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 hypertension  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 = splenorrenal; S-S = side-to-side, portacaval; E-S = end-to-side, portacaval.

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 pulmonale6: fatigue, dyspnea, exertional substernal pain, parasternal lift of the right ventricle, sharp accentuation of the pulmonic 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-
vations in the concentrations of alkaline phosphatase and of bilirubin in the serum. In many, the concentration of albumin in the serum was low. Anemia was uncommon. Four patients (T.K., J.S., R.B., and P.L.) had clinical manifestations of pulmonary hypertension with cor pulmonale. Each of these four patients had dyspnea. In addition, one patient (J.S.) displayed signs of right heart failure. All four patients had accentuation of the pulmonic component of the second heart sound, electrocardiographic pattern of right bundle-branch block or right ventricular hypertrophy, and radiologic evidence of cardiac enlargement and dilatation of the main branches of the pulmonary artery. It is noteworthy that prior to portal decompression these four patients had been normal with respect to physical examination of the chest, ECG, and chest roentgenogram. Representative chest x-rays from one patient are shown in figure 1.

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

Figure 1

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.

Figure 2

Photomicrograph showing intimal and medial thickening in a small pulmonary arterial vessel from a patient with cirrhosis, portacaval shunt, and pulmonary hypertension (× 70).
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>V₆₆/₆₆ (L/min/m²)</td>
<td>V₆₂/₆₂ (ml/min/m²)</td>
</tr>
<tr>
<td>T.K.</td>
<td>1.92</td>
<td>0.78</td>
<td>4.4</td>
</tr>
<tr>
<td>J.S.</td>
<td>1.79</td>
<td>0.80</td>
<td>6.1</td>
</tr>
<tr>
<td>R.B.</td>
<td>2.00</td>
<td>0.72</td>
<td>4.8</td>
</tr>
<tr>
<td>P.L.</td>
<td>1.80</td>
<td>0.80</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Group 1—Cirrhosis with clinical signs of pulmonary hypertension

Group 2—Cirrhosis without clinically apparent cardiorespiratory abnormality

A.R. | 2.02 | 0.71 | 5.4 | 160 | 35 | 93 | 30 | 7.45 | 40.5 |
J.E. | 2.00 | 0.80 | 4.3 | 131 | 34 | 100 | 32 | 7.41 | 38.1 |
E.M. | 1.72 | 0.80 | 2.8 | 100 | 25 | 100 | 39 | 7.41 | 47.2 |
G.F. | 1.40 | 0.93 | 5.7 | 130 | 27 | 93 | 36 | 7.40 | 46.8 |
M.G. | 1.58 | 0.79 | 4.5 | 137 | — | 94 | 25 | 7.38 | 33.0 |
R.E. | 1.68 | 0.82 | 5.9 | 142 | — | — | — | — | — |
M.E. | 2.08 | 0.73 | 3.1 | 127 | — | 96 | 40 | 7.38 | 54.0 |

