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Analysis of intrapulmonary right to left shunt in the hepatopulmonary syndrome

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Background/Aims: **Severe hypoxaemia in patients with chronic liver disease in the absence of intrinsic lung disease, the hepatopulmonary syndrome, is associated with pulmonary vascular dilatation and may be an indication for liver transplantation. Divergence between two methods of measuring right to left shunt (radiolabelled albumin macroaggregates and 100% oxygen breathing) has been described, but the mechanism and reason for the inter-patient variability for this shunt difference are not well understood.**

Methods: **Eight hepatopulmonary syndrome patients were studied, with characteristic pulmonary diffusion abnormalities (carbon monoxide transfer factor 41±5 (mean±SE)% predicted) and significant decreases in arterial oxygen saturation (%) on standing vs. supine (−10%±3) and on exercise vs. rest (−15%±2). All had hypoxaemia at rest (arterial oxygen tension 8.2±0.6 kPa), partially corrected by breathing 100% oxygen (48.2±8.8 kPa). Pulmonary angiography was performed and right to left shunt measured by two independent methods: (a) 100% oxygen breathing and (b) i.v. injection of radiolabelled microspheres.**

Results: **Measurement of right to left shunt with ^{99m}Tc-labelled albumin macroaggregates confirmed significant intrapulmonary microvascular dilatation, i.e. an "anatomical" shunt equalling 32±4% of cardiac output. Shunt measurements made simultaneously by the classical 100% oxygen technique were significantly smaller (19±3%, $p=0.01$). For individuals, the difference between the ^{99m}Tc-albumin macroaggregate shunt and the 100% oxygen shunt ranged from 2% to 30% absolute, convergence suggesting larger shunt channels (pure anatomical shunt) and divergence representing a combination of anatomical shunt and alveolar-capillary diffusion limitation (smaller microvascular channels).**

Conclusions: **Hypoxaemia in the hepatopulmonary syndrome may be due functionally either to right to left shunting or to diffusion limitation, depending upon the degree of dilatation of the pulmonary microvessels.**

Key words: **Cirrhosis; Hepatopulmonary syndrome; Right to left shunt.**

The hepatopulmonary syndrome (HPS) is now a well-recognised clinical syndrome, defined by the triad of chronic liver disease, abnormal pulmonary gas exchange and intrapulmonary vascular dilatation (1). The prevalence of this syndrome is unknown; arterial hypoxaemia is described in up to one-third of patients with liver failure, but HPS itself is less common (7.5–15%) (2). HPS has also been identified in patients who have only mild liver disease (2), or who have pre-sinusoidal portal hypertension associated with normal liver function (3). Portal hypertension is a prerequisite for the diagnosis of HPS. Although the pathogenesis of HPS is unclear, the pathological basis encompasses a range of vascular abnormalities, usually described as "intrapulmonary vasodilatation" (1). The most striking feature microscopically is gross dilatation of capillaries in the alveolar septa; diameters of 100 μm, as compared with the normal 7–15 μm, being described (4). The pulmonary angiogram may be normal or may have a diffuse "spongy" appearance with spidery vascular abnormalities; in one case, discrete arteriovenous communications (c. 1 mm) were seen (5). These dilated

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vessels are the main cause of the severe arterial hypoxaemia, acting either as a right to left shunt or as a barrier to diffusion at the alveolar level.

Characteristic clinical features of HPS, in addition to evidence of chronic liver disease, have been described. Patients frequently show clubbing and may display breathlessness on standing or arterial hypoxaemia which worsens on standing. They may have a hyperdynamic circulation (1). The arterial hypoxaemia is incompletely corrected by breathing 100% O_2. The pulmonary diffusing capacity for carbon monoxide (DLCO) [or transfer factor, TLCO] is typically <60% predicted (6). There is an intrapulmonary right to left shunt, shown by contrast-enhanced echocardiography or the extrathoracic appearance of intravenously injected radiolabelled albumin macroaggregates (^{99m}Tc-MAA).

In this report of eight patients with HPS, we focus on the divergence (previously described in a total of six patients (4,7–9)) between two measurements of the right to left shunt—the classical 100% oxygen breathing method and the ^{99m}Tc-MAA technique—and we propose that the magnitude of the difference relates to the size of the dilated microvascular channels.

