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Ventilation-perfusion inequality in patients with non-alcoholic liver cirrhosis

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Ventilation-perfusion inequality in patients with non-alcoholic liver cirrhosis. G. Hedenstierna, C. Söderman, L.S. Eriksson, J. Wahren.
ABSTRACT: Ventilation-perfusion relationships were studied in patients with non-alcoholic liver cirrhosis. Spirometry was essentially normal but the transfer factor of the lung (D_{LCO}) was reduced by on average 34% of predicted. Arterial oxygen tension (Pa_{O_2}) ranged from normal down to 6.9 kPa. Varying degrees of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) abnormalities (multiple inert gas elimination technique) were observed with increased dispersion of the perfusion distribution (log sd_Q, 0.90; range 0.32–1.71; upper normal limit, 0.60) and the presence of both regions of low $\dot{V}_A/\dot{Q}$ ratios (between 0.1 and 0.005) (mean 4.1%; range 0–18.8%) and shunt ($\dot{V}_A/\dot{Q}$ ratios below 0.005) (mean 3.9%; range 0–19.8%). There was a close similarity between measured and calculated Pa_{O_2} in normoxaemic patients, but calculated values exceeded measured Pa_{O_2} in hypoxaemic patients. The difference between calculated and measured Pa_{O_2} correlated inversely to D_{LCO} ($r=0.65$, $p<0.05$). An inverse correlation was also noted between D_{LCO} and the sum of shunt and low $\dot{V}_A/\dot{Q}$ regions ($r=0.87$, $p<0.001$). It is concluded that hypoxaemia in non-alcoholic liver cirrhosis patients can be accounted for by intrapulmonary shunting and $\dot{V}_A/\dot{Q}$ mismatch, and possibly a "diffusion-perfusion" defect in patients with more severe gas exchange impairment.
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Chronic liver disease with cirrhosis is frequently accompanied by impaired arterial oxygenation and sometimes hypoxaemia [1]. Using multiple inert gas elimination technique [2] several recent studies have demonstrated a ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch in severely liver-diseased patients, mainly with alcoholic cirrhosis, and with varying smoking habits [3–7]. In three of these studies, the $\dot{V}_A/\dot{Q}$ mismatch could to full extent explain the impaired arterial oxygenation [3–5]. However, additional factors such as diffusion limitation and extrapulmonary shunting were discussed in the two other papers on patients with more severe gas exchange impairment and considerable hypoxaemia [6, 7].

In patients with non-alcoholic cirrhosis impairment of arterial oxygenation has become an important issue, since severe hypoxaemia is a contraindication to liver transplantation [8]. To what extent intrapulmonary $\dot{V}_A/\dot{Q}$ mismatch, with or without other associated gas exchange disturbances, may explain the hypoxaemia in this group of patients has not been fully established. Better understanding of the causes of hypoxaemia may improve the perioperative care of the liver transplanted patient, and possibly widen the indications for such surgery.

In the present study we have evaluated the $\dot{V}_A/\dot{Q}$ relationships and diffusion capacity of the lung in essentially nonsmoking patients with advanced non-alcoholic liver cirrhosis and varying arterial oxygen tension (Pa_{O_2}).

Material and methods

Patients

Fourteen patients with liver cirrhosis admitted to the hospital for assessment of a possible liver transplantation were investigated (table 1). Their mean age was 37 yrs (range, 18–50 yrs), mean weight 65 kg (range, 51–83 kg) and mean height 171 cm (range, 155–197 cm). The diagnosis was primary sclerosing cholangitis in four patients, primary biliary cirrhosis in four, chronic active hepatitis in three, cryptogenic cirrhosis in two, and tyrosinaemia in one patient. One patient had previously had bleedings from oesophageal varices and nine had slight ascites. None of the patients had systemic hypertension or cardiac or renal dysfunction. All had normal chest X-ray. Two patients were moderate smokers (less than ten cigarettes per day) (patients no. 5 and 10). All patients were hospitalized at the time of the study. The study was approved by the local ethics committee, and informed consent was obtained from each patient.

