

The circulation, the lung, and finger clubbing in hepatic cirrhosis

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Haemodynamic and respiratory data were obtained by gasometric methods in two groups of patients with hepatic cirrhosis, who were distinguishable by the presence or absence of finger clubbing. Cardiac index and venoarterial admixture were significantly higher in cases with clubbing; these findings are discussed. However, levels of venoarterial admixture were normal in four with clubbing, which suggests that increased right-to-left shunt flow is not an essential factor in the pathogenesis of clubbing in liver disease.

Finger clubbing is most often seen in diseases of the lungs or heart, but it is also a common finding in hepatic cirrhosis. The pathogenesis of clubbing is not fully understood, but various studies (Mendlowitz, 1938; Charr and Swenson, 1946; Lovell, 1950; Wilson, 1952) have shown that it may be a consequence of digital vasodilatation. Furthermore, Hall (1959) suggested that venoarterial admixture might be responsible for clubbing in certain cardiopulmonary diseases; he proposed that a vasodilator substance normally detoxicated in the pulmonary capillary bed could thereby enter the systemic circulation and cause the associated digital vascular changes. Since venoarterial admixture in cirrhosis may result from both intrapulmonary arteriovenous (Rydell and Hoffbauer, 1956) or porta-pulmonary anastomoses (Calabresi and Abelmann, 1957), and peripheral vasodilatation may be widespread giving an increased cardiac output (Kowalski and Abelmann, 1953), it has seemed possible that this lung bypass mechanism might account for clubbing in liver disease (Stein and Stein, 1961; Bashour, McConnell, and Miller, 1967). Previous evidence concerning the association of clubbing and increased venoarterial admixture in cirrhosis has been conflicting: cases with cyanosis invariably have clubbing, but the converse has not been true and patients with clubbing may have normal arterial

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saturation (Abelmann *et al.*, 1961; Shaldon *et al.*, 1961). However, venoarterial admixture must be fairly large to reduce arterial saturation significantly (Georg *et al.*, 1960), especially in cirrhosis when increased peripheral blood flow is accompanied by a small arteriovenous oxygen difference.

The purpose of our study was to establish the interrelation of arterial hypoxaemia, venoarterial admixture, hyperkinetic circulation, and finger clubbing in chronic liver disease.

Subjects and methods

We investigated 24 volunteer patients with hepatic cirrhosis, 12 with and 12 without clubbing. No case was severely decompensated; none had ascites or more than mild encephalopathy. We deliberately selected cases, where necessary, to equalize the mean serum albumin levels in the two groups for the purpose of keeping the groups closely matched for liver failure. For comparison we assessed respiratory function in 12 healthy control subjects. All patients were studied at rest, supine, without sedation, and in the post-absorptive state.

A fine nylon microcatheter (Portex) was flow-guided to the pulmonary artery from the right antecubital vein using a pressure transducer and oscillographic recorder (Sanborn). A polyethylene cannula was placed in the right brachial artery. After an adequate settling down period, expired gas was collected for 3 minutes in a Douglas bag while the patient breathed ambient air using a mouthpiece, noseclip, and one-way valve. During this time mixed venous and arterial blood samples were drawn into heparinized syringes. Next the patient breathed 99.5 per cent oxygen for at least 15 minutes after which further blood samples were taken. PO₂, PCO₂, and pH of blood samples were measured by Radiometer electrodes. The

expired air was analysed for O_2 and CO_2 by the Haldane apparatus. Alveolar PO_2 was calculated by the alveolar air equation, assuming that arterial and alveolar PCO_2 were equal. The alveolar-arterial PO_2 difference ($A-aDO_2$) was obtained by subtraction. Oxygen contents of blood samples were calculated from their oxygen tensions using the data of Kelman and Nunn (1966) to determine oxygen saturation and the data of Christoforides and Hedley-Whyte (1969) to determine dissolved oxygen. Oxygen consumption was estimated from the composition of expired air, which allowed cardiac output (\dot{Q}_t) to be derived by the Fick principle. Venous admixture (\dot{Q}_{va}) was calculated from the measurements obtained during oxygen breathing using the standard shunt formula:

$$\frac{\dot{Q}_{va}}{\dot{Q}_t} = \frac{CC_{O_2} - CA_{O_2}}{CC_{O_2} - C\bar{V}_{O_2}}$$

Where CC_{O_2} , CA_{O_2} , and $C\bar{V}_{O_2}$ are the oxygen contents of end-pulmonary capillary, arterial, and mixed venous blood respectively; oxygen equilibration between end-capillary blood and alveolar gas was assumed to be complete. In our control subjects mixed venous blood was not sampled, but its oxygen content was assumed to be 4.5 volumes per cent less than arterial blood.

