Hypoxaemia and cirrhosis of the liver¹

AKIRA FUNAHASHI, AHAMED V. P. KUTTY,
and SANDRA L. PRATER

*Veterans Administration Center, Wood, Wisconsin and Departments of Medicine and Physiology
of the Medical College of Wisconsin, Milwaukee, Wisconsin, USA*

Funahashi, A., Kutty, A. V. P., and Prater, Sandra L. (1976). *Thorax*, 31, 303–308. **Hypoxaemia and cirrhosis of the liver.** In order to determine the frequency of hypoxaemia and to evaluate the role of increased closing capacity in producing hypoxaemia in patients with cirrhosis of the liver, 13 patients with well-established cirrhosis were studied. Arterial blood gases, spirometry, lung volume, and closing capacity measurements were made with the patients in the seated and recumbent positions after exclusion of cardiopulmonary dysfunction. Four of 13 and six of 12 patients exhibited significant hypoxaemia in the seated and recumbent positions respectively. Five of 13 patients showed a closing capacity greater than predicted. This frequency of increased closing capacity was not higher than in a group of smokers of the same age. Unlike Ruff *et al.* (1971), we did not find a consistent relationship between hypoxaemia and closing capacity.

The association between hypoxaemia and cirrhosis of the liver has been known since the report of Snell in 1935. Abnormal oxygen dissociation was initially thought to be the cause of this phenomenon, but subsequent studies showed that the change was not sufficient to explain the degree of hypoxaemia (Heinemann, Emirgil, and Mijnsen, 1960; Caldwell, Fritts, and Cournand, 1965). Portopulmonary or intrapulmonary shunts were postulated as a primary cause of hypoxaemia in cirrhotic patients since anatomical communications between the portal vein and the pulmonary venous system were observed in necropsy material (Calabresi and Abelmann, 1957) and produced in experimental animals (Khaliq, Kay, and Heath, 1972). The physiological significance of this shunt flow was studied by Nakamura *et al.* (1965) who found no positive correlation between such flow and hypoxaemia. The existence of intrapulmonary shunts has been well documented (Rydell and Hoffbauer, 1956; Hansoti and Shah, 1966; El Gamal *et al.*, 1970), but its incidence was found to be very low (Berthelot *et al.*, 1966; Stanley, Ackrill, and Wood, 1972).

In recent years ventilation-perfusion abnormality has been considered to be the major mechanism in causing hypoxaemia among patients

with cirrhosis of the liver (Karetzky and Mithoefer, 1967; Cotes *et al.*, 1968).

Since the introduction of the measurement of closing volume, it has been suggested that a smaller functional residual capacity (FRC) than closing capacity (CC) may be a cause of ventilation-perfusion abnormality leading to hypoxaemia (Craig *et al.*, 1971) on the basis that if CC is greater than FRC the airways of dependent parts of the lung are closed during a part of the normal respiratory cycle. If perfusion continues through these areas during airway closure, it will result in a shunt and lead to arterial hypoxaemia. The CC tends to remain unchanged for both sitting and recumbent positions while FRC usually is smaller in the recumbent than in the sitting position. Therefore, the CC may exceed FRC only in the recumbent position (Leblanc, Ruff, and Milic-Emili, 1970). This relationship has been suggested as a mechanism for hypoxaemia seen only in the recumbent position (Hamosh and DaSilva, 1973).

Ruff and his associates (1971) studied the closing capacity of cirrhotic patients who had hypoxaemia and found that the CC was uniformly increased. They further reported that the CC was greater than FRC in most of their patients.

The purpose of the present study was to determine the frequency of hypoxaemia in patients

¹This work is a result of VA project No. 2965-05.

with cirrhosis of the liver who had no appreciable cardiopulmonary abnormalities, and to determine the significance of the FRC-CC value in producing hypoxaemia.

MATERIAL AND METHODS

Thirteen patients were selected for the study. All had cirrhosis of the liver, 10 had moderate to marked ascites, and three had no ascites. The criteria for selection were: (1) cirrhosis of the liver verified by biopsy; (2) absence of cardiopulmonary abnormalities including airways obstruction; and (3) normal chest radiograph. Informed consent was obtained from all subjects.

