Pulmonary Hypertension Associated with Cirrhosis of the Liver and with Portacaval Shunts

By ROBERT M. SENIOR, M.D., RICHARD C. BRITTON, M.D., GERARD M. TURINO, M.D., JOHN A. WOOD, M.D., GLENN A. LANGER, M.D., and ALFRED P. FISHMAN, M.D.

SUMMARY
Pulmonary hemodynamics were studied in 11 patients with hepatic cirrhosis who had undergone surgical portal decompression several years earlier. Four of the patients had both clinical and physiological evidence of pulmonary hypertension; two others had mild, subclinical pulmonary hypertension. Autopsy examination of two patients who had clinical evidence of pulmonary hypertension revealed thickening of the small pulmonary arteries and multiple small pulmonary emboli. Before the portosystemic venous Anastomosis was created, all of the patients had had normal cardiorespiratory performance. These studies suggest that emboli from the portal vein may have been involved in the genesis of the pulmonary hypertension in these patients. The role of surgical portal decompression is unclear. Retrospective studies of 70 clinical records and of 17 autopsy protocols in a similar group of patients did not clarify the role of the surgical decompression in the genesis of the pulmonary hypertension.

Additional Indexing Words:
Pulmonary hypertenion Chronic cor pulmonale Pulmonary thromboemboli Cirrhosis Portacaval shunt

PULMONARY HYPERTENSION and chronic cor pulmonale may result from recurrent pulmonary embolism.1 Although most pulmonary emboli originate in the veins of the lower extremities, they may also arise from other venous beds and from the right side of the heart.2 A few reports have suggested that the portal venous system may occasionally be involved in the pathogenesis of thromboembolic pulmonary hypertension.3-5

The present study extends these earlier observations by considering the occurrence and mechanism of pulmonary hypertension in patients in whom surgical communications between the portal and systemic veins were created for the relief of portal hypertension.

Subjects and Methods
This report deals with 81 patients who survived surgical decompression of portal venous hypertension for at least 2 years. All of the patients had cirrhosis of the liver and in each instance portal decompression had been done to control hemorrhagic complications of portal hypertension. The data were obtained in two general ways: (1) from clinical, anatomical, and physiological observations, and (2) from review of clinical and autopsy records and from autopsy material ("retrospective").

Clinical and Physiological Observations
The clinical and physiological observations were made on 11 patients. These patients are identified, and some relevant features of their liver disease and of their surgically-created shunts appear in
Table 1

General Hepatic and Portosystemic Features in Eleven Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Liver biopsy</th>
<th>Type of shunt</th>
<th>Years post shunt</th>
<th>Serum albumin (g/100 cc)</th>
<th>Serum bilirubin (mg/100 cc)</th>
<th>Serum alk. phos. (K.A. units)</th>
<th>Hemoglobin (g/100 cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.K.*</td>
<td>33</td>
<td>M</td>
<td>Laennec</td>
<td>SR</td>
<td>10</td>
<td>4.4</td>
<td>0.3</td>
<td>21</td>
<td>13.4</td>
</tr>
<tr>
<td>J.S.‡</td>
<td>58</td>
<td>F</td>
<td>Laennec</td>
<td>S-S</td>
<td>6</td>
<td>2.8</td>
<td>6.4</td>
<td>54</td>
<td>12.0</td>
</tr>
<tr>
<td>R.B.*</td>
<td>46</td>
<td>M</td>
<td>Post-nec</td>
<td>S-S</td>
<td>9</td>
<td>3.6</td>
<td>1.0</td>
<td>12</td>
<td>16.0</td>
</tr>
<tr>
<td>P.L.</td>
<td>59</td>
<td>M</td>
<td>Laennec</td>
<td>E-S</td>
<td>8</td>
<td>2.2</td>
<td>9.2</td>
<td>24</td>
<td>13.0</td>
</tr>
<tr>
<td>A.R.</td>
<td>58</td>
<td>M</td>
<td>Laennec</td>
<td>E-S</td>
<td>9</td>
<td>2.9</td>
<td>0.8</td>
<td>11</td>
<td>14.0</td>
</tr>
<tr>
<td>J.E.</td>
<td>51</td>
<td>M</td>
<td>Laennec</td>
<td>E-S</td>
<td>3</td>
<td>4.0</td>
<td>0.6</td>
<td>17</td>
<td>14.5</td>
</tr>
<tr>
<td>E.M.</td>
<td>50</td>
<td>F</td>
<td>Laennec</td>
<td>SR</td>
<td>11</td>
<td>4.4</td>
<td>0.4</td>
<td>9</td>
<td>12.5</td>
</tr>
<tr>
<td>G.F.</td>
<td>45</td>
<td>F</td>
<td>Laennec</td>
<td>SR</td>
<td>4</td>
<td>2.5</td>
<td>0.4</td>
<td>15</td>
<td>10.8</td>
</tr>
<tr>
<td>M.G.§</td>
<td>31</td>
<td>F</td>
<td>Post-nec</td>
<td>E-S</td>
<td>17</td>
<td>2.0</td>
<td>2.5</td>
<td>39</td>
<td>11.5</td>
</tr>
<tr>
<td>R.E.</td>
<td>59</td>
<td>M</td>
<td>Post-nec</td>
<td>S-S</td>
<td>3</td>
<td>2.9</td>
<td>2.0</td>
<td>15</td>
<td>9.5</td>
</tr>
<tr>
<td>M.E.</td>
<td>55</td>
<td>M</td>
<td>Post-nec</td>
<td>S-S</td>
<td>2</td>
<td>3.8</td>
<td>1.0</td>
<td>19</td>
<td>13.8</td>
</tr>
</tbody>
</table>

