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Research Article

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Regional Lung Function in Patients with Hepatic Cirrhosis

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ABSTRACT The lung volume at which the dependent lung zones begin to trap gas as a result of airway closure (i.e., the "closing volume") was measured with ^{133}Xe in 10 seated patients with hepatic cirrhosis. In all of them the closing volume was increased above normal, and in eight it was greater than the functional residual capacity, indicating the presence of airway closure and gas trapping during resting tidal volume breathing. Direct measurements made with ^{133}Xe in five cirrhotic patients (*a*) confirmed the presence of increased gas trapping in the lower lung zones both at residual volume and at functional residual capacity, and (*b*) indicated that in liver cirrhosis the ventilation-perfusion ratio of the dependent lung zones may be very low, primarily as a result of decreased ventilation due to airway closure. It is concluded that in hepatic cirrhosis, gas trapping in the dependent lung zones may be an important cause of impaired gas exchange within the lungs. It is suggested that the premature airway closure observed in this disease may be due to mechanical compression of small airways by dilated blood vessels and/or interstitial pulmonary edema.

INTRODUCTION

Arterial oxygen desaturation is often present in cirrhosis of the liver (1–13). This phenomenon was first attributed to decreased affinity of hemoglobin for oxygen (14), but the shift to the right of the oxyhemoglobin dissociation curve has been shown to be too small and/or infrequent to explain the observed degree of arterial oxygen desaturation (3, 8, 15). It is now generally agreed that the desaturation is caused chiefly by lowered arterial oxygen tension. The latter is not due to hypoventilation, as patients with hepatic cirrhosis are known to hyperventilate (3, 6, 8–10, 16). Increased venous admixture either through porto-pulmonary shunts (3, 8–10, 17–23) and intrapulmonary shunts (5, 24–26), or through spider nevi on pleural surfaces (11, 13) has been often quoted as the cause of lowered arterial oxygen tension in hepatic cirrhosis, but recent studies have shown that a ventilation/perfusion imbalance must contribute significantly to the arterial hypoxia (6, 16, 26–28). In the present investigation we have used radioactive xenon (^{133}Xe) in cirrhotic patients in an attempt to elucidate the nature of their ventilation/perfusion imbalance.

METHODS

All patients studied had the classical clinical and laboratory evidence of hepatic cirrhosis. Their physical characteristics, type of cirrhosis, smoking histories, and plasma proteins concentrations are listed in Table I. None of the patients had clinical evidence of cardiorespiratory disease, and none had ascites at the time of the study. The chest radiographs of some showed ill-defined lower zone nodularity of the type that has previously been described in hepatic cirrhosis (11). In most, plasma albumin concentration was reduced, its average value amounting to 2.8 g/100 ml of plasma.

Total lung capacity and its subdivision were measured using a body plethysmograph, and their predicted normal values were obtained according to Bates and Christie (29). Predicted values for 1 sec forced expiratory volumes were computed according to Gaensler and Wright (30). Carbon monoxide diffusing capacity of the lungs was measured by the single breath method (31). The alveolar-arterial O_2 differences were computed using the "ideal" alveolar air equation (32). Measurements of A-aDO_2 were done both during room air and 100% oxygen breathing. At least 30 min of O_2 breathing was required before samples were

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TABLE I

Physical Characteristics, Type of Cirrhosis, Smoking History, X-Ray Findings, and Plasma Protein Concentrations of Patients

Subject	Sex	Age	Weight	Height	Type of cirrhosis*	Cigarettes per day	Years of smoking	Chest X-ray nodularity	Albumin	Globulins
		yr	*kg*	*cm*					*g/100 ml of plasma*	
K. T.	F	11	30	141	ACH	0	0	+	2.4	3.8
R. G.	M	18	54	169	CRYPT	0	0	—	2.0	7.5
L. M.	F	29	78	172	ACH	7‡	7	+	3.0	3.8
D. T.	M	31	76	183	ALC	0	0	+	3.3	4.0
C. P.	F	37	65	164	ACH	10‡	10	+	2.6	3.9
G. P.	M	24	82	186	ACH	0	0	—	3.9	3.2
M. S.	M	40	69	174	ALC	10	30	—	1.7	4.3
H. M.	M	43	63	171	ACH	10	25	—	1.7	8.3
T. M.	M	45	62	173	CRYPT	20‡	30	—	3.2	3.1
M. W.	F	60	60	168	ALC	5	30	—	4.1	1.9
P. R.	M	61	67	158	CRYPT	10	40	—	2.7	4.1

*ACH, active chronic hepatitis; ALC, alcoholic cirrhosis; CRYPT, cryptogenic.
‡During last 2 yr smoking reduced to occasional cigarette.

taken. The arterial-alveolar N_2 differences were measured by gas chromotography according to Farhi, Edwards, and Homma (33). In our laboratory, the normal upper limit for a-AD_{N_2} is 10 mm Hg. The percentage shunt during O_2 breathing was computed according to Beggren (34).

The equipment used in the ^{133}Xe regional lung function studies has been previously described in detail (35). In five patients the regional subdivisions of lung volume as well as the regional distribution of resting ventilation and pulmonary blood flow were measured, while the closing volume was measured in 10 subjects. All measurements were made in the sitting position.