Spirometry was measured with a Stead-Wells spirometer and the lung volumes were determined by the helium dilution method (Meneely *et al.*, 1960). The closing volume was measured by the single breath nitrogen washout method described by Buist and Ross (1973) using an expiratory flow rate below 0.3 l/s. The closing volume was that between the point of terminal rise in nitrogen concentration and the end of expiration. Closing volume plus residual volume was termed closing capacity. Only tracings showing a distinct rise in N_2 concentration were used, and tracings which had a vital capacity deviating more than $\pm 10\%$ from that of the initial measurement with the Stead-Wells spirometer were discarded. Closing capacity is expressed either as a per cent of total lung capacity or as an actual volume. The coefficient of variation of repeated measurements of closing capacity/TLC in normal subjects in our laboratory, 8.7%, is similar to that reported by others (McFadden, Holmes, and Kiker, 1975).

Arterial blood was obtained from the brachial artery by an arterial puncture with a 20 gauge

needle, and oxygen tension (P_{aO_2}), carbon dioxide tension (P_{aCO_2}), and pH were measured with the Radiometer gas analyzer. All measurements were performed in both sitting and recumbent positions. The sequence of study was: (1) collection of arterial blood, (2) spirometry, (3) lung volume measurements, and (4) closing volume. The patients assumed each position for a minimum of 15 minutes before the start of the study to allow the redistribution of perfusion.

Eleven healthy smokers of age comparable to that of the cirrhotic patients were selected to measure the effect of cigarette smoking alone on closing volume and arterial blood gases as well as to see the relationship between FRC and CC. The predicted values for spirometry were based on the Veterans Administration and Army Cooperative Study (Kory *et al.*, 1961).

RESULTS

Table I shows the age, smoking history, and spirometric measurements of 13 cirrhotic patients. Cases 3, 4, and 10 showed moderate reduction of FVC, but FVC was normal or near normal in the remaining cases. In all cases forced expiratory volume in one second (FEV_1)/FVC was greater than 70%, indicating that there was no large airway obstruction. Table II shows the age, smoking history, spirometric measurements, and P_{aO_2} of 11 healthy smokers. FVC and FEV_1 /FVC were normal except in cases 2 and 9, who had a minimally low FEV_1 and FEV_1 /FVC ratio, respectively. Arterial oxygen tension (P_{aO_2}) was generally above 80 mmHg except for cases 2 and 9, who had slight hypoxaemia.

The P_{aO_2} for both sitting and recumbent positions are shown in Figure 1. The shaded area

TABLE I
AGE, SMOKING HISTORY, AND SPIROMETRY OF PATIENTS WITH CIRRHOSIS OF THE LIVER

	Case	Age	Smoking ¹	FVC (l)	FEV_1 /FVC (%)
Cirrhotic patients with ascites	1	56	30	4.35 (96) ²	79
	2	52	25	3.70 (85)	77
	3	50	25	1.93 (50)	74
	4	46	20	3.36 (63)	81
	5	59	35	2.82 (79)	76
	6	41	20	4.75 (102)	79
	7	32	15	3.63 (75)	85
	8	68	40	2.75 (100)	76
	9	66	40	3.92 (98)	76
	10	48	28	1.66 (45)	71
Cirrhotic patients without ascites	11	48	20	4.59 (87)	79
	12	51	30	4.01 (105)	81
	13	57	30	3.05 (94)	85
	Mean	52	27	83%	

¹Pack years.

²Percent of predicted value.

TABLE II
AGE, SMOKING HISTORY, AND SPIROMETRY OF
HEALTHY SMOKERS

Case	Age	Smoking ¹	FVC	FEV ₁ /FVC	PaO ₂
1	48	30	4.10 (105) ²	85	93
2	56	56	3.76 (82)	76	72
3	44	28	5.78 (116)	75	93
4	54	76	3.61 (94)	80	111
5	53	35	4.80 (111)	84	86
6	59	10	3.76 (94)	81	84
7	40	36	4.30 (91)	80	86
8	58	100	3.90 (90)	84	85
9	57	34	4.57 (112)	69	76
10	59	21	3.90 (93)	77	84
11	50	12	4.35 (98)	78	91
Mean	52	40	99%		

¹Pack years.

²Percent of predicted value.

