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BLOOD GAS CHANGES AND PULMONARY HEMODYNAMICS IN PORTAL HYPERTENSION DUE TO SCHISTOSOMIASIS MANSONI

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SUMMARY

Data on 134 patients with portal hypertension due to schistosomiasis and on 23 individuals, taken as controls, is presented. According to the room air PaO_2 and the A-aDO_2 gradient on 100% oxygen, patients were divided in three groups: Group I, normals PaO_2 and A-aDO_2 gradient (96 patients); Group II, low PaO_2 and normal A-aDO_2 gradient (16 patients); Group III, low PaO_2 and elevated A-aDO_2 gradient (10 patients), normal PaO_2 and elevated A-aDO_2 gradient (12 patients). These result showed that hypoxemia, as manifested by a low room air PaO_2, occurred in 26 patients (19.4% of the 134 patients). However, it was not related to abnormal shunting of blood in the 16 patients who comprised Group II (61.5% of the hypoxemics). In 12 patients of Group III hypoxemia was apparent only during 100% oxygen breathing. This indicates that in patients with portal hypertension due to schistosomiasis an oxygen test should be performed in order to rule out hypoxemia. A low mean $PaCO_2$ was observed in all three groups. In Group I, $PaCO_2$ showed a significant inverse correlation with the pulmonary arteriolar resistance index. Pulmonary hypertension was more commonly observed in Group III patients, who also presented a higher frequency of gastrointestinal bleeding and esophageal varices.

INTRODUCTION

Chronic Cor pulmonale and the so called "cyanotic syndrome" have been described as the major manifestations of pulmonary involvement in schistosomiasis [3,5,6,11,14,16]. These two clinical entities represent advanced stages of this disease. However, subclinical pulmonary involvement in schistosomiasis has not been well documented. Thus, pulmonary hemodynamics have been studied in those patients with clinical, electrocardiographic and radiologic signs of pulmonary hypertension [3,5]. In addition, the usual methods employed for detection of hypoxemia have failed to disclose subclinical cases because the criteria of a low arterial oxyhemoglobin saturation, which have been currently used for diagnosis of hypoxemia are not entirely satisfactory [3,5]. Indeed, once there is a shift to the left of the oxyhemoglobin dissociation curve, mild degrees of hypoxemia, as evidenced by a low arterial blood PO_2 may exist in the presence of normal values for the arterial oxyhemoglobin saturation [1].

The methodology of detection of subclinical cases of pulmonary schistosomiasis is im-

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portant in order to determine the frequency with which the lung is involved in this disease, as well as to provide a standard method for the longitudinal study of the natural history of pulmonary schistosomiasis. Beyond the identification of hypoxemia by more sensitive methods, an understanding of the pathogenesis may be gained by the study of refractoriness to 100% oxygen. In the majority of cases reported in the literature, hypoxemia, when present, is secondary to an increased right to left pulmonary shunt [6,11,14,16,17]. These findings, however, are related to a small number of patients, and may not reflect the true frequency with which a measurable right to left shunt will give rise to hypoxemia in patients with portal hypertension due to schistosomiasis. No conclusions have been made as to whether the presence of hypoxemia and pulmonary hypertension are independent phenomena, representing different types of lung injury of this parasitic disease.

The aim of the present study is to determine in a large group of patients with portal hypertension due to schistosomiasis: 1) the presence of hypoxemia and 2) the relationship between hypoxemia and pulmonary hypertension without previous selection based on clinical, radiographic and electrocardiographic manifestations suggestive of pulmonary schistosomiasis.

MATERIAL AND METHODS

One hundred sixty five patients with portal hypertension due to schistosomiasis were studied. Complete studies were obtained in 134 patients (68 males and 66 females), whose age ranged from 10 to 74 years, mean of 31.9. Adequate blood gas data could not be obtained in the other 31 patients, who were excluded from the present series. The diagnosis of schistosomiasis was based on the demonstration of eggs of **S. mansoni** in the stools (131 patients, 97.8%) and/or a liver biopsy revealing the Symmers type of portal fibrosis (45 patients, 33.6%).

Classification of portal hypertension was based on the presence of enlargement of the left lobe of the liver associated with splenomegaly. All but eleven patients presented with the compensated form of hepatosplenic schistosomiasis, characterized by the absence of ascites and leg edema [15]. In these eleven patients, ascites alone was present in eight individuals and associated with leg edema in three.

All the patients were submitted to right and left heart catheterization in a fasting state, and received 10 mg of Diazepan, orally, 30 minutes before the procedure. While supine, right heart catheterization was performed by the insertion of an indwelling nylon catheter (i.d. 1.0 mm; o.d. 1.4 mm) into an antecubital vein, by the Seldinger technique. The catheter was advanced into the pulmonary artery while the intravascular pressure pulse was monitored to confirm the location of the catheter tip. A similar catheter was inserted by the same technique into the femoral artery and was advanced to the thoracic aorta. After the insertion of the catheters, the patient rested for fifteen minutes in order to return to a steady state prior to the measurements. Thereafter, the arterial catheter was advanced into the left ventricle and pressures in the pulmonary artery, left ventricle and thoracic aorta were measured in rapid succession by means of a P23Db Statham strain gauge and a Philips electromanometer, and recorded in a Cardiopan 573, simultaneously with lead II of the electrocardiogram. Zero reference point was taken 10 cm below the sternal angle.

Arterial and mixed venous blood samples were drawn into heparinized syringes while the patient was breathing room air and after 20 minutes of breathing 100% humidified oxygen. The oxygen was supplied through a mouthpiece with a nonrebreathing valve while the nose was occluded. A 10 inch length of wide-bore rubber tubing was attached to the exhaust limb of the valve to prevent back flow of air through the valve during the initial moments of respiration. During the period of oxygen breathing appropriate ventilation of the lungs was assured by three deep breaths every five minutes [8].

