was used for the entire study. Two pairs of these electrodes bonded to a
Methods

Simultaneous recording of electrocardiogram (ECG), phonocardiogram (PCG) and carotid pulse were obtained initially. Then ECG, PCG and the first derivative of impedance cardiogram (dZ/dt) were obtained (fig. 2). The following data were calculated averaging five consecutive complexes:

1. Electromechanical systole (QS) — from the onset of the QRS complex of the ECG to the first high frequency component of aortic closure.
2. Left ventricular ejection time (LVET) — from the onset of the upstroke of the carotid pulse to the nadir of the dicrotic notch.
3. Pre-ejection period (PEP) by the formula QS — LVET.
4. PEP/LVET ratio from uncorrected values.
5. Stroke volume (SV) from the impedance cardiogram by the formula:

\[ SV = p \times \left( \frac{L}{Z_0} \right)^3 \times \text{VET} \times \frac{dZ}{dt} \text{ min} \]

Where \( L \) = mean distance between the inner electrodes in centimeters, \( p \) = resistivity constant of blood at 37°C calculated from hematocrit,\(^\text{17}\) \( Z_0 \) = the mean transthoracic electrical impedance in ohms, \( \text{VET} \) = ventricular ejection time in seconds calculated from a point of \( dZ/dt \) waveform intersecting zero calibration line to a clear dip (X point) synchronous to aortic closure, \( dZ/dt \text{ (min)} = \text{amplitude of } dZ/dt \text{ in ohm/sec.} \)
6. Heart rate — from RR interval.
7. Cardiac output = SV \times heart rate (stroke index and cardiac index obtained from standard nomograms).
8. RZ interval = the distance between the peak of the R wave of ECG and of \( dZ/dt \).\(^\text{18}\)
9. \( (dZ/dt)/RZ \text{ index} \).\(^\text{18, 19}\)

The time intervals were corrected by standard regression equation used in our laboratory.\(^\text{11}\) QS\(_\text{a}\) index = 1.85 HR + observed value. PEP index = 0.44 HR + observed value. LVET index = 1.42 HR + observed value. RZ index = 0.75 HR + observed value.

The data were calculated serially without any knowledge of the drug status. The results were divided and analyzed by ICL 1904 computer with standard statistical methods (Student's t-test and analysis of variance).

Results

Group I subjects were on placebo, group II on \( \beta \) methylidigoxin and group III on diuretics during the study. (Throughout the text \( \beta \) methylidigoxin is referred to as digoxin and the sea level data after five days of drug therapy before induction to high altitude as control values and the basal sea level values before drugs as day 0 data.)

Placebo (table 1)

The heart rate increased from 58/min at sea level to 73/min on the tenth day at high altitude. The PEP index increased from a control level of 131 msec at sea level to 146 msec on the fifth and tenth days at high altitude. The values returned to normal on third day of return to sea level. The
### Table 1. Alterations of 17 Subjects on Placebo

<table>
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<tr>
<th>HR</th>
<th>SI (ml/m²)</th>
<th>CI (L/min/m²)</th>
<th>PEPI (msec)</th>
<th>LVET I (msec)</th>
<th>PEPI/LVET (× 1000)</th>
<th>RZI (msec)</th>
<th>dZ/dt</th>
<th>RS</th>
<th>QS</th>
<th>PEP/LVET &gt;400</th>
<th>PEP/LVET &gt;600</th>
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<td>383 (10)</td>
<td>346 (30)</td>
<td>161 (12)</td>
<td>13.3 (1.7)</td>
<td>518 (16)</td>
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<td>0</td>
</tr>
<tr>
<td>Drug +5</td>
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<td>60 (9)</td>
<td>3.5 (0.6)</td>
<td>131 (9)</td>
<td>388 (10)</td>
<td>346 (30)</td>
<td>160 (10)</td>
<td>13.0 (2.0)</td>
<td>516 (13)</td>
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<tr>
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<td>59 (12)</td>
<td>3.4 (0.4)</td>
<td>132 (9)</td>
<td>388 (9)</td>
<td>349 (23)</td>
<td>161 (12)</td>
<td>13.0 (1.6)</td>
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<td><strong>High altitude</strong> (induction by air to 3658 m)</td>
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<tr>
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<td>382 (11)</td>
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<td>12.6 (2.0)</td>
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<td>370 (11)</td>
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<td>45**(*) (10)</td>
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<td>373 (13)</td>
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<tr>
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<td>2.8**(*) (0.6)</td>
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<td>363**(*) (14)</td>
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<td>170**(*) (13)</td>
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<td>352**(*) (19)</td>
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<tr>
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<td>371 (10)</td>
<td>381 (36)</td>
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<td>14.0 (2.5)</td>
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<tr>
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<td>3.5 (0.5)</td>
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<td>372 (9)</td>
<td>368 (33)</td>
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<tr>
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<td>376 (9)</td>
<td>358 (45)</td>
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<td>504 (14)</td>
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</table>

