Left Ventricular Function, Metabolism, and Blood Flow in Chronic Cor Pulmonale

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SUMMARY
Left ventricular function, oxidative metabolism, and coronary blood flow were evaluated in 11 patients with chronic cor pulmonale (mean age 53 years) at rest and during stress, and compared with 11 normal subjects (mean age 29 years) studied under similar conditions. The left ventricles of patients with chronic cor pulmonale were normal in regard to contractile state, preload, afterload, coronary blood flow, and myocardial oxidative metabolism. However, the mean cardiac index, stroke volume, stroke work, and left ventricular ejection fraction were below normal, and end-systolic volume was elevated. These differences in performance are consistent with the older mean age of the patients. An alternative explanation is the limit placed on right ventricular stroke volume by the increased afterload (pulmonary vascular resistance). Allowance for these factors permits the conclusion that the left ventricles of patients with chronic cor pulmonale are normal unless involved by a second disease process.

Additional Indexing Words:
Oxidative metabolism  Chronic cor pulmonale  Pulmonary vascular resistance

Chronic cor pulmonale has been defined by a World Health Organization committee as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease." Whether the left ventricle may be involved as a result of cor pulmonale is controversial. Such involvement has been inferred from the postmortem observation of left ventricular hypertrophy in some patients with chronic pulmonary disease, from clinical evidence of apparent left ventricular failure in others, from elevated left ventricular end-diastolic pressure in three of the eight patients in the latter series, and from the finding that an angiotensin-induced increase in afterload elicited reduction in left ventricular performance in 12 of 15 patients with cor pulmonale. However, left ventricular hypertrophy has been absent in other series, and end-diastolic pressures were normal in all cor pulmonale patients studied (total 28) in two recent investigations of left ventricular function, and no abnormalities of function resulted in cor pulmonale when afterload increases were produced using methoxamine. None of the previous studies has evaluated the force-velocity (contractile) or length-work (Frank-Starling) relations. In view of the controversy regarding the left ventricle in cor pulmonale, the present study was undertaken in order to evaluate the state of the left ventricle more completely by means of nearly simultaneous measurement of preload, afterload, contractility, pump performance, coronary hemodynamics, and myocardial oxidative metabolism.

Materials and Methods
Eleven patients with chronic cor pulmonale were studied by combined left and right heart catheterization. The important clinical findings for these patients are outlined in table 1. Each patient fulfilled one or more criteria for right ventricular overload; RVH by ECG, right ventricular heave, or right ventricular enlargement by X-ray. None was in right heart failure
Clinical Findings

<table>
<thead>
<tr>
<th>Pt</th>
<th>RVF</th>
<th>RVE</th>
<th>RVH on PE</th>
<th>RAD</th>
<th>Psv</th>
<th>Clinical diagnosis</th>
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<td>R.R.</td>
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<td>+</td>
<td>+</td>
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<td>0</td>
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<td>H.G.</td>
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<td>J.F.</td>
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<td>+</td>
<td>0</td>
<td>Pulmonary TB with LUL bronchiectasis</td>
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<tr>
<td>G.M.</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>R.F.</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RVF = previous right ventricular failure; RVE = right ventricular enlargement on X-ray; RVH on PE = right ventricular hypertrophy (left parasternal or subxiphoid heave) on physical examination; RAD = right-axis deviation (> +110°); Prom R-aVR = dominant late R wave in lead aVR in a vertical heart; Ppulm = Ppulmonale; bron = chronic bronchitis; emph = chronic pulmonary emphysema; fibr = chronic pulmonary fibrosis.

at the time of study. None of the patients had evidence of other types of cardiovascular disease, and none was diabetic. The mean age of this group was 53 years, and the mean arterial oxygen saturation 88% following maximum benefit from therapy for their pulmonary disease. These were compared with 11 normal subjects, mean age 29 years and mean arterial oxygen saturation 96%, evaluated by the same methods.

