

## SOURCES OF VENOARTERIAL ADMIXTURE IN PORTAL HYPERTENSION \*

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It has been shown that cirrhosis of the liver is often accompanied by admixture of venous blood to the arterial blood, sometimes to a degree producing cyanosis (1-8). Two possible routes have been demonstrated morphologically: intrapulmonary arteriovenous shunts (2, 9), and channels connecting the portal circulation through esophageal and mediastinal veins with pulmonary veins (10, 11). The aim of the present study was to evaluate the physiological significance of these communications.

### MATERIALS AND METHODS

The sex, age, and clinical data of the 20 patients examined are presented in Table I. Eighteen patients had cirrhosis of the liver, the diagnosis in all cases confirmed by liver biopsy or necropsy. Two patients (no. 13 and 16) had extrahepatic portal hypertension. In Patient 13, it was caused by a congenital malformation of the portal vein, and in Patient 16, by portal vein thrombosis. In Patients 12 and 16, portacaval anastomosis had been performed before the investigation, but in both it was non-functioning.

The patients showed no signs of congestive heart failure or intracardiac shunts. Patient 11 had a small basal infiltrate in the left lung; the remaining patients had normal lungs, judged from X rays. Pulmonary function studies were carried out in 10 patients, revealing in one patient (no. 16) a moderate obstructive ventilatory insufficiency. This patient had a functional residual volume of 55% of the total lung volume and a forced expiratory volume in the first second of 53% of the vital capacity. None of the patients was cyanotic and none had arterial oxygen saturation lower than 92%. Three had clubbing of the fingers (no. 1, 16, and 20); two (no. 4 and 10) had spider nevi. Twelve patients had experienced hematemesis or melena on one or more occasions. Fourteen patients had radiographical signs of varices of the esophagus, and in four, filling of esophageal veins was demonstrated by splenoportography. The portal pressure was elevated in all patients but two (no. 8 and 9).

*Analytical methods.* Oxygen tension of the arterial blood was measured by a polarographic method (12); pH

was measured electrometrically, and carbon dioxide tension was estimated by the interpolation method (13). Tritium ( $T_2$ ) and tritiated water (THO) were analyzed by the method of Lassen, Mellemgaard, and Georg (14). The portal pressure was measured with a Tybjaerg Hansen capacitance manometer (15) through a needle (intrasplenic pressure) or catheter (wedged hepatic venous pressure).

*Procedure.* The patient was placed in the supine position. An indwelling arterial needle was introduced into the right femoral artery. A solution containing  $T_2$ , THO, and Evans' blue dye in saline was then administered as a rapid iv injection. Five seconds later, anaerobic sampling of arterial blood was started and continued at a constant rate until about 30 seconds after the injection. The duration of the sampling was timed, with a Millikan ear oximeter to indicate the first passage of Evans' blue dye through the ear lobe. The sampling was discontinued 5 seconds after the maximal dye concentration was observed.

Percutaneous splenic puncture was carried out not earlier than 15 minutes after the iv injection of  $T_2$ . When reproducible intrasplenic pressures were obtained, a sample of arterial blood was drawn for blank determinations of THO, and a solution identical with that used for iv injection was injected rapidly into the spleen. Arterial blood was sampled during the same period as used after the iv injection, and a second sample was collected during the next 30 seconds. The needle was left in the spleen during the sampling and afterwards employed for a splenoportography.

On a separate occasion, arterial blood was drawn for the determination of oxygen tension and carbon dioxide tension, after respiration in pure oxygen for at least 15 minutes.

*Calculations.* By total venoarterial admixture we mean the combined effect of all sources carrying desaturated blood to the arteries. "Right-to-left shunt" designates the fraction of the mixed venous blood (i.e., blood in the right heart and the pulmonary artery) that reaches the systemic arteries without passing air-filled alveoli. By "portopulmonary shunt" we mean the fraction of the portal blood flow that bypasses the pulmonary capillaries.