Regional subdivisions of lung volume were measured by the method of Sutherland, Katsura, and Milic-Emili (36). Regional distribution of ventilation was studied by modification of the method of Sutherland et al. (36). Briefly, starting from functional residual capacity, the subject inhaled a small breath of air labeled with ^{133}Xe. Inspiration of the labeled gas was made at normal (resting) flow rates. After inspiration of the labeled gas, the subject was rapidly switched to a spirometer containing room air and continued to inspire until full inspiration was achieved. Breath was held at full inspiration until count rates were recorded over the chest. Regional count rates were then converted into regional ^{133}Xe concentrations using the equilibration procedure described by Ball, Stewart, Newsham, and Bates (37). To facilitate comparison, regional ^{133}Xe concentrations were expressed as a percentage of the concentration expected had the inspired ^{133}Xe been distributed uniformly throughout the lungs. Expressed in this way, our data of regional ventilation are an index of the regional ventilation distribution "per alveolus" (36).

The regional distribution of perfusion was determined by rapidly injecting 1–2 mCi of ^{133}Xe dissolved in 5 ml saline through a polyethylene catheter inserted into an antecubital vein. The injections were made at functional residual capacity (FRC), while the subject, with glottis open, held his breath (about 15 sec). This was followed by a maximal inspiration of room air, the subject holding his breath at total lung capacity (TLC) until regional count rates were recorded. The results are expressed as distribution of perfusion per alveolus, as described by Anthonisen and Milic-Emili (38).

The closing volume, i.e. the lung volume at which the dependent airways begin to close, was measured on 10 patients with the ^{133}Xe bolus technique described by Dollfuss, Milic-Emili, and Bates (39). Briefly, this method consists of having the subject expire maximally, and at full expiration (RV), while the subject is holding his breath, a 1–2 ml bolus of air containing 1–2 mCi of ^{133}Xe is injected into the mouthpiece. He then makes a slow vital capacity (VC) inspiration from a spirometer containing room air. After this, he makes a slow VC expiration over a period of 10–15 sec while the ^{133}Xe concentration in expired gas and the volume expired are continuously measured and recorded on an X-Y recorder (model 2D-2AM; Hewlett-Packard Co., Moseley Div., Pasadena, Calif.). Expired ^{133}Xe concentration is measured with a scintillation counter placed on the mouthpiece. The output of the counter is fed to a rate meter, and from here to the Y-axis of the X-Y recorder, the X-axis of which is driven by a potentiometer attached to the spirometer.

Fig. 1 shows a sample recording from a seated patient. Four phases are shown (39): dead space gas (I), mixed alveolar and dead space gas (II), "alveolar plateau" (III), and a terminal and abrupt change in the slope of the alveolar plateau (IV). This terminal change in concentration of the alveolar plateau (phase IV) has been attributed to closure of airways, starting in the most dependent parts of the lungs and moving progressively upward as residual volume is approached. It is known that after ^{133}Xe bolus inspiration at residual volume the intrapulmonary ^{133}Xe concentration is greatest near the lung top (39). Thus, when the dependent airways begin to close, the expired ^{133}Xe concentration must necessarily increase because of greater contribution to the expirate from the upper lung regions (whose ^{133}Xe concentration is highest). Consequently, the junction between phases III and IV is taken as representing the lung volume at which the dependent airways start to close, i.e., the closing volume.

TABLE II

Results of Pulmonary Function Tests of Cirrhotic Patients

Subject	TLC	VC	RV	FRC	FEV_1	D_{LCO}	Closing volume
			liters			*ml/min per mmHg*	*% TLC*
K. T.	2.93	2.15	0.78	1.26	1.85	11.5	47.1
	(2.78)	(2.28)	(0.50)	(1.19)	(2.00)	(20.0)	(30.0)
R. G.	5.22	4.00	1.22	2.58	3.20	11.8	50.0
	(6.49)	(4.97)	(1.52)	(3.43)	(3.90)	(33.0)	(34.0)
L. M.	6.59	4.42	2.17	3.64	3.05	14.2	66.5
	(5.81)	(4.07)	(1.74)	(3.22)	(3.70)	(29.5)	(39.5)
D. T.	6.06	4.35	1.71	3.66	4.20	10.6	—
	(7.65)	(5.51)	(2.14)	(4.15)	(4.05)	(36.0)	
C. P.	5.02	3.72	1.30	2.50	3.00	3.7	57.9
	(4.60)	(3.30)	(1.30)	(2.67)	(3.20)	(26.0)	(43.3)
G. P.	11.09	7.03	4.06	6.83	4.90	29.5	47.7
	(7.96)	(5.84)	(2.12)	(4.30)	(4.30)	(39.0)	(36.7)
M. S.	7.02	5.00	2.02	3.40	3.70	19.5	55.5
	(6.60)	(4.61)	(1.99)	(3.69)	(3.50)	(31.0)	(45.0)
H. M.	5.78	4.13	1.65	3.18	3.55	23.5	52.8
	(6.32)	(4.38)	(1.94)	(3.51)	(3.30)	(29.0)	(46.3)
T. M.	6.04	3.78	2.26	3.02	3.10	9.6	58.9
	(6.48)	(4.45)	(2.03)	(3.69)	(3.30)	(30.0)	(47.5)
M. W.	4.75	3.35	1.40	2.15	2.60	11.4	58.7
	(5.15)	(3.30)	(1.85)	(3.04)	(2.70)	(25.0)	(55.0)
P. R.	5.37	3.40	1.97	2.69	2.50	26.0	59.6
	(4.64)	(2.93)	(1.71)	(2.88)	(2.35)	(22.0)	(55.5)

TLC, total lung capacity; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; FEV_1, 1 sec forced expiratory volume; D_{LCO}, CO-diffusing capacity of the lungs measured by the single breath method (31). The predicted normal values are in parentheses beneath the measured values. Predictions for subdivisions of lung volume were obtained according to Bates and Christie (29); for FEV_1 according to Gaensler and Wright (30); for D_{LCO} according to Ogilvie, Forster, Blakemore, and Morton (31); for closing volume according to Lablanc, Ruff, and Milic-Emili (40).

