THE EFFECTS OF HIGH ALTITUDE ON PULMONARY HYPERTENSION OF CARDIOPATHIES, AT LA PAZ, BOLIVIA

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The altitude of the Medical School of La Paz, Bolivia, is 3,701 m above sea level and the mean atmospheric pressure averages about 490 mm Hg. This provides an inspired oxygen tension (PIO2) of 93 and an average alveolar PO2 (PAO2) of about 60 mm. Hg. which corresponds to breathing 13.1% oxygen at sea level. Since the classical experimental observations in 1946 by Von Euler and Liljestrand (1951), concentrations of inspired oxygen of less tham 15% were in the majority of experiments on intact animals (Reeves and Leathers, 1964) and in man (Defares, Lundin, Arborelius, Jr., Strombland and Svanberg, 1960) associated with an elevation in pulmonary artery pressure and probable vasoconstriction in the pulmonary circulation. Recent cardiac catheter data derived from normal subjects above 3,000 m in Leadville, Col. (Volgel, Rose, Blount Jr. and Grover, 1962), the Indian Himalayas (Roy, Singh, Bhatia and Khanna, 1965), and Morococha, Peru (Banchero, Sime, Peñaloza, Cruz, Gamboa and Marticorena, 1966), where PIO2 is less tham 100 mm Hg, showed raised mean resting pulmonary artery pressures and frank pulmonary hypertension during exercise.

Congenital heart disease with large pulmonary blood flows has a high incidence at high altitude (Alzamora, Rotta, Battilana, Abugattas, Rubid, Buroncl, Zapata, Santa-María, Binder, Subiría, Paredes, Pando and Graham, 1953) and Pe-

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naloza, Arias-Stella, Sime, Recavarren and Marticorena, (1964) drew attention to the increased incidence of patent ductus arteriosus at high altiude. In the cuorse of six month's atiendance at a weekly cardiac clinic at the Instituto Nacional de Tórax. La Paz, 94 patients were seen by two of us. In twenty-eight patients congenital heart disease with large left to right shunts was present which in twelve was clinically attributable to uncomplicated patent ductus arteriosus. While patent ductus arteriosus thus constituted almost 13% in this group of cardiac patients, severe pulmonary hypertensión was seen in 50% of the total group which included eight with mitral stenosis and four patients with chronic mountain sickness or Monge's disease.

In a clinical appraisal of the various cardiopathies common to the population of La Paz, which are in themselves frequently associated with pulmonary hypertension at sea level, it seemed of interest to us to attemp to separate the physiological component of pulmonary hypertension associated with the altitude of La Paz from that which could be reasonably attributed to the underlying cardiopathy. The summation of these two components sharply accentuoates the clinical sigss of pulmonary hypertension in the La Paz patients and a possible separation is calculated to improve an understanding of residual physical signs following successful surgical correction of mitral stenosis, atrial and ventricular septal defects as well as closure of patent ductus arteriosus. Unlike successful surgery for these uncomplicted cardiopathies at sea level, some pulmonary hypertension will persist in the La Paz patients as a consequence of altitude.

This report confines itself to a comparison of respiratory and hemodynamic observations derived from eleven patients who were free from significant cardio-pulmonary disease and a group of ten patients suffering from various cardiopathies known to increase pulmonary vascular resistance either as a result of large pulmonary blood flows from left to right shunts or from mitral stenosis. The twenty-one patients comprising this studuy y came to the Instituto Nacional Torax from the different hospitals in La Paz and include two with Monge's disease. The latter while free from obvious cardio-pulmonary disorders, showed evidence of polycythemia, central cyanosis, finger clubbing, severe pulmonary hypertension, alveolar hypoventilation and respiratory acidosis peculiar to this sydrome (Monge, 1943).

Table I gives the diagnoses of the twenty-one patients selected for this investigation.

Hypertension of Cardiopathies, at La Paz, Bolvia

Table I. Patient-Material catheterized at La Paz, (altitude 3.701 m)

METHODS

Catheterization of the right heart was explained to the patient in detail 24 h before the procedure and was conducted in the routine manner at the Instituto Nacional de Torax, La Paz. Patients were fasting on the morning of the test and considered to be in a basal state having also received sodium seconal 50 mg. 30 min prior to the procedure.