Results

The clinical and physiological findings are shown in the Table. Mild arterial hypoxaemia was common in the patients with cirrhosis. In the group with clubbing the mean arterial PO_2 was slightly lower and the mean $A-aDO_2$ was slightly higher than in the group without clubbing, but neither difference was significant ($P > 0.5$, and $0.1 < P < 0.2$). Cardiac indices (Fig. 1) were higher ($P = 0.001$) and arteriovenous O_2 differences were lower ($0.001 < P < 0.005$) in the patients with clubbing compared with those without clubbing. Venous admixture was higher in cases with clubbing than in those without clubbing ($0.01 < P < 0.05$), but normal levels were found in several patients from each group (Fig. 2). A positive correlation was obtained between the increases of cardiac index and venous admixture (Fig. 3). This was significant when the results of both groups of patients were pooled ($r = 0.74$, $P < 0.001$). When taken as separate populations this correlation was still significant in the cases with clubbing ($r = 0.66$, $0.01 < P < 0.05$) but was not significant in the group without clubbing ($r = 0.49$, $P = 0.1$).

Discussion

Our results confirm an earlier impression that the hyperdynamic circulation of hepatic cirrhosis is often pronounced in patients with finger clubbing (Bashour *et al.*, 1967). The similar levels of arterial O_2 tensions in our

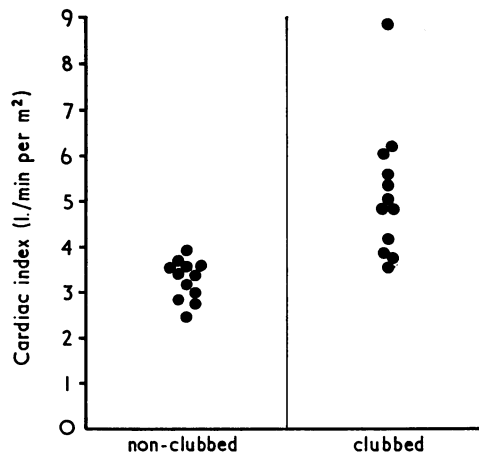
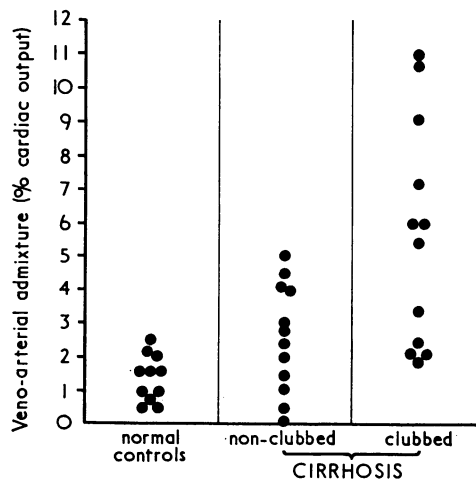


FIG. 1 Levels of cardiac index in cases of hepatic cirrhosis with and without clubbing.

patients with and without clubbing also agree with previous reports in which no correlation was found between clubbing and arterial unsaturation in hepatic cirrhosis (Abelmann *et al.*, 1961; Shaldon *et al.*, 1961). Thus it is interesting that venous admixture was significantly higher in the cases with clubbing compared to those without clubbing. This paradox was largely due to the smaller arteriovenous O_2 differences in the patients with clubbing, which had lessened the reduction of their arterial O_2 tensions by a given amount of venous admixture.

The regional circulatory disturbances in cirrhosis are complex, but it would be sur-

FIG. 2 Levels of venous admixture in normal subjects and cases of hepatic cirrhosis with and without clubbing.



prising if some were not interrelated in their causation. A characteristic microvascular change at many sites is the opening of arterio-venous anastomoses, but the vasodilator mechanism for this is obscure, and multiple factors may be involved. The presence of these anastomoses in the pulmonary circulation is well established as the chief cause of the raised venoarterial admixture in liver disease. It has also been suggested that increased anastomotic flow in the peripheral and digital circulations, respectively, may account for the high cardiac output in cirrhosis (Silverstein, 1956) and the increased digital blood flow associated with clubbing (Lovell, 1950; Wilson, 1952). However, it remains conjectural whether or not the correlation found between clubbing, increased venoarterial admixture, and hyperkinetic circulation in our patients was due to a common response in their digital, pulmonary,