RESULTS

As shown in Table II, the subdivisions of lung volume and FEV_1 were essentially within normal limits, except for subject G. P. in whom all volumes were much greater than the predicted values. The diffusing capacity for carbon monoxide was below predicted normal values in most patients, particularly in subject C.P.

The arterial oxygen tension during room air breathing was less than 80 mm Hg in all patients, except for subjects G. P. and H. M. (Table III). These two subjects also had a normal $A\text{-}aD_{O_2}$ and $a\text{-}AD_{N_2}$, whereas these values were increased above the normal limits in the other subjects. The alveolar-arterial oxygen difference during 100% O_2 breathing and the corresponding calculated percentage shunt (% $\dot{Q}s/\dot{Q}t$) were markedly increased in only three of the patients (K.T., L.M., and D.T.). Except in subjects G.P. and M.S., the arterial CO_2 tension was reduced below the normal values.

Fig. 2 illustrates the regional distribution of gas at full expiration (residual volume) in four patients together with results obtained by Sutherland et al. (36) on eight seated normal young subjects. Regional lung volumes at full expiration (i.e. regional residual volumes) are expressed as a percentage fraction of the corresponding regional total lung capacities (% TLC_r), i.e., of the regional volumes at full inspiration. It can be seen that in all four cirrhotic patients the regional residual volume increased markedly towards the lung bases, contrary to the results in normal subjects. Indeed, in three patients (Fig. 2) the regional residual volumes in the most dependent lung zones exceeded 50% of the volume of these regions at full inspiration, indicating marked gas trapping in the dependent lung zones, presumably caused by premature closure of small airways.

Fig. 3, which illustrates the regional distribution of gas at functional residual capacity, indicates that in the four patients with hepatic cirrhosis gas trapping in dependent lung zones was also present at the end of a

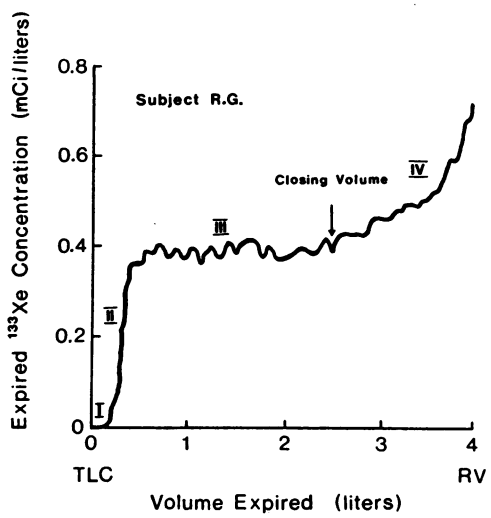

FIGURE 1 Relationship between ^{133}Xe concentration in expired air and expired volume after an inspiratory VC maneuver during which a bolus of ^{133}Xe was inhaled at RV. Arrow indicates closing volume. In patient R. G., aged 18 yr, the closing volume amounted to about 35% of the vital capacity. In normal subjects of comparable age, the closing volume is less than 10% of the vital capacity (40).

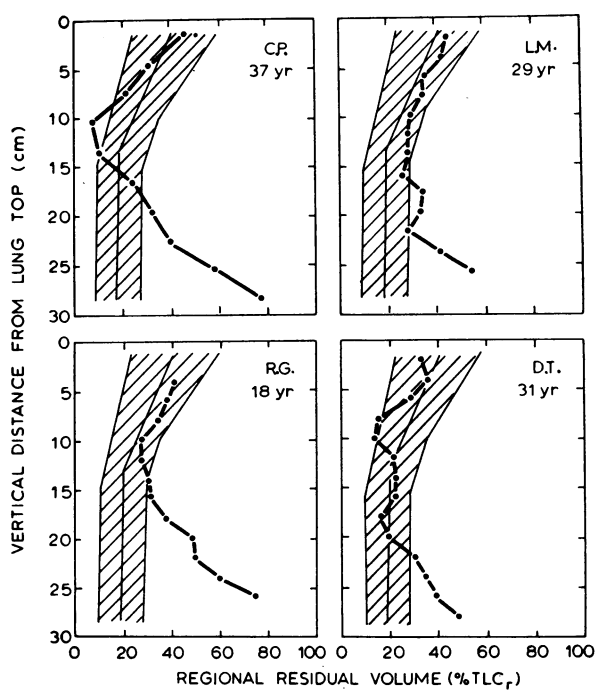

FIGURE 2 Regional distribution of gas at full expiration (residual volume) in four cirrhotic patients. Average results ±2 SD (hatched areas) on eight normal seated subjects of comparable age are also shown. Regional residual volumes are expressed as a percentage fraction of the volume of each region at full inspiration, i.e., as a percentage of the corresponding regional total lung capacity (% TLC_r). Note the marked increase in regional residual volume towards the lung bases in all four cirrhotic patients.