Materials and Methods

Subjects

Eight patients (one female, age range 24–54 years, mean 41 years) were studied. Clinical details are given in Table 1. All patients had had pulmonary angiography to exclude the presence of large, discrete pulmonary arteriovenous malformations. No patient had renal impairment. Six patients had cirrhosis proven on liver biopsy. Patient no. 5 had diffuse nodular regenerative hyperplasia of the liver with gastric and oesophageal varices and gross splenomegaly (splenectomy performed) and had portal hypertension of unknown aetiology. Patient no. 8 with clear-cut intrapulmonary shunting was very ill when the diagnosis of HPS was first entertained and liver biopsy was deferred because of severe thrombocytopenia; the diagnosis of cirrhosis and portal hypertension was "presumptive". Five of the eight patients had been identified previously as likely to have hepatopulmonary syndrome while being assessed for liver transplantation. Serial measurements were obtained on one patient (no. 5) over 3 years. Local Ethical Committee approval was obtained for the study and all patients gave fully informed consent.

Pulmonary function and exercise studies

Forced expired volume in the first second (FEV_1) and vital capacity (VC) were measured using a dry wedge spirometer, recording the best of three attempts. Single-breath carbon monoxide transfer factor (TLCO) (or diffusing capacity, DLCO) was measured in duplicate or triplicate and corrected to a standard haemoglobin concentration of 14.6 g/dl. The percentage predicted values were derived from European standards (10). Arterial oxygen saturation was measured using an Ohmeda Biox 3700 pulse oximeter.

Postural changes in arterial oxygen saturation (SaO_2) were assessed with the patient supine for 10 min, then standing erect for 10 min. SaO_2 was recorded at 1-min intervals and the mean value between 7 and 10 min was recorded.

Patients exercised using a cycle ergometer, with incremental increases in workload at the end of each minute, until symptom-limited maximum exertion was reached. Workload was increased by 15 or 30 W at each stage depending on exercise capacity. Arterial oxygen saturation and heart rate were monitored via a pulse oximeter with an ear probe.

Measurement of right to left shunt using ^{99m}Tc-MAA injection

Subjects received an intravenous injection of ^{99m}Tc-labelled macroaggregated albumin (^{99m}Tc-MAA), fol-

TABLE 1

Clinical details at presentation

Patient	Age	Sex	Hb g/dl	Diagnosis	PHT	Child-Pugh Grade/Score
1	38	M	17.4	Hepatitis B cirrhosis	+	B 9
2	53	M	12.3	Cryptogenic cirrhosis	+	C 9
3	40	M	10.7	Cryptogenic cirrhosis	+	C 10
4	30	M	14.0	Cryptogenic cirrhosis, pancytopenia	+	B 9
5	34	F	12.5	Diffuse nodular hyperplasia	+	C 11
6	54	M	14.7	Alcoholic cirrhosis	+	C 10
7	53	M	17.1	Cryptogenic cirrhosis	+	A 6
8	24	M	12.3	Pancytopenia, ?cirrhosis	n/a	A 6

Clinical details, including age, sex and underlying diagnosis. PHT indicates presence of portal hypertension (+), measurements unobtainable in one patient (n/a). Child-Pugh grade (A least and C most severe) and score (max. 15) assesses severity of liver disease.

lowed by gamma camera imaging, as previously described (11). Briefly, the method employs albumin macro-aggregates of 20–60 μm diameter (Amersham Pulmonate II, Amersham International, UK) which are too large to traverse normal pulmonary capillaries. However, in HPS a proportion of MAAs bypasses the normal pulmonary vasculature via the abnormally large shunt vessels and thus reaches the systemic circulation, in proportion to the right to left shunt (as a fraction of cardiac output). Conversely, the number of MAAs, as a fraction of the injected dose, remaining trapped in the lungs reflects the non-shunted blood. In the present studies, 50 MBq of ^{99m}Tc-MAAs were injected in the gamma-camera room. Images were obtained of the upper abdomen, in posterior and lateral views, and of the lungs. Thus, total counts were obtained from regions of interest over the right kidney and both lungs. The total injected radioactivity was measured by counting the syringe which contained the dose, before and after injection, on the gamma camera. The right kidney is assumed to receive 10% of the systemic cardiac output, based on radionuclide studies in normal subjects (12), although this has not been verified in HPS patients. To the extent that renal blood flow (as a proportion of cardiac output) is reduced, the ^{99m}Tc-MAA shunt will be underestimated.