All subjects were studied in the fasting state following mild barbiturate sedation which was adjusted according to body weight and the level of hypoxemia. The pulmonary artery was entered through a right antecubital vein and the coronary sinus through a left antecubital vein. Care was taken to place the coronary sinus catheter high enough to avoid right atrial venous admixture. The left ventricle was entered in a retrograde fashion via the right brachial artery using an NIH catheter which was positioned in midcavity. The aortic root was entered via the left brachial artery by the Stille-Seldinger technic using a polyethylene catheter (1 1.3 mm, 70 cm long). Simultaneous pressures were recorded using Statham P23Gb pressure transducers and an oscillographic recorder (Electronics for Medicine). The zero pressure level was established at a point halfway between the manubrium and the table top. The first time derivative of the ventricular pulse was obtained using a resistance-capacitance differentiating circuit (time constant 1.1 msec) connected to the output of the ventricular channel. The catheter of this system was connected directly to the external transducer. This conventional system has been found to be linear up to a dP/dt maximum of 2500 mm Hg-sec and exhibits an error of between 5 and 10% between 2500 and 3000 mm Hg-sec, if care is taken to eliminate overt motion artifact by careful positioning of the catheter tip.

The left ventricular ejection fraction was measured by indicator dilution as we have previously described. Indocyanine green dye was introduced into the left ventricle by sudden injection, and blood was sampled at rates of 2.0 ml/sec through the aortic catheter and a Gifford densitometer by means of a Harvard withdrawal pump. The sampling dead space was approximately 1.0 ml, and the 90% response time for the catheter-densitometer system was less than 0.6 sec. For these curves concentrations were plotted semilogarithmically as a function of stroke number. Except for the initial one or two beats on some curves, concentrations uniformly fell on a single slope of exponential decay. From this slope the ejection fraction, which is the ratio of stroke volume to end-diastolic volume, was calculated as 1 – (Cn+1/Cn), where Cn is the concentration on any beat, Cn+1 is the concentration on the succeeding beat, and the concentration ratio (Cn+1/Cn) is obtained as the kth root of 0.1, where k is the number of beats required for a 1 log decade fall in concentration. The results of two or more measurements of ejection fraction were averaged in each subject for each state evaluated. We have previously reported, on the basis of 146 measurements in 34 human subjects, a mean coefficient of variation of 5.1% for measurement of ejection fraction by this method.

Cardiac output was obtained from aortic dilution curves following the sudden injection of indocyanine green into the pulmonary artery. For these curves, concentration was plotted semilogarithmically as a function of time and extrapolated to 1% peak concentration. Areas were obtained by summation of the concentrations, and forward flow was calculated by...
the method of Kinsman, Moore, and Hamilton. Mean stroke volume was obtained as the average from two or more such curves in each state, and the end-diastolic volume of the left ventricle was calculated as the ratio of mean stroke volume to mean ejection fraction. End-diastolic volume measured by this technic does not differ significantly from sequential measurements obtained by single-plane cineangiography.\textsuperscript{16, 17}

Left ventricular coronary blood flow was measured using \textsuperscript{85}Kr-saturated saline, following 15-sec infusions into the left ventricle, by semicontinuous sampling from the coronary sinus washout. The results of this method have been found to differ insignificantly from the nitrous oxide method.\textsuperscript{18, 19} Blood was withdrawn simultaneously from both the arterial circulation and the coronary sinus before and after each coronary period, for the measurement of lactate\textsuperscript{20} and pyruvate\textsuperscript{21} and during the fifth minute following krypton infusion for analysis of oxygen by the method of Van Slyke and Neill.\textsuperscript{22} In addition, blood was withdrawn shortly before each krypton infusion to obtain background radioactivity. Each \textsuperscript{85}Kr specimen was counted for gamma-activity in a well counter for a total of 5000 or 10,000 counts with the center of the counter window at 51 kev. The radioactivity of the eight specimens minus the background radioactivity was plotted on semilog paper, and the line of best fit for the washout slope was drawn or obtained mathematically. The time for a 1 log decade fall was measured, and the \textsuperscript{85}Kr coronary flow was calculated from the Kety formula and expressed as ml/100 g LV/min. A partition coefficient of 1.0 and a specific gravity for myocardium of 1.05 have previously been reported.\textsuperscript{18} Myocardial oxygen consumption was then calculated as the product of coronary flow and the arterial coronary sinus oxygen difference.