*P = <0.01, **P = <0.001 as compared to drug + 5.

Figures in parentheses indicate standard deviation.

Drug + 5 = data after 5 days of drug therapy.

Drug - 2 = data after 2 days of withdrawal of drugs.

Abbreviations: HR = heart rate; SI = stroke index; CI = cardiac index; PEPI = pre-ejection period index; LVET I = left ventricular ejection time index; RS = reversion of normal; dZ/dt = amplitude of impedance cardio gram in ohms/sec divided by RZ interval in seconds.

### Table 2. Alterations of 17 Subjects on β Methyl Digoxin

<table>
<thead>
<tr>
<th>HR</th>
<th>SI (ml/m²)</th>
<th>CI (L/min/m²)</th>
<th>PEPI (msec)</th>
<th>LVET I (msec)</th>
<th>PEPI/LVET (× 1000)</th>
<th>RZI (msec)</th>
<th>dZ/dt</th>
<th>RS</th>
<th>QS</th>
<th>PEP/LVET &gt;400</th>
<th>PEP/LVET &gt;600</th>
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<tr>
<td>Day 0</td>
<td>60 (9)</td>
<td>54 (8)</td>
<td>3.2 (0.4)</td>
<td>129 (6)</td>
<td>384 (10)</td>
<td>343 (22)</td>
<td>162 (10)</td>
<td>13.3 (1.6)</td>
<td>512 (12)</td>
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<td>0</td>
</tr>
<tr>
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<td>50 (7)</td>
<td>3.0 (0.3)</td>
<td>130 (8)</td>
<td>374 (11)</td>
<td>359 (31)</td>
<td>164 (9)</td>
<td>13.2 (2.3)</td>
<td>508 (14)</td>
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</tr>
<tr>
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<td>56 (7)</td>
<td>3.1 (0.3)</td>
<td>128 (5)</td>
<td>379 (10)</td>
<td>346 (16)</td>
<td>162 (10)</td>
<td>13.7 (1.3)</td>
<td>507 (13)</td>
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<td><strong>High altitude</strong> (induction by air to 3658 m)</td>
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<tr>
<td>Day 1</td>
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<td>50 (8)</td>
<td>3.2 (0.4)</td>
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<td>376 (14)</td>
<td>361 (27)</td>
<td>163 (11)</td>
<td>14.1 (2.1)</td>
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<tr>
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<td>3.2 (0.3)</td>
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<td>388 (54)</td>
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<td>370 (12)</td>
<td>368 (25)</td>
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<td>Day 5</td>
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<td>366 (12)</td>
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<tr>
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<td>Day 1</td>
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<tr>
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<td>55 (8)</td>
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<td>492 (27)</td>
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**β** methyl digoxin (table 2)

The subjects receiving digoxin showed an increase in heart rate by 8 beats/min on the tenth day at high altitude. The PEP index did not change significantly from the control levels of 130 msec. The control LVET index at sea level was 374 msec. This came down to 354 msec on the tenth day at high altitude and the change was statistically not significant.
Table 3. Alterations of 17 Subjects on Diuretics