FIG. 1. Level of arterial oxygen tension of cirrhotic patients in both sitting and recumbent positions. An arrow indicates the change from sitting to recumbent position; — indicates no change: ○ patient with ascites and normal PaO₂; ● patient with ascites and hypoxaemia; △ patient without ascites and normal PaO₂; ▲ patient without ascites and hypoxaemia.

is mean ± 1 SD for PaO₂ in healthy subjects (Sorbini *et al.*, 1968). In the sitting position four of 10 patients with ascites showed hypoxaemia and three of them had PaO₂ values below 66 mmHg. None of the patients without ascites showed hypoxaemia. Most of the patients with ascites showed a slight hyperventilation, with arterial carbon dioxide tension (Paco₂) in the range of 31 to 35 mmHg, except case 9, who showed a marked hyperventilation (Paco₂ of 23 mmHg and PaO₂ of 120 mmHg). There was no appreciable change in Paco₂ between the sitting and recumbent position in any patient studied. In the recumbent position for which the changes of PaO₂ from the sitting

position are indicated by the arrow in Fig. 1, five of nine patients with ascites showed hypoxia. One patient (10), who was hypoxaemic in the sitting position, was unable to assume the recumbent position because of a large amount of ascites and, therefore, was not included. Three patients, two with ascites and one without ascites, became hypoxaemic in the recumbent position. The degree of hypoxaemia was not altered significantly with a change in body position for three subjects who were hypoxaemic while both sitting and recumbent. Figure 2 shows the CC of all 13 patients, superimposed on the shaded area which indicates the predicted normal value according to Buist (1973). Five of 10 ascitic patients showed an increased CC, whereas all three non-ascitic patients were within the normal range. Of the five who had increased CC, two had hypoxaemia, whereas two patients with hypoxaemia had a normal CC. Of 11 healthy smokers measured for this study, five showed an increased CC. In two normal smokers with hypoxaemia, one had an increased CC while the other had a normal CC.

The relationship between FRC and CC in cirrhotic patients is shown in Figure 3. Most of the patients in the sitting position who had a normal PaO₂ had FRC greater than CC. In the four patients who had a low PaO₂, however, two showed FRC greater than CC (FRC-CC > 0), and two showed FRC smaller than CC (FRC-CC < 0). In the recumbent position most of the hypoxaemic patients had an FRC value smaller than CC (FRC-CC < 0). However, there was a wide scatter

FIG. 2. Closing capacity (CV + RV)/TLC of cirrhotic patients. Shaded area is a predicted normal from Buist and Ross (1973) (see text): ○ patient with ascites and normal PaO₂; ● patient with ascites and hypoxaemia; △ patient without ascites and normal PaO₂; ▲ patient without ascites and hypoxaemia.

FIG. 3. FRC-CC value (litre) of cirrhotic patients in both sitting and recumbent positions. An arrow indicates the change from sitting to recumbent: ○ patient with ascites and normal PaO_2 ; ● patient with ascites and hypoxaemia; △ patient without ascites and normal PaO_2 ; ▲ patient without ascites and hypoxaemia.

FIG. 4. FRC-CC value (litre) of healthy smokers in sitting position: ○ subject with normal PaO_2 ; ● subject with hypoxaemia.

of the FRC-CC value in patients who showed normal PaO_2 in the recumbent position. Figure 4 shows this FRC-CC value among the healthy smokers. Again there was a wide scatter of this value. Two subjects who had hypoxaemia showed FRC value smaller than CC. On the other hand, four subjects without hypoxaemia had FRC-CC value below zero.

DISCUSSION

The incidence of hypoxaemia among patients with cirrhosis of the liver has been reported in various series (Blackburn *et al.*, 1960; Rodman, Sobel,

and Close, 1960; Bashour, Miller, and Chapman 1961), though pulmonary disease or congestive heart failure, both of which may cause hypoxaemia, were not carefully excluded. In the present study we excluded hypoxaemia due to cardio-pulmonary dysfunction, yet still found the frequency of hypoxaemia to be surprisingly high. Since many patients with cirrhosis have associated pulmonary disease or congestive heart failure, the overall prevalence of hypoxaemia would be even higher.

Hypoxaemia was more frequent in the recumbent position. The degree of hypoxaemia, however, did not differ in two patients with ascites who were hypoxaemic in both sitting and recumbent positions, and one patient who was hypoxaemic only in the recumbent position did not have ascites. These observations suggest that the mechanical disturbance of diaphragmatic movement due to ascites was probably not a major factor in producing hypoxaemia among these patients. It has been well established that smokers have a higher incidence of increased CV and CC (Buist, 1973; Funahashi, Melville, and Hamilton, 1975). In the present series, the incidence of increased CC among the subjects with cirrhosis of the liver was no greater than that in healthy smokers with a comparable smoking history. This suggests that cirrhosis of the liver, even with the presence of a moderate to marked degree of ascites, did not specifically alter the CC. That conclusion differs from that of Ruff *et al.* (1971), though the reason is not apparent. It may be due to the difference of subjects studied or the different method used to measure the closing capacity. In their series none had ascites and all but two had hypoxaemia, whereas a majority of our patients had moderate to marked ascites and only four had hypoxaemia in a sitting position. Two of these four hypoxaemic patients, however, had normal CC. If high CC were secondary to increased interstitial fluid around the small airways, as postulated by Ruff *et al.* (1971), one might expect to see any effect of cirrhosis exaggerated by the presence of ascites.