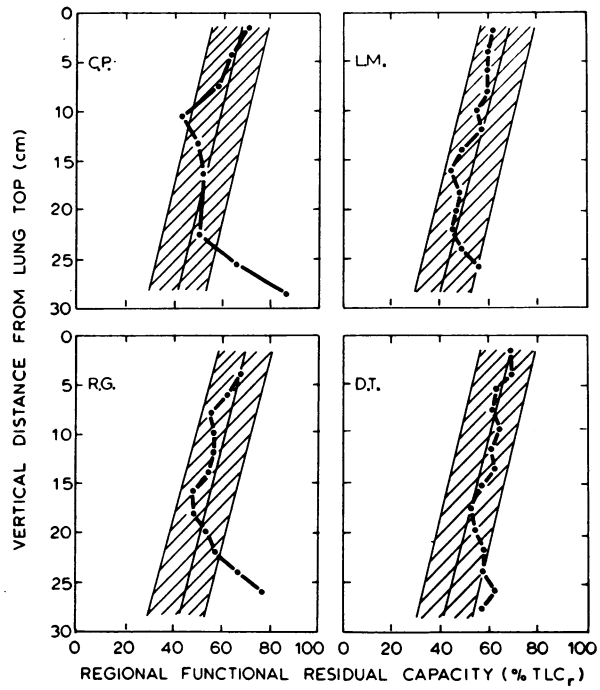

FIGURE 3 Regional distribution of gas at functional residual capacity in same four patients of Fig. 2. Average results ±2 SD (hatched areas) on eight normal young seated subjects are also shown. Note the increase in regional FRC towards the lung bases in all four cirrhotic patients.

normal expiration. Indeed, in all four subjects the regional functional residual capacity increased towards the lung bases, while in normal subjects it decreases progressively from lung top to bottom (36).

TABLE III

Blood Gas Data of Cirrhotic Patients

Subject	$Paco_2$	Pao_2	A-aDo_2 (air)	a-AD_{N_2}	A-aDo_2 (oxygen)	$\dot{Q}_s/\dot{Q}_T$ (oxygen)
			mm Hg			%
K. T.	24	46	76	11	590	35.0
R. G.	31	75	35	14	40	3.5
L. M.	31	65	50	19	150	13.9
D. T.	31	41	—	—	—	40.0
C. P.	21	54	71	12	—	6.0
G. P.	39	95	10	6	—	—
M. S.	38	71	31	17	15	0.9
H. M.	32	85	25	—	40	3.0
T. M.	36	65	45	10	65	6.7
M. W.	32	69	42	17	70	6.9
P. R.	31	78	39	—	21	1.9

The alveolar-arterial O_2 differences were computed using the ideal alveolar air equation (32); the arterial-alveolar N_2 differences were measured according to Farhi et al. (33); the percentage shunt (% $\dot{Q}_s/\dot{Q}_T$) was computed according to Berggren (34).

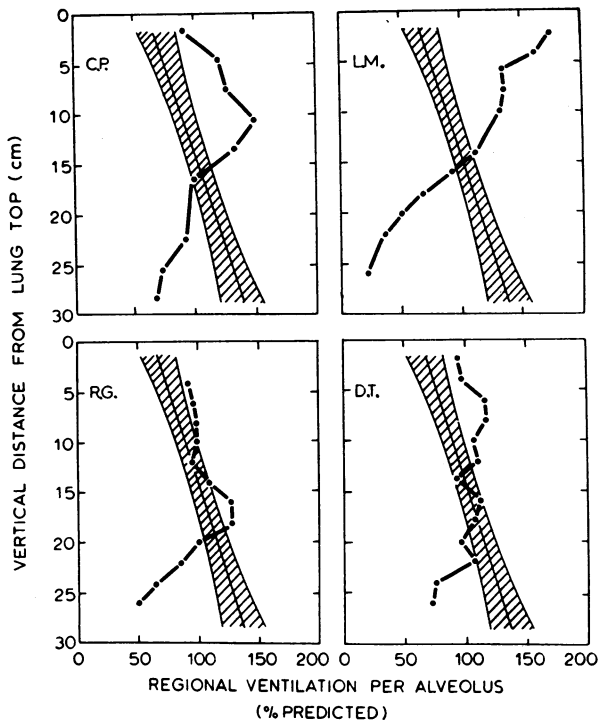

FIGURE 4 Regional distribution of ventilation during tidal breathing in four subjects of Figs. 2 and 3. Regional ventilation is expressed as a percentage of the ventilation per alveolus predicted had the inspired tidal volume been distributed uniformly to all alveoli of the lungs. Average results ±2 SD (hatched areas) on eight normal seated young subjects are also shown. Note that in normal subjects ventilation per alveolus increases progressively from lung top to bottom, while in all patients it is decreased at the lung bases.

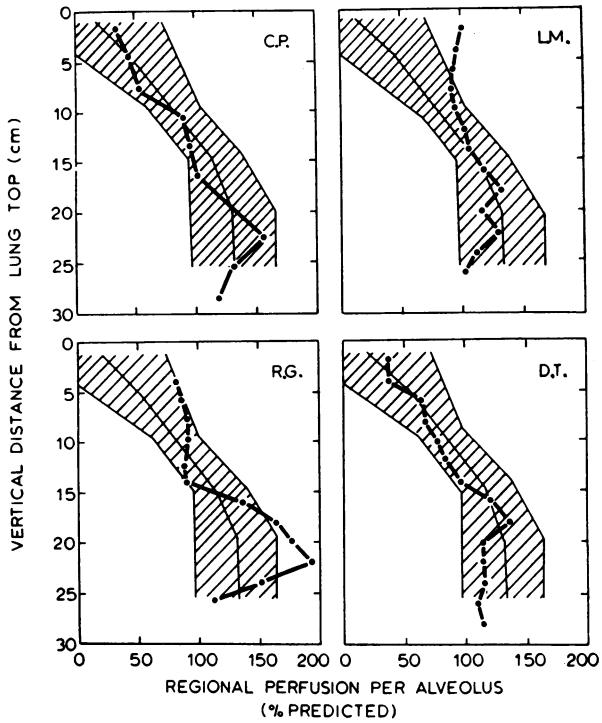

FIGURE 5 Regional distribution of resting pulmonary blood flow. Regional perfusion is expressed as a percentage fraction of the perfusion per alveolus predicted if all alveoli had received a uniform blood flow. Average results ±2 SD (hatched areas) on eight normal young seated subjects are also shown.