Table 1. – Clinical, laboratory and spirometric data on the patients

Patient no.	Age yrs	Sex	Smoking Cig·day^{-1}	Diagnosis	ALAT	Alkaline phosphatase	Prothrombin complex (normotest)	Albumin	Haemoglobin	VC %pred	FEV_1/FVC %	DLco %pred	Kco %pred
1	39	F	0	CAH	0.92	4.5	55	25	130	-	-	-	-
2	49	F	0	PBC,PC	1.68	7.1	140	18	110	74	63	-	-
3	47	F	0	PBC	2.87	32.3	100	27	113	103	80	-	-
4	35	M	0	PSC	1.11	16.2	95	40	122	102	79	80	93
5	29	F	10	CAH	0.50	1.9	50	32	104	123	79	64	60
6	22	M	0	PSC	0.86	22.7	125	32	109	103	80	84	100
7	24	M	0	PBC	1.04	5.2	36	29	111	-	-	-	-
8	37	F	0	PSC	1.28	14.0	58	21	81	108	89	-	-
9	50	M	0	PSC	2.57	32.9	200	25	109	73	83	63	64
10	35	F	10	CAH	0.80	6.5	39	22	137	135	65	69	47
11	38	F	0	CC	0.71	17.2	65	27	112	108	78	65	66
12	18	F	0	T	1.66	35.0	45	25	110	119	75	44	41
13	43	M	0	CC	0.51	13.7	590	32	143	80	74	51	65
14	45	F	0	PBC	2.55	11.0	79	30	100	106	80	77	84
Mean	36.5				1.36	15.7	81.2	27.5	113.6	103	77	66	69
SEM	2.7				0.21	3.0	12.5	1.5	4.3	6	2	4	7

ALAT: alanine amino-transferase; CAH: chronic active hepatitis; CC: cryptogenic cirrhosis; PSC: primary sclerosing cholangitis; PBC: primary biliary cirrhosis; PC: pancreatic cancer; T: tyrosinaemia; VC: vital capacity; FEV_1/FVC: forced expired volume in one second in % of the forced vital capacity; DLco: transfer factor of the lung; Kco: DLco corrected for haemoglobin concentration and divided by alveolar volume [9]. Ref. values ALAT<0.7 μkat·l^{-1}, alkaline phosphatase<4.2 μkat·l^{-1}, prothrombin complex 70–130%, albumin 35–46 g·l^{-1}, haemoglobin 115–145 g·l^{-1}.

Lung function tests

Slow (static) and forced vital capacity manoeuvres (VC and FVC) were recorded by a low resistive bellows spirometer (Ohio 810), and the forced expired volume in one second as a percentage of FVC (FEV_1/FVC) was calculated. The transfer factor of the lung was analysed by the single breath CO method (DLco) (equipment: Mijnhardt diffusimat), and calculated according to standard techniques [9]. It was also corrected for haemoglobin concentration in blood and divided by alveolar volume to normalize for lung volume (alveolar volume) (carbon monoxide transfer coefficient: Kco).

Reference values for spirometry were calculated by means of the European Summary equations [10], and reference values for DLco and Kco were calculated according to those referred by COTES [9].

Catheterization and haemodynamic measurements

The studies were performed with the patient in the supine position. A triple lumen thermistor-tipped catheter (Swan Ganz 7F Edwards Laboratories, Santa Ana, CA) was introduced percutaneously after local anaesthesia into the right femoral vein and advanced under fluoroscopy to a right-sided hepatic vein (ten patients). The occlusion pressure, obtained by inflating the balloon at the tip of the catheter, and the free hepatic venous pressure were measured. The difference between the two pressures thus reflects the hepatic venous pressure difference. The catheter was then advanced to the heart and into the pulmonary artery. Pulmonary vascular pressures, related to atmospheric pressure, were recorded, and mixed venous blood was drawn for gas analysis as described below. The brachial artery was cannulated for pressure recordings and blood sampling, and an additional venous catheter was inserted into the opposite arm for infusion of inert gases. Cardiac output was determined by thermodilution. A 10 ml bolus of ice-cold 5% glucose was injected into the right atrium and the dilution curve was analysed by a cardiac output computer (model 9520A, Edwards Laboratories). Four measurements of cardiac output were made, and the mean value was calculated.

Ventilation-perfusion relationships

Six gases (sulphur hexafluoride (SF_6), ethane, cyclopropane, enflurane, diethylether, and acetone) were dissolved in isotonic saline and infused into a vein at a rate of 3 ml·min^{-1}. After 40 min of infusion, under steady-state conditions, arterial and mixed venous blood samples were taken and mixed expired gas collected for analysis by gas chromatography (Sigma 3, Perkin Elmer). Blood gas partition coefficients were determined by a two-step procedure. For technical details, see [11]. Arterial/mixed venous and mixed expired/mixed venous gas concentration ratios (retention and excretion, respectively) were plotted against blood gas partition coefficients. By formal mathematical analysis with enforced smoothing these relationships were transformed into a multicompartmental plot of blood flow and ventilation against $\dot{V}_A/\dot{Q}$ [2, 12]. Of the available information related to the $\dot{V}_A/\dot{Q}$ distribution data are presented on the mean $\dot{V}_A/\dot{Q}$ ratio of the ventilation and perfusion distributions (V_{mean}, Q_{mean}),