The force-velocity-length relationship was expressed using an index of contractility previously described.\textsuperscript{23} The index is calculated as (MRPR/MIP)/2πr, where MRPR is the maximum rate of left ventricular pressure rise, MIP the maximum isovolumetric pressure which is a linear function of tension during the isovolumetric period, and 2πr the mean circumferential fiber length at end-diastole. The numerator approximates the velocity of the contractile element at peak isometric stress, while the denominator normalizes the index for differences in heart size. Changes in contractile element performance are thus manifested as changes in MRPR out of proportion to changes in MIP (afterload) or fiber length (preload).

Work generated by the left ventricle, in g-m/beat, was calculated from the formula: W = (LVMSP - LVEDP) (SV) (1.36)/100, where LVMSP = left ventricular mean systolic pressure, LVEDP = left ventricular end-diastolic pressure, SV = stroke volume, and 1.36 is the factor to convert mm Hg to cm H$_2$O. For calculating the left ventricular work index, the above was divided by the body surface area of the individual patients.

Each patient was studied at rest, and then an attempt was made to study supine exercise on a bicycle ergometer. It proved to be difficult or impossible to reach and maintain a steady state in many of these patients because of the impairment in their pulmonary function. Only three successful studies were achieved during exercise. Therefore, it was elected to utilize an isoproterenol infusion at a rate which previous experience had demonstrated would result in heart rates similar to those achieved during moderate exercise on a bicycle ergometer.

The results of the study were evaluated using conventional statistical technics for small samples. Differences between patients with chronic cor pulmonale and normal subjects were compared using Student's $t$ test for unpaired samples. The data from three patients studied during exercise and four during isoproterenol infusion were similar and therefore were pooled under the title of "Stress." These were then compared with normal subjects who had been studied during exercise. The changes from rest to stress were also evaluated by comparing mean percent changes for the chronic cor pulmonale patients with those for the normal subjects.

**Results**

The results of this study appear in tables 2 and 3. In the patients with cor pulmonale, mean heart rate, left ventricular systolic and end-diastolic pressures, aortic mean pressure, and total peripheral resistance were normal while the pulmonary vascular resistance was significantly elevated. The mean cardiac index in patients with chronic cor pulmonale was below that of the normal subjects (2.77 vs 3.34 liters/min/m$^2$), but this difference was only of borderline significance ($P < 0.1$).

Left ventricular coronary blood flow, myocardial oxygen extraction, and myocardial oxygen usage as well as the coronary vascular resistance were within normal limits (table 2). There was no evidence for coronary inadequacy, since in each patient the coronary arteriovenous differences for blood lactate were positive, the coronary sinus lactate-pyruvate ratios were normal, and there was no excess lactate production. Moreover the mean resting coronary sinus oxygen content ($5.2 \pm 0.3$ vol %) did not differ significantly from normal ($5.4 \pm 0.6$).

Left ventricular contractility was normal in patients with cor pulmonale, and the variables used to make this calculation were also within normal limits (table 3). There was no important correlation between age and our index of contractility in either patients with chronic cor pulmonale ($r = 0.25$) or normal subjects ($r = 0.12$). Patients over 50 years of age had almost the identical mean value for this index as patients under 50 years of age. There was also no relationship between the degree of arterial hypoxemia and the status of the force-velocity relationship. However, patients with chronic cor pulmonale had a significantly smaller stroke volume.
Table 2

