Failure of Hypoxic Pulmonary Vasoconstriction in Patients with Liver Cirrhosis

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ABSTRACT The combination of arterial hypoxemia and low pulmonary vascular resistance in patients with liver cirrhosis is unexplained. Pulmonary microcirculatory dilation, but not gross arterio-venous shunts, has been the usual postmortem finding in patients with liver cirrhosis. When 10 patients with alcoholic liver cirrhosis breathed 10% oxygen in nitrogen, they failed to increase their pulmonary vascular resistance. However, four patients with functional murmurs, three patients with hyperkinetic heart syndrome, six patients with normal pulmonary artery pressures and intracardiac left to right shunts, and five patients with renal failure and anemia all increased their pulmonary vascular resistances when they breathed 10% oxygen in nitrogen. These findings suggested that in liver cirrhosis the normal regulating mechanism (hypoxic vasoconstriction) of the pulmonary circulation may be impaired, resulting in failure of the lung to match perfusion with ventilation.

INTRODUCTION

Patients with liver cirrhosis have increased pulmonary flow (1), arterial oxygen desaturation (2), low pulmonary vascular resistance (3), and hyperventilation (4). Various explanations have been offered for the arterial hypoxemia, but none has proved satisfactory. The shift to the right in the oxyhemoglobin dissociation curve (5) is insufficient to explain the degree of desaturation that occurs (6). The normal diffusing capacity (4), the increased alveolar-arterial oxygen tension gradient (7), the failure to fully saturate arterial blood during oxygen breathing (4, 7), and the results of isotope gas studies (8) have been presented in favor of venous admixture as the cause of the arterial hypoxemia. Necropsy studies, however, in patients with liver cirrhosis have revealed intrapulmonary arterio-venous anastomoses or portopulmonary venous communications in only a few patients (9, 10).

Recently Cotes, Field, Brown, and Read (11) postulated that, in the absence of a ventilatory defect, the arterial hypoxemia might be ascribed to inappropriate distribution of pulmonary flow relative to ventilation. If the lungs were unable to regulate perfusion, then the paradoxical combination of arterial hypoxemia and low pulmonary vascular resistance might occur. We postulated that impairment of the hypoxic vasoconstricting mechanism might be responsible for both low pulmonary vascular resistance and arterial hypoxemia in patients with liver cirrhosis.

In this study we attempted to compare the effects of inspiratory hypoxia in patients with cirrhosis, in normal subjects, and in patients who had certain clinical features simliar to those of patients with cirrhosis, namely, increased pulmonary flow, anemia, and the presence of a chronic debilitating illness. Failure of cirrhotic patients, compared to the controls, to increase pulmonary vascular resistance during hypoxia would favor the hypothesis.

METHODS

Liver cirrhosis. We selected for study 10 patients (six males and four females, ages 30–56 yr) with severe alcoholic liver cirrhosis who had evidence of a hyperkinetic circulatory state as judged by tachycardia, bounding pulses, and warm-flushed extremities. Hepatomegaly was present in all patients; splenomegaly, ascites, pedal edema, cutaneous spiders, and esophageal varices in nine patients and icterus in seven. In six patients liver biopsy confirmed the presence of liver cirrhosis. In four, biopsy could not be done because of massive ascites and elevated prothrombin times. None had detectable intrinsic pulmonary disease. At the time of the study nine patients were receiving chlorothiazide, seven were receiving an aldosterone antagonist, and eight were receiving vitamin supplement.

Control groups. The 18 patients used as controls (8 males and 10 females, ages 15–42 yr) were classified into

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the following groups. (*a*) Four patients with systolic murmurs had normal chest roentgenograms, electrocardiograms, and normal findings by heart catheterization and angiography (normal group). (*b*) Three patients had a hyperkinetic heart syndrome as defined by systemic hypertension, tachycardia, and high cardiac output. (*c*) Six patients had intracardiac left-to-right shunts (ASD 4, VSD 1, PDA 1). In five of them, the lesion was subsequently confirmed at surgery. (*d*) Five patients had chronic renal failure and anemia.