the dispersion around the means, expressed as the logarithmic standard deviation of ventilation and perfusion distributions (log SDV, log SDQ), shunt (percentage perfusion of lung regions with $\dot{V}_A/\dot{Q}$ ratios <0.005), "low $\dot{V}_A/\dot{Q}$ regions" (Qlow; percentage perfusion of lung regions with 0.005 <$\dot{V}_A/\dot{Q}$ ratios <0.1), "high $\dot{V}_A/\dot{Q}$ regions" (Vhigh); percentage ventilation of lung regions with 10<$\dot{V}_A/\dot{Q}$ ratios <100), and dead space (VD; percentage ventilation of lung regions with $\dot{V}_A/\dot{Q}$ ratios >100).

Blood gas analysis

Arterial and mixed venous blood were drawn for blood gas analysis, using standard techniques (analyser: ABL-2, Radiometer).

Statistics

Standard statistical methods were employed, using Student's t-test and linear regression analysis when necessary. Data in the text and tables are presented as mean±SE.

Results

Lung function

FEV_1/FVC was at the lower normal limit in two patients (patients no. 2 and 10). Otherwise there were no signs of airway obstruction. Mild reductions in vital capacity were shown in two patients (patients no. 2 and 9). The transfer factor, whether it was expressed in absolute value (DLCO), or after correcting for haemoglobin concentration and normalizing for alveolar volume (KCO), was moderately reduced. Individual data are shown in table 1.

Circulation

Cardiac output ranged from normal to high values (4.4–15.7 $l \cdot min^{-1}$), maintained by a heart rate of mean 75 beats/min^{-1} and a large stroke volume in most patients [13] (table 2). Pulmonary artery pressures were all normal to low and the pulmonary capillary wedge pressure was also within normal limits. The calculated pulmonary vascular resistance was in the lower range of normal [13]. Systemic vascular pressures and the calculated systemic vascular resistance were normal or low. The arterial-mixed venous oxygen content difference was low in most patients, and ranged from 18–47 $ml \cdot l^{-1}$ blood (table 2).

The hepatic venous pressure difference was increased in 5 of 10 patients studied, the highest value being 27 mm Hg (upper normal limit used in our laboratory, 9 mm Hg) (table 2).

Gas exchange and ventilation-perfusion relationships

Minute ventilation was normal to high (table 2) and arterial carbon dioxide tension normal to low (table 3). The measured Pa_{O_2} was 11.4 kPa (85 mm Hg) or less in six patients. This value is used as the lower normal limit at our laboratory for the present age group (see also [14]). Severe hypoxaemia was seen in patients no. 10, 12 and 13 (table 3). Mixed venous oxygen tension was normal to high in all patients, even in those with more severe arterial hypoxaemia (table 3).

The technical quality of the derived $\dot{V}_A/\dot{Q}$ distributions was assessed by summing up the squared differences between measured and predicted retentions of the six infused inert gases (remaining sum of squares, (RSS)). An indication of acceptable quality of the $\dot{V}_A/\dot{Q}$ distributions is a RSS of 6 or less in half of the experimental runs [15]. In this study it was 6 or less in 11 of 14 experiments. The calculated distributions

Table 2. – Ventilatory and haemodynamic variables

Patient no.	$\dot{V}_E$ $l \cdot min^{-1}$	$\dot{Q}_T$ $l \cdot min^{-1}$	HR $b \cdot min^{-1}$	$C(a-\bar{v})O_2$ $ml \cdot l^{-1}$	$\overline{RA}$ mmHg	$\overline{PA}$ mmHg	$\overline{PCW}$ mmHg	$\overline{PS}$ mmHg	PVR $mmHg \cdot l^{-1} \cdot min$	SVR $mmHg \cdot l^{-1} \cdot min$	HVPG mmHg
1	7.2	4.4	110	45.5	10	10	5	97	1.32	19.7	-
2	6.8	5.8	87	34.3	10	7	2	73	1.02	10.9	2
3	6.8	7.1	73	35.0	8	15	12	93	0.42	11.0	14
4	7.5	7.2	58	36.7	-	10	7	90	0.42	11.5*	20
5	6.1	8.1	75	29.7	4	12	9	71	0.63	8.3	6
6	6.0	5.0	60	46.5	8	12	8	87	0.80	15.7	-
7	9.0	15.7	91	25.9	2	7	4	83	0.19	5.2	-
8	7.3	10.4	81	18.0	13	16	11	95	0.48	7.9	-
9	9.1	7.3	68	46.9	9	11	4	78	0.97	9.5	7
10	6.4	7.5	62	28.8	7	15	9	82	0.80	10.0	12
11	7.3	7.0	70	32.3	4	11	7	80	0.57	10.9	27
12	8.6	6.3	68	37.0	8	10	8	100	0.60	14.6	6
13	14.2	7.1	72	37.9	7	15	11	92	0.57	12.0	16
14	8.1	6.0	80	39.4	8	16	9	81	1.17	12.2	4
Mean	7.9	7.5	75.4	35.3	7.5	11.9	7.6	85.9	0.71	11.4	11.4
SEM	0.6	0.7	3.7	2.2	0.8	0.8	0.8	2.4	0.08	1.0	2.5

