Bradycardia, increased cardiac output, and reversal of pulmonary hypertension in altitude natives living at sea level¹

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Eleven healthy young men native to high altitude underwent haemodynamic studies at their original place of residence and after two years' residence at sea level. The investigation sought to determine the long-term effects of the suppression of the hypoxic stimulus upon heart rate, cardiac output, and pulmonary artery pressure of highlanders. For comparative purposes the influence of oxygen inhalation at high altitude was also studied.

The heart rate fell at sea level and bradycardia was seen in most of the cases. The fall in heart rate is probably related to an increase in the predominance of the parasympathetic nervous system of highlanders after the relief of hypoxia. Oxygen inhalation at high altitude produced a smaller reduction in heart rate than after descending to sea level. The increase in heart rate during exercise was similar in both environments.

Cardiac output increased moderately with the descent to sea level. This change was not associated with changes in oxygen uptake, but with a reduction in the values of haemoglobin, arterial oxygen content, and arteriovenous difference of oxygen. Stroke index increased significantly on descent to sea level, mainly as a consequence of the reduction in heart rate. At both altitudes exertion caused a similar increase in cardiac output which was related to the increase in heart rate rather than to stroke index which did not show significant variations. Oxygen inhalation at high altitude did not alter cardiac output and stroke index.

Mean resting pulmonary arterial pressure fell to normal after two years' residence at sea level, but the pressure response to exercise was similar to that observed at high altitude and greater than that seen in healthy lowlanders. Oxygen inhalation at high altitude produced only a partial reduction in pulmonary hypertension. A recurrence of pulmonary hypertension was observed on return to high altitude. These observations emphasize the importance of the structural characteristics of the pulmonary vessels of highlanders in the mechanism of high altitude pulmonary hypertension.

Previous investigations have shown that high altitude natives have a mild to moderate degree of pulmonary hypertension associated with a normal cardiac output and heart rate (Rotta *et al.*, 1956; Peñaloza *et al.*, 1963; Sime *et al.*, 1963; Hultgren, Kelly, and Miller, 1965a). Physical exertion produces an increase in pulmonary arterial pressure whereas the response of the heart rate and cardiac output is no different from that observed in the sea level resident submitted to comparable degrees of exercise (Banchero *et al.*, 1966).

There is little information about the circulatory modifications which occur in highlanders when the hypoxic stimulus is suppressed. Hultgren, Kelly, and Miller (1965b) studied the effect of 100 per cent oxygen inhalation during 10 to 15 minutes, and found a partial reduction of pulmonary arterial pressure. Hartley *et al.* (1967) studied natives from Leadville, Colorado (10,200 feet of altitude), after 10 days of residence at sea level, and observed a slight increase of cardiac output at rest. On exertion, heart rate and pulmonary pressure increased less than at altitude while the rise in cardiac output was greater. Grover *et al.* (1966) studied a girl with severe pulmonary hypertension from Leadville,

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Colorado, and noted a great reduction in pulmonary pressures after 11 months' residence at sea level.

We had the opportunity to perform physiological studies in a group of high altitude soldiers at their original place of residence and after a prolonged residence at sea level. The main purpose of this investigation was to ascertain the changes occurring in pulmonary arterial pressure, cardiac output, and heart rate, both at rest and on exertion. Preliminary information on this subject has been published (Peñaloza *et al.*, 1962; Sime *et al.*, 1966).

Subjects and methods

Eleven Peruvian Andean recruits born in the highlands surrounding Cerro de Pasco (14,200 feet of altitude), aged 18 to 23 years, were selected from a group of volunteers on the basis of their clinical normality shown by physical examination, chest x-ray, electrovectorcardiographic studies, and some laboratory tests. Haemodynamic studies by right heart catheterization were carried out in all of them at Morococha at 14,900 feet of altitude (mean barometric pressure of 445 mmHg) and after two years of continuous residence at Lima at 500 feet of altitude (mean barometric pressure of 750 mmHg). Once the selection of the subjects was accomplished at Cerro de Pasco, they were taken up to Morococha two weeks before the baseline haemodynamic study. During this period the subjects were made familiar with the physiological procedure, mainly with the bicycle ergometer which was used to perform exercise.

Right heart catheterization was carried out at rest and on exertion with the subject in the supine position, in fasting conditions, and without medication. Two catheters were passed through two different veins of the antecubital space to register pressures easily and rapidly during exercise. A polyethylene catheter was introduced into the brachial artery also. At rest, blood pressures were registered from the right atrium, right ventricle, pulmonary artery, pulmonary wedge position, and brachial artery. Blood samples from the pulmonary and brachial arteries, and expired air were collected simultaneously. These observations were then repeated after the subjects had been breathing 35 per cent oxygen in nitrogen gas mixture giving a P_{O_2} similar to that at sea level during 15 minutes. The exercise was performed using a bicycle ergometer. The subject pedalled for 7 minutes with a work load of 300 kg m/min per m^2 at the rate of 60 rpm controlled with a metronome. During the fourth and fifth minutes blood samples were withdrawn from the pulmonary and brachial arteries and at the same time the expired air was collected. After the sixth minute of exercise, blood pressures were registered from pulmonary wedge position, right ventricle, right atrium, and brachial and pulmonary arteries.