Systemic and Coronary Hemodynamics in Chronic Cor Pulmonale

<table>
<thead>
<tr>
<th>Pt group</th>
<th>HR  (beats/min)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>AoMP (mm Hg)</th>
<th>TPR (dynes/sec/cm²)</th>
<th>PAR (dynes/sec/cm²)</th>
<th>CI (liters/min)</th>
<th>CBF (ml/100 g LV/min)</th>
<th>MVO₂ (ml/100 g LV/min)</th>
<th>C(A-V)O₂ (vol %)</th>
<th>CRI (mm Hg/ml/100 g LV/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCP resting mean (N = 11)</td>
<td>89</td>
<td>112</td>
<td>8</td>
<td>89</td>
<td>1695</td>
<td>519</td>
<td>2.77</td>
<td>88</td>
<td>9.7</td>
<td>11.0</td>
<td>1.04</td>
</tr>
<tr>
<td>SEM</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>186</td>
<td>165</td>
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<td>0.6</td>
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<td>Normal resting mean (N = 11)</td>
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<td>113</td>
<td>9</td>
<td>92</td>
<td>1367</td>
<td>141</td>
<td>3.34</td>
<td>86</td>
<td>10.2</td>
<td>11.9</td>
<td>1.10</td>
</tr>
<tr>
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<td>6</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>96</td>
<td>26</td>
<td>0.22</td>
<td>5</td>
<td>0.8</td>
<td>0.8</td>
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<td>&lt;0.9</td>
<td>&lt;0.6</td>
<td>&lt;0.5</td>
<td>&lt;0.2</td>
<td>&lt;0.05</td>
<td>&lt;0.1</td>
<td>&lt;0.8</td>
<td>&lt;0.6</td>
<td>&lt;0.3</td>
<td>&lt;0.5</td>
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<tr>
<td>CCP stress mean (N = 7)</td>
<td>116</td>
<td>122</td>
<td>7</td>
<td>92</td>
<td>1305</td>
<td>230</td>
<td>3.85</td>
<td>124</td>
<td>12.9</td>
<td>10.8</td>
<td>0.77</td>
</tr>
<tr>
<td>SEM</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>169</td>
<td>61</td>
<td>0.35</td>
<td>9</td>
<td>0.4</td>
<td>0.9</td>
<td>0.06</td>
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<tr>
<td>Normal stress mean (N = 8)</td>
<td>110</td>
<td>128</td>
<td>13</td>
<td>104</td>
<td>1009</td>
<td>97</td>
<td>4.89</td>
<td>126</td>
<td>15.1</td>
<td>12.1</td>
<td>0.81</td>
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<tr>
<td>SEM</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>94</td>
<td>3</td>
<td>0.32</td>
<td>6</td>
<td>0.8</td>
<td>0.6</td>
<td>0.04</td>
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<tr>
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<td>&lt;0.5</td>
<td>&lt;0.02</td>
<td>&lt;0.2</td>
<td>&lt;0.2</td>
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<td>&lt;0.05</td>
<td>&lt;3.3</td>
<td>&lt;0.6</td>
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</table>

Mean % change from rest to stress:

| CCP (N = 7)                           | 27              | 7             | -7            | 3             | -26                 | -22                 | 44              | 30                    | 34                       | -2              | -23                        |
| SEM                                   | 6               | 2             | 21            | 3             | 5                   | 9                   | 7               | 9                     | 7                        | 4               | 5                          |
| Normal (N = 8)                        | 32              | 13            | 57            | 11            | -13                 | -27                 | 54              | 49                    | 49                       | 0               | -23                       |
| SEM                                   | 5               | 2             | 23            | 2             | 8                   | 12                  | 7               | 7                     | 12                       | 4               | 4                          |
| P value                               | <0.6            | <0.1          | <0.1          | <0.2         | <0.8                | <0.5                | <0.3            | <0.3                  | <0.7                     | <0.9            |                            |

Abbreviations: CCP = chronic cor pulmonale; HR = heart rate; LVSP, LVEDP, and AoMP = left ventricular systolic, end-diastolic, and aortic mean pressures; TPR and PAR = total peripheral and pulmonary arteriolar resistance; CI = cardiac output; CBF and MVO₂ = coronary blood flow and myocardial oxygen consumption; C(A-V)O₂ = coronary arteriovenous oxygen difference; CRI = coronary resistance index.
## Table 3