$\dot{V}_E$: minute ventilation; $\dot{Q}_T$: cardiac output; HR: heart rate; $C(a-\bar{v})O_2$: arterial-mixed venous oxygen content difference; $\overline{RA}$: mean right atrial; $\overline{PA}$: mean pulmonary arterial; $\overline{PCW}$: mean pulmonary capilliary wedge; $\overline{PS}$: mean systemic arterial; PVR: pulmonary vascular resistance; SVR: sytemic vascular resistance; HVPG: hepatic venous pressure gradient; *: RA assumed to be 7.5 mmHg.

Table 3. – Respiratory and inert gas variables

Patient no.	$Pa_{O_2}m$	$Pa_{CO_2}m$	$P\bar{v}_{O_2}$	Shunt	Low $\dot{V}_A/\dot{Q}$	$\dot{Q}_{mean}$	Log SD$\dot{Q}$	$\dot{V}_{mean}$	Log SD$\dot{V}$	$Pa_{O_2}p$
1	13.8	4.3	5.5	0	0	0.77	0.55	1.03	0.51	13.7
2	14.4	3.9	5.8	0.8	0.9	0.90	0.57	1.04	0.32	14.6
3	11.8	5.1	5.9	5.3	0	0.60	0.39	0.74	0.61	11.8
4	13.1	4.7	6.0	2.9	0	0.70	0.39	0.83	0.41	13.1
5	13.2	4.2	6.2	0.2	4.7	0.48	1.07	0.80	0.55	13.1
6	11.4	4.2	4.5	0.3	0	0.67	0.32	0.74	0.32	11.3
7	13.5	3.6	6.0	1.9	3.1	0.59	0.93	0.84	0.45	13.3
8	11.7	4.0	6.5	0	18.8	0.40	1.45	1.07	0.64	12.3
9	11.8	4.7	5.7	0	6.7	0.67	0.90	1.00	0.48	12.1
10	8.7	4.2	5.8	3.4	9.2	0.34	1.32	0.91	0.96	9.1
11	11.2	3.9	5.7	2.7	1.3	0.46	0.81	0.70	0.66	11.1
12	6.9	4.7	4.9	19.8	10.4	0.57	1.71	1.59	0.68	7.4
13	7.7	3.9	5.3	17.2	0	0.98	1.09	2.84	0.88	8.3
14	10.0	4.6	4.8	0.7	3.0	0.63	1.03	1.23	0.69	10.3
Mean	11.4	4.3	5.6	3.9	4.1	0.63	0.90	1.10	0.58	11.5
SEM	0.6	0.1	0.2	1.7	1.4	0.05	0.11	0.15	0.05	0.6

$\dot{V}_{mean}$, $\dot{Q}_{mean}$: mean $\dot{V}_A/\dot{Q}$ of ventilation and perfusion distributions; log SD$\dot{V}$ or $\dot{Q}$: log standard deviation of the ventilation and perfusion distribution around $\dot{V}_{mean}$ and $\dot{Q}_{mean}$, respectively; shunt: perfusion of non-ventilated lung regions ($\dot{V}_A/\dot{Q}<0.005$) in % of cardiac output; "low $\dot{V}_A/\dot{Q}$": perfusion of poorly ventilated (relative perfusion) lung regions ($0.005<\dot{V}_A/\dot{Q}<0.1$) in % of cardiac output; $Pa_{O_2}m$, $Pa_{CO_2}m$: measured arterial oxygen and carbon dioxide tensions; $P\bar{v}_{O_2}$: mixed venous oxygen tension; $Pa_{O_2}p$: predicted Pa_{O_2} (from $\dot{V}_A/\dot{Q}$) (blood gas tension in kPa).