The total venoarterial admixture was estimated by Berggren's principle (16). This entails the determination of the alveolar-arterial oxygen tension gradient following respiration in pure oxygen for at least 15 minutes. The procedure eliminates contributions from diffusion and distribution factors to the alveolar-arterial oxygen tension gradient, so that the latter solely represents the effect of

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TABLE I  
Clinical data of 20 patients studied\*

Patient no.	Sex	Age	Ascites	Clubbing	Spider nevi	Hematemesis or melena	X-ray signs of varices of esophagus	Filling of esophageal veins by splenoportography	Portal pressure
									<i>mm Hg</i>
1	F	62	+	+	-	+	+		33
2	M	77	-	-	-	-	-		19†
3	M	67	+	-	-	-	+		31†
4	F	67	+	-	+	+	+	+	30
5	F	55	-	-	-	-	+	+	12
6	M	69	-	-	-	+	+	-	28
7	M	42	-	-	-	-	-	-	29
8	F	56	-	-	-	-	-	-	10
9	F	59	-	-	-	-	-	-	12
10	M	40	+	-	+	-	+		
11	F	60	+	-	-	+	-		43
12	F	65	+	-	-	+	+	-	31
13	M	20	-	-	-	+	+	+	31
14	M	56	-	-	-	+	+	-	33
15	M	50	-	-	-	+	+	-	25
16	M	64	-	+	-	+	+	+	25
17	F	66	-	-	-	+	-	-	23
18	F	76	-	-	-	+	+	-	22
19	F	47	-	-	-	+	+	-	16
20	M	33	-	+	-	+	+	+	27

\* Patients 13 and 16 had extrahepatic portal hypertension; the remaining patients suffered from cirrhosis of the liver.

† The portal pressure indicates intrasplenic pressure, except in cases marked †, where wedged hepatic venous pressure has been substituted.

venoarterial admixture. The admixture was calculated from

$$\frac{Q_{va}}{Q_t} = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - CvO_2} = \frac{Aad}{Aad + avd} \quad [1]$$

where  $Q_{va}/Q_t$  is the ratio of venoarterial admixture to cardiac output, and  $Cc'O_2$ ,  $CaO_2$ , and  $CvO_2$  are the oxygen contents of pulmonary end-capillary blood (estimated from the calculated alveolar oxygen tension), arterial blood, and mixed venous blood, respectively. The numerator  $Aad$  is the alveolar-arterial oxygen difference, which when arterial saturation is complete, can be calculated from the alveolar-arterial oxygen tension gradient and the solubility of oxygen in blood. The denominator is the sum of the  $Aad$  and the arteriovenous oxygen difference ( $avd$ ), assumed to be 4.5% by volume.

The right-to-left shunt was estimated from the results of analysis of arterial blood after a rapid iv injection of  $T_2$ , a radioactive inert gas. The low solubility of this gas [the blood/gas partition coefficient is 0.017 (17)] results in its almost complete escape during the first passage through the lung capillaries. THO was employed as a nonvolatile diffusible reference substance.

Estimation of the ratio of concentrations in arterial blood of  $T_2$  and THO permits calculation of the fraction of the "labeled" blood (in this case, mixed venous blood) that reaches the arterial blood without passing air-filled alveoli (14). The recovery  $R$  of  $T_2$  gas in the arterial blood was expressed as a percentage of the expected recovery, assuming no loss of gas had taken place:

$$R = \frac{r_a}{r_s} \times 100 = \frac{Ca_{T_2}/Ca_{THO}}{C_{ST_2}/C_{STHO}} \times 100. \quad [2]$$

The numerator gives the observed ratio  $r_a$  of the  $T_2$  concentration  $Ca_{T_2}$  to that of labeled water  $Ca_{THO}$  in the arterial sample. The denominator expresses the corresponding ratio  $r_s$  in an anaerobically produced blood standard;  $r_s$  is thus taken to express the ratio that would have been found in the arterial sample if all mixed venous blood had bypassed the alveoli.