The presence of gas trapping at the end of a normal expiration (FRC) implies that the distribution of resting ventilation must also be altered. That this is the case is indicated in Fig. 4, which illustrates the regional distribution of the small tidal breaths of ^{133}Xe taken from functional residual capacity. As shown in this figure, in all four patients ventilation distribution to the dependent lung zones was grossly reduced.

The distribution of pulmonary blood flow in the four cirrhotic patients is shown in Fig. 5. It can be seen that three of the patients (C.P., L.M., R.G.) had a small zone of reduced blood flow at the lung bases, and two (L.M. and R.G.) had increased blood flow to the apical lung regions. These abnormalities of perfusion distribution were, however, considerably less pronounced than the abnormalities of ventilation distribution (Fig. 4).

Measurements such as are shown in Figs. 2–5 were also made on the subject K.T., whose age was 11 yr. Her results are summarized in Fig. 6. It can be seen that the regional distribution patterns are essentially the same as in the older patients.

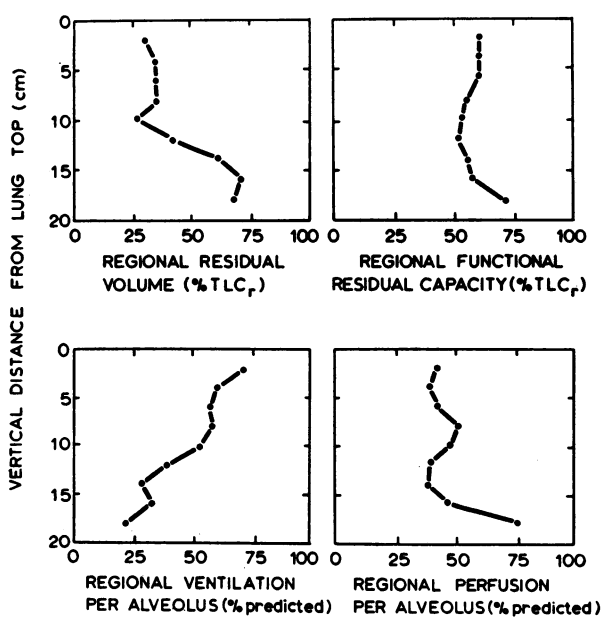

FIGURE 6 Regional lung function data on patient K. T., aged 11 yr. Her vertical lung height was about 20 cm. Ordinates and abscissae as in Figs. 2–5.

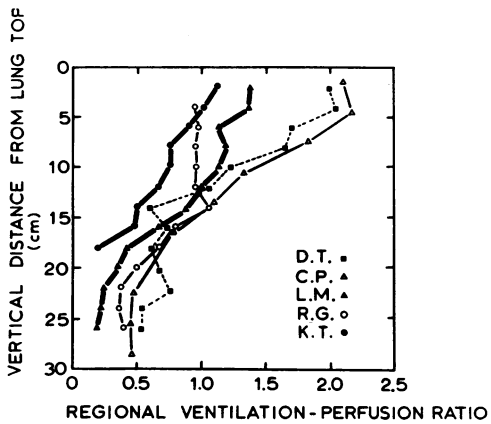

FIGURE 7 Regional distribution of ventilation-perfusion ratios computed from data in Figs. 4–6, taking into account the over-all ventilation-perfusion ratio which was measured separately on each subject. Note that in the dependent lung zones the ventilation-perfusion ratio was less than 0.5 in four out of five patients, indicating gross underventilation.

In all five patients whose results are shown in Figs. 2–6, the reduction in lower lung zones perfusion (if present) was less marked than the reduction in ventilation, leading to a decreased ventilation-perfusion ratio in the lower third of the lung. Indeed, the ventilation-perfusion ratio in the dependent lung zones was in general lower than 0.5 (Fig. 7).

The radioactive xenon studies described are rather timeconsuming and involve complex and expensive equipment. Furthermore, because of radiation exposure the measurements cannot be repeated at frequent intervals. Recently, however, a new technique that has

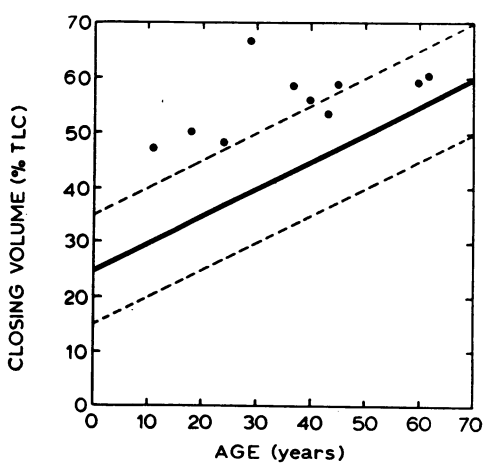

FIGURE 8 Relationship between closing volume and age in 10 seated patients with hepatic cirrhosis (solid circles). Average relationship ±2 SD between closing volume and age on 80 normal seated subjects is also shown. Closing volume is expressed as a percentage fraction of the total lung capacity.