Blood samples were iced immediately and analysed for oxygen and carbon dioxide tensions, and pH, with the highest oxygen tensions being measured within five minutes of collection. Determinations were performed

with a Radiometer pH meter no. 27 with a gas monitor. The arterial (PaO_2) and mixed venous ($P\bar{v}O_2$) oxygen tensions were measured with an oxygen electrode calibrated according to the anticipated oxygen tension of water at 38°C. For arterial samples obtained during oxygen breathing, calibration was accomplished with humidified oxygen. The measured tensions were corrected for a factor of 1.05 [13].

The alveolar arterial oxygen gradient ($A\text{-}aDO_2$) was calculated by subtracting the arterial oxygen tension measured during oxygen breathing from the theoretical alveolar oxygen tension. Alveolar oxygen tension was assumed to be equal to the barometric pressure minus the combined tensions of alveolar CO_2 (presumed equal to the measured arterial PCO_2) and water vapor at 38°C.

Oxyhemoglobin saturation were measured in an AO oximeter, model no. 108000. Hemoglobin concentration was determined by the cyanomethemoglobin method.

From the oxygen tension, saturation, and hemoglobin concentration, the per cent anatomic sunt was calculated:

$$\dot{Q}s/\dot{Q}T = \frac{Cc - Ca}{Cc - Cv}$$

The cardiac output was calculated by the Fick principle. The assumed oxygen consumption was based on age, sex, and heart rate, as recommended by LAFARGE & MIETTNEN [10]. From the oxygen tension, saturation, and hemoglobin concentration obtained while the patient was breathing room air the arterial and venous oxygen contents were calculated.

The pulmonary arteriolar resistance index was calculated by the following formula:

$$PaRI\ (Dynes/sec/cm^{-5}/M^2) = \frac{\overline{PA}(mmHg) - LVED\ (mmHg) \times 60 \times 1330}{CI\ (ml/min/M^2)}$$

where:
$\overline{PA}$ = pulmonary artery mean pressure
LVED = left ventricular end-diastolic pressure
CI = cardiac index.

Control values for the parameters under study were obtained in 23 individuals without schistosomiasis: 10 with minor surgical problems and no evidence of cardiopulmonary disease, and 13 who had cardiac catheterization performed because of the presence of heart murmurs. Their age ranged from 10 to 49 years (mean of 22.9). Fourteen were males and nine females. The control mean values plus minus two times the correspondent standard deviation ($\bar{X} \pm 2SD$) were taken as the upper and lower limits of normal, respectively.

Calculations were made on a HP 9100 B — Calculator. Significance differences between means were calculated using a non paired **t** test; for the differences between proportions an appropriate test was used [2]. Correlation coefficients were calculated by regression analysis.

RESULTS

Since one of the main purposes of this investigation was concerned with the problem of hypoxemia in portal hypertension due to schistosomiasis, the patients under study were divided in groups according the values obtained for their PaO_2 while breathing room air, and for their $A\text{-}aDO_2$ gradient during the administration of 100% oxygen. Based on these criteria 3 groups emerged: Group I, patients with normal PaO_2 and normal $A\text{-}aDO_2$ gradient (96 patients); Group II, patients with low PaO_2 (< 87.2 mmHg) and normal $A\text{-}aDO_2$ gradient (16 patients); Group III, patients with normal or low PaO_2 and elevated $A\text{-}aDO_2$ gradient (> 121.0 mmHg) (22 patients).

Table I contains the range, mean value, and standard deviation for age in each one of these 3 groups and in the control group. It also shows the **p** value obtained from the statistical comparisons performed between each group and the control group and among the groups themselves. Table II shows identical values for the arterial blood oxygen saturation (SaO_2), PaO_2, $PaCO_2$ and paH, while breathing room air, and for the arterial blood PO_2 and PCO_2, $A\text{-}aDO_2$ gradient, and $\dot{Q}s/\dot{Q}t$,

while breathing 100% oxygen. Corresponding values for the mean pulmonary artery pressure ($\overline{PA}$), left ventricular end-diastolic pressure (LVED), cardiac index (CI), pulmonary arteriolar resistance index (PaRI), and hemoglobin concentration are shown in Table III. Tables IV and V contains the individual values for the parameters under consideration obtained in Groups II and III.

GROUP I — age ranged from 12 to 74 years, mean of 31.6. Pulmonary hypertension ($\overline{PA}$ above 20.0 mmHg) was present in 10 patients (10.4%), being severe in 2 ($\overline{PA}$ of 58.9 and 62.1 mmHg), moderate in 4 ($\overline{PA}$ > 35 mmHg and < 50 mmHg), and mild in 5 ($\overline{PA}$ > 20 mmHg and < 35 mmHg). All these patients showed also an increased pulmonary arteriolar resistance index, which was markedly elevated in those with severe pulmonary hypertension (1,385.1 and 1,056.6 dynes/sec/cm^{-5}/M^2). Correlation analysis between $PaCO_2$ and pulmonary artery mean pressure and between $PaCO_2$ and arteriolar resistance index showed a significant inverse correlation ($r = -0.2765$, $p < 0.01$ and $r = -0.3113$, $p = 0.02$).

In relation to the controls, their mean age (31.6 years) and mean pulmonary arteriolar resistance index (211.9 dynes/sec/cm^5/M^2) were significantly higher ($p < 0.01$ and $p < 0.05$, respectively), Tables I and III. On the other hand, their mean arterial blood PCO_2 (38.5 mmHg) and mean hemoglobin concentration (12.3 gm%) were significantly lower ($p < 0.001$ and $p < 0.05$, respectively), Tables II and III, and Fig. 1. An elevated mean value for the arterial blood pH (7.41) was also observed, but the difference was not significant, Table II.

TABLE I

Range, mean values and standard deviation for age in the three groups of patients with portal hypertension due to schistosomiasis mansoni and in the control group (*)

Values	AGE IN YEARS			
	Controls (23)	GI (96)	GII (16)	GIII (22)
Range	10 — 49	12 — 74	14 — 53	10 — 60
Mean	22.9	31.6	33.7	30.6
SD	8.4	14.1	12.8	14.4
P (**)		< 0.01 (vs C)	< 0.01 (vs C)	< 0.05 (vs C)
		—	NS (vs GI)	NS (vs GI)
		—	—	NS (vs GII)

(*) Between parenthesis are the number of patients in each group. See text for details concerning the composition of the groups.

