Respiration and Circulation in Patients with Portal Cirrhosis of the Liver

By H. O. Heinemann, M.D.

It is generally known that cirrhosis of the liver may be accompanied by marked changes in the hepatic and splanchnic vasculature, which in turn lead to reduced hepatic blood flow, increased portal venous pressure, and the development of collateral vessels permitting bypass of the diseased liver. Less well known is the fact that cirrhosis of the liver may also be associated with changes in the respiratory pattern, the pulmonary vasculature, and the systemic circulation. Information on this subject is at present incomplete. It may even seem questionable that impairment of the function of a single organ can lead to such a varied pathologic pattern. This review attempts to fulfill a dual purpose: first, to draw attention to the above-mentioned, less well known complications of cirrhosis of the liver, and, secondly, to present a more unified concept of the respiration and circulation in patients with this disease.

Patients with cirrhosis of the liver may hyperventilate at rest in the absence of reduced hemoglobin content of the blood and without apparent increase in oxygen consumption. This leads to the development of mild respiratory alkalosis. To explain the hyperventilation in the face of reduced carbon dioxide tension and normal, or slightly elevated, pH of the arterial blood, the assumption is often made that the respiratory center is stimulated by ammonia, because the blood level of this metabolite is frequently elevated in patients with liver disease. Poor correlation between the ammonia content of arterial blood and the minute ventilation casts some doubt on the significance of ammonia as a respiratory stimulus and leaves this problem open for further investigation. Another stimulus that must be considered to explain the hyperventilation is the low oxygen tension of arterial blood, not infrequently observed in patients with cirrhosis of the liver. Determination of the partial pressure of oxygen in arterial blood reveals tensions, however, which are not of the order of magnitude commonly assumed to be necessary to increase ventilation, and the mechanism maintaining hyperventilation in the absence of adequate physiologic stimuli (pCO₂, pH, and pO₂) remains, at present unsatisfactorily explained.

The above-mentioned low arterial oxygen tension, observed in some patients with cirrhosis of the liver, leads to an increased gradient in the partial pressure of oxygen between the blood and alveolar air. This gradient is further accentuated by the high alveolar oxygen tension caused by hyperventilation. The low arterial oxygen tension in cirrhosis of the liver might be due to hyperventilation of well-perfused lung tissue, because of elevation of the diaphragm secondary to ascites, or these patients may have intrinsic lung disease with reduced diffusing capacity for oxygen. Pulmonary function remains within normal limits and unsaturation of arterial blood persists, however, irrespective of the presence or absence of ascites, and paracentesis has no apparent effect on ventila-
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It is also conceivable that changes in the hemoglobin molecule, leading to a shift in the oxygen dissociation curve, may be responsible for the hypoxemia in liver disease. Such a mechanism can similarly be excluded, however, because blood of hypoxemic patients becomes fully saturated by equilibration in vitro with gas mixtures containing oxygen at tensions similar to the ones observed in vivo.

These considerations leave shunting of venous blood into the systemic circulation as a third possibility to explain the hypoxemia of liver disease. The presence of such veno-to-arterial shunts is made likely by the fact that administration of 100 per cent oxygen does not abolish either the increased gradient for oxygen tension between alveolar air and arterial blood, nor the hypoxemia in patients with marked unsaturation. In adults with portal cirrhosis, in contrast to patients with so-called juvenile cirrhosis, these shunts are apparently not located between the pulmonary arteries and pulmonary veins. Abnormal vascular channels, which could account for extrapulmonary shunting of venous blood into the systemic circulation, have been documented by Calabresi and Abelman, who demonstrated communications between the portal vascular bed and the pulmonary veins via periesophageal and mediastinal veins. The volume of portal venous blood entering the systemic circulation per unit of time must depend on the available pressure gradient between the portal and pulmonary veins and may, therefore, vary considerably during the respiratory cycle because of the unusual location across the diaphragm.

Unpublished observations indicate that cirrhosis of the liver may in some instances be associated with changes in the pulmonary arteries (vasculitis†) and an elevated pulmonary artery pressure. The underlying mechanism is at present not understood. But the question arises whether there is a relationship between the pulmonary hypertension and the fact that metabolites, originating from the gastrointestinal tract, have direct access to the pulmonary arteries via acquired or surgically induced anastomoses of portal vein to vena cava. It is tempting to compare this situation with the pulmonary hypertension in patients with the carcinoid syndrome, where serotonin escapes hepatic inactivation because of overproduction or metastases beyond the liver and then affects the pulmonary vessels. At present, however, there is no evidence to suggest that the changes in the pulmonary arteries, occasionally observed in patients with cirrhosis of the liver, are due to a specific metabolite such as serotonin.*