As a measure of the right-to-left shunt, the  $T_2$  recovery gives an overestimation on account of the contribution to the  $T_2$  recovery caused by "back-pressure" from the alveolar  $T_2$  tension, which builds up during the passage. This can, however, be corrected by calculation (18) or by simultaneous use of two gases with different solubilities (17).

For the estimation of portopulmonary shunt, a solution of the same composition as that used intravenously was injected into the spleen. The recovery of  $T_2$  gas was calculated as mentioned above. Again, the recovery is taken to indicate the fraction of the labeled blood (in this case, blood leaving the spleen) that bypasses the pulmonary capillaries.

## RESULTS

The arterial oxygen tension (Table II) was normal in most cases and moderately reduced in some. On the average, it was reduced to 87 mm

Hg as compared with 95 mm Hg found in normal subjects by the present method. The arterial hydrogen ion concentration differed only slightly from normal values, the average pH being 7.39. The arterial carbon dioxide tension showed a tendency towards reduced values, the average  $p\text{CO}_2$  being 36.5 mm Hg.

Determination of venoarterial admixture by the present technique has given in normal subjects an average value of 2.5% of the cardiac output, with SD of 1.6% (5). Eight of the 20 patients (Table II) had venoarterial admixture exceeding the upper normal limit, i.e., 6% of the cardiac output, the maximal value being 21% (Patient 11). The average venoarterial admixture of the 20 patients was 6.6%. Both patients with extrahepatic portal hypertension showed normal venoarterial admixture.

Recovery of  $T_2$  after iv injection in normal subjects has been found to be, on the average, 1.1%, with SD of 0.5% (14). In the present study (Table II), the  $T_2$  recovery after iv injection exceeds 2.5% (regarded as the upper normal limit) in eight of the 20 patients, thus demonstrating the existence of abnormal right-to-left shunt in these

subjects. Of the eight patients with venoarterial admixture exceeding 6% of the cardiac output, five had  $T_2$  recoveries greater than 4%; in the remaining three, it was 1.0, 1.2, and 2.1%, respectively.

The portopulmonary shunt has not been measured in normal subjects. The recovery of  $T_2$  after intrasplenic injection was in six of the ten patients studied by this technique (Table II) considerably (i.e., from 2 to 8 times) greater than that following iv injection. Thus, in these six patients, the blood leaving the spleen bypasses the pulmonary capillaries to a greater extent than mixed venous blood does. This group includes three of the four patients with abnormal venoarterial admixture. It is not possible to demonstrate any significant correlation between the portal pressure and intrasplenic/intravenous recovery ( $r = 0.4$ ,  $p > 0.10$ ) or the total venoarterial admixture ( $r = 0.6$ ,  $p > 0.05$ ).

#### DISCUSSION

Decreased oxygen saturation of arterial blood could be the result of decreased arterial oxygen tension, or of abnormalities of the hemoglobin

TABLE II

Results of analysis of arterial oxygen tension, estimation of total venoarterial admixture ( $\dot{Q}_{va}/\dot{Q}_t$ ) by analysis of oxygen tension of arterial blood during respiration in pure oxygen, and results of analysis of arterial blood after tritium injection\*

Patient no.	Hemoglobin	Arterio-venous oxygen difference	Arterial oxygen tension	$\dot{Q}_{va}/\dot{Q}_t$ Percentage of cardiac output	Recovery of tritium injected	
					Intravenous	Intrasplenic
	g/100 ml	ml/100 ml	mm Hg		%	%
1	10.5		77	9	1.0	
2	11.6	4.8	80	9	1.2	
3	9.8	3.8	80	12	4.1	
4	10.7	3.7	90	2	0.7	
5	9.7		98	4	1.5	
6	12.1		94	6	3.0	
7	11.1		96	3	2.3	
8	12.8		85	8	2.1	
9	14.8		92	4	2.1	
10	12.7			4	3.5	
11	9.6		70	21	11.3	8.1
12	12.4	6.0	84	8	4.2	36.5
13	13.3	3.6	100	3	3.6	4.4
14	12.3	4.3	92	5	1.6	0.9
15	12.3		88	8	6.1	13.6
16	13.5	5.1	87	2	0.9	4.1
17	9.5		80	6	1.8	6.5
18	11.7		76	12	8.5	16.7
19	12.1		96	4	1.5	9.8
20	13.0		95	2	1.8	1.5
Average	11.7		87.4	6.6	3.14	