Blood pressures were registered using two Statham gauge (P23Db) and a Twin Viso Sanborn

recorder (model 60-1300). Zero was taken as the mid-point of the anteroposterior diameter of the thorax in the third intercostal space at the sternum. During exercise, values for systolic and diastolic pressures were obtained by averaging them over two respiratory cycles. Mean pressures were obtained by electrical integration.

Blood samples were withdrawn anaerobically and analysed for oxygen and carbon dioxide contents and for oxygen capacity in a Van Slyke and Neill manometric apparatus. Expired air was collected in a Tissot calibrated spirometer, and gas content was analysed in a Haldane-Henderson apparatus. This procedure allowed the calculation of the oxygen uptake, the arteriovenous (AV) oxygen difference, and the cardiac output by Fick's principle.

One week after the observations at high altitude had been performed, the subjects were taken down to Lima where they joined the Army, being recatheterized after two years of continuous residence at sea level. Haemodynamic studies were performed as described above, both at rest and on exertion. At the end of their military duties two of the cases (Cases 7 and 8) came back to Cerro de Pasco, where they were studied again one year later.

Data obtained from these subjects at rest and on exertion at Morococha and Lima and during the inhalation of 35 per cent oxygen at Morococha were compared in several ways. The significance of differences resulting from the paired comparison of data were evaluated by the Fisher's *t* test. In addition, analysis of covariance was used for testing the differences existing between the regression of mean pulmonary arterial pressure on cardiac index, calculated with paired values obtained at rest and on exertion from the 11 highlanders at high altitude and after residing at sea level, and from a comparable group of 17 lowlanders studied in a previous investigation (Banchero *et al.*, 1966). Correlation between these two variables has also been assessed.

Results

Characteristics of subjects in Morococha and after two years of residence at sea level are given in Table 1. Table 2 shows the results obtained from highlanders at rest, during exercise, and breathing 35 per cent oxygen at Morococha. The results obtained both at rest and during exercise in Lima are shown in Table 3. Observations performed in Cases 7 and 8 studied one year after return to 14,200 feet of altitude are shown in Table 4.

Physical and haematological characteristics

Mean weights were 55.0 ± 1.5 (S.E.) kg at altitude and 60.6 ± 1.8 kg at sea level. Individual increases on descent to sea level were highly significant ($P < 0.001$). Height figures did not change. Mean values of body surface were $1.54 \pm 0.03 m^2$ in Morococha and $1.62 \pm 0.03 m^2$ in Lima. Paired comparison of

TABLE I Characteristics of subjects studied at Morococha (14,900 feet) and after two years of residence at Lima (500 feet)

Case No.	Age (yr)		Height (cm)		Weight (kg)		BSA (m ²)		Hb (g/100 ml)		Haematocrit (%)	
	*M	L†	M	L	M	L	M	L	M	L	M	L
1	20	22	158	158	60.88	65.90	1.61	1.70	18.63	12.79	58.1	41.0
2	18	20	163	167	58.30	70.00	1.61	1.77	15.74	13.01	48.8	40.0
3	23	25	158	158	50.55	57.30	1.49	1.55	17.70	13.01	52.9	39.3
4	23	25	165	165	63.28	69.30	1.68	1.75	19.34	13.90	57.1	41.9
5	21	23	155	156	51.08	56.80	1.47	1.54	16.70	12.32	50.0	40.0
6	21	23	155	155	54.20	56.70	1.51	1.53	19.75	14.88	56.4	44.3
7	23	25	159	159	46.80	52.90	1.44	1.52	16.89	13.57	50.8	41.7
8	20	22	155	156	54.90	61.00	1.51	1.59	22.30	14.82	68.3	40.0
9	20	22	159	160	50.80	55.90	1.50	1.60	19.53	12.94	56.4	40.0
10	20	22	155	156	53.92	55.40	1.50	1.53	17.81	13.40	54.3	44.5
11	18	20	164	164	60.00	65.50	1.64	1.70	19.12	13.62	56.7	48.5
Mean	20.6	22.6	159	160	55.00	60.61	1.54	1.62	18.50	13.48	55.4	41.9
± S.E.	0.5	0.5	0.01	0.01	1.54	1.82	0.03	0.03	0.55	0.24	1.6	0.8
± S.M.	1.8	1.8	0.04	0.04	5.11	6.04	0.08	0.10	1.81	0.81	5.3	2.8

Significance of differences (d) between paired observations

$\bar{d}$	2	0.01	5.64	0.08	-5.02	-13.51
t	∞	2.19	7.26	7.45	12.20	7.68
P		<0.10	<0.001	<0.001	<0.001	<0.001

*M: Morococha. †L: Lima.

individual data indicates statistically significant increases which are related to weight increments.

Mean haemoglobin values were 18.5 ± 0.55 g/100 ml at high altitude and 13.5 ± 0.24 g/100 ml at sea level. Mean figures of haematocrit changed from 55.4 ± 1.6 per cent to 41.9 ± 0.8 per cent. Individual decreases in haemoglobin and haematocrit were highly significant ($P < 0.001$). The subnormal values obtained at sea level were not associated with any kind of symptoms.

Oxygen uptake and ventilation Mean oxygen uptake was 158 ± 4.7 ml/min per m² at altitude and 161 ± 3.7 ml/min per m² at sea level. On exertion, these values increased to 802 ± 28.8 and 866 ± 24.0 , respectively. The individual differences between altitude and sea level were not significant. The increments from rest to exercise were nearly similar for the same work load at both environments.