Procedure. Right and left heart catheterization were performed on each patient after an overnight fast and without premedication. Separate Cournand catheters were introduced into the pulmonary artery and the pulmonary capillary "wedge," so that both pressures could be measured simultaneously. Control measurements of the cardiac output were obtained by the direct Fick principle as has been described (12). Shortly after the collection of the expired air, cardiac output was also determined by the cardiogreen indicator dilution method except in the patients with intracardiac shunts. The patients then breathed hypoxic mixture (8–14% O_2 in N_2) for 10–15 min. During the hypoxia, pulmonary arterial, pulmonary capillary wedge, and systemic arterial pressures were simultaneously recorded every 2 min. The pressures used in the calculation of pulmonary vascular resistance were those nearest in time to the measurement of pulmonary flow. After 10 minutes of hypoxia, blood samples were taken for measurement of arteriovenous oxygen difference in all patients and cardiac output was measured by indicator dilution method in 14 patients. For the calculation of the cardiac output during hypoxia, we assumed that the oxygen uptake was equal to that measured during room air breathing (13). Indicator dilution curves used as a check showed good correlation (range ±20%) in the per cent change of cardiac output as measured by the two methods. Pulmonary vascular resistance (units), cardiac index (liters/min·m^2), venous admixture, and alveolar-arterial oxygen tension gradient were calculated utilizing conventional formulas. Statistical analysis of the differences in readings for liver cirrhosis and control patients was made using the "two factor experiment with repeated measures and unequal groups size" (14). Values during hypoxia which are different from the controls ($P < 0.05$) are indicated in Tables I and II.

TABLE I

Effects of Hypoxia in 10 Patients with Liver Cirrhosis

Age Sex	F_{IO_2}	PA	Mean pressure PA-PC	AO	HR	$\dot{Q}_{Pul}$	CI	PVR	Pa_{O_2}	Pa_{CO_2}	pH	RQ	A-a_{O_2}	Hct
			mm Hg			*liter/ min*	*liter/ min·m^2*	*"units"*	*mm Hg*	*mm Hg*			*mm Hg*	
39	0.21	12	6	88	90	9.4	4.1	0.6	82	38	7.42	—	—	36
M	0.08	13	7	70	100	10.2	4.4	0.7	36	29	7.50			
45	0.21	11	4	72	120	10.6	6.0	0.4	68	33	7.44	0.80	37	35
F	0.09	11	4	70	120	14.3	8.2	0.3	40	25	7.49			
32	0.21	11	6	62	100	8.0	4.9	0.7	90	30	7.39	0.80	18	21
F	0.09	13	6	62	104	17.0	10.3	0.4	32	32	7.51			
46	0.21	20	11	118	84	11.2	5.4	1.0	70	30	7.43	0.70	32	43
M	0.14	22	13	97	90	11.4	5.5	1.1	49	27				
39	0.21	10	3	80	90	8.2	5.3	0.4	76	28	7.51	0.99	41	35
F	0.08	12	6	60	96	10.9	7.0	0.5	35	25	7.55			
31	0.21	24	5	90	90	11.0	5.5	0.4	80	37	7.39	0.73	17	38
M	0.09	27	5	80	108	14.0	7.0	0.4	36	34	7.47			
35	0.21	17	6	80	105	13.5	8.2	0.4	78	25	7.53	1.06	42	30
F	0.08	16	4	80	110	14.2	8.6	0.3	34	23	7.61			
49	0.21	18	7	85	70	6.0	3.5	1.2	71	42	7.39	0.80	19	30
M	0.09	20	10	75	120	11.5	6.7	0.9	34	36	7.45			
57	0.21	10	5	68	84	6.3	3.7	0.8	73	38	7.43	0.76	24	34
M	0.09	20	5	70	90	9.5	5.5	0.5	34	29	7.49			
30	0.21	14	6	89	84	16.2	9.3	0.4	105	16	7.56	1.03	24	27
M	0.12	14	6	80	104	17.2	9.9	0.3	57	21	7.49			
Mean	0.21	15	6	84	92	10.0	5.6	0.6	79	32	7.45	1.85	28	36
±SD		5	2	15	13	3.1	1.8	0.3	10	7	0.06	0.13	9	10
Mean	0.10	17	7	76	103*	13.0*	7.3*	0.5	39*	28	7.51*			
±SD		5	3	11	10	2.6	1.8	0.2	8	4	0.06			