Measurement of R-L shunt using 100% oxygen

Patients breathed 100% oxygen from a Douglas bag for 20 min. A mouthpiece, two-way valve and noseclip were used to ensure delivery of 100% oxygen. An arterial blood gas sample was taken and analysed immediately for PaO_2. Using the SaO_2 (measured independently by oximetry) and PaO_2 values on 100% oxygen and current haemoglobin concentration, the shunt fraction was calculated from the classic equation (13). This shunt equation was also used to calculate the apparent shunt or "venous admixture" when the subjects were breathing air, calculating an ideal alveolar PO_2 from the measured $PaCO_2$ and a respiratory exchange ratio (assumed) of 0.8.

In three patients (nos. 3, 4 and 8) radioisotope shunt measurements were performed breathing both air and 100% oxygen. One-third of the microsphere dose was injected for the first measurement and two-thirds for the second, a method which we have previously shown allows accurate quantification of sequential shunt measurements (11). Both measurements of shunt (^{99m}Tc-MAA and 100% oxygen) were made simultaneously with the subjects lying supine.

Measurement of pulmonary haemodynamics

Pulmonary pressures and pulmonary arterial and aortic oxygen contents were measured at pulmonary angiography, prior to the injection of contrast medium. Mean pulmonary artery (PA) and pulmonary capillary wedge (PCW) pressures were measured via an end-hole catheter (7 French headhunter catheter, Cordis Europs N.V. 9301 LJ Roden, The Netherlands). Free main PA pressure was recorded and the catheter was advanced and wedged in a peripheral vessel until a wedge trace was obtained on the pressure tracing. Pulmonary vascular resistance was calculated using the Fick principle, assuming a resting oxygen consumption derived from standard tables (14) corrected for age, sex and calculated body surface area.

Measurement of arteriovenous oxygen difference

In three patients (nos. 4, 5 and 6) the arterial to mixed venous oxygen content difference was measured di-

TABLE 2

Measurements of lung volumes, transfer factor and postural change in SaO_2

Patient	FEV_1/VC	VC(%)	DLCO(%)	KCO(%)	SaO_2% (supine)	SaO_2% (erect)	ΔSaO_2%
1	0.76	107	45	53	93	88	−5
2	0.68	101	64	66	95	88	−7
3	0.84	100	50	52	96	92	−4
4	0.86	81	29	45	98	95	−3
5	0.90	45	33	61	93	82	−11
6	0.85	87	40	43	86	72	−14
7	0.71	71	47	63	87	78	−9
8	0.83	42	22	53	68	40	−28
Mean	0.80	79	41	55	89	80	−10
SD	0.08	25	13	8	9	16	8
SEM	0.03	9	5	3	3	5	3

Measurements of the forced expiratory volume in 1 s to slow vital capacity ratio (FEV_1/VC), slow vital capacity (VC), diffusing capacity for carbon monoxide (DLCO),diffusing capacity per unit alveolar volume (KCO), all as % predicted normal, and arterial oxygen saturation (SaO_2)% in the supine and erect posture, demonstrating enhanced arterial hypoxaemia in the erect posture.

rectly at pulmonary angiography. In two patients (nos. 1 and 3) arteriovenous difference was calculated using cardiac output measurements obtained at cardiac catheterisation. In the case of subject no. 7, the cardiac catheterisation data were not available and the mean value for the a–v difference of all other subjects was used. In the remaining two patients (nos. 2 and 8) Vo_2 and Q_P were measured using a mass spectrometer (Amis 2000, Innovision, Denmark) technique. Vo_2 was calculated from analysis of mixed expired gas. For measurement of Q_P, patients were switched to a closed circuit and breathed a gas mixture containing 0.3% acetylene, 3% SF_6, 35% oxygen and balance nitrogen. Acetylene concentrations during a rebreathing manoeuvre were monitored by mass spectrometry and flow was measured by pneumotachograph and spirometer. Q_P was thus calculated from the rate of alveolar uptake of the inert, soluble gas acetylene (15). These $(Ca–Cv)O_2$ differences were used in the calculation of the 100% oxygen shunt and the venous admixture.

Statistical analysis

All parameters measured are given as mean± standard error of the mean (SEM). Shunt differences were compared using the Wilcoxon matched pairs test for non-parametric data.