Mean value of ventilation was 5.24 ± 0.36 l./min per m² in Morococha and 4.80 ± 0.25 in Lima. These figures increased during exercise to 24.74 ± 1.07 and 19.88 ± 0.75 , respectively. Paired comparison of each individual datum indicates that ventilation at rest was slightly lower at sea level ($P < 0.30$) and that this difference was significant on exertion ($P < 0.01$). The lowering of ventilation at sea level is in accordance with the higher values of ventila-

tion which have been described in Andean natives living at high altitude (Hurtado *et al.*, 1956). Ventilation values of highlanders at sea level were still higher than those obtained in a comparable group of lowlanders studied by Banchero *et al.* (1966).

Arterial oxygen saturation, arterial and venous oxygen contents, and arterio-venous oxygen difference Mean arterial oxygen saturation was 78.48 per cent ± 1.25 at Morococha and 97.31 per cent ± 0.68 at sea level, the individual decreases being highly significant ($P < 0.001$). On exertion these values decreased to 69.20 ± 1.28 and 94.33 ± 0.57 , respectively. The decrements were significant in both environments ($P < 0.01$ and $P < 0.02$, respectively). The administration of oxygen at altitude increased the arterial oxygen saturation to 95.0 per cent ± 0.57 .

Mean arteriovenous oxygen content difference at rest was 4.22 ± 0.24 vol. per cent at altitude and 3.64 ± 0.11 vol. per cent at sea level. On exertion, these values changed to 10.66 ± 0.36 vol. per cent and 9.90 ± 0.21 vol. per cent, respectively. The individual decreases on descent to sea level were significant at rest ($P < 0.05$) and on exertion ($P < 0.01$). The reduction of the resting arteriovenous oxygen difference at sea level was principally due to the lowering of arterial oxygen content

TABLE 2 Physiological observations in 11 Andean natives studied at Morococha (14,900 feet)

Case No.	V_E BTPS (l./min/ m^2)	VO_2 STPD (ml/min/ m^2)	SAO_2 (%)	O_2 content, vol/100 ml			Heart rate (beat/ min)	Cardiac index (l./min/ m^2)	Stroke index (ml/ beat/ m^2)	Pulmon- ary total resis- tances (dynes/ sec/ cm^{-5})	Pressures (mmHg)			
				Arterial	Venous	AV O_2 diff					S	D	M	
A) Rest (room air)														
1	6.46	163	75.57	18.87	15.04	3.83	90	4.25	47.2	234	28	6	20	
2	6.08	152	81.22	17.13	12.52	4.61	74	3.31	44.7	300	31	7	20	
3	3.54	138	74.49	17.67	14.10	3.57	67	3.85	57.4	279	28	9	20	
4	5.17	165	79.00	20.47	17.03	3.44	73	4.81	65.9	257	36	15	26	
5	5.65	171	80.56	18.03	14.62	3.41	108	5.01	46.4	347	36	20	32	
6	5.28	135	80.09	21.20	16.65	4.55	85	2.97	34.9	356	30	11	20	
7	7.58	190	87.89	19.89	14.04	5.85	72	3.24	45.0	308	30	7	18	
8	4.56	151	77.04	23.06	19.48	3.58	78	4.23	54.2	388	42	16	31	
9	3.72	159	72.94	19.09	14.97	4.12	71	3.87	54.5	317	35	10	23	
10	4.61	149	75.06	17.91	12.73	5.18	68	2.88	42.3	574	42	13	31	
11	4.98	162	79.46	20.36	16.03	4.33	63	3.73	59.3	313	32	11	24	
Mean.	5.24	158	78.48	19.43	15.20	4.22	77	3.83	50.2	334	34	11	24	
± SE	0.36	4.7	1.25	0.54	0.61	0.24	3.9	0.21	2.7	27.4	1.5	1.3	1.6	
± SD	1.18	15.4	4.16	1.77	2.02	0.78	12.9	0.71	8.9	90.9	5.0	4.3	5.2	

B) Exercise (300 kg m/min/m²)

1	18.40	654	67.52	17.67	7.77	9.90	135	6.61	48.9	263	54	20	35
2	23.39	724	74.06	17.08	5.83	11.25	142	6.44	45.4	424	70	40	55
3	26.36	881	75.33	18.60	6.62	11.98	125	7.36	58.9	262	56	15	36
4	24.37	779	67.28	17.89	9.21	8.68	142	8.98	63.2	371	95	60	70
5	29.75	969	65.08	15.06	4.44	10.62	175	9.13	52.2	334	70	40	56
6	27.81	759	63.67	16.95	8.24	8.71	150	8.72	58.1	273	60	30	45
7	30.38	910	65.73	16.23	3.77	12.46	190	7.31	38.5	494	75	40	65
8	23.49	840	70.39	21.38	10.42	10.96	130	7.66	58.9	484	82	41	70
9	23.14	813	71.32	19.45	8.15	11.30	156	7.19	46.1	407	70	25	55
10	22.05	783	65.71	17.00	6.18	10.82	125	7.23	57.9	442	80	40	60
11	22.97	709	75.11	19.53	8.92	10.61	112	6.69	59.7	350	58	26	48
Mean	24.74	802	69.20	17.89	7.23	10.66	144	7.57	53.4	373	70	34	54
±SE	1.07	28.8	1.28	0.53	0.62	0.36	6.9	0.29	2.3	25.6	3.8	3.8	3.7
±SD	3.54	93.1	4.25	1.76	2.05	1.19	23.0	0.95	7.7	84.8	12.6	12.6	12.2