<table>
<thead>
<tr>
<th>Sea level</th>
<th>HR (m/sec)</th>
<th>SI (m/sec)</th>
<th>CI (m/sec)</th>
<th>PEPI (msec)</th>
<th>LVET I (msec)</th>
<th>PEP/LVET (X 1000)</th>
<th>RZI (msec)</th>
<th>dZ/dt (RZ)</th>
<th>QSf (msec)</th>
<th>PEP/LVET &gt;400</th>
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<td>63 (10)</td>
<td>57 (11)</td>
<td>3.5 (0.6)</td>
<td>134 (8)</td>
<td>384 (9)</td>
<td>350 (29)</td>
<td>161 (12)</td>
<td>13.0 (1.9)</td>
<td>517 (11)</td>
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<td>0</td>
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<td>Drug +5</td>
<td>62 (10)</td>
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<td>2.6 (0.5)</td>
<td>139 (11)</td>
<td>369 (16)</td>
<td>399 (43)</td>
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<td>3.5 (0.7)</td>
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<td>High altitude (induction by air to 3658 m)</td>
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<td>443 (92)</td>
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<td>12.5 (2.7)</td>
<td>482 (24)</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Return to sea level (by air)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>61 (7)</td>
<td>46 (12)</td>
<td>2.9 (0.6)</td>
<td>140 (8)</td>
<td>361 (12)</td>
<td>412 (34)</td>
<td>171 (11)</td>
<td>13.8 (2.3)</td>
<td>494 (26)</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>61 (9)</td>
<td>49 (10)</td>
<td>3.0 (0.5)</td>
<td>138 (11)</td>
<td>361 (13)</td>
<td>405 (42)</td>
<td>173 (10)</td>
<td>13.3 (2.0)</td>
<td>493 (27)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Drug -5</td>
<td>61 (8)</td>
<td>62 (12)</td>
<td>3.7 (0.6)</td>
<td>130 (6)</td>
<td>382 (11)</td>
<td>344 (14)</td>
<td>163 (13)</td>
<td>13.0 (2.2)</td>
<td>514 (25)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The PEP/LVET index increased from the control level of 0.359 to 0.379 on the tenth day at high altitude. Values of PEP/LVET ratio above 0.400 were observed in 1, 2, 3, 5, 4 and 5 subjects on days 1, 2, 3, 4, 5 and 10, respectively, at high altitude. No subject had values above 0.500. The RZ interval, (dZ/dt)/RZ index, stroke index and cardiac index did not change significantly.

Diuretics (table 3)

The subjects of group III showed an increase in heart rate from the control values of 62/min to 75/min on the tenth day at high altitude. The PEP index was 134 msec before drugs at sea level and increased to 139 msec after diuretics. Exposure to high altitude resulted in a further increase to 152 msec on the tenth day. The maximal reduction of 25 msec in the LVET index on the tenth day at high altitude was not statistically significant. The PEP/LVET ratio was 0.350 prior to drug intake. This increased to 0.399 after five days of diuretics. On exposure to high altitude a further increase to 0.482 was seen on the fifth day. PEP/LVET ratio over 0.400 was observed in eight subjects after drug administration at sea level. On exposure to high altitude, values above 0.400 were noted in 12, 13, 14, 15 and 15 subjects on days 1, 2, 3, 4, 5 and 10, respectively.

Values above 0.500 were observed in 3, 5, 4, 4, 6 and 3 subjects at high altitude on days 1 to 10, respectively.

The RZ interval increased by 10 msec on first day at sea level, but the change was not statistically significant. The (dZ/dt)/RZ index showed significant reduction on days 3, 4 and 5 at high altitude.

The stroke index was 57 ml prior to drug therapy. Administration of diuretics resulted in a moderate diuresis (mean increase in urine output 987 ± 340 ml) and a reduction in stroke index to 41 ml. Exposure to high altitude resulted in a further decrease to 34 ml (P < 0.01). The cardiac index came down from 3.5 to 2.6 L/min/m² after diuretic intake. Exposure to high altitude did not result in further significant decrease, the reduction in stroke index being compensated by the tachycardia.