*Esophageal varices.
‡Spider angiomata.
§Ascites.
SR = splenorenal; S-S = side-to-side, portacaval; E-S = end-to-side, portacaval.

Table 1. Necropsy studies were obtained in two of these patients.

Clinical

In addition to the medical history and physical examination, a variety of other studies were done, including ECG, chest x-ray, blood count, and liver function tests. Particular attention was paid to the following clinical features of pulmonary hypertension and cor pulmonale: fatigue, dyspnea, exertional substernal pain, parasternal lift of the right ventricle, sharp accentuation of the pulmonary component of the second heart sound, pulmonic ejection click, electrocardiographic evidence of right ventricular hypertrophy, and right ventricular enlargement associated with abnormal prominence of the main branches of the pulmonary artery in chest x-rays. Patients who had parenchymal disease of the lungs, or rheumatic, congenital, hypertensive, or arteriosclerotic forms of heart disease were excluded from this report.

Physiological

The physiological appraisal of these subjects included: (1) measurement of lung volumes and maximum ventilatory capacity, (2) assessment of the uniformity of distribution of inspired air, (3) determination of the gaseous composition of arterial blood and the analysis of respiratory gas exchange, and (4) measurement of pulmonary arterial blood pressure and flow. The methods used to make these physiological measurements have been described previously.7

Retrospective Study

The clinical records of 70 patients were reviewed; in 17 of these, autopsy records and autopsy material were also examined. Particular attention was paid in the clinical record to episodes of proven or suspected pulmonary embolization, unexplained dyspnea, and unexplained cardiac enlargement. From the autopsy protocols, estimates were obtained of the thickness of the right ventricular free wall, degree of pulmonary arteriosclerosis, and the presence of thromboemboli in the major branches of the pulmonary artery. Lung sections were reexamined by light microscopy for arterial emboli and for changes in the small arterial vessels consistent with pulmonary hypertension.8

Results

Clinical, Anatomic, and Physiological Observations

Clinical

As shown in table 1, all of the subjects were adults and, with two exceptions, were between 40 and 60 years of age. Cirrhosis was of either the portal or the postnecrotic type. Portacaval shunts had been done 2 to 17 years before study; in most patients the shunt was more than 4 years old. Only two patients (J.S. and M.G.) were debilitated at the time of study. Only one patient (T.K.) had not had arrest of gastrointestinal hemorrhage following portal decompression. No patient had clubbing of the digits, one patient (M.G.) had ascites, and one patient (J.S.) had spider angiomata. Several patients had moderate ele-
Roentgenograms of the chest in a patient with cirrhosis and portacaval shunt. Left. Before shunting, the heart and lungs appear normal. Right. Nine years after portal decompression the heart, pulmonary outflow tract, and main branches of the pulmonary artery are enlarged.