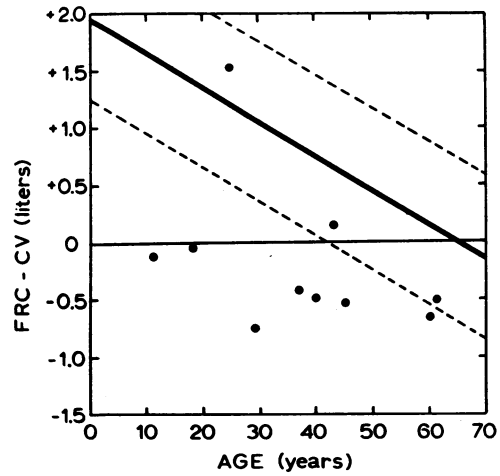

FIGURE 9 Difference between FRC and closing volume (CV), in liters, as a function of age in 10 cirrhotic patients (solid circles). Average relationship ±2 SD on 80 normal seated subjects is also shown. Note that in 8 out of the 10 patients, the closing volume exceeded the FRC, indicating the presence of airway closure in the resting tidal volume range.

none of these disadvantages has been developed to detect increased gas trapping in the lungs. This is the ^{133}Xe bolus technique (39, 40), by which measurement may be made of the closing volume, i.e., the lung volume at which the lungs begin to trap gas. Using this technique we have measured the closing volume in 10 of our patients. The results are shown in Fig. 8, where closing volume, expressed as the percentage fraction of the total lung capacity, is plotted against age. The average relationship ±2 SD of closing volume with age for normal seated subjects is also shown (40). It can be seen that in all cirrhotic patients there was a considerable increase in closing volume, reflecting increased gas trapping in the lungs.

In most patients the closing volume was greater than the functional residual capacity. This is shown in Fig. 9, where the difference between FRC and closing volume, expressed in liters, is plotted against age. The average relationship ±2 SD for normal seated subjects is also shown (40). In normal seated subjects, the critical age at which the closing volume begins to exceed FRC averaged about 65 yr. Although all cirrhotic patients were younger than this, in 8 out of 10 the closing volume exceeded the FRC. This implies that in most of our cirrhotic patients some of the dependent lung units were closed either throughout or during part of the resting breathing cycle; hence ventilation distribution to the lower lung zones was decreased (40, 41). In this connection it should be noted that in order for all closed airways to reopen the lung volume must exceed the closing volume by about 5% TLC

(41). A direct confirmation of lower zones hypoventilation is provided by results such as are shown in Figs. 4 and 6.

DISCUSSION

In normal seated subjects, the ventilation to the apical alveoli is roughly half that of the dependent alveoli (36). This distribution pattern is determined almost entirely by the gravity-dependent pleural pressure gradient down the lungs acting in combination with the nonlinear volume elasticity of the lungs (36). In the patients with liver cirrhosis, the distribution of a breath taken from resting lung volume (FRC) was not preferential to the lower lung zones, but there was a marked reduction in lower zones ventilation. This was associated in some patients with a somewhat reduced lower zones perfusion. Compression of lung tissue by ascitic fluid cannot be invoked to explain these abnormalities since all of our patients were free of ascites. Neither can they be ascribed to underlying chronic bronchitis or emphysema as our patients had no clinical, radiological or spirometric (Table II) evidence of chronic lung disease, although some of them were or had been smokers (Table I). In this connection it should be noted that the abnormalities or regional lung function in cirrhotics who smoked were similar to those in the patients who did not smoke. For example, patients R. G. and D. T. in Figs. 2–5 are nonsmokers, whereas the other two patients whose results are shown in the same illustrations have been moderate smokers for several years.

The reduced ventilation to the basilar lung zones in our cirrhotic patients is probably caused by airway narrowing or closure in the dependent lung zones. Indeed, in most patients studied the closing volume was considerably increased (Fig. 8), and in 8 out of 10 patients the closing volume exceeded the functional residual capacity (Fig. 9), indicating that in these 8 patients some of the dependent airways must have been closed during resting breathing. An increase in closing volume can be caused by an increase in the magnitude of the pleural pressure gradient down the lungs, by loss of the elastic recoil of the lungs, particularly if it occurs in the dependent lung zones, and/or by decreased resistance to collapse of the dependent small airways (41). The latter can be caused by several factors, such as: (*a*) loss of surfactant in the small airways, (*b*) changes in bronchomotor tone, (*c*) mechanical compression of small airways from distended vessels, and (*d*) interstitial pulmonary edema (41, 42). Although at present it is impossible to make any definite conclusions concerning which factors change in hepatic cirrhosis, for reasons discussed below, we favor mechanisms (*c*) and (*d*).

Since some of the pulmonary bronchial veins drain into the azygos vein, the azygos hypertension in hepatic cirrhosis (43) may well be associated with distension of bronchial vessels, leading to mechanical compression of the airways. The dilatation of the precapillary vessels in the lung, which has been observed at necropsy by Berthelot, Walker, Sherlock, and Reid (11) in patients with hepatic cirrhosis, may also lead to a similar effect. In this connection it should be noted that in dogs raising left atrial pressure results in increased small (peripheral) airway resistance, even in the absence of evident interstitial edema (44). This phenomenon may well be explained by competition for space between airways and dilated blood vessels.

The present findings on cirrhotics also appear to be consistent with the development of peribronchial and perivascular edema in the lower lung regions causing regionally increased vascular and/or airway resistance. Reduced dependent lung zones ventilation (44) and perfusion (44, 45) distribution has been observed previously in patients with mitral stenosis, and it has been suggested that interstitial edema is the initial cause of reduction of blood flow in the dependent lung zones (46). Furthermore, recent work on dogs (44) has shown that in lungs with acute interstitial edema the small airways in the dependent lung zones are compressed. However, while in mitral stenosis the increased interstitial fluid is caused chiefly by increased pulmonary vascular pressures, other mechanisms must be involved in liver cirrhosis, since the pulmonary vascular pressures are, in general, either normal or only slightly increased (10, 47).