Pressures from the right heart and pulmonary artery and wedge position as well as from a systemic artery were measured by means of Sanborn physiological pressure transducers and inscribed on a direct writing Sanborn recorder. Mean pressure was registered by direct electronic integration. All pressures were referred to atmospheric zero-level at 10 cm above the X-ray table op.

Resting minute ventilation (VE), respiratory frequency (f/min), tiaal volume (VT), minute oxygen consumption (VO2), and carbon dioxide elimination (VCO2) were obtained from a four minute expired air collection in a Douglas bag. All gas volumes are expressed as V or V = (BTPS)2 ml, or l/min/m2, except for VO2 and VCO2 which are given at STPD3. Oxygen and carbon dioxide contents (FEO2 and FECO2) in expired air were analyzed in duplicate by the Roughton-Scholander technique.

2 BTPS - Body temperature/ambient barometric pressure/full water vapour saturation.

3 SAPD - 0° C/760 mm. Hg/dry.

Simultaneous blood samples were aspirated anaerobically during the four minutes of expired air collection from both a pulmonary and systemic artery. All blood analyses were corried out at the Instituto Boliviano de Biologia de Altura. Hemoglobin content of the blood samples was measured photometrically. Blood P02 determinations were by polarography using the Clark electrode attachment of the radiometer micro-Astrup assembly. Blood pH measurements at 37° C. were by radiometer glass electrode, which mas standardised daily with fresh ampoules of pH 7.381 radiometer phosphate buffer, while blood PCO2 was calculated from the pH of blood tonometered with 3.7 and 7.4% and CO2 gas mixtures and the Sigaard-Anderson alignment nomogram. Oxygen saturations of pulmonary and arterial blood samples were read

off the Severinghaus blood O2 dissociation nomogram utilizing PO2 of the bloods and allowing for temperature and pH effects.

For the computation of cardiac output by application of the direct Fick method the arterio-venous oxygen content difference was derived from the oxygen saturation and oxygen capacity of the blood samples.

Physiological dead space (VDS) was calculated from the Bohr equation using PaCO2 instead of PACO2, inasmuch as PA — a CO2, gradients were found in related studies to be small (Cudkowicz, 1968). Resting alveolar ventilation (VA BTPS) were obtained from VA = VE — VDS — VDS = minute dead space ventilation BTPS) as well as from

$$VA = \frac{VCO2 \times 863}{PaCO2}$$

Alveolar ventilation and physiological dead space were corrected for aparatus dead space.

Total pulmonary vescular resistance (TPR), pulmonary arteriolar resistance (PAR) and systemic vascular resistance (SVR) were calculated in the standar manner and are expressed as dynes/sec/cm-5.

Exercise han to be carried aut on the X-ray table by straight leg raising against resistance, there being no ergometer available at the Instituto Nacional de Torax, and lasted for 4 min. Similarly, oxygen breathing and acetyl choline infusions were conducted for the same period, and the effect of these procedures on pulmonary vascular pressures was followed at intervals of 1 min.

While the actual work load during effort could not be calculated, it was of sufficient magnitude to significantly increase pulmonary artery pressure in each patient.

RESULTS

Statistical analysis of the data from the control and cardiopathy series, giving means, standard errors and probabilities are shown in tables II and VII. The information obtained from the two patients with Monge's disease is thought to be of special interest which merits separation of their data from that of the contral and cardiopathy series.