Anatomic

Two patients (T.K. and P.L.) with clinical pulmonary hypertension came to autopsy. In both, there was marked right ventricular hypertrophy associated with dilatation and atherosclerosis of the pulmonary artery and its main branches. Although neither patient had gross thromboemboli in the pulmonary vasculature, both had microscopic evidence of thromboembolism in small pulmonary arterial vessels. These abnormalities (fig. 2) included intimal thickening, medial hypertrophy, and partial occlusion and recanalization of vessel lumens. However, examination of the surgical postacaval shunts and of other venous beds...
### Table 2

*Pulmonary Gas Exchange and Arterial Blood Values in Eleven Subjects with Cirrhosis and Portacaval Shunts at Rest*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Surface area (m²)</th>
<th>Pulmonary Gas Exchange</th>
<th>Arterial blood gas composition</th>
<th>Serum CO₂ (vol %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R (L/min/m²²)</td>
<td>V₁, O₂ (ml/min/m²²)</td>
<td>V₁/V₁ × 100 (%)</td>
</tr>
<tr>
<td>T.K.</td>
<td>1.92</td>
<td>0.78</td>
<td>4.4</td>
<td>151</td>
</tr>
<tr>
<td>J.S.</td>
<td>1.79</td>
<td>0.80</td>
<td>6.1</td>
<td>145</td>
</tr>
<tr>
<td>R.B.</td>
<td>2.00</td>
<td>0.72</td>
<td>4.8</td>
<td>151</td>
</tr>
<tr>
<td>P.L.</td>
<td>1.80</td>
<td>0.80</td>
<td>5.3</td>
<td>162</td>
</tr>
</tbody>
</table>

**Group 1—Cirrhosis with clinical signs of pulmonary hypertension**

**Group 2—Cirrhosis without clinically apparent cardiorespiratory abnormality**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Surface area (m²)</th>
<th>Pulmonary Gas Exchange</th>
<th>Arterial blood gas composition</th>
<th>Serum CO₂ (vol %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.R.</td>
<td>2.02</td>
<td>0.71</td>
<td>5.4</td>
<td>160</td>
</tr>
<tr>
<td>J.E.</td>
<td>2.00</td>
<td>0.80</td>
<td>4.3</td>
<td>131</td>
</tr>
<tr>
<td>E.M.</td>
<td>1.72</td>
<td>0.80</td>
<td>2.8</td>
<td>100</td>
</tr>
<tr>
<td>G.F.</td>
<td>1.40</td>
<td>0.93</td>
<td>5.7</td>
<td>130</td>
</tr>
<tr>
<td>M.G.</td>
<td>1.58</td>
<td>0.79</td>
<td>4.5</td>
<td>137</td>
</tr>
<tr>
<td>R.E.</td>
<td>1.68</td>
<td>0.82</td>
<td>5.9</td>
<td>142</td>
</tr>
<tr>
<td>M.E.</td>
<td>2.08</td>
<td>0.73</td>
<td>3.1</td>
<td>127</td>
</tr>
</tbody>
</table>

R = respiratory exchange ratio; V₁ = minute ventilation (BTPS); V₁, O₂ = volume of oxygen taken up (STPD); V₁/V₁ = ratio of volume of respiratory dead space to tidal volume; SaO₂ = oxyhemoglobin saturation of arterial blood; P<sub>CO₂</sub> = partial pressure of carbon dioxide in arterial blood.
Table 3
Pulmonary and Systemic Pressures and (Fick) Cardiac Output in Eleven Subjects with Cirrhosis and Portacaval Shunts

<table>
<thead>
<tr>
<th>Subject</th>
<th>Flow Cardiac index (L/min/m²)</th>
<th>Pulmonary artery systolic (mm Hg)</th>
<th>Pulmonary artery diastolic (mm Hg)</th>
<th>Pulmonary artery mean (mm Hg)</th>
<th>Brachial artery systolic (mm Hg)</th>
<th>Brachial artery diastolic (mm Hg)</th>
<th>Right ventricle end-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.K.</td>
<td>3.2</td>
<td>75</td>
<td>29</td>
<td>51</td>
<td>96</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>J.S.</td>
<td>2.7</td>
<td>80</td>
<td>28</td>
<td>51</td>
<td>135</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>R.B.</td>
<td>3.3</td>
<td>86</td>
<td>42</td>
<td>60</td>
<td>150</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>P.L.</td>
<td>4.0</td>
<td>63</td>
<td>34</td>
<td>43</td>
<td>168</td>
<td>70</td>
<td>9</td>
</tr>
</tbody>
</table>

Group 1—With clinical signs of pulmonary hypertension

Group 2—Without clinically apparent cardiorespiratory abnormalities

A.R. 0.71 3.6 60 22 35 178 85 6 8
J.E. 0.80 3.1 23 16 17 139 83 — —
E.M. 0.80 3.1 14 6 11 143 86 — —
G.F. 0.93 5.4 19 5 11 146 80 — —
M.G. 0.79 5.1 31 6 19 135 72 — —
R.E. 0.82 8.1 27 10 16 135 60 — —
M.E. 0.73 5.0 39 17 26 165 80 — —

Figure 3
Cardiac index and mean pulmonary arterial blood pressure during the basal state in 11 patients with cirrhosis and portacaval shunts.