Results

Of the eight patients with microvascular intrapulmonary shunting studied, six had proven cirrhosis, one presumed cirrhosis and one HPS secondary to portal hypertension (Table 1). The severity of hypoxaemia (PaO_2 breathing air or 100%) (Table 2) was not related to the severity of liver disease (Child-Pugh score, Table 1). All patients had had pulmonary angiography to exclude macroscopic pulmonary arteriovenous malformations.

Pulmonary function tests

Pulmonary function and arterial oxygen saturation data are shown in Table 2. There was mild airways obstruction in patients 2 and 7, who were ex-smokers. The vital capacity was greater than 70% predicted in all but two patients (nos. 5 and 8), both of whom were very disabled by the time of study. In contrast, a marked reduction in diffusing capacity (transfer factor) was seen in all patients, with a mean TLCO of 41±5 (mean±SEM)% and KCO of 55±3% predicted. All but three patients had a reduced resting SaO_2 (<95%) when measured supine (mean 90±3%, range 68–98%). There was a detectable fall in the SaO_2 in all patients when measured in the standing position, to a mean of 80±5%, range 40–95% ($p<0.001$), a mean reduction of SaO_2 of 10±3% (Fig. 1A).

Exercise studies

Five patients exercised to a mean of 48±8% predicted workload (range 30–180 Watts) and to 79±4% of their predicted maximum heart rate (Table 3). This was despite a marked and progressive arterial desaturation in all patients (mean fall in SaO_2 with maximum exercise 14±2%, range 6–19%) (Fig. 1B).

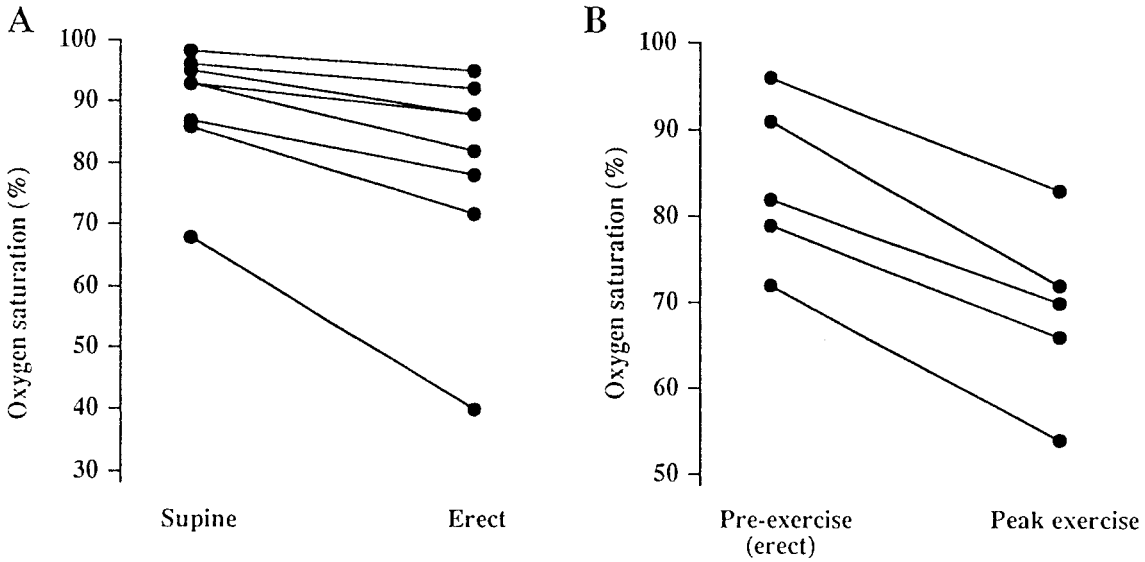

Fig. 1. Worsening hypoxaemia in the erect posture and on exercise in patients with hepatopulmonary syndrome. ***A.*** *Arterial oxygen saturation (SaO_2)% measured in the supine posture and after standing for 10 min.* ***B.*** *Arterial oxygen saturation (SaO_2)% measured immediately before and at maximum exercise.*

TABLE 3

Exercise studies of patients

Patient: study	SaO_2% Rest	SaO_2% Ex	ΔSaO_2	Max Watts (ex)	Watts% pred.	HR (max ex)	HR% pred (max ex)
3	91	72	−19	180	82	155	90
4	96	83	−13	120	55	152	84
5	82	70	−12	45	38	138	78
6	72	54	−18	30	16	100	61
7	79	66	−13	90	43	123	76

Arterial oxygen saturation (SaO_2) is shown at rest (erect posture) and at maximum exercise. Work at maximum exercise is given in Watts and as % predicted. Heart rate (HR) at maximum exercise per minute and as % predicted is also shown. Patient 8 was too unwell to perform exercise studies. Patients 1 and 2 were not studied for logistic reasons.