(**) Non-paired t test.

GROUP II — in this group age ranged from 14 to 53 years, mean of 33.7. As shown in Table II the low PaO_2 ranged from 75.6 to 87.1 mmHg, mean of 83.3, while the arterial oxyhemoglobin saturation was still within the normal limits, varying between 92% and 96%, mean of 94%.

An elevated mean pulmonary artery pressure was documented in 3 patients (18.7%), being of a severe degree in patient no. 4 (55.4 mmHg), moderate in patient no. 46 (40.0 mmHg), and mild in patient no. 23 (27.7 mmHg). According to the degree of pulmonary hypertension, the pulmonary arteriolar resistance index showed marked elevation in patient no. 4, moderate in patient no. 46 and mild in patient no. 23, Table IV.

When compared to the controls, the patients in this group presented a significantly higher mean age (33.7 years, $p < 0.01$), a significantly lower mean arterial oxyhemoglobin saturation (94%, $p < 0.01$) and a significantly

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TABLE II

Range, mean values and standard deviation for the arterial blood gas tensions (PaO_2 and $PaCO_2$), oxygen saturation (SaO_2) and pH (paH), and for the alveolar arterial oxygen gradient ($A\text{-}aDO_2$) and per cent anatomic shunt ($\dot{Q}s/\dot{Q}t$) in the three groups of patients with portal hypertension due to schistosomiasis mansoni and in the control group (*)

Groups	Values	AIR				OXYGEN			
		SaO_2 %	PaO_2 mmHg	$PaCO_2$ mmHg	paH	PaO_2 mmHg	$PaCO_2$ mmHg	$A\text{-}aDO_2$ mmHg	$\dot{Q}s/\dot{Q}t$ %
C	Range	93-98	89.2-102.9	37-45	7.35-7.42	556.5-672.0	26-41	7.9-109.9	0.62-8.60
(23)	Mean	96	97.2	41.2	7.39	606.6	34.4	64.4	4.89
	SD	2.5	5.0	3.2	0.16	29.4	3.8	28.3	2.0
G. I	Range	94-98	88.2-111.3	34-46	7.34-7.53	556.5-672.0	25-43	0.7-105.0	0.01-8.93
(96)	Mean	96	97.7	38.5	7.41	606.6	34.2	64.5	5.03
	SD	1.0	4.3	3.0	0.03	27.8	3.2	26.4	2.2
G. II	Range	92-96	75.6-87.1	34-50	7.36-7.46	556.5-645.7	30-42	39.5-115.4	2.46-9.82
(16)	Mean	94	83.3	38.3	7.41	559.7	34.7	75.0	5.34
	SD	1.0	3.4	4.2	0.03	26.8	3.4	23.8	2.0
G. III	Range	72-97	44.0-102.9	34-45	7.37-7.52	120.7-546.0	28-52	124.2-547.1	8.90-36.20
(22)	Mean	93	85.2	39.4	7.42	472.4	35.6	197.7	14.52
	SD	5.8	14.9	2.9	0.14	98.6	5.0	100.2	6.8
	GI vs C	NS	NS	< 0.001	NS	NS	NS	NS	NS
	GII vs C	< 0.01	< 0.001	< 0.05	NS	NS	NS	NS	NS
P	GIII vs C	< 0.05	< 0.001	NS	NS	< 0.001	NS	< 0.001	< 0.001
	GI vs GII	< 0.001	< 0.001	NS	NS	NS	NS	NS	NS
	GI vs GIII	< 0.001	< 0.001	NS	NS	< 0.001	NS	< 0.001	< 0.001
	GII vs GIII	NS	NS	NS	NS	< 0.001	NS	< 0.001	< 0.001

(*) Values obtained breathing room air (AIR) and 100% oxygen for 20 minutes (OXYGEN)

TABLE III

Range, mean values and standard deviation for the mean pulmonary artery pressure ($\overline{PA}$), left ventricular end-diastolic pressure (LVED), cardiac index (CI), pulmonary arteriolar resistance index (PaRI) and hemoglobin concentration in the three groups of patients with portal hypertension due to schistosomiasis mansoni and in the control group.

Groups	Values	$\overline{PA}$ mmHg	LVED mmHg	Cardiac Index L/min/M^2	PaRI dynes/sec/cm^{-5}/M^2	Hemoglobin gm%
C	Range	8.1 — 18.7	6.7 — 11.9	2.6 — 5.3	17.4 — 171.5	10.4 — 15.7
(23)	Mean	14.1	9.0	3.9	108.6	13.1
	SD	2.9	1.4	0.8	60.4	1.3
GI	Range	7.4 — 62.1	2.4 — 12.7	2.2 — 5.3	18.6 — 1385.2	8.3 — 15.8
(96)	Mean	17.3	8.7	3.6	211.9	12.3
	SD	8.7	3.1	0.7	230.2	1.6
GII	Range	10.5 — 55.4	3.2 — 13.7	2.3 — 5.2	46.4 — 1780.2	8.2 — 14.8
(16)	Mean	19.3	8.7	3.6	320.7	12.6
	SD	12.6	3.1	0.8	499.2	1.7
GIII	Range	10.7 — 62.7	3.2 — 16.1	2.5 — 6.6	30.6 — 1498.9	9.9 — 15.2
(22)	Mean	20.2	7.9	3.9	298.2	12.1
	SD	12.4	2.7	0.9	359.0	1.5
	GI vs C	NS	NS	NS	< 0.05	< 0.05
	GII vs C	NS	NS	NS	NS	NS
	GIII vs C	< 0.05	NS	NS	< 0.05	< 0.05
	GI vs GII	NS	NS	NS	NS	NS
	GI vs GIII	NS	NS	NS	NS	NS
	GII vs GIII	NS	NS	NS	NS	NS

lower mean $PaCO_2$ (38.3 mmHg, $p < 0.05$), Fig. 1. Their mean arterial blood pH (7.41) was also higher than the control (7.39), but the difference was not significant, Table II. In relation to Group I patients, they showed only a significant lower mean arterial blood PO_2 ($p < 0.001$).