R = respiratory exchange ratio; V₆₆ = minute ventilation (BTPS); V₆₂ = volume of oxygen taken up (STPD); V₆₆/₆₆ = ratio of volume of respiratory dead space to tidal volume; SaO₂ = oxyhemoglobin saturation of arterial blood; P_CO₂ = 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>R</th>
<th>Flow Cardiac index (L/min/m²)</th>
<th>Pulmonary artery Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Mean (mm Hg)</th>
<th>Pressures</th>
<th>Brachial artery Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Right ventricle End-diastolic (mm Hg)</th>
<th>Pulmonary arterial wedge pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.K.</td>
<td></td>
<td>3.2 75 29 51</td>
<td></td>
<td></td>
<td></td>
<td>Group 1—With clinical signs of pulmonary hypertension 96 49 3 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.S.</td>
<td>0.80</td>
<td>2.7 80 28 51</td>
<td></td>
<td></td>
<td></td>
<td>Group 2—Without clinically apparent cardiorespiratory abnormalities 135 65 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.B.</td>
<td>0.72</td>
<td>3.3 86 42 60</td>
<td></td>
<td></td>
<td></td>
<td>150 100 12 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.L.</td>
<td>0.80</td>
<td>4.0 63 34 43</td>
<td></td>
<td></td>
<td></td>
<td>168 70 9 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.R.</td>
<td>0.71</td>
<td>3.6 60 22 35</td>
<td></td>
<td></td>
<td></td>
<td>178 85 6 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.E.</td>
<td>0.80</td>
<td>3.1 23 16 17</td>
<td></td>
<td></td>
<td></td>
<td>139 83 —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.M.</td>
<td>0.80</td>
<td>3.1 14 6 11</td>
<td></td>
<td></td>
<td></td>
<td>143 86 —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.F.</td>
<td>0.93</td>
<td>5.4 19 5 11</td>
<td></td>
<td></td>
<td></td>
<td>146 80 —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.G.</td>
<td>0.79</td>
<td>5.1 31 6 19</td>
<td></td>
<td></td>
<td></td>
<td>135 72 —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.E.</td>
<td>0.82</td>
<td>8.1 27 10 16</td>
<td></td>
<td></td>
<td></td>
<td>135 60 —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.E.</td>
<td>0.73</td>
<td>5.0 39 17 26</td>
<td></td>
<td></td>
<td></td>
<td>165 80 —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3

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

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

Circulation, Volume XXXVII, January 1968
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 pulmone-
is chronic parenchymal lung disease, congenital heart disease, and left ventricular failure could not be implicated in any of these patients. It is noteworthy that the majority of the patients with the combination of hepatic cirrhosis, portosystemic venous shunts, and pulmonary hypertension who had comparable hepatic and pulmonary ventilation and alveolar gas exchange than patients with cirrhosis but normal pulmonary hemodynamics in earlier observations did not display any greater derangements in ventilation and alveolar gas exchange than patients with cirrhosis. In these reports, several mechanisms were considered as likely bases for the pulmonary hypertension.}

Table 5

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Number of cases</th>
<th>Cirrhosis</th>
<th>Portal hypertension</th>
<th>Physiological data</th>
<th>Arterial blood (O₂ sat.)</th>
<th>Presumed basis for pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantz and Craige⁴</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>Emboli</td>
</tr>
<tr>
<td>Owen and associates⁴</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>(spontaneous)</td>
<td>—</td>
<td>Emboli</td>
</tr>
<tr>
<td>Murray, Dawson, and Sherlock¹⁷</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>4.93 44 26 34 84 94</td>
<td>&quot;Unknown&quot;</td>
</tr>
<tr>
<td>Naeve⁵</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>—</td>
<td>Emboli-5; idiopathic-1 IDiopathic</td>
</tr>
<tr>
<td>Kerbel¹³</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>4.92 — — 60 93 —</td>
<td>Hypervolemia</td>
</tr>
<tr>
<td>Bayley, Segel, and Bishop¹⁴</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>—</td>
<td>5.13 39 17 24 84 99.7</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Cohen and Mendelow¹⁵</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

Table 5 summarizes the previous descriptions of the association of pulmonary hypertension with cirrhosis of the liver or portal hypertension. 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.
PULMONARY HYPERTENSION

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 portosystemic 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

The authors are indebted to Dr. G. Richard Dickerson, of The Brockton Hospital, Brockton, Massachusetts, for autopsy data and autopsy material on patient T. K. and to the Veterans Administration Hospital, West Roxbury, Massachusetts, for report of cardiac catheterization (#135).

References

7. Bergofsky, E. H., Turino, G. M., and Fish-


Pulmonary Hypertension Associated with Cirrhosis of the Liver and with Portacaval Shunts
ROBERT M. SENIOR, RICHARD C. BRITTON, GERARD M. TURINO, JOHN A. WOOD, GLENN A. LANGER and ALFRED P. FISHMAN

Circulation. 1968;37:88-96
doi: 10.1161/01.CIR.37.1.88
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/37/1/88

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/