Measurements of right to left shunt

All eight patients were hypoxaemic breathing air (mean PaO_2 8.2±0.6 kPa), with a mean PaO_2 of 48.2±8.8 kPa breathing 100% oxygen (Table 4).

Mean right to left shunt measured by the radioisotope method (^{99m}Tc-MAA) was 32±4% of cardiac output. In the calculation of the 100% oxygen shunt, the measured arteriovenous difference was lower than the standard value of 50 $ml \cdot l^{-1}$ used in the shunt equation, reflecting the high cardiac output often present in these patients. In all cases the right to left shunt values obtained by the 100% oxygen method were less than those obtained by the ^{99m}Tc-MAA method ($p=0.002$). In most cases, however, the ^{99m}Tc-MAA shunt value was close to the venous admixture ["physiological" shunt breathing air] (32±4% compared with 32±4%, $p=0.97$). The relationships between shunt measurements and venous admixture are shown in Fig. 2.

In three patients, radioisotope shunt measurements were performed with the patients breathing 100% oxygen and then air. There was no significant difference between the ^{99m}Tc-MAA results on air or on 100% oxygen, i.e 11.4% on air versus 12.2% on oxygen for patient 3, 16.6% vs 16.2% for patient 4 and 23% vs 26% for patient 6.

Pulmonary haemodynamics

Measurements were obtained in seven patients prior to pulmonary angiography (Table 5). Cardiac output, derived from $(Ca–Cv)O_2$ and Vo_2, was high in all but one patient, with a mean value of 9.1±1.2 $l \cdot min^{-1}$. This was similar to the values obtained in patients with macroscopic pulmonary arteriovenous malformations (16) with equivalent levels of right to left shunt. Arteriovenous oxygen difference ranged from 20–48 $ml \cdot l^{-1}$, with a mean of 32±3 $ml \cdot l^{-1}$. PVR was reduced in all cases (mean 0.44±0.04 $mmHg \cdot l^{-1} \cdot min$) in comparison with the normal range of 0.80±0.04 $mmHg \cdot l^{-1} \cdot min$ (17). There were no correlations between cardiac output or PVR and either shunt measurement or the difference between the two shunt measurements.

TABLE 4

Measurements of PaO_2 on air and 100% oxygen and calculations of shunt by 100% oxygen rebreathing and microsphere methods

Patient: study	$PaCO_2$ kPa (air)	PaO_2 kPa (air)	PaO_2 kPa (100% O_2)	$CaO_2–CvO_2$ (ml/l)	Q_S/Q_T(%) 100% oxygen	Q_S/Q_T (%) MAA	Venous admixture (%)
1	2.7	6.5	50.8	32	20	50	45
2	3.1	9.2	63.9	36	21	25	40
3	4.8	11.1	75.0	20	12	32	20
4	4.3	10.4	79.2	36	5	16	19
5	4.0	6.8	13.6	35	24	36	32
6	4.4	7.5	46.0	28	24	26	44
7	3.9	7.3	44.1	23	15	25	22
8	4.4	6.5	13.1	48	32	48	35
Mean	3.9	8.2	48.2	33	19	32	32
SD	0.7	1.8	25.0	8	8	12	11
SEM	0.3	0.6	8.8	3	3	4	4

Arterial blood gas measurements were performed with the patient breathing air and 100% oxygen. Right to left shunt was measured in two ways: by 100% oxygen rebreathing and using ^{99m}Tc-MAA.