**Hemodynamics Data in Chronic Cor Pulmonale**

<table>
<thead>
<tr>
<th>Pt group</th>
<th>MRPR (mm Hg/sec)</th>
<th>MIP (mm Hg)</th>
<th>2(r) (cm)</th>
<th>CyIx (g·cm/beat)</th>
<th>SW (ml/m²)</th>
<th>SV (ml/m²)</th>
<th>EDV (ml/m²)</th>
<th>ESV (ml/m²)</th>
<th>SV/EDV</th>
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<td>72</td>
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<td>1.18</td>
<td>65</td>
<td>32</td>
<td>88</td>
<td>58</td>
<td>0.37</td>
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<tr>
<td>SEM</td>
<td>136</td>
<td>2</td>
<td>0.4</td>
<td>0.35</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>0.03</td>
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<tr>
<td>Normal resting mean (N = 11)</td>
<td>1783</td>
<td>74</td>
<td>19.7</td>
<td>1.22</td>
<td>91</td>
<td>41</td>
<td>77</td>
<td>35</td>
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<tr>
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<td>113</td>
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<td>74</td>
<td>34</td>
<td>90</td>
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<td>4</td>
<td>8</td>
<td>6</td>
<td>0.03</td>
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<tr>
<td>Normal stress mean (N = 8)</td>
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<td>82</td>
<td>20.5</td>
<td>1.47</td>
<td>117</td>
<td>46</td>
<td>85</td>
<td>39</td>
<td>0.54</td>
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<tr>
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<td>4</td>
<td>7</td>
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<td>0.03</td>
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<tr>
<td><em>P</em> value</td>
<td>&lt;0.95</td>
<td>&lt;0.1</td>
<td>&lt;0.8</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.7</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
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</table>

Mean % change from rest to stress, CCP (N = 7)
| (N = 7)                      | 50               | 1           | 1           | 53              | 23         | 15         | 3           | 2           | 12     |
| SEM                          | 6                | 3           | 1           | 10              | 8          | 9          | 5           | 6           | 6      |

Normal (N = 8)
| (N = 8)                      | 37               | 8           | 4           | 23              | 29         | 18         | 14          | 13          | 4      |
| SEM                          | 6                | 2           | 3           | 7               | 8          | 9          | 9           | 14          | 4      |
| *P* value                    | <0.2             | <0.05       | <0.4        | <0.05           | <0.7       | <0.9       | <0.4        | <0.4        |

Abbreviations: MRPR = maximum rate of pressure rise; MIP = maximum isovolumetric pressure; 2\(r\) = end-diastolic fiber length; CyIx = contractility index; SW = stroke work; SV = stroke volume; EDV = end-diastolic volume; ESV = end-systolic volume; SV/EDV = left ventricular ejection fraction.
delivered from a normal left ventricular end-diastolic volume. Thus, the ejection fraction (the extent of fiber shortening) of the left ventricle was reduced and the end-systolic volume elevated. The reduced stroke volume at normal systemic pressures resulted in a stroke work significantly less than that found in normal subjects (table 3).

During stress, the absolute values of those variables which were lower than normal at rest tended to remain lower (tables 2, 3). For example, the mean cardiac output during stress was lower than that found in normal subjects (3.85 vs 4.89 liters/min/m², P < 0.05). However, the response to stress, expressed as the mean percentage change from control values, did not differ in the two groups. Specifically, both groups experienced comparable degrees of cardiaacceleration, increases in systemic blood flow and pressure, decreases in total systemic resistance, and increments in coronary flow and myocardial oxygen usage. While the mean left ventricular end-diastolic pressure was slightly lower in the cor pulmonale group, this was probably the result of differences in the kind of stress (exercise in all normal subjects, isoproterenol in four of the seven patients). Elevation of the legs to the pedals of a bicycle ergometer in the supine position is often responsible for some augmentation in end-diastolic pressure, whereas isoproterenol routinely produces a decrease.