Figure 4
Ventilation and arterial blood gases in 11 patients with cirrhosis and portacaval shunts. The bar indicates one standard deviation about the mean.

disclosed no probable sources of the pulmonary thromboemboli.

Physiological

Spirometry and distribution of inspired air. Lung volumes, maximum ventilatory capacity, and the distribution of inspired air were normal in all subjects.

Respiratory gas exchange and arterial blood gas composition. The values for respiratory gas exchange and arterial blood gas composition are summarized in table 2. In this table, and in table 3, the subjects have been divided into two groups according to the presence (group 1) or absence (group 2) of clinical manifestations of pulmonary hypertension and cor pulmonale. Resting ventilation was abnormally elevated in all of the patients in group 1 and in all but two patients (E.M. and M.E.) in group 2. Also, except for these two patients, arterial carbon dioxide tensions and serum bicarbonate were below normal in all patients. Arterial oxyhemoglobin
PULMONARY HYPERTENSION

Table 4
Comparison of Right Ventricular Wall Thickness

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Cirrhosis</th>
<th>Cirrhosis and shunt*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Mean thickness (mm)</td>
<td>3.5</td>
<td>3.3</td>
<td>3.6</td>
</tr>
<tr>
<td>sd</td>
<td>± 1.1</td>
<td>± 1.0</td>
<td>± 1.7</td>
</tr>
</tbody>
</table>

*On the average, surgical shunts had been created about 5 years before death.

saturations were slightly below normal in all of the patients in group 1 and in two of the patients (A.R. and G.F.) in group 2.

Pulmonary and systemic hemodynamics and cardiac output. The values of right ventricular, pulmonary arterial, pulmonary arterial wedge, and brachial blood pressures and cardiac output are presented in table 3. In the four patients of group 1, pulmonary arterial pressure was considerably increased; the mean pressures in the main pulmonary artery ranged from 43 to 60 mm Hg. The corresponding pulmonary arterial wedge pressures and cardiac outputs were normal. Although three patients (J.S., R.B., and P.L.) had abnormally high end-diastolic pressures in the right ventricle, only J.S. demonstrated clinical heart failure. Two patients (A.R. and M.E.) in group 2 had elevated pulmonary arterial blood pressures; that is, mean pressures of 35 and 26 mm Hg, respectively. The cardiac index was above normal in patient M.E., but was normal in patient A.R. The other patients of group 2 had normal pulmonary arterial blood pressures even though the cardiac outputs were abnormally high in three (fig. 3). In figure 4, ventilation and arterial blood gas composition of the patients with elevated pulmonary arterial blood pressure is schematically contrasted with the values obtained in the patients with normal blood pressure in the pulmonary artery. It is apparent that in these respects all of the patients were similar.

Retrospective Study

Medical Records

The review of the clinical records of the 70 patients whose portacaval shunts had been performed an average of 7 years earlier failed to reveal a single instance of clinical pulmo-

nary hypertension or cor pulmonale. In only one patient had there been a recognized pulmonary infarction, and this had occurred approximately 2 weeks after portal decompression.

Autopsy Records and Autopsy Material

The review of 17 autopsy protocols failed to reveal any instances of notable pulmonary arteriosclerosis, emboli in the large pulmonary arteries, or right ventricular hypertrophy. In one patient, microscopic examination disclosed numerous thromboembolic occlusions of the small pulmonary arterial vessels. As may be seen in table 4, there was no significant difference between the thickness of the right ventricular wall in the three groups.

Discussion

In recent years, several studies have dealt with the pulmonary circulation in patients with cirrhosis of the liver. The reasons for these studies have been either clubbing of the digits or disturbances of ventilation and of arterial blood oxygenation in these patients. As a consequence of these studies, several disorders of the pulmonary circulation have been described: (1) spontaneous portopulmonary and intrapulmonary arteriovenous anastomoses, (2) arteriolar dilatation, and (3) spider angiomata of the visceral pleura. A number of reports have also provided evidence for the coexistence of liver disease and abnormal portal and pulmonary hemodynamics.