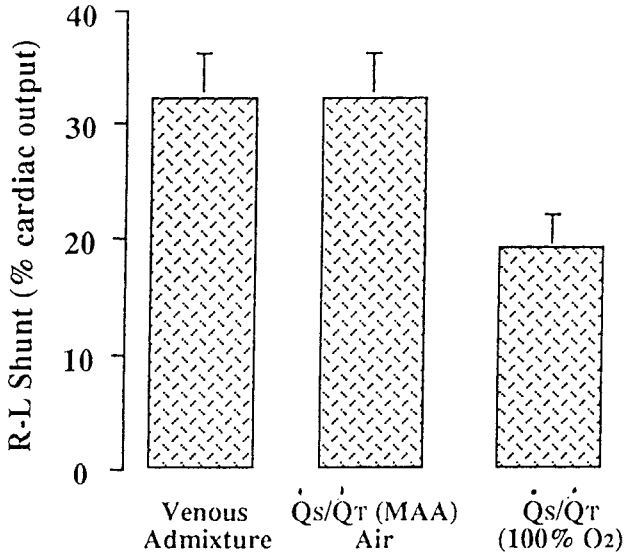

Fig. 2. Measurements of right to left (R-L) shunt from PaO_2 breathing 100% oxygen, after intravenous ^{99m}Tc-MAA and from PaO_2 breathing air (venous admixture). ^{99m}Tc-MAA shunt measurements on air (32+4%) were not significantly different from venous admixture (32+4%, p=*0.97) but were significantly greater than measurements on 100% oxygen (19+3%,* p=*0.002).*

Serial measurements of pulmonary function, arterial oxygenation and right to left shunt in patient no. 5

This patient was studied on three occasions over a 3-year period, as she deteriorated and her exertional dyspnoea increased. As shown in Fig. 3, there was a progressive decline in her diffusing capacity, arterial saturation and exercise capacity. The right to left shunt increased and there was a widening of the difference between the values obtained by oxygen and radioisotope methods.

Discussion

Difference between the radioisotope (^{99m}Tc-MAA) and 100% oxygen right to left shunts

This is the first systematic evaluation, in the hepatopulmonary syndrome, of the difference between the radioisotopic (^{99m}Tc-MAA) and the physiological (100% oxygen) measurement of intrapulmonary anatomic shunt. In a pure right to left anatomic shunt, there will be no difference between the ^{99m}Tc-MAA and 100% oxygen shunt measurements, as is found in the large shunt channels associated with macroscopic intrapulmonary arteriovenous malformations (18). Nevertheless, in a proportion of our patients with HPS the 100% oxygen shunt is less than the ^{99m}Tc-MAA shunt, which is consistent with previous case reports (4,7–9). In our patients the anatomic intrapulmonary shunt measured with ^{99m}Tc-MAAs exceeded the "functional" anatomic shunt using 100% oxygen breathing by a mean of 13% absolute, or 68% in relative terms. There was, however, a wide spectrum of ^{99m}Tc-MAA–100% oxygen differences (+2% to +30%, Fig. 4).

How do these findings help us explain the mechanisms of hypoxaemia in HPS? Anatomic shunt is a reasonable explanation for the findings in patients such as nos. 2 and 6, where the ^{99m}Tc-MAA and 100% oxygen shunts tend to converge; presumably, as supported by histological studies (5), the dilated channels must be too large to permit oxygen diffusion equilibrium, even when PaO_2 exceeds 87 kPa. However, large anatomic shunts cannot be reconciled with the findings in the majority of subjects, where there is a large difference between the 100% oxygen and MAA shunt measurements. The most likely explanation in this situation is that the shunt channels are large enough for 20–60 μm ^{99m}Tc-MAA particles to pass through, but small enough in diameter to permit partial oxygen equilibration when PaO_2 is raised to 87 kPa, as suggested by Genovesi et al. (7). At lower FIO_2, such as when breathing air, diffusion limitation for oxygen will tend to become infinite and the difference between the ^{99m}Tc-MAA shunt and the oxygen shunt ("venous admixture") will disappear (Table 4, Fig. 2).