Gas Exchange, Alveolar and Dead Space Ventilations

Table II shows that the control and cardiopathy patients were of similar build and that no statistically significant dif-

ferences emerged in respect of Hb/g/100 ml, O2 capacity vols/100 ml, minute ventilation (VE L/min/m2) expressed at either BTPS or STPD, frequency of respiration (f/min), minute oxygen consumption (VO2 STDP/ml/min/m2), or minute carbon dioxide output (VCO2 STPD/ml/min/m2). The mean age of the patients was greater, and their tidal volumes smaller. The two patients with Monge's disease showed striking differences in that their mean BSA/m2 was 31.1 vols/100 ml. Their mean VE falls between the means of the controls and the patients with cardiopathies, but this, in spite of a larger tidal volume, becomes much reduced if expressed as alveolar ventilation (VA L/min/m2 BTPS), inasmuch as the Monge patients have a considerable increase in physiological dead space (VDs/BTPS/ml m2). Their dead space ventilation (VDS 1/min/m2 BTPS) is greater than in the controls and cardiopthy series and both mixed expired CO2 concentrations (FECO2) and arterial PCO2 (PaCO2) are elevated suggesting overall alveolar hypoventilation (table III). By contrast table III indicates a statistically significantly lower FECO2 and VDS in the patients with cardiopathies.

Blood Gas Tensions, pH and Oxygen Saturations

Table IV shows the differences concerning PO2, pH, oxygen saturation and oxygen content in volumes/100 ml in the bloods from the pulmonary and systemic artery. The pH of both pulmonary and systemic artery bloods in the patients series is significantly higher than in the controls, that of the pulmonary artery is best explained by the inclusion of five patients with left to right shunts. The corresponding means in the Monge patients show an expected reduction in pH of the respective bloods as well lower PO2 and oxygen saturations in systemic arterial blood, confirming the respiratory acidosis and alveolar hypoventilation. The mean arterio-venous oxygen difference is also slightly higher than in the control and cardiopathy groups and the oxygen content in corresponding bloods is considerably increased as a result of the high Hb concentrations.

Cardiac Output and Shunt Flows

Table V shows that no statistically significant differences could be established in respect of the means for resting cardiac output (Q Fick), cardiac indices (CI), heart rates (HR), stroke volumes (SV) and stroke indicess I) of the two main series. The

Monge patients had a lower mean heart rate and this explains the larger mean stroke volume and index in these two patients. The mean pulmonary blood flow in the five patients with left to right shunts was 2.49 l/min/m2 above the mean cardiac index of 3.24 l/min/m2. For the shunt calculations the SA-PA AV O2 difference was used while the Q Fick calculation was based on superior vena cava systemic arterial blood oxygen content difference. (SA-SVC AV O2 difference).

Right Heart and Pulmonary Vascular Pressures

The differences in mean pressures are shown in table VI. The means of right ventricular systolic pressure, mean right ventricular (MRVP), and the means of pulmonary artery pressures (MPAP) were statistically significantly higher in the patient series. No significant difference emerged in respect of the means of right atrial (RAP), pulmonary wedge (PCU) and systemic artery pressures (SAP. The corresponding means of pressures in the two patients with Monge's disease resembled those of the patient series, but mean pulmonary artery pressure was slightly higher at 51.5 mm Hg contrasted with that of 50.0 mm Hg in the cardiopathy group

The mean pulmonary artery pressure of 22.9 mm Hg in the control group is well above the mean of 14.0 mm Hg usually found at sea level (Holmgren, Jonsson, Sjostrand, 1960) and in similar to the pulmonary artery pressure found at rest at altitudes above 10,000 ft (Vogel, Rose and Blount, Jr., 1962). No statistically significant difference emerged in respect of pulmonary wedge pressure.

Pulmonary and Systemic Vascular Resistance

Table VII depicts the differences in the means of total pulmonary vascular (TPR in dynes/sec/cm-5), pulmonary arteriolar (PAR) and systemic resistances (SVR). Mean TPR and PAR in the cariopathy patients exceed those of the controls by 68 and 137% respectively, whereas the highest mean TPR and PAR were present in the two patients with Monge's disease. No significant difference was established in respect of the means of systemic vascular resistance. The means of TPR and PAR of the control group exceed those established for sea level by more than 100% (Banchero, Sime, Penaloza, Cruz, Gamboa and Marticorena, 1966).