Patients with cirrhosis of the liver may have unexplained cardiac hypertrophy. Lunseth, Olmstead, and Abboud reported such cardiomegaly in 12 out of 108 autopsies on patients with portal cirrhosis, an incidence of 11 per cent. Coronary artery disease and hypertension are generally considered to be less common in these patients. To account for this abnormality, one has therefore to consider other mechanisms. One possibility would be that portal cirrhosis is associated with a specific type of myocardial disease. Such a mechanism is not unlikely because microscopic examination of the myocardium in the patients studied by Lunseth, Olmstead, and Abboud and others revealed an unusual type of diffuse fibrosis, often only in portions of a single muscle fiber.

Predominant right ventricular hypertrophy is another characteristic feature of the cardiomegaly in patients with cirrhosis of the liver. This may be due to the occasionally observed increased pulmonary artery pressure. It is also known that patients with cirrhosis of the liver may have a high cardiac output at rest, irrespective of the presence or absence of collateral circulation, portocaval shunt, anemia,

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* Rydell and Hoffbauer** observed arteriovenous anastomoses between the pulmonary artery and the pulmonary vein in a patient with juvenile cirrhosis.
† The so-called shunt equation cannot be applied to calculate the volume of blood flowing through these vascular communications because the oxygen content of portal blood is not readily measurable.

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*The serotonin content in blood of patients with cirrhosis of the liver is reported to be lower than in normal subjects.
or nutritional deficiencies. Such persistent elevation of the cardiac output could account for cardiac hypertrophy. The increase in cardiac output is not associated with increased oxygen consumption and is therefore different from the circulatory pattern observed in the so-called hypermetabolic state. The rise in cardiac output is similar to the change noted in patients with arteriovenous fistulae and thiamine deficiency. All these syndromes have in common a reduction of the peripheral resistance.

It is conceivable that cardiomegaly, perhaps in combination with degenerative changes in the myocardium, may lead to cardiac failure. No adequate information, however, is available on the incidence of such a complication in patients with cirrhosis of the liver. Dyspnea and cough, frequently noted in these patients, is usually ascribed to the elevated diaphragm because of ascites and the higher susceptibility to respiratory infections. Peripheral edema is as frequent as ascites in these patients and may occur irrespective of the presence or absence of fluid in the abdomen. Hydrothorax may develop, most commonly in association with ascites. Pulmonary infections or leakage of ascitic fluid into the pleural cavity is usually implicated as a cause. If heart failure, indeed, complicates cirrhosis of the liver, it may be difficult to detect because most symptoms can also be ascribed to the underlying disease. Measurement of venous pressure and the response to a cardiotonic regimen may be helpful in differentiating the cause of fluid retention. Furthermore, coincidence of cirrhosis of the liver and heart failure does not imply a causal relationship, because both conditions have a high incidence in the same age group. However, 2 well-documented cases of high output failure have been reported in the literature. Emphasis, therefore, on high output failure as a potential complication of cirrhosis of the liver seems justified and may lead to more frequent recognition.

The increased cardiac output in patients with cirrhosis of the liver is presumably due to decreased peripheral resistance and the resulting increased peripheral blood flow. These changes in the hemodynamic pattern are clinically discernible by the increased pulse pressure, flushed palms, and capillary pulsations. The mechanism responsible for the reduction in peripheral resistance is unknown. It has been postulated that either increased production or diminished inactivation of vasoactive substances is involved. Such a substance, originating from the area drained by the splanchnic vessels and normally inactivated by the liver, could escape hepatic inactivation and gain access to the systemic circulation via collateral vessels. Increased levels of circulating estrogen have also been implicated as a cause for both the development of palmar erythema (peripheral vasodilatation) and the appearance of arterial spiders.

Cirrhosis of the liver is occasionally accompanied by hypertrophic osteoarthropathy. The cause of clubbing remains unknown, but it has been postulated that this abnormality is related to increased peripheral blood flow, increased cardiac output, or shunting of venous blood into the systemic circulation, changes also observed in patients with portal cirrhosis of the liver. But hypertrophic osteoarthropathy is apparently more often observed in patients with biliary cirrhosis, where such a hemodynamic pattern seems not to occur.