GROUP III — age ranged from 10 to 60 years, mean of 30.6. As seen in Table V, arterial blood PO_2 while breathing room air was low in 10 patients, the lowest value being observed in patients no. 6 and 159 (51,4 and 44 mmHg), who presented clinically with cyanosis and clubbing. In 4 of these 10 patients, the arterial oxyhemoglobin saturation was also low, varying between 72 and 90%. During 100% oxygen breathing, all the patients presented an elevated A-aDO_2 gradient, a low PaO_2 (< 547.8 mmHg) and a high $\dot{Q}s/\dot{Q}t$ (> 8.89%). As illustrated in Fig. 2 and 3, when the A-aDO_2 gradient was compared with the $\dot{Q}s/\dot{Q}t$ and with the room air PaO_2, a highly significant coefficient of correlation was obtained ($r = 0.9002$, $p < 0.0001$ and $r = -0.8047$, $p < 0.0001$).

Five of the 20 patients (25%) in whom the mean pulmonary artery pressure was measured had pulmonary hypertension, which was severe in patient no. 116 (62.7 mmHg), moderate in patient no. 12 (47 mmHg) and mild in patients no. 6, 30 and 37, Table V. The pulmonary arteriolar resistance index was also elevated in these patients, except for patient no. 6, who presented a normal value. This latter patient was one of the 2 cyanotic studied, who also had a high cardiac index (6.57 L/min/M^2), Table V.

In comparison to the controls their mean room air arterial blood PO_2 (85.2 mmHg) and oxyhemoglobin saturation (93%) showed significant lower values ($p < 0.001$ and $p < 0.05$). On the other hand the mean pulmonary artery pressure and arteriolar resistance index showed significant higher mean values (20.2 mmHg, $p < 0.05$ and 298.2 dynes/sec/cm^{-5}/M^2, $p < 0.05$). As occurred in the other two groups, their mean $PaCO_2$ was also lower than the control, but the difference was not significant, Fig. 1. The reason for that, however, was related to the relatively high $PaCO_2$ presented by patients no. 31 and 155 (45 and 44 mmHg), Table V. Once these values were taken out of the series, the mean $PaCO_2$ decreased to 38.8 mmHg, and the difference with the controls became significant at the 5 per cent level.

In comparison to Group I patients, the significance of the differences were the same as those observed with the controls when oximetric and gasometric values obtained while breathing room air and 100% oxygen were considered, Table II. However, the mean pulmonary artery pressure, mean arteriolar resistance index and mean hemoglobin concentration showed similar values.

In comparison to Group II, Group III patients presented a significant lower mean PaO_2 a significant higher mean A-aDO_2 gradient and a significant higher mean $\dot{Q}s/\dot{Q}t$ ($p < 0.001$) while breathing 100% oxygen.

Although pulmonary hypertension was more frequent in Group III patients, the difference was significant only in relation to Group I patients ($p < 0.05$).

DISCUSSION

The mean ages of the three groups of patients studied are similar but significantly higher than the age of the controls (Table I). This could have affected the statistical comparisons performed. On the other hand, this is unlikely since in the present series the physiological data in Group I patients are very similar to the control group, except for the means $PaCO_2$, pulmonary arteriolar resistance index and hemoglobin concentration (Tables II and III) whose values are not influenced by age.

Evidence of a disturbance in the oxygenation of the blood was present in patients of Group II and III, a total of 38 patients (28.3%) of the 134 patients studied. Hypoxemia while breathing room air, characterized by a low room air PaO_2, occurred in all patients of Group II and in 10 patients of Group III, giving an over-all frequency rate for this abnormality of 19.4%. In 12 patients of Group III, hypoxemia only became apparent during 100% oxygen breathing, as manifested by the

TABLE IV

Individual values for age, sex, arterial blood gas tensions (PaO_2 and $PaCO_2$), oxygen saturation (SaO_2), and pH (paH), for the alveolar arterial oxygen gradient ($A\text{-}aDO_2$), per cent anatomic shunt ($\dot{Q}s/\dot{Q}t$), mean pulmonary artery pressure ($\overline{PA}$), left ventricular end-diastolic pressure (LVED), cardiac index (CI), pulmonary arteriolar resistance index (PaRI), and hemoglobin concentration (Hb) of 16 patients with portal hypertension due to schistosomiasis mansoni and a low room air PaO_2 (Group II).

Patients			AIR									OXYGEN		
No.	AGE (years)	SEX	SaO_2 %	PaO_2 mmHg	$PaCO_2$ mmHg	paH	$\overline{PA}$ mmHg	LVED mmHg	CI L/min/M²	PaRI dynes/sec/cm-⁵/M²	Hb gm %	PaO_2 mmHg	$A\text{-}aDO_2$ mmHg	$\dot{Q}s/\dot{Q}t$ %
4	32	F	95	84.0	36	7.46	55.4	3.2	2.34	1780.1	9.8	609.0	65.2	4.50
23	33	F	95	87.1	50	7.41	27.7	4.0	4.14	456.8	13.6	556.5	106.2	9.82
32	14	M	95	81.9	39	7.37	17.9	8.4	3.19	237.6	11.5	619.5	54.4	3.58
46	31	M	92	78.7	37	7.39	40.0	11.4	3 32	687.4	12.0	567.0	103.8	6.31
47	21	M	94	82.9	41	7.39	14.6	12.5	3.61	46.4	13.1	619.5	50.2	3.48
48	53	M	95	87.1	37	7.42	11.6	13.7	3.20	—	11.7	609.0	62.6	3.48
52	19	F	95	87.1	36	7.42	13.2	10.3	3.61	64.1	13.4	598.5	70.5	4.83
54	48	F	94	81.9	36	7.42	10.5	8.9	2.73	46.8	13.7	556.5	115.4	6.53
55	46	M	94	84.0	34	7.45	11.2	5.3	4.78	98.5	12.1	598.5	76.0	6.63
56	43	F	94	86.1	36	7.40	13.0	7.2	3.24	142.8	13.5	609.0	62.3	4.60
59	22	M	93	75.6	38	7.42	12.5	9.2	3.21	82.0	14.8	588.0	82.5	5.18
61	20	F	94	84.0	36	7.41	14.8	11.6	3.58	71.3	14.6	630.0	45.4	3.68
78	49	M	94	86.0	45	—	15.6	—	4.32	—	13.1	630.0	39.5	2.46
152	41	F	96	86.1	38	7.38	15.2	—	—	—	13.5	577.5	97.4	6.33
161	45	M	93	80.8	—	7.36	—	8.4	—	—	13.3	645.7	—	—
165	23	M	95	79.8	35	7.41	16.3	7.6	5.18	134.0	8.2	580.7	93.9	8.66