The results of the present study support the notion that occasionally cirrhosis of the liver and portosystemic communications may be complicated by pulmonary arterial hypertension and chronic cor pulmonale. Six patients with cirrhosis and surgically created portosystemic venous shunts also had pulmonary hypertension. Four of the patients displayed typical clinical manifestations of pulmonary hypertension and right ventricular enlargement. Two patients came to necropsy and both had small pulmonary thromboemboli, dilatation of the main pulmonary arteries, and right ventricular hypertrophy. Usual causes of pulmonary hypertension, that
is, chronic parenchymal lung disease, congenital heart disease, rheumatic heart disease, and left ventricular failure, could not be implicated in any of these patients.

It is noteworthy that the patients with the combination of hepatic cirrhosis, portosystemic venous shunts and pulmonary hypertension displayed no greater derangements in ventilation and alveolar gas exchange than patients who had comparable hepatic and portal disease but normal pulmonary hemodynamics. In accord with earlier observations on cirrhosis of the liver, patients in both groups showed abnormally high levels of minute and alveolar ventilation, and slight reductions in arterial oxyhemoglobin saturation.

**Previous Reports of Combined Liver Disease and Portal and Pulmonary Hypertension**

Table 5 summarizes the previous descriptions of the association of pulmonary hypertension with cirrhosis of the liver or portal hypertension alone. Only half the observations included measurements of pulmonary arterial pressure; in the others, pulmonary hypertension was suspected on clinical or anatomic grounds. In these reports, several mechanisms were considered as likely bases for the pulmonary hypertension.

**Idiopathic changes in the pulmonary vessels**

Kerbel,^{13} and Cohen and Mendelow,^{15} described two young adult women with cirrhosis and proven pulmonary hypertension. At postmortem examination their lungs displayed only abnormalities of vessel walls, and during life both patients conformed to the common picture of idiopathic pulmonary hypertension.^{19} These cases probably represent the accidental coincidence of two disorders.

**Expansion of the pulmonary blood volume due to expanded total blood volume**

Bayley and associates^{14} attributed the occurrence of moderate pulmonary hypertension in 15 patients with hepatic cirrhosis to an expanded circulating blood volume. Apparently consistent with their physiological observations are the anatomic observations^{16} which indicate that cardiomegaly, affecting
primarily the right ventricle and without manifest cause, is not uncommon in hepatic cirrhosis. However, the studies of Massumi and co-workers suggest that the association of an expanded blood volume and pulmonary hypertension may be coincidence rather than cause and effect, since they did not find pulmonary hypertension in any of their 25 patients with hepatic cirrhosis even though many had abnormally large circulating blood volumes.

Thromboemboli from the portal venous system

At least three authors have reported examples of thromboembolic pulmonary hypertension and cor pulmonale in which the portal vein appeared to be the source of recurrent emboli. In five of the patients reported by Naeye, cirrhosis was the probable cause of portal hypertension. In his sixth case and in the single cases reported by Mantz and Craige, and by Owen and associates, portal vein disease seemed to be a primary event. All of these patients had developed porto-systemic collateral vessels, usually through gastric and esophageal varices, but a few had spontaneous direct portacaval shunts. From the postmortem findings of portal vein thrombi in conjunction with large direct vascular pathways to the lungs, these authors suggested that the portal vessels were the origin of pulmonary emboli.

Others have also shown that thrombi commonly develop in the portal venous tracts when there is portal hypertension. All of the patients of this report had liver disease and portal hypertension for many years prior to the discovery of abnormalities in pulmonary hemodynamics. Also, all of the patients had undergone manipulation of the portal vessels during surgical portal decompression and had surgical communications established between the veins of the portal bed and the inferior vena cava. Consequently, the possibility exists that the portal venous bed is the site of origin of the pulmonary emboli. However, this possibility remains unproved for several reasons: (1) In none of the patients were thrombi found in the portal vein at the time of surgical decompression of the portal vein, (2) esophageal bleeding did not recur after portal decompression, suggesting that the shunts were functional, and (3) anatomic studies at necropsy in two patients failed to disclose macroscopic thrombotic material in either the surgical shunts or in the adjacent vessels.

An additional uncertainty is contributed by numerous reports concerning the natural history of surgical portal decompression which make no reference to pulmonary emboli or to unexplained pulmonary hypertension and cor pulmonale. In view of these uncertainties, the role of the surgical portal vein-systemic vein shunt in the genesis of the pulmonary hypertension remains unsettled. But, the fact that all of these patients had normal cardiorespiratory performance prior to surgery suggests that emboli from the portal venous system may have led to the pulmonary hypertension.

Acknowledgment

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