Gas exchange on exercise

Patients with HPS showed significant worsening of hypoxaemia on exercise, with mean SaO_2 falling from 84% at rest to 69% at maximum exercise. This could be due to an increase in shunting, where the channels are large, or to an increase in diffusion limitation where the channels are smaller. A fall in mixed venous oxygen content will exaggerate the effect of a given shunt flow

TABLE 5

Measurements of resting pulmonary haemodynamics

Patient	Q_T $l \cdot min^{-1}$	Mean PAP mmHg	PCW mmHg	PVR mmHg · min · l^{-1}
1	7.6	7	4	0.39
2	8.1	9	4	0.62
3	12.3	18	12	0.48
4	7.4	15	12	0.41
5	8.7	11	7	0.46
6	14.5	10	6	0.28
8	5.4	15	12	0.41
Mean	9.1	12	8	0.44
SD	3.1	4	4	0.10
SEM	1.2	1	1	0.04

Pulmonary haemodynamics measured at rest prior to angiography. Mean pulmonary artery pressure (PAP) and wedge pressure (PCW) were measured using an end-hole catheter and PVR was calculated.

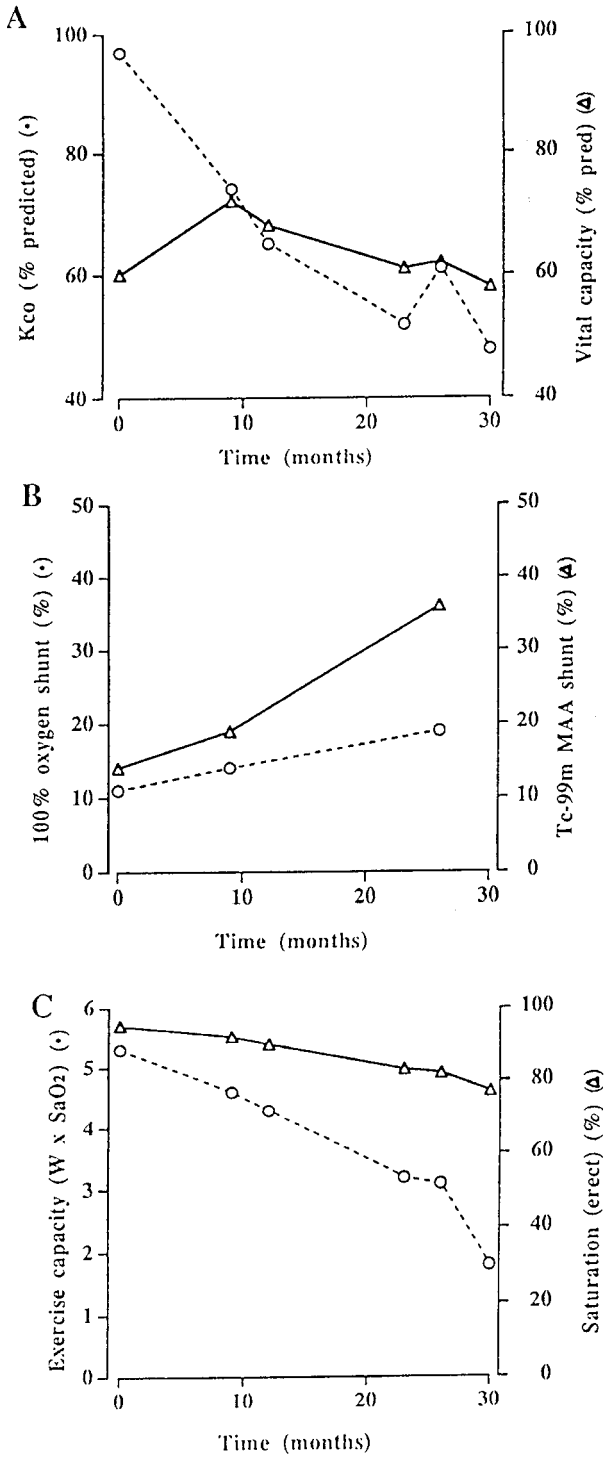

Fig. 3. Serial measurements of pulmonary function, exercise capacity and right to left shunt over 30 months in patient no. 5 with the hepatopulmonary syndrome. ***A.*** *Diffusing capacity (Kco) and vital capacity (VC) as % predicted.* ***B.*** *Right to left shunt measured by 100% oxygen and using ^{99m}Tc-MAA.* ***C.*** *"Exercise capacity" (product of workload (W) and oxygen saturation (SaO_2) at maximum exercise) and arterial oxygen saturation in the erect posture.*