Patients with cirrhosis of the liver have frequently an enlarged total blood volume. This is mainly due to an increase in the plasma fraction, the red cell mass being within normal limits. This leads to lowering of the hematocrit level, a fact that should be taken into consideration if the anemia of liver disease is to be evaluated. A normal hematocrit value in patients with cirrhosis of the liver, in the face of an elevated blood volume, represents a rise in red cell mass. It is conceivable that hypoxemia, if present, may stimulate red cell production and induce a relative or absolute polycythemia. Two such patients with cirrhosis of the liver and secondary polycythemia have been reported in the literature. The mechanism causing the rise in plasma volume is unknown. But a similar hypervolemia is observed in other conditions associated with
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decreased peripheral resistance, such as arteriovenous fistulas, thiamine deficiency, and pregnancy. Reduction of the peripheral resistance, due to whatever mechanism, may conceivably initiate a cycle of events that ultimately leads to an increased plasma volume.

From the foregoing review, one can conclude that cirrhosis of the liver may be accompanied by marked changes in the respiratory pattern, pulmonary vasculature, and systemic circulation. Information about the incidence of these changes and their relationship to the stages of the disease and the type of cirrhosis is at present not available. Most observers have limited their studies to individual phenomena, such as the cardiac output, in selected patients. Rydell and Hoffbauer, on the other hand, performed a careful study in a single patient with so-called juvenile cirrhosis and were able to define a disease entity characterized by hypoxemia, secondary polycythemia, high cardiac output, heart failure, and, apparently in contrast to adults with portal cirrhosis, multiple intrapulmonary arteriovenous fistulas. Comparable studies are not available in adults with cirrhosis of the liver. Such observations are necessary, however, before a similar disease entity can be confidently described for portal cirrhosis. As a working hypothesis for future studies, one can separate the changes observed in adults with portal cirrhosis into 3 different groups.

First, communications between the portal vascular bed and either the pulmonary veins or the venae eavae may (a) permit venous blood to enter the systemic circulation and cause hypoxemia or (b) may allow intestinal metabolites to escape hepatic inactivation and gain direct access to the systemic circulation.

Secondly, metabolites escaping hepatic inactivation may be responsible for the changes in the pulmonary vessels, pulmonary hypertension, reduced peripheral resistance, and hyperventilation.

Finally, reduction of the peripheral resistance leads to a rise in cardiac output and perhaps also the plasma volume. The increased cardiac output may eventually cause cardiac hypertrophy and heart failure, a complication difficult to recognize in older patients in whom heart disease may occur independently and fluid retention and dyspnea can be attributed to the underlying disease.

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Addendum

Since this paper was submitted for publication, another well-documented example of arterial hypoxemia in cirrhosis of the liver has been described by Rodman and associates.

Sumario in Interlingua

Es generalmente cognoscite que cirrhosis del hepatex pote esser accompaniante de marcate alterationes in le vasculatura hepatic e splanchnie e que isto, de su parte, resulta in un reduction del fluxo hepatic de sanguine, in un augmento del tension venose portal, e in le disveloppamento de vasos collateral que permitte le circuitio del hepatex morbide. Es minus ben cognoscite que cirrhosis del hepatex pote etiam esser associate con alterationes del respiratio, del vasculatura pulmonar, e del circulation major. Le presente articulo ha le duple objective de (1) signalar le supra-mentionate, minus ben cognoscite complicationes de cirrhosis del hepatex e (2) presentar un plus unificite conception del respiratio e del circulation in patientes con ille disordine.

In summation de su argumento e como base pro futur studios, le autor presenta le hypothese que le alterationes observate in patientes adulte con cirrhosis portal pote esser separate in tres differente gruppos.

1. Communicationes inter le vasculatura portal e, de un latere, le venas pulmonar o, del altere latere, le venas eavae pote resultar in (a) le entrada de sanguine venose in le circulation major con le effecto de hypoxemia o (b) le non-inactivation de metabolitos intestinal per le hepatex e le consequente transition directe de ille metabolitos a in le circulation major.

2. Metabolitos que escappa al inactivation per le hepatex pote devenir responsable pro alterationes in le vasos pulmonar, pro hypertension pulmonar, pro le reduction del resistencia peripherie, e pro hypertension.

3. Le reduction del resistencia peripherie resulta in un augmento del rendimento cardiae e forsan etiam del volumene de plasma. Le augmentate rendimento cardiae pote, in le curso del tempore, devenir le causa de hypertrophia cardiae e disfallimento del corde—un complication que es difficile a identificar in patientes de etates plus avantiate, proque in tales le
References
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Medical Eponyms

By Robert W. Buck, M.D.

The true worth of an experimenter consists in his pursuing not only what he seeks in his experiment, but also what he did not seek.—Claude Bernard. (Submitted by H. M. Marvin, M.D.)

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