F_{IO_2} indicates the fractional concentration of oxygen in the inspired gas. Individual data, mean values and one standard deviations are given for mean pulmonary arterial pressures (PA), pulmonary arterial pressure minus pulmonary capillary "wedge" pressure (PA-PC), mean aortic pressure (AO), heart rate (HR), pulmonary flow ($\dot{Q}_{Pul}$), cardiac index (CI), pulmonary vascular resistance (PVR), arterial oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tensions, arterial pH (pH), respiratory quotient (RQ), alveolar-arterial oxygen tension (A-a_{O_2}) and hematocrit (Hct).

* Indicate mean values which differ ($P < 0.05$) from the control.

TABLE II

Effects of Hypoxia in Control Subjects

	F_{IO_2}	PA	Mean pressure PA-PC	AO	HR	$\dot{Q}_{Pul}$	CI	PVR	Pa_{O_2}	Pa_{CO_2}	pH	RQ	$A\text{-}a_{O_2}$	Hct
		mm Hg				*liters/ min*	*liters/ min·m²*	*"units"*	*mm Hg*	*mm Hg*			*mm Hg*	
Normals (4)														
Mean	0.21	15	6	104	80	6	3.2	1.0	86	38	7.37	0.80	12	43
±SD		1	2	28	8	1	0.4	0.3	4	8	0.04	0.04	8	4
Mean	0.10	24*	17*	108	87	8	4.6	2.1*	36*	32	7.48*			
±SD		3	4	13	16	2	1.1	0.5	4	8	0.05			
Hyperkinetic heart syndrome (3)														
Mean	0.21	12	6	97		10	5.4	0.6	106	33	7.42	0.97	4	43
±SD		5	1	16		2	1	0.1	9	8	0.10			5
Mean	0.09	21*	14*	96		11	6	1.3*	38*	30	7.48			
±SD		4	1	16		1	0.6	0.2	4	4	0.05			
Intracardiac LT-RT shunt (6)														
Mean	0.21	17	8	94	94	9‡	6.3	0.8‡	97	35	7.40	0.87	9	40
±SD		6	3	4	12	2	1.8	0.1	7	5	0.03	0.07	3	4
Mean	0.09	31*	23*	82*	111*	12‡	9.0	1.9*‡	38*	32	7.43			
±SD		9	8	9	16	4	3.5	0.8	4	4	0.04			
Renal failure														
Mean	0.21	18	6	124	93	7	4.1	1.0	95	36	7.36	0.8	5	27
±SD		10	1	13	35	1	0.6	0.4	14	4	0.06	0.17	10	2
Mean	0.09	26	13*	127	103*	9	6.0	1.4*	42*	32	7.48*			
±SD		11	5	20	16	2	1	0.4	5	6	0.06			

The abbreviations are given in Table I.

* Indicate mean values which differ ($P < 0.05$) from control.

‡ Two patients who had A-V O_2 differences less than one had calculated values of pulmonary flow greater than 25 liters/min, and are not included in flow and resistance columns.

RESULTS

Room air. The mean pulmonary arterial pressure and pressure gradient between pulmonary artery and pulmonary capillary wedge in patients with liver cirrhosis were within normal limits and did not differ from those found in the control groups. In the cirrhotic and control groups there was good agreement of left ventricular diastolic and pulmonary wedge pressures and only wedge pressures are presented. The large variation in pulmonary arterial pressure in patients with renal failure reflected various degrees of left ventricular failure. The pulmonary blood flows were abnormally high and the pulmonary vascular resistances were low in patients with liver cirrhosis, left to right shunts, and hyper-

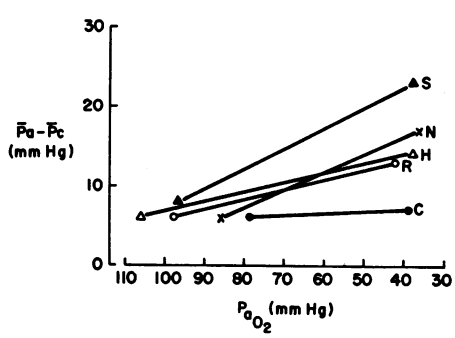

FIGURE 1 The effects of hypoxia on the pressure gradient between pulmonary artery and pulmonary capillary wedge (PA-PC). Patients with cirrhosis (C), normal subjects (N), hyperkinetic syndrome (H), intracardiac left to right shunts (S), and renal failure (R).