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TABLE V

Individual values for age, sex, arterial blood gas tensions (PaO_2 and $PaCO_2$), oxygen saturation (SaO_2), and pH (paH), for the alveolar arterial oxygen gradient ($A\text{-}aDO_2$), per cent anatomic shunt ($\dot{Q}s/\dot{Q}t$), mean pulmonary artery pressure ($\overline{PA}$), left ventricular end-diastolic pressure (LVED), cardiac index (CI), pulmonary arteriolar resistance index (PaRI) and hemoglobin concentration (Hb) of 22 patients with portal hypertension due to schistosomiasis mansoni and an elevated $A\text{-}aDO_2$ gradient while breathing 100% oxygen (Group III).

Patients			AIR									OXYGEN		
No.	AGE (years)	SEX	SaO_2 %	PaO_2 mmHg	$PaCO_2$ mmHg	paH	$\overline{PA}$ mmHg	LVED mmHg	CI L/min/M²	PaRI dynes/sec/ cm⁻⁵/M²	Hb gm %	PaO_2 mmHg	$A\text{-}aDO_2$ mmHg	$\dot{Q}s/\dot{Q}t$ %
6	20	M	94	51.4	35	7.46	21.1	6.4	6.57	178.5	12.2	252.0	420.5	36.20
12	19	F	97	96.6	41	7.45	47.0	6.7	3.42	940.3	12.4	514.5	153.9	12.01
13	13	M	93	87.1	43	7.45	16.3	7.0	4.16	178.4	11.6	409.5	242.3	11.60
20	42	M	96	99.7	35	7.42	18.0	8.4	3.08	248.7	11.6	483.0	185.3	13.64
24	26	M	97	98.0	40	7.41	14.0	3.2	3.05	282.6	12.0	504.0	165.1	10.96
26	25	M	96	90.3	35	7.42	10.7	7.6	3.26	75.9	12.2	504.1	169.7	11.80
27	14	F	92	89.2	43	7.45	20.0	16.1	3.18	97.9	11.7	430.5	244.4	16.62
30	34	M	95	81.9	34	7.52	25.3	7.4	2.88	496.0	10.6	525.0	154.5	8.90
31	39	M	95	87.1	45	7.37	13.3	8.3	4.83	82.6	11.4	504.0	168.6	14.45
35	22	M	97	98.0	42	7.41	15.0	9.4	5.19	86.1	12.5	535.0	140.1	14.73
37	45	F	93	87.1	42	7.45	26.6	6.7	2.55	622.7	9.9	498.1	172.8	10.32
38	19	F	95	89.2	40	7.41	13.3	5.4	3.39	186.0	10.2	525.0	145.7	9.93
45	17	M	96	92.4	42	7.40	13.3	11.4	4.96	30.6	11.3	535.5	132.0	11.20
49	35	M	95	86.1	41	7.42	11.7	8.8	4.17	55.5	15.2	535.5	134.1	9.32
85	42	M	95	92.4	38	7.38	15.4	—	4.16	144.1	14.6	546.0	124.2	9.32
94	30	M	96	96.6	36	7.43	13.2	—	3.75	113.0	10.4	504.0	167.3	11.57
116	60	F	90	73.5	35	7.37	62.7	5.6	3.04	1498.9	11.3	535.0	138.1	10.25
124	54	M	94	88.2	34	7.39	—	—	3.04	—	15.2	482.0	193.4	10.88
155	56	F	90	65.1	44	7.38	—	—	—	—	—	472.5	187.3	—
156	36	F	97	102.9	39	7.45	16.0	9.3	—	—	13.6	525.0	144.7	—
159	10	F	72	44.0	41	7.39	13.7	—	3.86	120.1	12.0	120.7	547.1	29.34
160	16	M	95	79.8	41	7.44	18.3	6.5	4.14	227.4	12.0	451.5	218.6	18.14

GUIMARAES, A. C.; ALVES JUNIOR, A. R.; SANTOS FILHO, A.; ESTEVES, J. P.; VINHAES, L. S. A.; ABREU, W. N.; SOUZA, J. A. de A.; BINA, J. C. & PRATA, A. R. — Blood gas changes and pulmonary hemodynamics in portal hypertension due to schistosomiasis mansoni. **Rev. Inst. Med. trop. São Paulo** 19:80-93, 1977.

elevated A-aDO_2 gradient. This elevated frequency of hypoxemia in patients with portal hypertension due to schistosomiasis contrasts with the occasional cases reported in the literature [3,5,6,11,14,16]. The reason for this discrepancy becomes apparent if we consider that in the present investigation hypoxemia was defined in terms of a low PaO_2, either during room air or 100% oxygen breathing, instead of a low oxyhemoglobin saturation, as has been reported [5,3]. Actually by this latter criteria, only 4 of these 38 patients would have been considered as hypoxemic, thus reducing the frequency rate of this disturbance to 3%. Normal values for the oxyhemoglobin saturation associated to low values for the room air PaO_2 may be explained by the tendency of these patients to show elevated paHs, shifting the oxyhemoglobin dissociation curve to the left.