Figure 1 depicts the effects of four minutes of oxygen breathing on mean pulmonary artery pressure and pulmonary

wedge pressure in the three goups. The means only are shown. The maximun efect became apparent at the end of the second minute and thereafter the mean pressures levelled out. In the two patients with Monge's disease the mean drop in MPAP was 16.5 mm Hg. or 33% with the mean pressure becoming steady at 34.0 mm Hg. In the cardiopathy group the pressure fell by 12.5 mm Hg or 25%, steadying at 37.5 mm Hg. In the controls the mean PAP fell from 22.9 to 16.0 mm Hg, i. e. by 6.9 mm. Hg or 30%. The drop in mean PCP was minor and averaged 0.45 in the cardiopathy group and 0.4 mm. Hg in the controls, while no significant drop was seen in the Monge patients.

The effects of exercise on mean pulmonary artery pressure and mean PCP are presented in figure 2. Mean PAP in the cardiopathy group rose from 50.0 to 97.0 mm Hg at the end of the fourth minute providing an increase of 74%. In the Monge patients mean PAP rose from 51.5 to 93.0 mm Hg which is 81%. In the controls the corresponding rise, in mean PAP was from 22.9 to 49.0 mm Hg or an increase of 109%. Mean pulmonary wedge pressure rose from a mean of 6.8 to 9.8 mm Hg in the controls; i. e. bz 44%, whereas in the cardiopathy group the increase was much greater namely 7.3 mm Hg or 92%. This is again explicable on the basis of the inclusion in this series of two patients with mitral stenosis, whose mean PCP elevation on effort considerably influenced the statistical mean. The increase in mean PCP in the two Monge patients was from 7.4 to 8.9 mm Hg, a mean of 1.5 mm Hg or 20%.

Acetyl choline was infused into the pulmonary artery at the rate of 5 μg/min. Figure 3 shows that the mean pulmonary artery pressure in the cardiopatry series fell from 50.0 to 40.1 mm Hg or by 20% while mean PCP remained unchanged. In the controls the drop in mean MPAP amounted to 4.9 mm Hg or 168% which is considerably less than the drop seen during oxygen breathing, while the mean PCP fell from 6.8 to 5.4 mm Hg; a change of 1.4mm Hg or 17%. Information of the effect of actyl choline infusion in Monge's disease is aviala-ble on one patient. This showed a drop in MPAP from 52.0 to 43,5 mm Hg. This mean drop of 8.5 mm Hg or 16% is once again less than the drop of 33% seen with oxygen breathing. No change occurred in mean PCP.

DISCUSION

With surgical correction of mitral stenosis or a left to right shunt the cardiac output of the cardiopathy patients can be

expected to return to conrol levals similar to those usually found at sea level. Their mean pulmonary artery pressure, however will probably reach levels approximately 6 mm Hg above the mean pulmonary artery pressure of 22.9 mm Hg of the controls, while a return to sea level in patients with chronic mountain sickness will probably effect a reduction of MPAP by approximately 8 mm Hg above that of the altitude control patients. TPR can be expected to approach control level for high altitude in surgically corrected patients with uncomplicated left to right shunts, but PAR is calculated to remain about 100% above that of the high altitude controls.

The effects of oxygen breathing and the acetyl choline infusions at the altitude of La Paz are best explained on the basis of an increase in pulmonary arteriolar muscle bulk (Arias-Stella and Saldana, 1963) and irreversible intimal changes in the pulmonary arteries (Heath and Edwards, 1958). In patients with Monge's disease these changes are probably mainly in the pulmonary arteries to the upper lobes, reducing the total cross sectional area of the pulmanary artery tree. The partial elimination of the vasoconstrictive component due to high altitude alveolar hypoxia alone in the controls seems more effective with oxygen than acetyl choline. No ready explanation is available for this difference in response. Pulmonary arteriolar resistance in the cardiopathies does not return to control levels with either oxygen or acetyl choline, and structural changes in the pulmonary arteries have to be invoked as an alternativa explanation. Current investigations (Cudkowicz, 1969) suggest that upper lobe perfusión, particularly in patients with Monge's disease, does not significantly change with the adoption of recumbency. This as well as the large physiological dead space demonstrated in these patients suggests that the upper lobe pulmonary arteries might well be structuralley abnormal.