\* In estimating  $\dot{Q}_{va}/\dot{Q}_t$ , an arteriovenous oxygen difference of 4.5% by volume has been assumed in all cases, even when the arteriovenous oxygen difference has been measured.

causing a decrease in the oxygen affinity of hemoglobin. The latter explanation was advanced by Keys and Snell (19) as a cause of cyanosis in liver disease. Later investigations into the oxygen-hemoglobin dissociation curve of blood from patients with cirrhosis of the liver, however, have not confirmed this finding (20), and reduced oxygen tension of arterial blood has been reported in a number of such patients (4-8, 20-21).

Low arterial oxygen tension may result from uneven distribution of inspired air in the lungs, diffusion difficulties, or venoarterial admixture. The diffusion capacity for oxygen has been determined in patients with cirrhosis of the liver (4, 20, 21) and found to be normal. Estimation of venoarterial admixture by direct measurement of the arterial oxygen tension during oxygen respiration has been reported in a number of patients with cirrhosis of the liver. Wilson and associates (1) found an average venoarterial admixture of 5.8% of the cardiac output in ten patients; Williams (4) reported an average admixture of 9.7% in nine patients; Georg, Mellemgaard, Tygstrup, and Winkler (5) found a venoarterial admixture of 1 to 49%, averaging 9.5%, in 19 patients; and Bashour, Miller, and Chapman (8) obtained an average value of 18% in 15 patients. Apparently, whereas gross shunting causing arterial unsaturation is not often found, abnormal degrees of venoarterial admixture are common in cirrhosis of the liver. In the twenty patients studied, the average venoarterial admixture (6.6%) was only slightly elevated, but eight of the patients had values exceeding the upper normal limit.

Since calculation of the relative venoarterial shunt in each patient is based on an assumed arteriovenous oxygen difference, the result must be taken as an approximate value only. The arteriovenous oxygen difference does not deviate much from 4% by volume in normal resting subjects (22), but may be somewhat lower in patients with cirrhosis of the liver, owing to a tendency in these patients to increased cardiac output. Direct measurement of arteriovenous oxygen difference has been carried out in few patients with cirrhosis of the liver. From the data of Abelman, Kowalski, and McNeely (23) an average arteriovenous oxygen difference of 3.4% by volume in eleven patients can be calculated. Georg

and associates (5) reported an average arteriovenous oxygen difference of 4.0% by volume in four patients. The above-mentioned estimations of venoarterial shunt in patients with cirrhosis of the liver (1, 4, 5, 8) have all been carried out with assumed arteriovenous oxygen differences of 4.3 to 5% by volume, and therefore probably represent minimal values. In the present study, an assumed arteriovenous oxygen difference of 4.5% was chosen to allow the results to be compared with those of previous workers. The average value, however, of the actually measured arteriovenous oxygen differences in seven patients (Table II) is 4.5% by volume.

Measurements of venoarterial admixture based on oxygen tension determinations give an overall estimation, but do not supply any information concerning the channels through which the admixture occurs. An approach to this problem based on the use of inert gases of low solubility has recently been developed (14, 24-26). When such gases (krypton<sup>85</sup>, T<sub>2</sub>) are injected intravenously as a physical solution, they will to a large extent leave the blood during the first passage through normal lung capillaries, whereas blood bypassing air-filled alveoli will carry the gas to the arterial blood. Analysis of the arterial blood thus permits an estimation of this bypass.