Shunting of blood through porto-pulmonary anastomoses as a consequence of portal hypertension, or through pulmonary micro arterious-venous fistulae has been considered the major cause of hypoxemia in patients with portal hypertension due to schistosomiasis [6,7,11,14,16,17]. This type of hypoxemia should be expected to be associated to a high A-aDO_2 gradient and $\dot{Q}s/\dot{Q}t$ during inhalation of 100% oxygen, for, at least, 10 minutes [12]. In emphysematous patients the time required to achieve a steady state is higher, but rarely exceeds 20 minutes [12]. Despite the absence of pulmonary emphysema in our patients, all of them received 100% oxygen, for 20 minutes. Then, the elevated values for the A-aDO_2 gradient and $\dot{Q}s/\dot{Q}t$ observed in patients of Group III can be interpreted as the result of abnormal shunting of blood, through one or both of these anatomic pathways. In addition to the amount of blood being shunted, the A-aDO_2 gradient may also be influenced by the oxygen content of this blood [4,12]. In group III, however, the A-aDO_2 gradient was mainly dependent of the $\dot{Q}s/\dot{Q}t$, as demonstrated by the significant direct correlation between these 2 parameters, Fig. 2. On the other hand, the highly significant inverse correlation between the A-aDO_2 gradient, while breathing 100% oxygen, and the room air PaO_2 also indicates this type of hypoxemia as the major determinant of the low room air PaO_2 observed in 10 patients of this group, Fig. 3.

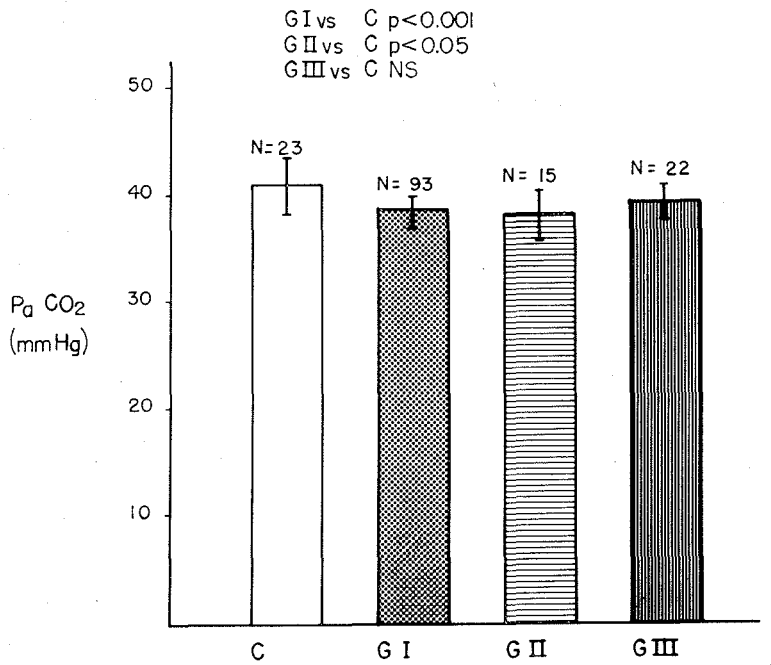

Fig. 1 — Arterial blood carbon dioxide tension in the three groups of patients with portal hypertension due to schistosomiasis and in the control group.

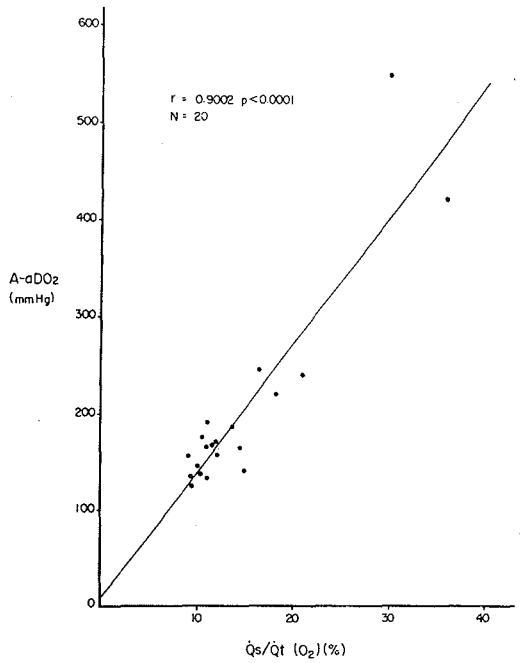

Fig. 2 — Correlation between the A-aDO$_2$ gradient and the $\dot{Q}s/\dot{Q}t$ while breathing 100% oxygen in a group of patients with portal hypertension due to schistosomiasis (Group III). As expressed by the high coefficient of correlation the elevation of the gradient is mainly a function of the elevation of $\dot{Q}s/\dot{Q}t$.

The observation, in 12 patients of Group III, of a normal room air PaO_2 associated with an elevated A-aDO$_2$ gradient during 100% oxygen breathing is very interesting and deserves some comments. In 6 patients, inhalation of 100% oxygen, was associated with an average fall of 24.3% in the pulmonary arteriolar resistance and a 9.8% mean increase in cardiac index, except for patient no. 24 who showed a mild decrease (2%) in this latter parameter. These findings suggest that inhalation of 100% oxygen was associated with openning or widening of anatomic pathways that by-passes pulmonary alveoli, leading, then, to an increase in shunting of blood through the lungs. In support of this hypothesis there is the demonstration that pulmonary arterious-venous fistulae may exist in the lungs of some patients with portal hypertension due to schistosomiasis[6,7,11,17]. In 4 patients, however, 100% oxygen administration caused a 13.3% mean fall in cardiac index, associated with a 13.9% increase in the pulmonary arteriolar resistance index. In these patients (no. 38, 45, 85 and 94, Table V) with mild elevation of the $\dot{Q}s/\dot{Q}t$, the slightly abnormal A-aDO$_2$ gradient may be explained by the decrease in the oxygen content of the