In theory, interstitial edema in hepatic cirrhosis can be caused by the combined effects of several mechanisms.

(*a*) *Decreased colloidal osmotic pressure.* The plasma albumin concentration, which is the main determinant of the colloidal osmotic pressure, is almost invariably decreased in hepatic cirrhosis (1, 48). In our patients, the average plasma albumin concentration amounts to 2.8 g/100 ml. No close correlation was found however, between plasma albumin concentration and the degree of lung function abnormality. This apparent discrepancy can probably be explained by the fact that several other mechanisms contribute to the development of pulmonary edema in hepatic cirrhosis, and the effect of these mechanisms may vary from one patient to another.

(*b*) *Increased capillary permeability.* Increased capillary permeability in hepatic cirrhosis has been documented by Cachera and Darnis (49).

(*c*) *Hormonal influence.* Various hormones may be responsible for water retention in hepatic cirrhosis (43, 50).

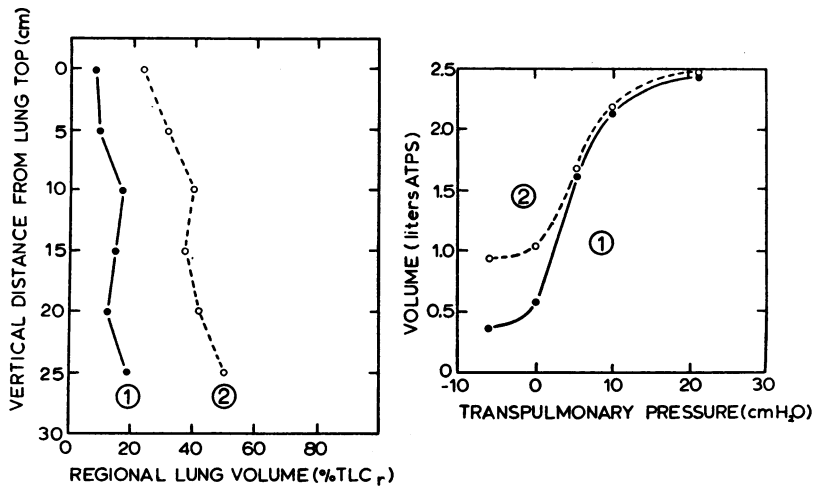

FIGURE 10 *Right:* Static deflation volume-pressure relationships of an isolated perfused dog lung before (*1*) and after (*2*) the development of interstitial pulmonary edema. Note the great increase of the trapped gas volume (i.e. the volume of gas remaining in the lungs at a transpulmonary pressure of −6 cm H_2O) after edema. *Left:* Regional distribution of trapped gas before (*1*) and after (*2*) the development of edema. Regional trapped gas volume is expressed as a percentage fraction of the volume of each region at full inflation, i.e., of the volume at a transpulmonary pressure of +22 cm H_2O (% TLC_r). Note that after edema the trapped gas volume in the dependent lung zones exceeds 50% of the volume of the same regions at full inflation. After Hughes and Rosenzweig (42).

(*d*) *Renal effects.* Modifications of renal blood flow in hepatic cirrhosis could lead to an increase in the tubular reabsorption of sodium.

(*e*) *Porto-mediastinal-pulmonary shunts.* These relatively high pressure channels may provide an additional route for increased fluid movement into the interstitial space of the lungs. In the normal lung there is probably a continuous net movement of fluid from the bronchial capillaries (part of the systemic circulation) into the interstitial pulmonary space. Since some of the pulmonary bronchial veins drain into the azygos vein, the azygos hypertension in hepatic cirrhosis (43) may well be associated with increased filtration of liquid into the interstitial space of the lungs

(*f*) *Decreased pulmonary lymph drainage.* The lymphatic flow through the thoracic duct can be greatly increased in hepatic cirrhosis, and the duct may be dilated (50, 51). As a result, lymphatic drainage from the lungs may be impaired.

Clearly, in hepatic cirrhosis there are several systemic (*a–d*) and local (*e, f*) mechanisms which, potentially, may produce pulmonary edema. Furthermore, since accumulation of fluid around the conducting airways and blood vessels of the dependent lung regions is probably the earliest phase of pulmonary edema (52), an increase in lower zones airway and vascular resistance, such as evidenced in the present study, would be expected to be one of its first consequences. In this connection, it should be noted that pulmonary edema is commonly found postmortem in lungs of cirrhotic patients (53). Thus, the regional ventilation and perfusion abnormalities of our cirrhotic patients may be, at least in part, the consequence of interstitial edema in the dependent lung zones. Further evidence supporting this hypothesis is provided below.