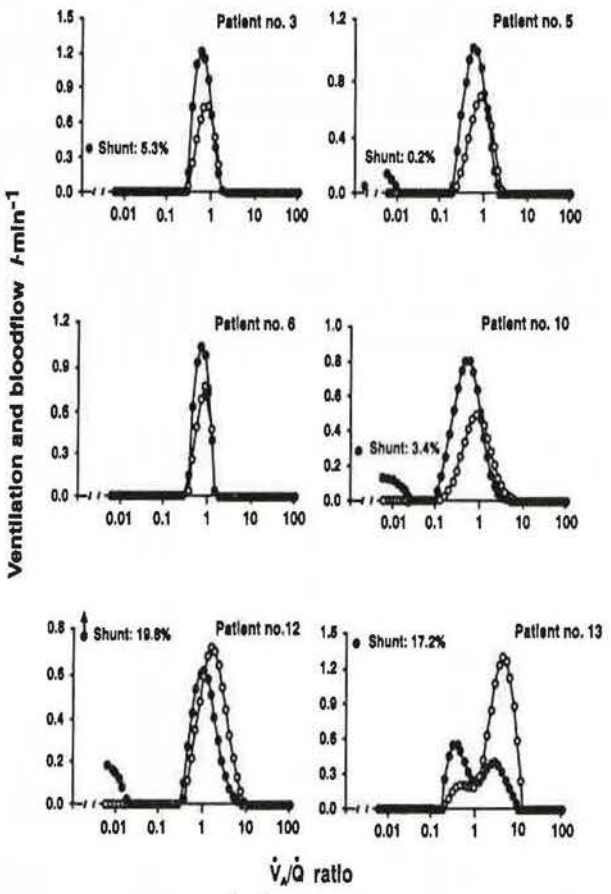

Fig. 1. – Examples of $\dot{V}_A/\dot{Q}$ distributions from 6 patients. Only one patient (no. 6) had a normal $\dot{V}_A/\dot{Q}$. All other patients had widened $\dot{V}_A/\dot{Q}$ distributions and/or varying degrees of perfusion to "low" $\dot{V}_A/\dot{Q}$ regions ($0.005<\dot{V}_A/\dot{Q}<0.1$) and shunt ($\dot{Q}s/\dot{Q}T$). ●: blood flow; ○: ventilation.

showed a wide range of $\dot{V}_A/\dot{Q}$ abnormalities (table 3, fig 1). Only one patient (patient no 6) had a clearly normal $\dot{V}_A/\dot{Q}$ distribution with normal log SD$\dot{Q}$, no regions of low $\dot{V}_A/\dot{Q}$ and almost no shunt (fig 1). Two patients had normal log SD$\dot{Q}$, no perfusion of low $\dot{V}_A/\dot{Q}$ regions, but moderately increased shunts (patients no. 3 and 4). Another 2 patients had borderline values on log SD$\dot{Q}$ (upper normal limit 0.60) [16], no or minor perfusion of low $\dot{V}_A/\dot{Q}$ regions, and no or very low shunt (patients no. 1 and 2). In the remaining nine patients log SD$\dot{Q}$ was clearly increased, well beyond the upper normal limit. In all these patients there was considerable perfusion of low $\dot{V}_A/\dot{Q}$ regions with extreme values of 9, 10 and 19% of cardiac output in patients no. 10, 12 and 8, respectively. In addition, a significant shunt was seen in 4 of these patients. Thus, a total of 6 patients had shunts which accounted for more than 2% of cardiac output with extreme values of 17 and 20% in patients no. 13 and 12, respectively (table 2).

Knowing the $\dot{V}_A/\dot{Q}$ distribution, cardiac output, mixed venous oxygen tension (P_{O_2}), the haemoglobin concentration and the slope of the dissociation curve, the arterial P_{O_2} can be calculated by means of an iterative procedure [17, 18]. All parameters were measured or calculated, except for P_{50} (a determinant of the slope of the haemoglobin dissociation curve) which was assumed to be 3.8 kPa (28.5 mm Hg), corresponding to the mean of data presented in previous studies [3, 6, 7]. However, the calculated Pa_{O_2} does not take any diffusion limitation for O_2 into account, nor will it be affected by extrapulmonary right to left shunting. A higher calculated than measured Pa_{O_2} may thus indicate an additional cause of hypoxaemia besides intrapulmonary shunt and $\dot{V}_A/\dot{Q}$ mismatch. A comparison of calculated and measured Pa_{O_2} showed a good correspondence in