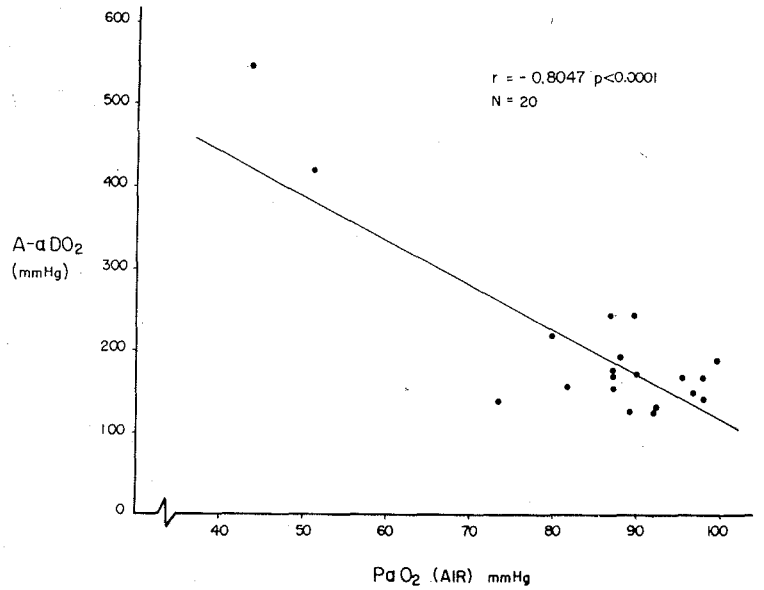

Fig. 3 — Correlation between the A-aDO$_2$ gradient, while breathing 100% oxygen, and the room air PaO_2 in a group of patients with portal hypertension due to schistosomiasis (Group III). As expressed by the high negative coefficient of correlation, to the lowest room air PaO_2 corresponds the highest oxygen gradient.

mixed venous blood as consequence of the decline in cardiac index. In the other 2 patients (no. 124 and 156) the cardiac index and pulmonary arteriolar resistance index, during 100% oxygen breathing, could not be obtained.

In the 16 patients of Group II, with a normal A-aDO_2 gradient while breathing 100% oxygen, the low room air PaO_2 cannot be explained on basis of abnormal shunting of blood through the lungs. These patients represent 47.3% of the 38 patients considered as having a disturbance in the oxygenation of the blood, and 61.5% of those with a low room air PaO_2. Then, these figures suggest, against the current belief, that the more frequent cause of a low room air PaO_2 in portal hypertension due to schistosomiasis is not an increased pulmonary anatomic shunt. Two possibilities should be further evaluated: uneven ventilation and a decrease in pulmonary diffusing capacity.

Uneven ventilation may represent an important cause of hypoxemia in these patients as suggested by recent findings in this laboratory related to the effects of intravenous reserpine upon the pulmonary circulation of patients with portal hypertension due to schistosomiasis (unpublished data). The injection of this drug into the pulmonary circulation, as a bolus, in doses of 0.04 mg/kg of body weight, has produced, specially in hypoxemic patients, a further drop of the PaO_2 associated with a decrease in the pulmonary arteriolar resistance index. Indeed, these findings are consistent with abolition of the Liljestrand reflex, propitiating an increase in perfusion of underventilated alveoli. Further evidence in this regard has been obtained in a hypoxemic patient who presented a drop in the PaO_2 from 80 mmHg to 60 mmHg, 30 minutes after 2.0 mg of reserpine, but did not change her PaO_2 while breathing 100% oxygen. It should be pointed out that no effects of this drug has been observed upon the $PaCO_2$.

The role that a decrease in the pulmonary diffusing capacity may play in the genesis of this type of hypoxemia remains to be determined. It has been measured occasionally in a few patients with visceral schistosomiasis, who have shown normal values at rest and a subnormal increase with exercise [9].

In our patients, hypoxemia, whatever its basic mechanism, tended to be mild to moderate in degree. The more severe cases of hypoxemia, as clinically manifested by the so called "cyanotic syndrome" were observed only in two patients. Both patients belong to Group III (no. 6 and 159, Table V) and had this severe degree of hypoxemia associated with very high values for the A-aDO_2 gradient and for the per cent anatomic shunt. This is in agreement with the relatively rarity that similar cases have been reported in the literature [6,11,14,16].

Alveolar hyperventilation at rest was present in several of the patients under study, as indicated by a mean $PaCO_2$ lower than the control, in all 3 groups. This kind of respiratory disturbance has also been documented by ZAKY et al. [18] in patients with portal hypertension due to schistosomiasis. In this study a low alveolar PCO_2 has been associated to an increase in the ventilatory equivalent and a decrease in pulmonary compliance. The high ventilatory equivalent is a consequence of the large physiologically dead space presented by these patients, which has been considered to be secondary to the obliterative lesions of the pulmonary arterioles by eggs of **S. mansoni.** The decrease in pulmonary compliance has been related to peribronchial and peri-bronchiolar fibrosis consequent to eggs' granulomatas, in addition to the vascular lesions. In this series, higher levels of pulmonary artery pressures were associated with lower levels of pulmonary compliance. In support to these findings are the significant inverse correlation between $PaCO_2$ and mean pulmonary artery pressure and between $PaCO_2$ and pulmonary arteriolar resistance index found in Group I. Therefore, it is conceivable that this decrease in pulmonary compliance could have played a role in the uneven ventilation postulated as the most probable basic mechanism responsible for the hypoxemia documented in Group II patients.

Pulmonary hypertension, of mild to severe in degree, was present in all three groups of patients with schistosomal portal hypertension. In all but one of them (no. 6) it was

associated with a correspondent increase in the pulmonary arteriolar resistance index, which is a characteristic of this condition [5]. Nevertheless, case no. 6, one of the cyanotics of this series (Group III, Table V), illustrates that in some patients, mild to moderate increases in pulmonary flow and elastic resistance may combine to give rise to a mild degree of pulmonary hypertension. In this patient, the level of the pulmonary arteriolar resistance index, though in the normal range, was not low enough to avoid the increase in pulmonary artery mean pressure in response to the increase in pulmonary flow.