Recently, Hughes and Rosenzweig (42) showed that interstitial pulmonary edema results in an increase in trapped gas volume, particularly in the dependent lung zones. Since knowledge of their study appears to be helpful for explaining the present results, we will review it in some detail. Using an isolated perfused dog lung preparation, with the lung suspended vertically, Hughes and Rosenzweig measured the static deflation volume-pressure relationship of the lung both under control conditions and after the development of interstitial lung edema. Edema was evidenced by increased lung weight and the presence of peribronchial and perivascular cuffs on histological examination. An example of their results is shown in Fig. 10 (*right*), where it can be seen that in the edematous lung there was a marked increase in trapped gas volume, i.e., the volume of gas left in the lungs at a negative (− 6 cm H_2O) transpulmonary pressure was increased. This marked increase in trapped gas volume is due to the fact that

in the edematous lungs small airways close at higher lung volumes than under control conditions (42). Since fluid accumulation in the perivascular and peribronchial spaces of the dependent lung zones is probably the earliest phase of pulmonary edema (52), the trapped gas volume should be greatest in the dependent lung regions. Hughes and Rosenzweig also measured the regional distribution of the trapped gas volume, using radioactive xenon, and found that in the lower regions of the lungs with interstitial edema the trapped gas volume did, indeed, often exceed 50% of the maximum volume (Fig. 10, *left*). Clearly, the striking similarity between our measurements of the regional distribution of residual volume (Figs. 2 and 6) and the data in Fig. 10 (*left*) suggest that increased gas trapping in dependent lung zones of cirrhotic patients may well be caused, at least in part, by peribronchial edema. The fact that the closing volume was increased in all cirrhotic patients (Fig. 8) also supports this view because, as pointed out above, in edematous lungs airway closure occurs at higher lung volumes than in normal lungs (Fig. 10, *right*).

Whatever the mechanisms causing the distribution abnormalities in hepatic cirrhosis, our results indicate that in this disease there may be a marked ventilation-perfusion impairment on a regional basis. Indeed, as shown in Fig. 7, in our patients the ventilation-perfusion ratio in the dependent lung zones was in general very low. Here it should be noted that, particularly in the lower lung zones, the $\dot{V}/\dot{Q}$ data in Fig. 7 are an underestimate of the impairment in gas exchange because our measurements of regional $\dot{V}/\dot{Q}$ fail to detect differences that may exist within each region. Since the lower lung zones (lower counting fields) in cirrhotic patients presumably contain both open and trapped units during quiet breathing, the $\dot{V}/\dot{Q}$ abnormality (and hence the impairment of gas exchange) must be much greater than the present techniques have revealed. In other words, some airways in the lower lung zones may attain the opening pressure at the beginning of inspiration, while others may only open towards the end of inspiration, i.e., when pleural pressures are most negative (41). Similarly, some airways may reach the closing pressure at the beginning of expiration while others will close only towards the end of expiration, i.e., when pleural pressures are most positive. In addition, some units may remain closed throughout the breathing cycle. Therefore, it is most likely that the lower lung zones contain units of different ventilation-perfusion ratios caused by uneven ventilation, which are hidden within the counting field and are not accessible to external counting. This spread of $\dot{V}/\dot{Q}$ ratios within the lower lung zones must necessarily lead to greater impairment of regional gas exchange than that revealed by the technique of external counting used in the present study. Thus, our results indicate that in hepatic cirrhosis there are low $\dot{V}/\dot{Q}$ areas in the dependent lung zones which must contribute substantially to decreased arterial oxygen tension and increased alveolar-arterial oxygen tension differences. In the only two patients (G. P. and H. M.) in whom the FRC was greater than the closing volume and who presumably had normal ventilation distribution, the arterial O_2 tension was within normal limits (Table III). In all other patients in whom there was evidence of airway closure in the resting tidal volume range, the arterial O_2 tension was substantially reduced. The reduction in arterial P_{O_2} and the increase of A-aD_{O_2} (air) was associated with an increase in a-AD_{N_2}, another parameter confirming the presence of low $\dot{V}/\dot{Q}$ areas in the lungs of cirrhotic patients (Table III). In seven of our patients the shunt ($\dot{Q}_s/\dot{Q}_T$) measured during 100% O_2 breathing was either within normal limits or only slightly increased (Table III). This slightly increased shunt may reflect the presence of lung units whose airways remained closed throughout the breathing cycle. In three patients (K. T., L. M., and D. T.), on the contrary, the shunt was markedly increased and was probably due not only to airway closure, but also to substantial contributions from porto-pulmonary and intrapulmonary shunts.

In some of our patients particularly in subject C. P., we also found a reduction in the diffusing capacity of the lungs (Table II), which may have contributed to arterial hypoxia. This probably cannot be ascribed to fibrosing alveolitis (54), as our patients had no evidence of restrictive lung disease. Some reduction of $D_{L_{CO}}$ may be related to alveolar wall edema causing an increased diffusion pathway by thickening the alveolar-capillary membrane (52, 55). Alternatively, the low values of $D_{L_{CO}}$ could reflect some pattern of pulmonary inhomogeneity.

In most of our patients the arterial CO_2 tension was reduced (Table III). This is in line with previous observations that chronic hyperventilation is a common feature in hepatic cirrhosis.

In conclusion, our results indicate that patients with hepatic cirrhosis can have maldistribution of pulmonary blood flow and, in particular, of ventilation which may cause considerable impairment of gas exchange within the lungs. The marked abnormalities of distribution of gas within the lungs of cirrhotic patients are compatible with the hypothesis that the maldistribution is caused by dilatation of blood vessels within the lungs and/or the interstitial pulmonary edema. Indeed, the gas distribution abnormalities are exactly what one expects them to be on the basis of the studies of Hughes

and Rosenzweig (42). If interstitial edema plays a major role in causing the regional distribution abnormalities in hepatic cirrhosis, one would expect to find similar distribution abnormalities in other pathological conditions associated with interstitial pulmonary edema. Indeed, regional distribution patterns similar to those obtained in our cirrhotic patients have been recently observed on patients in acute left heart failure.[1] It should be noted, however, that in the cirrhotic patients of the present study we had no direct evidence of interstitial pulmonary edema, and hence our tentative explanation of the results must necessarily remain speculative.

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[1] Zidulka, A., N. R. Anthonisen, and J. Milic-Emili. Unpublished observations.

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