None of the subjects on digoxin or diuretics developed any significant side effects.

Discussion

Elucidation of the physiological alterations secondary to high altitude exposure has been the subject of extensive research in a number of centers. The role of left ventricular dysfunction at altitude has been a subject of conjecture and controversy. Hultgren et al. felt that left ventricular dysfunction did not occur at altitude.2, 17 They were supported by other workers who based their opinion on the demonstration of a normal wedge pressure during acute high altitude pulmonary edema.1 18-20 Kowalski and Anthony subjected volunteers to short-term hypoxia in a chamber and demonstrated an improvement in left ventricular function which was attributed to increased sympathetic activity.21 On the other hand, a large number of other workers have been strongly propounding the development of left ventricular dysfunction at altitude.22-25

In 1975, we reported the results of a preliminary study in which 20 normal volunteers were serially studied after high altitude induction by air.22 A reduction in myocardial contractility was demonstrated by alterations in systolic time intervals. This study was further extended to cover 83 more subjects who were serially studied at sea level, on high altitude induction by air and road and on deinduction. In these volunteers also we could clearly demonstrate development of left ventricular dysfunction from the second day of exposure gradually deteriorating until 10 days and returning to normal on deinduction.16

The alterations in stroke volume and cardiac output on high altitude exposure have been the subject of a similar controversy. Earlier workers have felt that stroke volume was unaltered and cardiac output showed a mild increase.26, 27 Later reports, however, showed a reduction of stroke volume and cardiac output.23, 24 We had demonstrated a clear reduction of stroke volume on high altitude exposure in 50 subjects in whom the parameters were estimated by electrical impedance plethysmography.25

These observations suggested that left ventricular dysfunction could be the cause for the reduction in stroke volume. The current study was, therefore, carried out to support this hypothesis and to demonstrate the effect of a positive inotropic agent, i.e., digoxin, and a diuretic on left
ventricular function at high altitude. The drugs were chosen with a view to their possible use as prophylactic agents in high altitude illnesses. The placebo group was similarly studied to confirm our earlier findings and to obtain comparative data simultaneously. As these drugs were known to affect these parameters at sea level also, control values were obtained after five days of drug ingestion before high altitude induction and subsequent statistical comparisons obtained from these control values. Noninvasive assessment of left ventricular function was serially performed by calculating pre-ejection period, left ventricular ejection time, PEP/LVET ratio and \((\frac{dZ}{dt})/RZ\) index. Stroke index and cardiac index were obtained by electrical impedance plethysmography. These techniques permitted a rapid accumulation of the relevant data within three hours every day noninvasively. This eliminated diurnal variations of these values and enabled the studies to be completed within the expected peak effect periods of the drugs. The reliability of systolic time intervals as indices of myocardial contractility and electrical impedance plethysmography for estimating stroke volume have been extensively reported.\(^{23-25}\) The \(RZ\) interval and \((\frac{dZ}{dt})/RZ\) index have been found to be useful indicators of myocardial contractility by Siegal et al. and Hill and Merrifield.\(^{18, 19}\)

The alterations of these parameters in the placebo group were similar to our previous reports. A reduction in stroke index, cardiac index, LVET index, \((\frac{dZ}{dt})/RZ\) index and prolongation of PEP index and PEP/LVET ratio were clearly demonstrated. The group receiving diuretics showed a different response. The contractility parameters deteriorated on exposure to high altitude. The subjects on digoxin showed only mild changes in heart rate, stroke index, cardiac index and the contractility parameters.

The implications from the data obtained from the study are manifold. It has been established beyond reasonable doubt that air induction to an altitude of 3658 m causes distinct reduction of resting stroke volume and cardiac output. Simultaneously the noninvasive indices of left ventricular function are also markedly altered. These changes are aggravated by diuretics and administration of an inotropic agent effectively prevents their development at high altitude. Under these circumstances, it is reasonable to conclude that reduction in myocardial contractility plays a major role in the pathogenesis of reduction in stroke volume. This correlation has been postulated by a number of workers and our findings lend further objective support to their contention.\(^{23-25}\)

A distinct possibility now arises regarding use of inotropic agents as prophylaxis for high altitude illness. We have clearly demonstrated that the comparable groups on placebo and digoxin had distinctly different cardiovascular response to high altitude exposure. The placebo group had reduced myocardial function and those on digoxin had more or less normal values. This demonstration of normalization of objectively demonstrated parameters of myocardial function suggests a possible role for digoxin as a useful agent worth further exploration in this field.