In the patients with cor pulmonale, the ventricle continued to eject a smaller stroke volume from a normal end-diastolic volume and, consequently, the end-systolic volume of the ventricle was elevated and the stroke work was less than that found in normal subjects. However, contractility did not differ significantly from normal nor did any of the variables used to make this calculation (table 3). Left ventricular coronary blood flow did not differ from normal, but the absolute value for myocardial oxygen usage was significantly greater during stress in the normal subjects than in patients with cor pulmonale. This was felt to be due to the larger pressures generated in the left ventricle as well as the somewhat larger amount of useful work produced. No evidence of coronary inadequacy developed during stress. In each patient, the coronary arteriovenous difference for blood lactate was positive, the lactate-pyruvate ratio was normal, and there was no excess lactate production. It is probable that the amount of stress achieved by the normal subjects during exercise was somewhat greater than that found in patients with cor pulmonale.

Discussion

The results of this study demonstrate that the cor pulmonale group differed from the normal in having lower cardiac index, stroke volume, stroke work, and ejection fraction, and higher left ventricular end-systolic volume. These differences in left ventricular performance were not the result of abnormality in left ventricular preload, afterload, contractile state, coronary perfusion, or oxidative metabolism since these were all within normal limits. Without other demonstrable pathophysiology in that chamber, the possibility must be entertained that the reduced left ventricular pump performance is due to a phenomenon other than left ventricular pathology.

Neither anatomic nor functional abnormality of the left ventricle need be invoked to explain its reduced pump performance in cor pulmonale. Increased right ventricular afterload resulting from high pulmonary vascular resistance necessitates a larger portion of the right ventricle's contractile activity being expended in pressure work and a proportionately smaller fraction in volume work. Khaja and Parker, studying the performance of both ventricles in chronic obstructive lung disease, found that, in relation to its filling pressure, right ventricular stroke work was normal but its stroke volume diminished. Since the pump function of the left ventricle is, after all, contingent upon that of the right ventricle, subnormal stroke volume and cardiac index, as well as elevated left ventricular end-systolic volume, may be expected in severe right heart pressure overloads.

Another explanation for reduced left ventricular performance without other functional abnormality in that chamber reflects a difficulty with previous studies as well as our own, namely that of obtaining a suitable control group. Appropriate control subjects must be of similar age to the cor pulmonale patients, clinically normal, and therefore without indications for study, but willing to give informed consent for the necessary systemic, pulmonary, and coronary measurements. We did not find it possible to obtain an age-matched control group, and the question must, therefore, be asked whether the disparities in performance simply reflect the age difference. The available data indicate that this is so. Brandfonbrener and his associates have demonstrated that cardiac output decreases progressively with age and that a substantially lower
cardiac output, measured by the same technic used in the present study, is a consistent finding in older normal subjects. Their subgroup with mean age of 34 years and our normal subjects, with mean age of 29 years, had mean cardiac indices of 3.54 and 3.34 liters/min/m², respectively, and their subgroup with mean age of 55 years and our cor pulmonale patients, with mean age of 53 years, had mean indices of 2.78 and 2.77 liters/min/m², respectively.

Thus, deficits of left ventricular performance in cor pulmonale need not predicate anatomic or functional impairment of that chamber. They are explicable either in terms of the ordinarily older age of such patients, as in our series, or, in patients with more severe pulmonary hypertension, in terms of impaired right ventricular pumping.

Aside from impaired resting pump performance, the left ventricular abnormalities reported in cor pulmonale have consisted of occasional instances of elevated end-diastolic pressure and a depressed response to increased afterloading. However, increased end-diastolic pressure is recognized to be an unreliable index of expanded left ventricular volume and, therefore, of failure. Moreover, with elevated systemic venous pressure and hyperoxemia, a common presentation in decompensated cor pulmonale, increases in pericardial pressure may account for over three fourths of the left ventricular end-diastolic pressure. In regard to abnormal responses to afterloading, these were not observed when the afterload rise was produced with methoxamine but only with angiotensin, a drug which has been shown to be negatively inotropic in the intact heart.