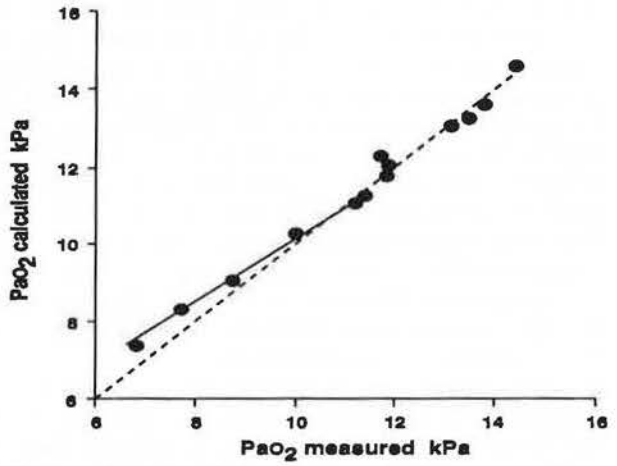

Fig. 2. – Comparison between measured arterial oxygen tension (Pao_2m) and that calculated from the $\dot{V}A/\dot{Q}$ distributions (Pao_2c). Note the similarity between measured and calculated values in the normoxaemic range, and the increasing difference when Pao_2 is reduced. Broken line: identity line; solid line: regression line,for the six hypoxaemic patients (Pao_2m<11.5 kPa): $Pao_2c = 1.68+0.85\ Pao_2m$; r=0.99, p<0.001. (See also text).

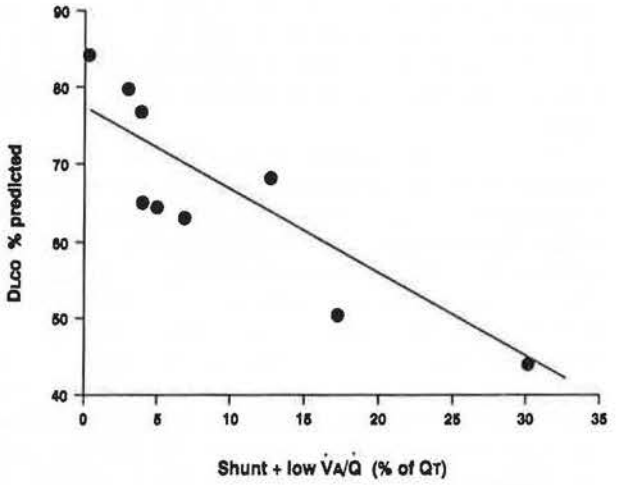

Fig. 3. – Correlation between DLCO and the degree of gas exchange abnormality, expressed as the sum of shunt and perfusion of lung regions with low $\dot{V}A/\dot{Q}$ ratios (low $\dot{V}A/\dot{Q}$), in percentage of cardiac output. Regression equation: DLCO = 77.3 - 1.19 (shunt + low $\dot{V}A/\dot{Q}$); r=0.87, p<0.001, n=9. A similar but weaker correlation was noted between KCO and the sum of shunt and low $\dot{V}A/\dot{Q}$ (not shown in figure; r=0.75, p<0.01).

normoxaemic patients with values scattered around the identity line, see fig 2. However, in the hypoxaemic patients (Pao_2 <11.5 kPa; n=6) calculated Pao_2 was on an average 0.3 kPa higher than the measured values (p<0.05), the correlation equation being $Pao_2c = 1.68 + 0.85 \times Pao_2m$; r =0.99, p<0.001 (c: calculated; m: measured). The difference increased when Pao_2 was reduced according to the equation: $Pao_2c - Pao_2m = 1.68 - 0.15\ Pao_2m$; r = 0.94, p<0.01. (Similar analysis on the whole material showed also significant correlations according to $Pao_2c = 1.16 + 0.91\ Pao_2m$; r = 0.99, p<0.001; and $Pao_2c - Pao_2m = 1.17 - 0.09\ Pao_2m$; r = 0. 69, p<0.01. However, an analysis on the whole

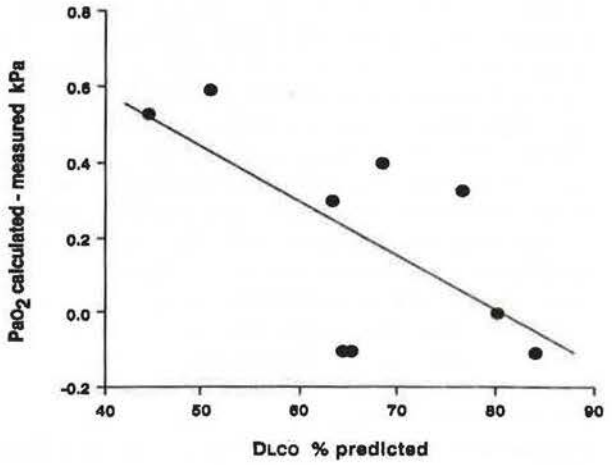

Fig. 4. – Correlation between the the difference of calculated and measured Pao_2 and DLCO. Regression equation: calculated Pao_2-measured Pao_2 = 1.15 - 0.014 DLCO; r=0.65, p<0.05, n=9.

material can be objected to, since the normal and the hypoxaemic values should not be expected to fit the same regression line).