C) Rest (35% oxygen)

1	12.23	305	95.96	24.48	19.05	5.43	80	5.61	70.1	142	26	8	16
2	6.59	206	95.67	21.47	15.98	5.49	70	3.75	53.6	225	27	6	17
3	4.05	136	93.30	22.40	17.60	4.80	65	2.84	43.7	265	25	6	14
4	4.37	156	94.33	24.71	20.22	4.49	80	3.49	43.6	273	36	13	20
5	5.97	201	92.18	24.67	19.68	4.99	88	4.03	45.8	197	29	8	15
6	8.68	295	98.01	24.74	17.65	7.09	88	4.16	47.2	200	23	7	15
7	5.94	212	95.69	28.91	24.06	4.85	72	4.38	60.8	278	36	10	23
8	3.43	146	93.35	24.70	20.13	4.57	73	3.19	43.7	334	32	7	20
9	9.39	252	95.85	23.14	17.41	5.73	64	4.40	68.7	230	30	8	19
10	3.84	132	94.54	24.56	19.79	4.77	68	2.77	40.7	300	27	7	17
Mean	6.45	204	94.99	24.48	19.16	5.22	75	3.86	51.8	244	29	8	18
±SE	0.90	20.1	0.57	0.62	0.71	0.25	2.8	0.27	3.5	17.9	1.4	0.7	0.9
±SD	2.86	73.5	1.79	1.97	2.23	0.77	8.8	0.86	11.0	56.6	4.4	2.1	2.8

Significance of differences (d) between paired observations

B	$\bar{d}$	19.50	644.18	-9.28	-1.53	-7.97	6.44	66.64	3.74	3.27	39.18	36.36	22.91	30.00
vs	t	18.58	23.77	4.54	3.06	19.92	18.45	10.85	13.80	1.18	1.37	12.42	6.86	9.43
A	P	<0.001	<0.001	<0.01	<0.02	<0.001	<0.001	<0.001	<0.001	<0.30	<0.30	<0.001	<0.001	<0.001
C	$\bar{d}$	1.25	47.70	16.61	4.81	3.90	0.92	0.70	0.15	1.25	-88.20	-4.30	-1.70	-5.70
vs	t	1.74	2.56	14.02	20.05	17.72	6.87	0.29	0.44	0.23	2.58	3.92	1.76	6.37
A	P	<0.20	<0.05	<0.001	<0.001	<0.001	<0.001	<0.80	<0.70	<0.90	<0.05	<0.01	<0.20	<0.001

TABLE 3 Physiological observations in 11 Andean natives studied after two years of residence at Lima (500 feet)

Case No.	V_E BTPS (l./min/ m^2)	VO_2 STPD (ml/min/ m^2)	SO_2 (%)	O_2 content, vol/100 ml Arterial Venous AV O_2 diff			Heart rate (beat/min)	Cardiac index (l./min/ m^2)	Stroke index (ml/beat/ m^2)	Pulmonary total resistances (dynes/sec/ cm^{-5})	Pressures (mmHg) Pulmonary artery S D M		
D) Rest													
1	4.72	162	97.81	17.01	13.49	3.52	63	4.59	72.9	113	29	3	11
2	4.00	148	94.97	16.81	12.46	4.35	53	3.40	64.2	200	30	8	15
3	4.55	145	100.39	17.77	14.54	3.23	57	4.47	78.5	139	25	5	12
4	4.25	155	98.25	18.58	15.29	3.29	48	4.71	98.1	117	24	4	12
5	4.61	186	96.59	16.18	12.69	3.49	67	5.34	79.7	97	25	6	10
6	4.38	158	98.12	19.86	16.63	3.23	68	4.88	71.7	139	22	5	13
7	5.90	108	97.60	17.94	14.38	3.56	55	3.03	55.2	173	30	—	10
8	4.75	159	94.74	19.10	15.07	4.03	68	3.95	58.1	178	26	6	14
9	4.01	165	95.51	16.81	12.85	3.96	53	4.17	78.6	156	26	7	13
10	6.69	169	101.53	18.50	14.57	3.93	53	4.31	81.3	182	27	8	15
11	4.94	164	94.92	17.58	14.10	3.48	60	4.70	78.3	100	26	5	10
Mean	4.80	161	97.31	17.83	14.19	3.64	59	4.32	74.2	145	26	6	12
± SE	0.25	3.7	0.68	0.33	0.38	0.11	2.1	0.20	3.6	10.7	0.8	0.5	0.6
± SD	0.82	11.5	2.25	1.11	1.25	0.37	7.0	0.67	12.0	35.5	2.5	1.6	1.9

E) Exercise (300 kg m/min/ m^2)