On theoretical grounds it would seem reasonable to assume that the combination of pulmonary vasoconstriction from high altitude alveolar hypoxia as well as an increase in pulmonary blood flow, stemming from a left to right shunt in particular, is calculated to considerably increase pulmonary arteriolar muscle wall development, wel documented in altitude dwellers (Arias-Stella and Saldana, 1963) and early surgery in permanent residents at La Paz is calculated to arrest this structural change and permit postoperative restoration of pulmonary arteriolar resistance to near control levels.

The gross increments in MPAP of 109% on exercise seen in the control patients at La Paz contrasts with the much smaller rises seen at sea level at high work levels (Slonim, Ravin, Balcaum and Dresser, 1954) Bevegard, Holmgren and Jonsson, 1963) and large pulmonary blood flows. The assumption has, therefore, to be made thet eary distension of the pulmonary capacitance vasculature occurs in normal residents at La Paz during moderate increases in cardiac output on effort, as a result of mainly anatomical restriction rather than vasoconstriction of the capacitance vasculature. In patients with cardiopathies and chronic mountain sickness (Monge's disease) additional structural abnormalities in the pulmonary vasculature are probable and similar to those seen in severe pulmonary hypertension at sea level (Heath and Edwards, 1958). The vasoconstrictive component in these patients accounts for about 30% of the resting MPAP. Developed finger clubbing, in contrast with secondary factors such as polycythemia, alveolar hypoventilation, and an expanded circulating blood volume in patients with chronic mountain sickness, also indicates the existence of a permanent vascular abnormality in the pulmonary circulation, namely pre-capillary broncho-pulmonary anastomoses found in patients with clubbing at sea level (Cudkowicz and Wraith, 1957). It is unlikely that such structural changes could regress on a change of residence from La Paz to the lowlands. Inasmuch as the main cardiac patient population of a capital city like La Paz could not be easily relocated the early recognition and surgical treatment of cardiopathies in particular is calculated to stabilize the wall thickness of the pulmonary arterioles similar to that extant in the normal controls. Early relocation of patients with Monlgé's disease, however, seems mandatory.

SUMMARY

This investigation concerns a comparison of hemodynamic data derived from eleven patients without cardio-pulmonary disease, living at La Paz, Bolivia, an ten patients with a variety of cardiopathies common to that city.

Alveolar hypoxia alone elevates mean pulmonary artery-pressure (MPAP) to 22.9 mm Hg. Mean total pulmonary vascular resistance (TPR) in the normals was 312 and mean pulmonary arteriolar resistance (PAR) 219 dynes/sec/ cm-5. The corresponding values in patients with different cardiopothies were MPAP - 50.0 mm Hg; TPR - 527.5 and PAR - 524.6 dynes/sec/cm-5 respectively. These differences were statistically

significant. In two patients with Monge's disease corresponding mean values were higher than in the patients with cardiopathies, namely MPAP - 51.5 mm Hg; TPVR - 668.5 and PAR - 568.5 dynes/sec/cm-5 respectively. No significant differences emerged in respect of 1. cardiac outpunt, 2. right atrial pressure, 3. pulmonary capillary pressure, 4. systemic artery pressure, 5. systemic vascular resistance.

These five parameters were essentially similar to those found at sea level.

Exercise raised MPAP by 109% in the controls and by 75% in the cardiopathy patients. MPCP rose by 44% in the controls, 92% in the cardiopathy patients and by 20% in the two Monge patients. Pure oxygen breathing over a four minute period reduced MPAP in all three gruops with the largest drop favouring the patients with Monge's disease. Acetyl choline infusions into the main pulmonary artery also produced a drop in MPAP, but this was less effective than that caused by oxygen.

An attempt has also been made to separate high altitude components on the afore-mentioned parameters from those attributable to underlying heart disease. The correction of the latter is not in itself calculated to restore MPAP and PAR to the control levels for La Paz and suggests that the combined effects of high altitude and heart disease irreversibly compromise the pulmonary vasculature.

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