Fritts and co-workers (18) used krypton<sup>85</sup> for the estimation of right-to-left shunt in 14 patients with cirrhosis of the liver and found the shunt to be insignificant. In one patient the shunt was calculated to be 3% of the cardiac output, in two patients 2%, and in the remaining patients less than 1%. In the present study, the T<sub>2</sub> recoveries indicate abnormal right-to-left shunts in eight of the 20 patients.

The nature of the right-to-left shunt cannot be evaluated with the present method. It might be effected through direct arteriovenous anastomoses as those demonstrated with special post-mortem technique (2, 9), or through totally atelectatic but perfused lung tissue. Four of the eight patients with abnormal right-to-left shunt had ascites and might therefore have had basilar atelectasis. Only one patient (no. 11) had abnormalities visible on radiography of the lungs. Without producing extensive atelectasis, ascites might give rise to uneven distribution of ventilation-perfusion ratios. In the authors' experience, however, even the se-

vere ventilation-perfusion disturbances of emphysematous lungs do not give rise to abnormal recoveries of  $T_2$ .

When iv injections are used, contributions to the admixture from other sources than the pulmonary artery will not be included. If, however, the gas is injected at other sites, different components of venoarterial admixture may be labeled. Attempts to label part of the portal blood in this way have been carried out. Fritts and co-workers (18) injected krypton<sup>85</sup> as a physical solution into the duodenum in four normal subjects and in five patients with cirrhosis of the liver, and compared the concentrations of the gas in blood from the pulmonary artery and the gas in blood from the brachial artery with those observed after iv injection. The patients with cirrhosis of the liver showed a greater krypton<sup>85</sup> concentration in arterial blood after instillation of the tracer into the duodenum than the normal subjects did. This indicates the existence of portopulmonary shunts in the patients, but gives no information concerning the magnitude of the blood flow through the channels.

Shaldon and colleagues (27) in 12 patients compared the arterial concentrations of krypton<sup>85</sup> in samples drawn during the first minute after iv injection and injection into the spleen of the same amount of krypton<sup>85</sup>. They found in 11 patients lower concentrations in arterial blood after injections into the spleen, but one patient showed a fourfold increase of the concentration of krypton<sup>85</sup> after injection into the spleen relative to that resulting from iv injection. This indicates that shunting of blood through portopulmonary channels occurred in at least one of the 12 patients studied. No definite conclusions can be drawn from the negative results, since slow emptying of the spleen will give rise to low concentrations that may mask portopulmonary shunt. The authors explored this problem in two patients by adding a nonvolatile tracer (radioactive human iodinated serum albumin) to the injection and found the absorption from the spleen to be incomplete in both cases.

In the present study, the calculations are based on the ratio of volatile ( $T_2$ ) to nonvolatile (THO) tracer, thus eliminating errors due to incomplete absorption. The recovery of  $T_2$  after intrasplenic injection indicates the proportion of the labeled

blood, i.e., the blood leaving the spleen, that reaches arterial blood without passing air-filled alveoli. The magnitude of this shunt in relation to the total cardiac output cannot be determined by the present method. A recovery value after intrasplenic injection considerably greater than that following iv injection signifies, however, that blood leaving the spleen bypasses the alveoli to a greater extent than mixed venous blood does. This is the case in six of the ten patients studied in this way.

The validity of  $T_2$  recovery values for estimation of pulmonary bypass depends on the same proportion of shunted and unshunted blood reaching the arterial sampling site during the sampling period and no recirculation occurring. It is possible that blood from the spleen, taking the normal route through the liver, passes more slowly than shunted blood, and this may result in overestimation of the portopulmonary shunt. To test this, the portopulmonary shunt in eight patients was calculated from samples drawn in the course of 60 seconds, which in most cases resulted in slightly smaller shunts than the usual 30-second samples. This decrease, however, did not exceed what might be accounted for by recirculation.