1	18.62	821	93.79	17.39	8.05	9.34	113	8.79	77.8	112	40	8	21
2	22.03	895	96.89	17.77	6.75	11.02	102	8.13	79.7	167	40	12	30
3	17.54	889	92.64	17.77	7.68	10.09	105	8.81	83.9	152	38	12	26
4	23.00	938	94.58	19.40	10.60	8.80	115	10.66	92.7	116	42	8	27
5	16.91	980	91.09	16.57	6.84	9.73	138	10.08	73.0	139	46	15	27
6	18.22	740	94.25	19.53	10.42	9.11	112	8.12	72.5	129	30	10	20
7	23.96	865	97.10	18.78	8.03	10.75	132	8.04	60.8	144	52	—	22
8	17.74	760	96.00	19.48	9.36	10.12	103	7.51	73.0	147	30	12	22
9	19.88	875	92.49	17.74	7.09	10.65	125	8.22	65.7	182	44	12	30
10	18.59	798	93.40	18.14	8.30	9.84	100	8.11	81.1	193	40	12	30
11	22.14	965	95.32	17.96	8.50	9.46	112	10.20	91.1	111	40	16	24
Mean	19.88	866	94.33	18.23	8.33	9.90	114	8.79	77.4	145	40	12	25
± SE	0.75	24.0	0.57	0.29	0.40	0.21	3.8	0.32	3.0	8.3	1.9	0.8	1.1
± SD	2.47	79.5	1.90	0.95	1.32	0.71	12.5	1.05	9.8	27.5	6.4	2.6	3.8

Significance of differences (d) between paired observations

E	$\bar{d}$	15.08	709.73	-2.99	0.40	-5.86	6.26	55.64	4.47	3.16	-0.18	13.82	6.00	13.09
vs	t	19.52	29.70	2.89	2.85	34.46	39.87	13.49	18.05	1.14	0.03	8.26	8.05	12.70
D	P	<0.001	<0.001	<0.02	<0.02	<0.001	<0.001	<0.001	<0.001	<0.30	—	<0.001	<0.001	<0.001

Significance of differences (d) between paired observations of Tables 2 and 3

D	$\bar{d}$	-0.44	-1.45	18.83	-1.59	-1.01	-0.58	-18.55	0.49	24.07	-189.00	-7.27	-6.10	-11.82
vs	t	1.13	0.17	12.15	3.97	1.95	2.47	6.07	2.35	7.31	7.61	2.83	4.35	7.58
A	P	<0.30	<0.90	<0.001	<0.01	<0.10	<0.05	<0.001	<0.05	<0.001	<0.001	<0.02	<0.01	<0.001
C	$\bar{d}$	1.63	50.80	-2.50	6.38	4.82	1.56	17.00	-0.36	-21.90	94.70	2.60	2.44	5.10
vs	t	2.04	2.25	3.00	11.60	7.31	6.09	5.48	1.03	3.77	4.49	1.34	2.23	6.20
D	P	<0.10	<0.10	<0.02	<0.001	<0.001	<0.001	<0.001	<0.40	<0.01	<0.01	<0.30	<0.10	<0.001
E	$\bar{d}$	-4.86	64.09	25.13	0.34	1.17	-0.76	-29.55	1.21	23.96	-228.36	-29.82	-22.00	-28.73
vs	t	3.86	1.98	19.33	0.67	2.50	3.62	6.72	3.56	12.04	10.06	7.47	5.03	8.03
B	P	<0.01	<0.10	<0.001	<0.60	<0.05	<0.01	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001

TABLE 4 Observations performed at altitude in highlanders returning from sea level, sea level subjects, and healthy altitude natives

	Age (yr)	BSA (m ²)	Hb (g/ 100 ml)	Hct (%)	V _E BTPS (l./min/ m ²)	VO ₂ STPD (ml/min/ m ²)	SaO ₂ (%)	O ₂ content, vol/100 ml Arterial Venous AV O ₂ diff			Heart rate (beat/ min)	Cardiac index (l./min/ m ²)
At Cerro de Pasco (14,200 feet)												
						Highlanders one year after return from sea level (Present study)						
C.L.D.	26	1.47	18.19	57.0	7.01	184	87.9	21.57	15.19	6.38	45	2.89
F.P.T.	23	1.55	23.25	70.0	6.07	158	78.7	24.61	20.78	3.83	68	4.11
Mean (2)	24	1.51	20.72	63.5	6.54	171	83.3	23.09	17.99	5.10	57	3.50
						Healthy natives (Peñaloza and Sime, 1971)						
Mean (12)	24	1.60	20.1	59.4	5.37	160	81.1	21.26	16.98	4.28	72	3.83
At Morococha (14,900 feet)												
						Sea level subjects after one year of residence (Rotta <i>et al.</i> , 1956)						
Mean (6)	21	1.66	19.0	—	6.45	136	84.0	—	—	4.58	74	3.00
						Healthy natives (Peñaloza, <i>et al.</i> , 1963)						
Mean (38)	22	1.54	19.5	59.1	5.27	160	78.4	20.24	16.10	4.14	69	3.71

Figures in parentheses represent number of cases.

which in turn was related to the subnormal values of haemoglobin observed in highlanders living at sea level.

Heart rate Mean heart rate was 77 ± 3.9 beat/min in Morococha and 59 ± 2.1 beat/min in Lima. Individual decreases on descent to sea level were highly significant ($P < 0.001$). In 7 of the 11 subjects heart rates were lower than 60 beats/min, which means a reduction to the range of bradycardia in highlanders living at sea level. On exertion mean heart rates increased to 144 ± 6.9 beat/min at altitude and 114 ± 3.8 beat/min at sea level. Individual differences between both levels during exercise were significant ($P < 0.001$). The magnitude of increment with exercise was similar in both environments and the lower values obtained at sea level are explained by the lower resting values. The administration of 35 per cent oxygen to highlanders while living at altitude produced an average reduction in heart rate of only 2 beats/min in contrast with 18 beats/min on descent to sea level.