Another aspect of the present study that needs to be considered is the possible effect of lung restriction due to ascites upon calculation of CC. The CC is calculated by adding RV to the closing volume and dividing by TLC. Therefore, if TLC decreased while RV remained unchanged, a net effect of low TLC upon calculation of CC would be an erroneous increase of calculated CC. In our series, RV was essentially within the normal range in those cases where there was a significant reduction of TLC. Since the frequency of increased

CC in our cirrhotic patients was no greater than that in healthy smokers, this possible effect of restrictive change due to ascites on the calculation of CC appears to be minimal.

Ruff *et al.* (1971) used a bolus gas technique whereas we used a single breath nitrogen washout method. These two methods are based on different principles but correlate well in healthy subjects (Travis, Green, and Don, 1973). It is, however, not certain that they correlate in disease. The possibility that a change of regional RV caused by ascites could have resulted in a low CC measurement is not entirely ruled out.

We were unable to find a correlation between FRC and CC relationships and hypoxaemia. This led us to search our files for this relationship among healthy smokers. To our surprise, four smokers out of 11 examined had a normal Pao₂ even though their FRC was much smaller than CC. Only two subjects with FRC smaller than CC exhibited hypoxaemia. It is, therefore, evident that having a CC larger than FRC does not necessarily result in hypoxaemia, although hypoxaemic subjects who were cirrhotic or were smokers tended to have FRC values smaller than CC. This lack of correlation may reflect the fact that lowered alveolar Pao₂ causes vasoconstriction and results in a redistribution of perfusion. Hypoxaemia may result only when, for some reason, this compensatory mechanism is lost and the under-ventilated areas continue to be perfused. It has been suggested that in patients with cirrhosis of the liver this regulatory mechanism may be lost (Daoud, Reeves, and Schaefer, 1972).

The present study suggests that the cause of hypoxaemia among cirrhotic patients is not directly attributed to an increased closing capacity. Severe hypoxaemia observed occasionally by others was probably due to a pulmonary capillary shunt, while in a large percentage of patients with slight to moderate hypoxaemia the most likely cause is a failure to control perfusion locally, leading to an increased ventilation-perfusion disproportion. In some patients this ventilation-perfusion mismatching may be the result of an increase in CC relative to the FRC.

We thank Lyle H. Hamilton, Ph.D. for his review of the manuscript and for valuable suggestions.