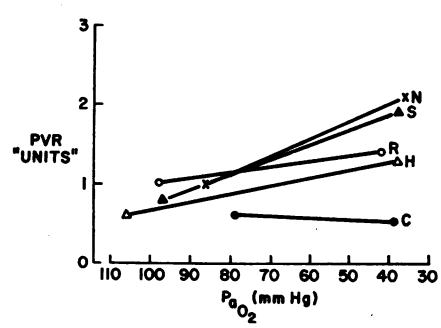

FIGURE 2 Effects of hypoxia on the pulmonary vascular resistance in patients with cirrhosis and control groups. Symbols used are the same as in Fig. 1.

kinetic heart syndromes. Although none of the cirrhotic patients was cyanotic, most had the previously described arterial hypoxemia and respiratory alkalosis and all had increased alveolar arterial oxygen tension gradients. The minute ventilation averaged 9.8±4.6 liters/min (BTPS) The calculated venous admixture was 24±5% which agreed with that reported by Massumi, Rios, and Ticktin (3).

Hypoxia. Inspiratory hypoxia decreased the mean arterial oxygen tensions to comparable values in all groups and increased the pulmonary blood flow approximately 2 liters/min in each of the groups studied. The mixed venous oxygen tension (30±4 mm Hg) in the cirrhotic group did not differ from those in the control groups. In the two patients in whom venous admixture could be calculated during hypoxia the percentage did not change. In these two patients the minute ventilation averaged 10.8 liters/min (BTPS). The pulmonary vascular pressure gradient across the lung (Fig. 1) and the pulmonary vascular resistance (Fig. 2) increased in each of the control groups but not in the patients with liver cirrhosis.

DISCUSSION

Failure of the patients with liver cirrhosis to respond to hypoxia apparently did not relate to the alkalosis, the anemia, the high output state, or the presence of chronic debilitating disease, since these conditions were present in one or more of the control groups. It was therefore concluded that failure of the response could conceivably be caused by (*a*) the presence of large pulmonary arterio-venous (A-V) [1] shunts or (*b*) the loss of the hypoxic vasoconstricting mechanism.

Barthelot, Walker, Sherlock, and Reid (15) recently examined the barium sulfate-injected lungs of 13 patients who died of liver cirrhosis. Detailed macroscopic as well as microscopic examination failed to demonstrate gross A-V shunts in the parenchyma of these lungs, although in one patient obvious A-V communications were found on the diaphragmatic surface of the lung. These investigators, however, did find dilatation of the pulmonary arteries and arterioles in all cases. These observations were supported by studies (unpublished) from our laboratory utilizing microradiography (16) and cleared whole lung sections from six additional patients who died of liver cirrhosis. The presence and extent of the microvascular dilatation in the lung may be related to both the severity and duration of the liver cirrhosis, since Barthelot et al. reported normal pulmonary vasculature in the lung of a patient who died with acute hepatic necrosis.

[1] *Abbreviations used in this paper:* A-a, alveolar-arterial; A-V, arterio-venous.

In the absence of gross A-V shunts, it may be presumed that the failure of the patients with liver cirrhosis to respond to hypoxia is due to an impairment or even absence of the hypoxic vasoconstricting mechanism A loss of this mechanism has not been reported previously. The cirrhotic patient may stand as a negative example of the teleological "purpose" for hypoxic vasoconstriction in the adult lung. Maintenance of a normal ventilation-perfusion relationship may depend on hypoxic vasoconstriction to sustain normal pulmonary vascular resistance and to regulate perfusion. Chronic impairment or loss of this mechanism may ultimately lead to a loss of the pulmonary arteriolar tone, consequent dilatation of the microvascular bed, and an inability of the lung to regulate perfusion. This abnormality could explain in patients with long standing cirrhosis, the low pulmonary vascular resistance, the increased A-a O_2 gradient, the arterial hypoxemia, and the dilatation of the pulmonary microcirculation.

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