Cardiac index and stroke index Mean values of cardiac index were 3.83 ± 0.21 l./min per m² in Morococha and 4.32 ± 0.20 l./min

per m² in Lima, the individual increases being significant ($P < 0.05$). On exertion, these values increased to 7.57 ± 0.29 l./min per m² at high altitude and 8.79 ± 0.32 l./min per m² at sea level. Individual differences on exercise between both levels were significant ($P < 0.01$). The magnitude of the cardiac output response to exercise was similar in both environments and the higher values obtained at sea level are due to the higher resting values. No changes in cardiac output at rest were obtained with 35 per cent oxygen inhalation while the subjects were living at altitude.

Mean values of stroke index were 50.2 ± 2.7 ml/beat per m² in Morococha and 74.2 ± 3.6 ml/beat per m² in Lima. Paired comparison of each individual's data indicates that stroke index was significantly higher at sea level ($P < 0.001$). On exertion, no significant changes were obtained both at high altitude and at sea level. The increased stroke index at sea level is the result of the slight but significant increase in cardiac index and mainly of the important reduction in heart rate. The 35 per cent oxygen inhalation at altitude did not produce modification of stroke index.

Pulmonary arterial pressures and resistances Average values of the mean pulmon-

Stroke index (ml/beat/ m ²)	Pulmonary total resistances (dynes/sec/ cm ⁻⁵)	Pressures (mmHg) Pulmonary artery		
		S	D	M
64.2	339	31	7	18
60.5	439	50	25	35
62.4	389	41	16	27
53.2	299	34	13	23
40.5	287	25	12	18
53.8	401	41	15	28

ary arterial pressure were 24 ± 1.6 mmHg at high altitude and 12 ± 0.6 mmHg at sea level, the individual decreases being highly significant ($P < 0.001$). On exertion, these values increased to 54 ± 3.7 mmHg in Morococha and 25 ± 1.1 mmHg in Lima, with significant individual differences between both levels ($P < 0.001$). The magnitude of the pulmonary pressure response to exercise was similar in both environments and the lower exercise levels obtained at sea level are explained by the lower resting values. The administration of 35 per cent oxygen while the subjects were living at altitude reduced significantly the mean pulmonary arterial pressure ($P < 0.001$). However, the decrease obtained in this way was less than that obtained after descending to sea level. In other words, oxygen inhalation produced a partial decrease of pulmonary hypertension, while residence at sea level was responsible for a complete reversal of pulmonary hypertension at rest.

Mean pulmonary resistances were 334 ± 27.4 dynes/sec per cm⁻⁵ in Morococha and 145 ± 10.7 dynes/sec per cm⁻⁵, with significant individual decreases on descent to sea level ($P < 0.001$). On exertion, no significant changes were observed both at high altitude and sea level. The inhalation of 35 per cent

oxygen at altitude produced a significant decrement of the total pulmonary resistances ($P < 0.05$).

Relation of pulmonary arterial pressure to cardiac index Pulmonary hypertension and normal cardiac index characterize Andean natives at high altitude. With residence at sea level, reversal of pulmonary hypertension occurs along with a moderate increase in cardiac index. On the other hand, the inhalation of oxygen at altitude produces a moderate decrease in pulmonary arterial pressure and no change in cardiac index (Fig. 1).

The flow-pressure relation has been calculated by using the values obtained in highlanders at Morococha and Lima as well as in a comparable group of lowlanders. The graphic representation of this relation is shown in Fig. 2. A significant relation between the two variables tested was observed. Correlation coefficients were 0.858 for highlanders at Morococha and 0.852 for the same people at Lima. The coefficient obtained in lowlanders was somewhat lower ($r = 0.674$).

On the other hand, the highest regression coefficient was observed for highlanders at Morococha and the lowest for lowlanders;

FIG. 1 Relation between resting mean pulmonary arterial pressure and cardiac index in highlanders. The illustration depicts the changes occurring in this relation when the hypoxic stimulus is suppressed. A comparison can be made between the effects of oxygen inhalation and descent to sea level. For comparative purposes the normal area (mean ± 2 SD) for this relation at sea level is shown. Solid symbols represent mean values.

the coefficient obtained in highlanders residing at sea level was intermediate between the previous two (regression coefficient = 7.355, 1.359, and 2.580, respectively). In other words, the increase in mean pulmonary arterial pressure to be expected for each litre of increase in cardiac index is higher for highlanders both at high altitude and after residing at sea level than for lowlanders.

The foregoing differences in the regression coefficients are reflected in the differences of slope existing between the corresponding regression lines shown in Fig. 2. In addition, it can be seen that the regression line representing highlanders at Morococha is, as expected, higher than the others. Differences of slope and height between regression lines obtained from highlanders at Morococha and Lima were tested by analysis of covariance; they proved to be significant in both cases ($P < 0.01$). This means that residence at sea level results in a lowering of mean pulmonary artery pressure in highlanders as well as a lower increase of pulmonary pressure in response to equivalent increases in cardiac index. On the other hand, no difference of elevation was discernible between regression lines of highlanders at Lima and lowlanders. Rather, significant differences of slope were found between the regression lines obtained from these two groups. This indicates that after residence at sea level the response of pulmonary artery pressure to a similar increase in cardiac index is still greater for highlanders than for lowlanders.