The use of furosemide as a prophylactic agent for prevention of high altitude pulmonary edema and acute mountain sickness has been advocated.\(^6\) The authors postulated oliguria as the dominant etiological factor, hypothesized that its correction will prevent such illnesses and reported useful results in an uncontrolled subjective study. On the other hand, Grey et al. reported that subjects started on furosemide on arrival at 5400 m quickly became medical casualties.\(^{36}\) In their experience, all five subjects so studied were incapacitated and would have been completely ineffective operationally. Hultgren and coworkers demonstrated that fluid retention and increase in plasma volume does not occur at high altitude.\(^{36}\) The subjects receiving furosemide prophylaxis had an increase in hematocrit by 10.3% and had no improvement in physical performance nor any amelioration of symptoms of acute mountain sickness. Five of the eleven subjects developed marked hypotension and syncope on quiet standing after mild exercise. Hultgren concluded that furosemide does not prevent acute mountain sickness.\(^37\) This study was, therefore, conducted with a slower acting diuretic combination with potassium-sparing capability, thus eliminating the effect of rapid diuresis and hypokalemia. However, no benefit could be demonstrated by this also.

Our limited and preliminary study seems to suggest a possible role for digoxin during high altitude induction. The number of subjects studied is small and the dosage schedule fixed and it is therefore not possible to dogmatically say that digoxin will be useful. It appears reasonable to conclude, however, that digoxin may be an avenue worth further exploration; results of more extensive studies may yield valuable clues regarding its use in the possible prevention of acute high altitude pulmonary edema.

**Acknowledgment**

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**References**

Pulmonary Hemodynamics and Right Ventricular Function in Hypertension

MARIA T. OLIVARI, M.D., CESARE FIORENTINI, M.D., ALVISE POLESE, M.D., AND MAURIZIO D. GUAZZI, M.D.

SUMMARY Pulmonary and systemic hemodynamics in 16 hypertensive subjects (group I) with left ventricular (LV) hypertrophy (ECG and echo criteria) and in 17 hypertensive subjects with ECG signs of LV strain (group II), were compared with those in 14 normal individuals. An augmented pulmonary arteriolar resistance (PAR) in group I and to a larger extent in group II accounted for the pulmonary pressure elevation in both groups. Increase in PAR was unrelated to pulmonary blood flow and volume, pleural pressure, arterial PO2, PCO2 and pH, and could not be explained entirely by the left ventricular end-diastolic pressure changes.

In group I, left (L.MSEJR) and right (R.MSEJR) mean systolic ejection rate, stroke index (SI) and mean velocity of circumferential fiber shortening (V_{ot}) were enhanced in spite of the heightened pressure load on both sides of the heart. In group II, a large reduction of SI, L.MSEJR, R.MSEJR and V_{ot}, as well as the relationship between ventricular filling pressures and SI, documented a compromised performance of both ventricles.

Findings indicate that: systemic hypertension is associated with elevation of pulmonary arterial pressure and of PAR which is not necessarily a consequence of impairment in LV function; LV hypertrophy is associated with enhanced performance of either ventricle; in coincidence with development of ECG signs of LV strain, the performance of both sides of the heart deteriorates.

A functional interdependence of the two ventricles is suggested.

AVAILABLE INFORMATION on the dynamics of the right side of the heart and lesser circulation in systemic hypertension is scanty and somewhat discordant. Normal values of pulmonary pressure in subjects with systemic hypertension have been recorded in some studies.\(^1\)\(^2\) Elevated values were detected in hypertensive patients with adaptation to low barometric pressure. Phil Trans Roy Soc London Ser B 203: 185, 1913


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