A significant inverse correlation between the transfer factor of the lung (DLCO, KCO), and gas exchange impairment, expressed as the sum of shunt and perfu-sion of low $\dot{V}A/\dot{Q}$ regions was noted (fig. 3). Separate analyses of DLCO on shunt and on low $\dot{V}A/\dot{Q}$ showed weaker correlations (r = -0.72 and -0.65, respectively). The possible impedance of arterial oxygenation by diffusion impairment was tested by comparing the difference between calculated and measured Pao_2 (Pao_2c - Pao_2m) with DLCO. An inverse correlation of borderline significance (r = 0.65, p<0.05) was noted, with increasing Pao_2c - Pao_2m when DLCO was decreased (fig. 4).

No correlations were seen between Pao_2 or any $\dot{V}A/\dot{Q}$ variable, on the one hand, and spirometry, on the other. Also, no correlation was shown between the degree of portal hypertension, as determined by the hepatic venous pressure gradient, and $\dot{V}A/\dot{Q}$ mismatching.

Discussion

The present study demonstrated that patients with non-alcoholic liver cirrhosis have a pulmonary dysfunction which produces both moderate areas of low $\dot{V}A/\dot{Q}$ ratios and shunt. These observations are similar to those made in patients with alcoholic cirrhosis [3–7]. However, in these studies, many patients were smokers, making it difficult to exclude smoking as a contributory factor to the $\dot{V}A/\dot{Q}$ disturbance. In the present investigation the patients were essentially nonsmokers, and no clinical and almost no functional signs of airway obstruction were seen. Two patients had slightly reduced vital capacities, and one of these (no. 2) had primary biliary cirrhosis which can be associated with fibrosing alveolitis [1]. However, a comprehensive clinical examination and chest X-ray

revealed no signs of fibrosis. Interstitial oedema in dependent lung regions and cranial displacement of the diaphragm because of ascites have also been suggested to cause hypoxaemia in cirrhotic patients, by compressing small airways and reducing ventilation in these regions [19, 20]. None of the present patients had signs of oedema, or a shift of the diaphragm, on chest X-ray. Moreover, ascites was minor in those who had it, and the two patients with the largest $\dot{V}A/\dot{Q}$ disturbances had no ascites at all, as assessed by clinical evaluation and ultrasound recording. It can thus be concluded that there were no clear findings of a ventilatory impairment, although subtle changes in the small airways may not be detected by the tests used. In two previous studies, no correlation was shown between tests on small airway function and respiratory and inert gas exchange data [3, 5].

Impaired hypoxic pulmonary vasoconstriction was proposed by DAOUD *et al.* [21] as a cause of hypoxaemia in patients with cirrhosis. More recently, it was suggested that cirrhotic patients exhibit progressive abnormalities of systemic and pulmonary haemodynamics together with increasing impairment of hypoxic pulmonary vasoreaction, and that this would be the main cause of the altered pulmonary gas exchange in cirrhosis [3]. It has also been shown that at least some cirrhotic patients have dilated microvascular channels which permit intravenously injected microspheres of 20–40μ in diameter to pass through the lung circulation [22–24]. It is tempting therefore to suggest that such vessels produce shunt, which, together with loss of hypoxic pulmonary vasoconstriction, cause the $\dot{V}A/\dot{Q}$ disturbance in liver cirrhosis. It has also been proposed that a diffusion gradient for oxygen may exist in dilated pulmonary vessels [25], resulting in a "diffusion-perfusion" defect [26]. This theory is supported by theoretical calculations of oxygen transport in larger vessels [27]. If present, such a mechanism may be contributing to reduced DLCO and hypoxaemia in liver cirrhosis. The present finding of an inverse correlation between gas exchange impairment (sum of shunt and perfusion of regions with low $\dot{V}A/\dot{Q}$ ratios), and reduction in the transfer factor of the lung (fig. 3) may indicate that both functional disturbances worsen in parallel, but it may also suggest that the reduced transfer factor merely reflects the ventilation-perfusion mismatch.