Discussion

Observations in high altitude natives after two years of residence at sea level have shown important circulatory modifications. The heart rate falls considerably whereas the cardiac output shows a moderate increase, resulting in an increased stroke index. Pulmonary pressures and vascular resistances fall to values similar to those seen in normal sea level residents.

Bradycardia One of the most striking findings of this investigation was a considerable reduction in heart rate of highlanders with the descent to sea level. On average the heart rate fell 18 beats/min, and a reduction to less than 60 beats/min was observed in 7 of the 11 cases. A lower heart rate in highlanders at the coast was also observed on exertion. This is due to the low heart rates at rest, since it must be stressed that the increase in heart rate in response to similar degrees of exercise is similar at sea level and at high altitude.

FIG. 2 Regression of mean pulmonary arterial pressure on cardiac index at rest and on exertion observed in highlanders at high altitude and after 2 years of residence at sea level and in lowlanders. Comparison of the regression lines shows that the slope and elevation corresponding to highlanders at altitude are clearly the highest as a consequence of the significant differences in pulmonary arterial pressures. Elevation of lines for Andean natives at sea level and sea level people are fairly similar, but the pulmonary pressure response to exercise of the former is significantly greater, thus determining a higher slope. Significance of differences in slope and elevation has been tested by analysis of covariance (see text).

Electrocardiographic observations previously performed in children and adults from high altitude (Peñaloza *et al.*, 1971) taken down to sea level have shown that the resting heart rate falls to even quite slow rates shortly after arrival. Likewise, Hartley *et al.* (1967) have described a slight reduction in heart rate of residents from Leadville, Colorado (10,200 feet of altitude), after 10 days of residence at sea level, both at rest and during exercise. This early fall of heart rate rules out the possibility that bradycardia observed in our cases resulted from physical training consequent to the military enrolment. The mechanisms mediating the reduction of heart rate of highlanders taken down to sea level is not clear as yet.

On the other hand, the present investigation showed at high altitude a slight reduction of heart rate as a consequence of 35 per cent oxygen inhalation during 15 minutes. Hultgren *et al.* (1965b) also obtained a reduction of 8 beats/min during the administration of

100 per cent oxygen to residents from La Oroya, Perú, at 12,300 feet of altitude. Marticorena *et al.* (1965) observed an important decrease of heart rate (mean fall of 17 beats/min) in unacclimatized Andean natives put inside an oxygen tent during 3 to 8 days. Recently, Carey and Schaefer (1970) have shown the occurrence of bradycardia as a result of the increased PO_2 in the inspired air of a hyperbaric environment.

The foregoing observations indicate that when the hypoxic stimulus is removed an early fall in heart rate occurs, the degree of this change being related to several factors such as concentration of oxygen, altitude of the place of residence, and clinical condition. It is possible that the suppression of the hypoxic stimulus accentuates even more the predominant parasympathetic activity which has been described in the high altitude native (Aste, 1936).

Increase of cardiac output and stroke volume The results confirm the finding of a normal cardiac output in Andean natives (Rotta *et al.*, 1956; Peñaloza *et al.*, 1963; Sime *et al.*, 1963; Hultgren *et al.*, 1965a) as opposed to the subnormal values described in the residents of Leadville, Colorado (Hartley *et al.*, 1967). Grover (1968) suggests that this difference is the result of a better acclimatization to altitude of Andean natives who have lived in an hypoxic environment over many generations.

The inhalation of 35 per cent oxygen during 15 minutes caused no significant modifications in cardiac output. Hultgren *et al.* (1965b) found no modification in cardiac output with the inhalation of 100 per cent oxygen either. In contrast, prolonged residence at sea level led in our cases to a significant increase of cardiac output. Such an increase was not related to changes in oxygen uptake, but was associated with a reduction in the arteriovenous difference of blood oxygen content, mainly a fall in the arterial oxygen content due to a reduced haemoglobin level.

Previous studies have shown the existence of a polycythaemic hypervolaemia (Hurtado, Merino, and Delgado, 1945; Merino, 1950) in the high altitude native. The observations of Reynafarje, Lozano, and Valdivieso (1959) have shown that the descent to sea level determines a reduction of polycythaemia and a proportionate increase in plasma volume, the total blood volume remaining unaltered during the first weeks of residence at the coast. Around the third or fourth months, total blood volume diminishes and red cell mass reaches subnormal values, producing a true

anaemia which gradually disappears during the subsequent months.

It is not clear why in the subjects of the present investigation anaemia persisted even after two years of residence at sea level. This finding cannot be ascribed to nutritional deficiencies because diet in the Peruvian army is well balanced. Since anaemia determines an increase in cardiac output at rest as a compensatory haemodynamic change, the slight degree of anaemia observed in highlanders after a long residence at sea level may explain the concomitant increase in cardiac output. It is worth mentioning that Hartley *et al.* (1967) observed a modest fall of haematocrit accompanying the slight increase of cardiac output in altitude dwellers after 10 days of residence at sea level.

The greater cardiac output observed in highlanders at the coast was also observed during exercise as a consequence of the higher resting values. However, the cardiac output response to similar degrees of exercise was similar in both environments. Hartley *et al.* (1967) have also observed greater figures of cardiac output in response to similar degrees of exercise in residents from Leadville, Colorado, restudied after 10 days of residence at sea level. The early increase of cardiac output elicited on exertion indicates a normal myocardial function and is in apparent disagreement with the hypothesis proposed by the same authors, which causally relates the depressant effect of hypoxia on the contractile myocardial force to the subnormal cardiac output found in the residents of Leadville.