The presence of patients with pulmonary hypertension in the three groups indicates that hypoxemia, whether refractory or not to oxygen, may occur as an independent phenomena. However, the significantly higher frequency of pulmonary hypertension in Group III in relation to Group I suggests that the development of this hypertension may be favored by the same basic factor leading to an increased A-aDO_2 gradient and $\dot{Q}s/\dot{Q}t$, on 100% oxygen. This factor may be a severe degree of portal hypertension leading to the development of a rich collateral circulation, through which massive embolization of the lungs by eggs of **S. mansoni** may take place. In some patients this latter phenomena may be responsible for both the development of a high pulmonary arteriolar resistance and abnormal shunting of blood through micro arterious-venous fistulae. In other patients, abnormal shunting of blood may take place independently, through porto-pulmonary anastomoses enlarged by the severity of the portal hypertension. A more severe degree of portal hypertension in Group III patients is suggested by a significant higher frequency of gastrointestinal bleeding in the patients of this group (50%) as compared to Group I (18.7%) and Group II patients (18.7%) ($p < 0.001$ and $p < 0.05$, respectively) Fig. 4. Furthermore, esophageal varices were demonstrated more times in patients of Group III (61.9%) than in those of Group I (32.3%) and Group II (37.5%). However only the difference between groups I and III reached statistical significance ($p < 0.01$), Fig. 5.

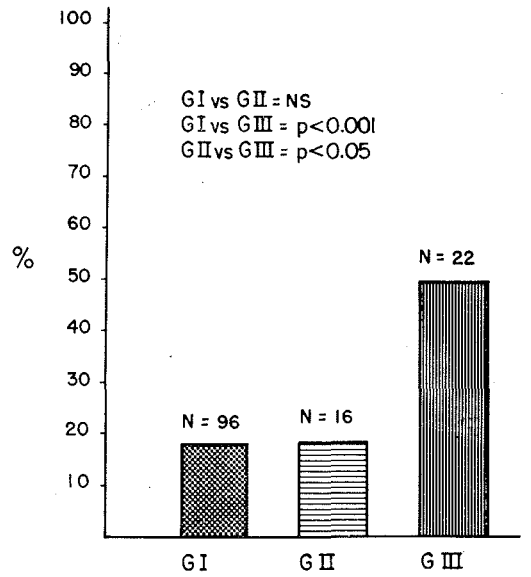

Fig. 4 — Frequency, in per cent, of episodes of gastrointestinal bleeding in the three groups of patients with portal hypertension due to schistosomiasis.

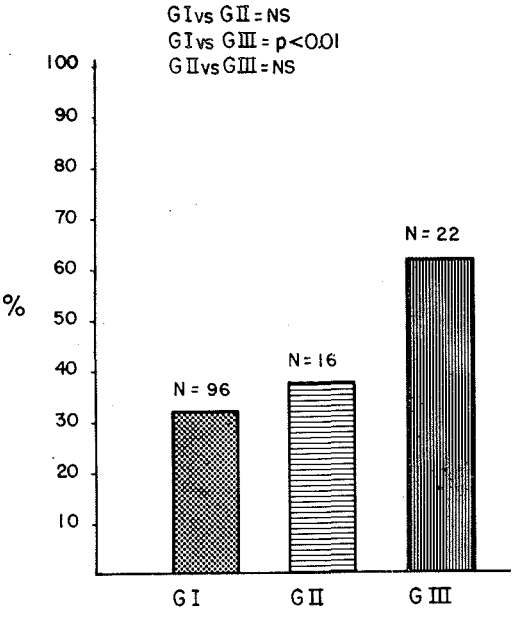

Fig. 5 — Frequency, in per cent, of esophageal varices demonstrated by x-ray in the three groups of patients with portal hypertension due to schistosomiasis.

In summary the present data documents different stages of physiological disturbances which may be induced in the lungs by schistosomiasis. It also shows that, once proper techniques are used, their frequency is relative-

ly high. In addition it illustrates that in patients with portal hypertension due to schistosomiasis, a low room air PaO_2 cannot be attributed to abnormal shunting of blood through the lungs unless a test with 100% oxygen is performed. On the other hand, a normal room air PaO_2 cannot rule out an elevated A-aDO_2 gradient during oxygen test. Finally, it shows that, in patients with schistosomiasis and severe clinical signs of portal hypertension, pulmonary hypertension and hypoxemia refractory to oxygen are more likely to occur.

RESUMO

Alterações dos gases sanguíneos e hemodinâmica pulmonar na hipertensão portal por esquistossomose mansoni

Os dados de 134 pacientes com hipertensão portal esquistossomótica e de 23 indivíduos, tomados como controles, são apresentados. Os pacientes foram divididos em três Grupos de acordo com a PaO_2 durante a respiração de ar atmosférico e com o gradiente A-aDO_2 durante oxigênio a 100%: Grupo I, PaO_2 e A-aDO_2 normais (96 pacientes); Grupo II, PaO_2 diminuida e A-aDO_2 normal (16 pacientes); Grupo III, PaO_2 diminuida e A-aDO_2 elevado (10 pacientes) e PaO_2 normal e A-aDO_2 elevado (12 pacientes).

Os resultados mostram que hipoxemia (baixa PaO_2) ocorreu em 26 pacientes (19,4% dos 134 pacientes), não estando relacionada a um desvio anormal de sangue nos 16 pacientes que compõem o Grupo II (61,5% dos hipoxêmicos). Em 12 pacientes do Grupo III, hipoxemia só foi demonstrada durante oxigênio a 100%. Isto indica que em pacientes com hipertensão portal esquistossomótica, um teste com oxigênio é necessário para se afastar a existência de hipoxemia.

Uma $PaCO_2$ diminuida foi observada nos três Grupos, sendo que no Grupo I mostrou correlação inversa significativa com o índice da resistência arteriolar pulmonar.

Hipertensão pulmonar foi mais freqüente no Grupo III, no qual houve maior freqüência de sangramento gastrintestinal e de varizes do esôfago.

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