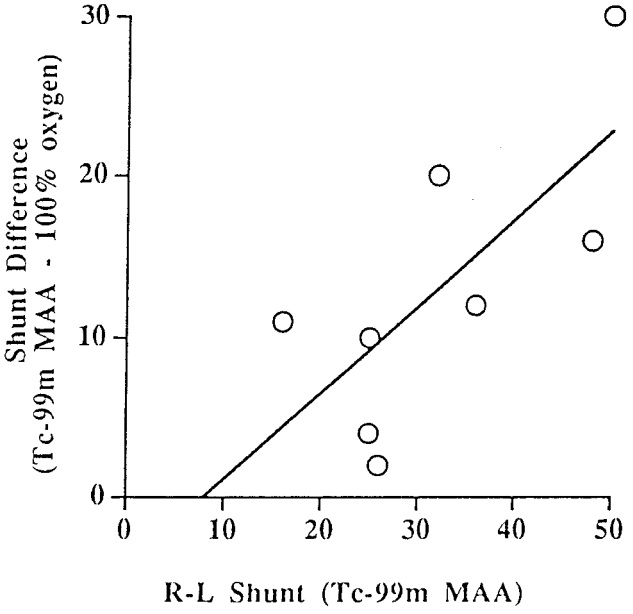

Fig. 4. ^{99m}Tc-MAA shunt minus 100% oxygen shunt plotted against ^{99m}Tc-MAA shunt for all subjects. The difference between the two shunt measurements correlates with the size of the anatomical shunt (r=+0.72).

on arterial saturation, and will increase the diffusion limitation by increasing the oxygen capacitance (β) of blood entering the capillary bed and shortening the capillary transit time. Thorens & Junod (19), in a single case of HPS, measured a shunt of 12% at rest (using 100% oxygen), which increased to 26% on exercise at 40 Watts. This is evidence in favour of shunt and/or diffusion limitation as the cause of arterial desaturation on exercise. It would be interesting to measure the ^{99m}Tc-MAA shunt on exercise in HPS.

Pulmonary haemodynamics

All patients studied had an elevated cardiac output and a low PVR at rest (Table 5), as previously reported (20,21). These findings are analogous to our previous studies in patients with macrovascular pulmonary arteriovenous malformations (16), where the elevated cardiac output allows maintenance of normal pulmonary blood flow (Q_P), even on exercise. In such patients, with no alveolar hypoxia and low pulmonary pressures, there is no constraint to increased right ventricular stroke volume to maintain oxygen delivery. This will also be the case in patients with HPS, and helps explain their reasonable exercise capacity (Table 3) despite profound hypoxaemia.

Pathogenesis

The underlying stimulus for microvascular remodelling in HPS is unknown. Recent reports, however, show

that hypoxaemia is reversed by liver transplantation (reviewed in Ref. 1), which is the most effective treatment for the hepatopulmonary syndrome. Vachiery et al. (22), in an analysis of Child-Pugh score and arterial PO_2 in 120 patients with cirrhosis, found that as a group those with $PaO_2 \leq 70$ mmHg ($n=17$) had significantly worse liver function. The correlation between Child-Pugh score and PaO_2 was weak (22), and no correlation was found in our study though the numbers were smaller. Since hypoxaemia is associated with more severe liver disease and with low PVR, failure of pulmonary hypoxic vasoconstriction has been postulated as a mechanism both of vascular dilatation and of V_A/Q mismatch (23). Nitric oxide has been suggested as a possible mediator of these effects (24). However, it is interesting that the non-selective pulmonary vasoconstrictor, almitrine, does not alter shunt size (21), nor does indomethacin (22).

Conclusions

In the hepatopulmonary syndrome, arterial hypoxaemia is predominantly due to two mechanisms: (a) intrapulmonary right to left shunting and (b) diffusion limitation. In the context of HPS, where alveolar to capillary tissue barrier thickness is normal (4), the distinction between "diffusion limitation" and an intrapulmonary "anatomic shunt" will be determined by the diameter of the microvessels in the alveolar septum in contact with alveolar PO_2. The wider the vessels, the more they act as pure shunts, diffusion limitation becoming infinite; moderate dilatation permits "partial" oxygen equilibration, particularly at high alveolar PO_2.

Interestingly, both mechanisms were demonstrated in a single individual as HPS evolved. As patient 5 deteriorated, the 100% oxygen and ^{99m}Tc-MAA shunts diverged (Fig. 3) which, from our analysis, would suggest the emergence of new, relatively small vascular shunts, rather than progressive enlargement of existing shunt channels.

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