With regard to the clinical bases for the presumption of left ventricular involvement in cor pulmonale, it must be noted that acute pulmonary congestion cannot confidently be attributed to left-sided heart failure in such patients since increases in pulmonary hypertension associated with bouts of respiratory failure may lead to pulmonary edema without involvement of the left heart. In addition, antemortem or postmortem demonstration of left ventricular hypertrophy may, in some patients, be coincidental and due to other causes. For example, coronary artery disease severe enough to produce myocardial infarction is known to occur without a history of chest pain or of documented myocardial damage. Moreover, myocardial ischemia with left ventricular dysfunction and even necrosis may occur with normal coronary arteriograms. It is especially likely that some patients with cor pulmonale will have an associated alcoholic cardiomyopathy. The high incidence of chronic pulmonary disease in alcoholics is well recognized, and left ventricular dysfunction has been demonstrated in alcoholics even without overt heart disease.

In proposing biventricular involvement in cor pulmonale, Scott and Garvin suggested that the syncytial arrangement of the myocardium resulted in a sharing of stresses by the two chambers. However, if this were the case, we should not expect the scanty and equivocal though provocative evidence of left ventricular involvement which has been reported; rather, clinical, physiologic, and pathologic documentation of left ventricular involvement should be the rule. If, therefore, the purported evidence of left ventricular involvement is valid, it is likely to be based upon a phenomenon other than the syncytial arrangement of the myocardium. Experimentally, hypoxemia and acidosis have been shown to depress left ventricular function. However, significant negative inotropy based on respiratory failure alone is unlikely until arterial pH is reduced to about 7.1. Furthermore, arterial hypoxemia rarely results in anaerobic metabolism, even with oxygen saturations below 60%, in patients with normal coronary arteries since it is myocardial oxygen tension and not arterial oxygen content which is the critical factor.

In the present study, there was no clinical evidence suggesting coronary disease; left ventricular coronary flow and myocardial oxygen consumption were normal, confirming the findings of Rose and Hoffman, Fukuda, and Moret and associates; and there was no metabolic evidence for myocardial hypoxia or coronary inadequacy based on coronary venous oxygen content, arteriovenous lactate extraction, coronary sinus lactate-pyruvate ratios, and excess lactate production.

In referring to cor pulmonale as "a disease of the whole heart," Altschule attributed the left-sided component partly to increased cardiac output, due to hypoxia and hypercarbia and shared by the two ventricles, and partly to a specific increase in left ventricular output due to bronchopulmonary shunting. However, earlier reports of increased cardiac output in lung disease have not been confirmed, and resting output has been described in recent reports, including the present one, as normal or reduced with an occasional high value attributed to the elevated oxygen consumption of increased respiratory effort or febrile infection. Increase in anastomotic bronchopulmonary flows does result in the output of the left ventricle exceeding that of.
the right. However, such shunting is confined to patients with bronchiectasis, silicosis, and other fibrosing disorders associated with finger clubbing. The difference between the two ventricular outputs is ordinarily small, uncommonly reaching levels of 25% excess of left ventricular output.\textsuperscript{50-52} It seems dubious that this stress is significant.

In terms of possible mechanisms underlying left ventricular involvement, Cudkowicz, in his recent review of left heart function in lung disease, while espousing the proposition that both ventricles are involved, concluded that left ventricular contractility in chronic lung disease appears to be within normal limits, that anoxia by itself is not a reasonable explanation for failure of the myocardium, that sustained but modest increases in left ventricular output are an inadequate explanation and, in general, that none of the known physiologic abnormalities constitutes a satisfactory pathogenetic mechanism for left ventricular involvement.\textsuperscript{53} We agree that there is no convincing explanation for left ventricular involvement. Moreover, on the basis of the present study and the above considerations, we conclude that there is no left ventricular involvement to be explained and that cor pulmonale is correctly defined by the World Health Organization as "a disease of the right ventricle."

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