REFERENCES

- Bashour, F. A., Miller, W. F., and Chapman, C. B. (1961). Pulmonary venoarterial shunting in hepatic cirrhosis. *American Heart Journal*, **62**, 350.
- Berthelot, P., Walker, J. G., Sherlock, S., and Reid, L. (1966). Arterial changes in the lungs in cirrhosis of the liver. Lung spider naevi. *New England Journal of Medicine*, **274**, 291.
- Blackburn, C. R. B., Read, J., McRae, J., Colebatch, H. J., Playoust, M. R., and Holland, R. A. B. (1960). Veno-arterial shunting of blood in chronic liver disease. *Australian Annals of Medicine*, **9**, 204.
- Buist, A. S. (1973). Early detection of airways obstruction by the closing volume technique. *Chest*, **64**, 495.
- and Ross, B. B. (1973). Predicted values for closing volumes using a modified single breath nitrogen test. *American Review of Respiratory Disease*, **107**, 744.
- Calabresi, P. and Abelman, W. H. (1957). Portocaval and porto-pulmonary anastomoses in Laennec's cirrhosis and heart failure. *Journal of Clinical Investigation*, **36**, 1257.
- Caldwell, P. R. B., Fritts, H. W. Jr., and Courmand, A. (1965). Oxyhemoglobin dissociation curve in liver disease. *Journal of Applied Physiology*, **20**, 316.
- Cotes, J. E., Field, G. B., Brown, G. J. A., and Read, A. E. (1968). Impairment of lung function after portacaval anastomosis. *Lancet*, **1**, 952.
- Craig, D. B., Wahba, W. M., Don, H. F., Couture, J. G. and Becklake, M. R. (1971). "Closing volume" and its relationship to gas exchange in seated and supine positions. *Journal of Applied Physiology*, **31**, 717.
- Daoud, F. S., Reeves, J. T., and Schaefer, J. W. (1972). Failure of hypoxic pulmonary vasoconstriction in patients with liver cirrhosis. *Journal of Clinical Investigation*, **51**, 1076.
- El Gamal, M., Stoker, J. B., Spiers, E. M., and Whitaker, W. (1970). Cyanosis complicating hepatic cirrhosis. *American Journal of Cardiology*, **25**, 490.
- Funahashi, A., Melville, G. N., and Hamilton, L. H. (1975). Ability of single-breath nitrogen closing volume to detect early airway obstruction. *Thorax*, **30**, 220.
- Hamosh, P. and DaSilva, A. M. T. (1973). Supine hypoxaemia and erythrocytosis due to airway closure at low lung volumes. *American Journal of Medicine*, **55**, 80.
- Hansoti, R. C. and Shah, N. J. (1966). Cirrhosis of liver simulating congenital cyanotic heart disease. *Circulation*, **33**, 71.
- Heinemann, H. O., Emirgil, C., and Mijnsen, J. P. (1960). Hyperventilation and arterial hypoxemia in cirrhosis of the liver. *American Journal of Medicine*, **28**, 239.
- Karetzky, M. S. and Mithoefer, J. C. (1967). The cause of hyperventilation and arterial hypoxia in patients with cirrhosis of the liver. *American Journal of Medical Sciences*, **254**, 797.
- Khalik, S. U., Kay, J. M., and Heath, D. (1972). Porta-pulmonary venous anastomoses in experimental cirrhosis of the liver in rats. *Journal of Pathology*, **107**, 167.

- Kory, R. C., Callahan, R., Boren, H. G., and Syner, J. C. (1961). The Veteran Administration-Army Cooperative Study of pulmonary function. *American Journal of Medicine*, **30**, 243.
- Leblanc, P., Ruff, F., and Milic-Emili, J. (1970). Effects of age and body position on "airway closure" in man. *Journal of Applied Physiology*, **28**, 448.
- McFadden, E. R. Jr., Holmes, B., and Kiker, R. (1975). Variability of closing volume measurement in normal man. *American Review of Respiratory Diseases*, **111**, 135.
- Meneely, G. R., Ball, C. O. T., Kory, R. C., Callaway, J. J., Merrill, J. M., Mabe, R. E., Roehm, D. C., and Kaltreider, N. L. (1960). A simplified closed circuit helium dilution method for the determination of residual volume of the lungs. *American Journal of Medicine*, **28**, 824.
- Nakamura, T., Nakamura, S., Tazawa, T., Abe, S., Aikawa, T., and Tokita, K. (1965). Measurement of blood flow through portopulmonary anastomosis in portal hypertension. *Journal of Laboratory and Clinical Medicine*, **65**, 114.
- Rodman, T., Sobel, M., and Close, H. P. (1960). Arterial oxygen unsaturation and the ventilation-perfusion defect of Laënnec's cirrhosis. *New England Journal of Medicine*, **263**, 73.
- Ruff, F., Hughes, J. M. B., Stanley, N., McCarthy, D., Greene, R., Aronoff, A., Clayton, L., and Milic-Emili, J. (1971). Regional lung function in patients with hepatic cirrhosis. *Journal of Clinical Investigation*, **50**, 2403.
- Rydell, R. and Hoffbauer, F. W. (1956). Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. *American Journal of Medicine*, **25**, 450.
- Snell, A. M. (1935). The effects of chronic disease of the liver on the composition and physical and chemical properties of blood: changes in the serum proteins: reduction in the oxygen saturation of the arterial blood. *Annals of Internal Medicine*, **9**, 690.
- Sorbini, C. A., Grassi, V., Solinas, E., and Muiesan, G. (1968). Arterial oxygen tension in relation to age in healthy subjects. *Respiration*, **25**, 3.
- Stanley, N. N., Ackrill, P., and Wood, J. (1972). Lung perfusion scanning in hepatic cirrhosis. *British Medical Journal*, **4**, 639.
- Travis, D. M., Green, M., and Don, H. (1973). Simultaneous comparison of helium and nitrogen expiratory "closing volumes". *Journal of Applied Physiology*, **34**, 304.

Requests for reprints to: Dr. A. Funahashi, Pulmonary Function Laboratory, Veterans Administration Center, Wood, Wis. 53193, USA.