It should be emphasized that the question of recirculation with the present method does not have the same critical importance as with the dye-dilution methods. The  $T_2$  gas itself will, for all practical purposes, disappear during the second passage through the lungs, whereas a small amount of recirculated THO may be added to the blood

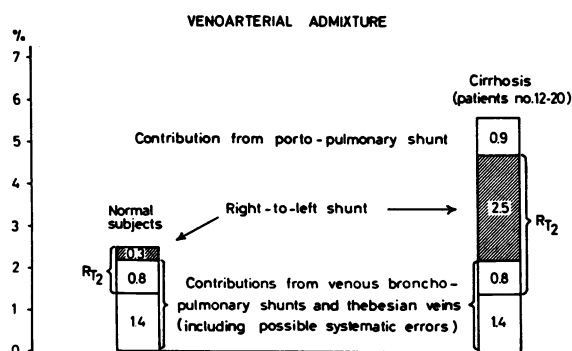


FIG. 1. ILLUSTRATION OF A ROUGH CALCULATION OF THE CONTRIBUTIONS OF THE RIGHT-TO-LEFT SHUNT AND THE PORTOPULMONARY SHUNT TO THE TOTAL VENOARTERIAL ADMIXTURE.  $R_{T_2}$  is recovery of tritium from the arterial blood after intravenous injection. For details, see text.

sample, resulting in a slight underestimation of the shunt.

Figure 1 shows an attempt to evaluate the relative contributions from various sources to the total venoarterial admixture in nine patients subjected to intrasplenic- and iv-injection studies. (Patient 11 has been omitted because of the great discrepancy between total venoarterial admixture and  $T_2$  recoveries, probably caused by a pulmonary infiltrate.) In normal subjects, an average  $T_2$  recovery of 1.1% has been found (14). In studies using simultaneous iv injections of  $T_2$  and krypton<sup>85</sup>, a right-to-left shunt averaging 0.3% has been calculated (17), the remaining  $T_2$  recovery being caused by alveolar back-pressure. Thus, the total venoarterial admixture of 2.5% found by the present method in normal subjects could be supposed to include a right-to-left shunt of 0.3% of the cardiac output, the remaining 2.2% being caused by blood flow through venous bronchopulmonary anastomoses and Thebesian veins (this includes a possible overestimation by the oxygen method). The average venoarterial admixture in the nine patients is 5.6%. The average recovery of  $T_2$  after iv injection is 3.3%. If contributions from venous bronchopulmonary and Thebesian veins (and any systematic error of the method) are considered identical with those in normal subjects, an amount of 0.9% of the cardiac output is left for contributions from portopulmonary shunts. If it is assumed that the greater part of the portal blood flow is labeled by the intrasplenic tracer injection, and this flow amounts to 20% of the cardiac output, this will, with the average portopulmonary shunt of 7.1% in excess of the right-to-left shunt, contribute 1.4% to the total venoarterial admixture.

These considerations are rough estimates based on possibly incorrect assumptions. They have been included to show that the right-to-left shunt and portopulmonary shunt together account for the entire increase in venoarterial admixture, and that right-to-left shunt is probably the more important source of venoarterial admixture in these patients.

#### SUMMARY

In 18 patients with cirrhosis of the liver and two patients with extrahepatic portal hypertension, the total venoarterial admixture was determined from

the alveolar-arterial oxygen tension gradient during oxygen respiration, and the right-to-left shunt was estimated with intravenous injections of tritium. Ten of the patients received intrasplenic injections of tritium for determination of portopulmonary shunt. The two patients with extrahepatic portal hypertension showed normal venoarterial admixture, whereas in eight patients with cirrhosis of the liver, the venoarterial admixture exceeded 6% of the cardiac output. The results of the tritium studies indicate that intrapulmonary shunts as well as portopulmonary shunts may be operative in patients with cirrhosis of the liver. Abnormal right-to-left shunts were demonstrated in a number of such patients, and the results confirm the occasional existence of considerable portopulmonary shunts in cirrhosis of the liver.

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