The moderate increase in cardiac output and mainly the great decrease of heart rate explain well the highly significant increase of resting stroke index observed in highlanders at sea level. This fact has also been described by Hartley *et al.* (1967). On exertion, the stroke index did not vary significantly either at high altitude or at sea level. In both environments the increase in heart rate is the main factor responsible for the increased cardiac output observed during exercise.

Reversal of pulmonary hypertension

After two years of residence at sea level pulmonary arterial pressures and vascular resistances reached levels similar to those found in the normal sea level resident at rest; the average descent of mean pulmonary artery pressure was 12 mmHg. The lower values of mean pulmonary arterial pressure found in highlanders at the coast were also observed on exertion. This is due to the lower pressure figures observed at rest. It is noteworthy that the pressure response to a similar degree of

exercise was similar at sea level and at high altitude.

Oxygen administration to highlanders at high altitude determined only a partial reduction of resting mean pulmonary arterial pressure (6 mmHg), which did not attain normal values for healthy sea level people. The partial decrease induced by oxygen was also observed by Hultgren *et al.* (1965b) in residents from lower altitudes. In one case with accentuated pulmonary hypertension observed by Grover *et al.* (1966) at Leadville, Colorado, oxygen inhalation did not normalize the pulmonary pressure figures.

These observations stress the importance of the structural characteristics of the pulmonary vasculature, determined by the arteriolar muscularization (Arias-Stella and Saldaña, 1963), in the mechanism of high altitude pulmonary hypertension. The partial decrease obtained by oxygen inhalation is due to the suppression of vasoconstriction. Normal pulmonary pressure values observed after a prolonged residence at sea level are probably related to the involution of the structural factor at the pulmonary arteriolar level.

There is little information about the early pressure response occurring with the descent to sea level. Hartley *et al.* (1967) did not observe significant modifications after 10 days of residence at lowlands. Peñaloza and Sime (1971) studied three cases of chronic mountain sickness after 3, 11, and 60 days of residence at the coast, respectively, observing that the reduction of pulmonary pressure was proportional to the time of residence at sea level. However, the case with the longest residence did not attain normal values of pulmonary pressure. Grover *et al.* (1966) observed in one case a fall of mean pulmonary arterial pressure up to 17 mmHg after 11 months of residence at sea level. These observations suggest that the pulmonary pressure of high altitude natives requires a prolonged stay at sea level to return to normal because of the slow involution of the anatomical changes of pulmonary vessels. The early pressure reduction is due first to the suppression of hypoxic vasoconstriction and then to the progressive lessening of polycythemia which occurs during the first three or four months of residence at sea level.

It is of interest to point out that even though pulmonary pressure at the coast reached normal resting values the pressure response on exercise was twice as high as that observed in normal residents at the coast. A moderate degree of exercise caused an increase in pulmonary pressure somewhat greater than 100 per cent in high altitude natives as compared

with the 50 per cent increase obtained in sea level residents in response to the same work load. The increases in cardiac output were similar. This difference in pulmonary pressure response is related to the fact that total pulmonary resistances remain unmodified in altitude natives during exercise while they decrease in lowlanders. This indicates that the involution of the structure of pulmonary vessels was not complete after two years of residence at sea level. It seems probable that the arteriolar compliance remains limited on exertion because of the partial persistence of muscle and double elastic layer in the arteriolar walls.

The observations performed in two of our cases studied again one year after return to altitude support this hypothesis. Pulmonary pressures obtained at rest and on exertion resembled those found in the baseline study performed at altitude (Table 4, Fig. 3). This behaviour is different from that observed by Rotta *et al.* (1956) in a group of sea level residents after one year of residence at high

FIG. 3 Behaviour of mean pulmonary arterial pressure and cardiac index observed in two highlanders at high altitude, after two years of residence at sea level and again one year after return to high altitude. At altitude and at sea level both subjects parallel the average response (mean ± 1 SE) of Andean natives in these situations (shaded areas). After the new prolonged exposure to high altitude blood flow remains almost unmodified at rest but is lower than formerly on exertion. Pressure response roughly resembles the pattern obtained in the baseline study.

altitude, in whom the mean pulmonary pressure increased but without attaining the figures observed in high altitude natives (Table 4). Since we should expect a similar degree of hypoxic vasoconstriction in both groups of subjects, the difference observed in the behaviour of pulmonary arterial pressure can be ascribed to the structural characteristics of pulmonary vessels of high altitude natives.

The effect of oxygen administration upon pulmonary circulation of highlanders during exercise has not been studied in this investigation. In the resident from Leadville studied by Grover *et al.* (1966), oxygen inhalation when performing a moderate degree of exercise produced a 75 per cent increase in mean pulmonary arterial pressure while the increase obtained before the oxygen was administered was 148 per cent. However, in spite of the suppression of vasoconstriction, pulmonary pressure response while breathing oxygen was 25 per cent greater than that observed in the normal sea level resident submitted to comparable degrees of exercise. This difference provides further evidence of the importance of the structural factor of the pulmonary vessels in the genesis of pulmonary hypertension commonly found in high altitude natives.

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