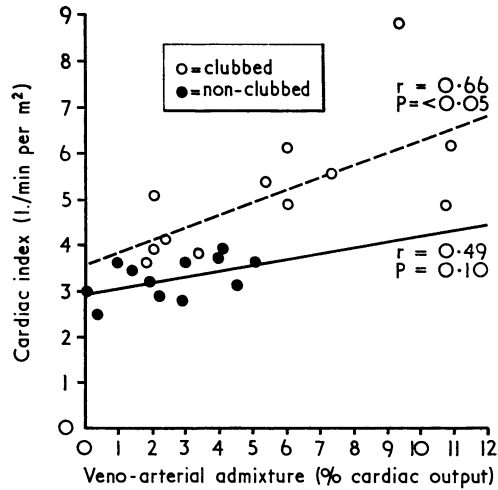


FIG. 3 Relation of cardiac index to veno-arterial admixture in cases of hepatic cirrhosis.

TABLE Clinical and physiological data in cases of hepatic cirrhosis with and without finger clubbing, and physiological data in healthy control subjects

Case No.	Age (yr)	Spiders	Jaundice	Spleen	Varices	Serum albumin (g/100 ml)	Arterial O ₂ tension (mmHg)	Alv.-art. O ₂ diff. (mmHg)	Cardiac index (l./min/m ²)	Art.-ven. O ₂ diff. (vol. %)	Veno-arterial admixture (% card. output)
Patients with clubbing											
1	61	-	+	-	-	4.3	78	22	4.2	3.2	2.4
2	53	-	-	-	-	3.9	91	20	5.1	2.9	2.1
3	52	+	+	+	-	3.2	85	31	3.8	3.4	3.4
4	47	+	+	-	-	3.4	88	30	6.1	2.4	6.2
5	30	+	-	+	-	4.0	69	43	5.6	3.6	7.3
6	17	-	+	-	-	1.8	66	41	6.2	3.1	11.0
7	43	-	+	+	-	4.0	84	23	3.9	4.5	2.1
8	45	+	+	+	+	3.5	105	26	4.9	1.8	6.2
9	45	-	-	+	+	3.4	82	29	5.4	2.7	6.1
10	26	+	+	+	-	3.5	85	27	8.8	1.3	9.2
11	61	+	+	-	-	3.1	78	39	3.6	3.2	1.9
12	59	+	-	-	-	3.4	67	43	4.9	2.5	10.8
Mean	45					3.5	81	31	5.2	2.9	5.7
SD	14					0.6	11	8	1.4	0.8	3.4
Patients without clubbing											
13	53	+	+	-	+	4.2	87	28	3.9	4.1	4.2
14	46	+	+	+	-	4.3	79	26	3.1	3.7	4.6
15	62	+	-	+	+	3.1	73	32	3.7	2.9	4.1
16	45	-	+	-	-	3.2	93	24	2.9	4.0	2.3
17	28	-	+	+	+	4.6	106	15	3.6	3.5	1.0
18	59	-	+	-	-	3.3	71	39	3.6	4.5	5.1
19	43	+	+	+	-	1.7	85	25	3.6	3.8	3.0
20	66	-	-	-	-	3.4	90	21	3.2	4.3	2.0
21	21	+	+	-	+	2.6	86	20	3.5	4.0	1.4
22	39	+	-	-	-	4.0	69	29	3.0	5.1	0
23	54	+	-	-	-	3.4	83	25	2.5	6.4	0.4
24	38	+	-	-	-	4.1	81	26	2.8	4.3	2.9
Mean	46					3.5	84	26	3.3	4.2	1.6
SD	14					0.8	10	6	0.4	0.9	1.7
12 healthy control subjects											
Mean	42						94	11			1.2
SD	14						8	7			0.8

and peripheral vascular beds to a single vasodilator mechanism.

The estimated levels of venoarterial admixture were normal in four patients with clubbing (Cases 1, 2, 7, and 11), but this finding requires further comment. Our methods tend to underestimate the total right-to-left shunt flow in cases with functioning porta-pulmonary anastomoses; the oxygen content of portal venous blood is high (Bradley *et al.*, 1953) and in our calculations we assumed that pulmonary arterial blood and blood traversing all right-to-left shunts were equally saturated. This assumption seems justifiable as flow through these porta-pulmonary anastomoses is comparatively small and has been found negligible in cases without prominent signs of a portal-systemic collateral circulation (Nakamura *et al.*, 1965). In particular, our four patients with clubbing and apparently normal levels of venoarterial admixture had no clinical or radiological evidence of such a collateral circulation, which makes a serious underestimate of their venoarterial admixture unlikely. Thus an increased right-to-left shunt flow does not seem essential for the development of clubbing in hepatic cirrhosis.

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