In an attempt to throw further light on the possibility of a diffusion limitation for oxygen, measured and calculated Pa_{O_2} have been compared in a number of recent studies, but varying results have been obtained. Thus, in studies on patients with no or only moderate hypoxaemia, all gas exchange impairment could be explained by intrapulmonary shunt and $\dot{V}A/\dot{Q}$ mismatch as evidenced by the corresponding measured Pa_{O_2} and calculated Pa_{O_2} [3–5]. On the other hand, in patients with more severe hypoxaemia a higher calculated than measured Pa_{O_2} indicated additional causes of hypoxaemia [6, 7]. In the present study we had the opportunity to examine both normoxaemic and severely hypoxaemic patients. We found a good correspondence between measured Pa_{O_2} and calculated Pa_{O_2} when oxygenation was normal, but an increasing difference between calculated and measured values with decreasing Pa_{O_2} as shown in figure 2. Thus, with increasing gas exchange impairment there was an increasing contribution to hypoxaemia by another factor than intrapulmonary shunt and $\dot{V}A/\dot{Q}$ mismatch, suggesting the coexistence of diffusion limitation for O_2. This was further supported when we compared the difference between calculated Pa_{O_2} and measured Pa_{O_2} ($Pa_{O_2}c$ - $Pa_{O_2}m$) with the reduction in DLCO. We found a weak correlation with increasing $Pa_{O_2}c$ - $Pa_{O_2}m$ when DLCO was decreased (fig. 4). On basis of these observations we propose that there is a diffusion limitation for both CO and O_2 which in some cases can cause reduced arterial oxygenation and add to the impaired oxygenation caused by shunt and $\dot{V}A/\dot{Q}$ mismatch. Since, to our knowledge, there is no morphological evidence of thickened alveolar-capillary membranes, we suggest that the higher $Pa_{O_2}c$ than $Pa_{O_2}m$ may be an indication of a "diffusion-perfusion" defect.

A weakness in the analysis of Pa_{O_2} is that a fixed slope factor (P_{50}) was used instead of constructed individual haemoglobin dissociation curves. However, the use of another P_{50} in all patients would not alter the correlation, only cause a parallel shift of the regression line. If, on the other hand, P_{50} varied considerably between the patients, the effect on the correlation will be less predictable.

Finally, the discussion on the difference between calculated and measured Pa_{O_2} postulates that any vessel dilatation has not produced intravascular inert gas gradients. Previous calculations suggest that the inert gases, as presently used, should not be diffusion limited [28]. Our own data showed a good fit of the derived $\dot{V}A/\dot{Q}$ distributions to the retention data (small remaining sum of squares, RSS), and no effect of the weight of the inert gases on their elimination could be disclosed. This would have been the case if there was a diffusion limitation for the inert gases. Thus, a heavy inert gas, such as enflurane, showed no greater error in fitting with the calculated retention curve (mean error, data from all patients: 0.24) than a light gas like ethane (mean error: -0.30; no significant difference between the two gases (paired t-test)).

In conclusion, patients with non-alcoholic liver cirrhosis suffer from $\dot{V}A/\dot{Q}$ mismatch and shunt similar to that shown in alcoholic cirrhosis. Moreover, with more prominent gas exchange impairment, the effect of an additional factor, probably diffusion limitation, for oxygen, emerges. The findings can fit with pulmonary vascular relaxation and dilated microvascular channels.

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Inégalité de ventilation-perfusion chez les patients atteints de cirrhose hépatique non éthylique. G. Hedenstierna, C. Söderman, L.S. Eriksson, J. Wahren.

RÉSUMÉ: Les relations ventilation-perfusion ont été étudiées chez des patients atteints de cirrhose hépatique non éthylique. La spirométrie est fondamentalement normale, mais le facteur de transfert pulmonaire (DLCO) est réduit en moyenne de 34% des valeurs prédites. La tension artérielle en oxygène (Pao_2) a des valeurs qui s'étalent depuis la normale jusqu'à 6.9 kPa. Différents degrès d'anomalies du rapport ventilation-perfusion ($\dot{V}A/\dot{Q}$) ont été observés au moyen de la technique d'élimination de gaz inertes multiples: il s'agit d'une accentuation de la dispersion de la distribution de la perfusion) log SDQ, 0.90; extrême 0.32–1.71: limite supérieure de la normale, 0.60) et de la présence de deux types de régions: celles avec une ratio $\dot{V}A/Q$ basse (entre 0.1 et 0.005) (moyenne 4.1%, extrême 0–18.8%) et celles avec shunt (ratio $\dot{V}A/\dot{Q}$ inférieure à 0.005) (moyenne 3.9%; extrême 0–19.8%). Chez les patients normoxémiques, il y a une similitude étroite entre la Pao_2 mesurée et calculée. Par contre, chez les sujets hypoxémiques, les values calculées sont supérieures aux values mesurées. La différence entre les valeurs calculées et mesurées de Pao_2 est en corrélation inverse avec la DLCO ($r=0.65$, $p<0.05$). L'on a noté également une corrélation inverse entre DLCO et la somme des régions à shunt et à rapport $\dot{V}A/\dot{Q}$ bas ($r=0.87$, $p<0.001$). L'on conclut que l'hypoxémie, chez les patients atteints d'une cirrhose hépatique non éthylique, peut être expliquée par le shunt intra-pulmonaire et par la non congruence de la ventilation et de la perfusion, et peut-être par un dèfect diffusion-perfusion chez les patients dont l'atteinte des échanges gazeux est plus sèvère.

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