Systolic Time Intervals in Chronic Obstructive Pulmonary Disease

By Robert G. Hooper, M.D., and Michael E. Whitcomb, M.D.

SUMMARY
In an attempt to clarify the relationship between left ventricular function and chronic obstructive pulmonary disease (COPD), systolic time intervals (STI) were measured in 12 control subjects and 28 patients with COPD who had only moderate arterial blood gas abnormalities and who had no cardiac symptomatology or clinical evidence of organic heart disease. The patients with COPD were divided into three groups of increasingly severe airway obstruction based on the percent predicted forced expired volume in one second.

Significant differences in pre-ejection period index (PEP_i) and left ventricular ejection time index (LVET_i) existed between the control subjects and the patients with the most severe lung disease (Group III). A highly significant difference in PEP/LVET existed between these two groups. The abnormalities of STI demonstrated in these patients are characteristic of left ventricular dysfunction and indicate that subclinical left ventricular dysfunction is frequently present in patients with moderate obstructive lung disease.

Additional Indexing Words:
Left ventricular function  Noninvasive studies  Lung disease

THE STATUS of left ventricular function in patients with chronic obstructive pulmonary disease (COPD) has been a controversial subject since early autopsy studies demonstrated left ventricular hypertrophy in a significant percentage of patients dying with COPD. These studies suggested that the left ventricle is adversely affected by long-standing obstructive lung disease, a concept in conflict with the traditional belief that chronic lung disease affects the right ventricle alone. Recent investigations have demonstrated definite abnormalities of the functional characteristics of the left ventricle in patients with COPD.1-3 Since many of the patients in these studies had significant hypoxemia, hypercapnia, and/or clinical cor pulmonale, it is unclear whether the left ventricular dysfunction was the result of these sequelae of COPD or more directly related to the effect of COPD on the heart.

In an attempt to clarify the relationship between left ventricular function and COPD, we have measured systolic time intervals (STI) in 28 patients with clinically stable COPD. These patients had only moderate arterial blood gas abnormalities and had no cardiac symptomatology, history of previous episodes of heart failure, or clinical evidence of organic heart disease. The measurement of systolic time intervals is a noninvasive technique which has been demonstrated to be a reliable index of left ventricular function.4-6 This study demonstrates that subclinical left ventricular dysfunction is frequently present in patients with obstructive lung disease and is not primarily the result of severe resting arterial blood gas abnormalities.

Methods

Patient Selection
Patients with chronic obstructive pulmonary disease who had been referred to the Pulmonary Function Laboratory, Walter Reed Army Medical Center, were evaluated for inclusion in this study. In order to be selected for the study, the patients had to have no clinical history suggestive of organic heart disease and no history of alcohol abuse. In addition the patients had to be normotensive and have a normal cardiac examination. All patients had a normal 12 lead electrocardiogram and normal cardiac silhouette on a standard PA chest roentgenogram. Patients with any other associated disease were excluded from the study. Twelve normal men were selected as control subjects. Patients and controls were not matched for age.

Pulmonary Function Testing
Routine spirometry was performed with a 13.5 liter Collins water seal spirometer. The vital capacity (VC), expiratory reserve volume and forced expired volume in one second (FEV_1), were calculated directly from the spirometry tracing. The functional residual capacity (FRC) was measured by the closed circuit helium dilution technique. The residual volume and total lung capacity (TLC) were calculated by standard methods. All results were expressed as volume at body temperature and pressure saturated with

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water (BTPS). Predicted values were those of Boren and associates.\textsuperscript{7} Arterial blood gases (PaCO\textsubscript{2} and PaO\textsubscript{2}) were measured by Clarke and Severinghouse electrodes utilizing an IL 513 blood gas analyzer.

Systolic Time Intervals

Polygraphic recordings were made on an Elema-Schonander (type EM-34) phonocardiogram at a paper speed of 125 mm per second. Simultaneous recordings were made of the electrocardiogram lead II, heart sounds at the lower left sternal border, and the carotid displacement pulse. All recordings were performed between 8 a.m. and noon. Patients in whom adequate recordings of heart sounds could not be obtained were excluded from the study.

Five consecutive cardiac cycles were measured and the results averaged. The R-R interval of the electrocardiogram (ECC) was used to calculate heart rate. Total electromechanical systole (QSE) was measured from the onset of the QRS of the ECC to the aortic closure sound. The onset of the rapid upstroke of the carotid pulse to the carotid incisural notch was measured as the left ventricular ejection time (LVET). The pre-ejection period (PEP) was calculated by subtraction of the LVET from QSE. The ratio of the PEP to LVET (PEP/LVET) was calculated from the measured intervals. The PEP and LVET have been corrected for rate by using the regression equation of Weisler et al.\textsuperscript{4} The rate corrected PEP and LVET were expressed as the PEP index (PEPI) and LVET index (LVEt).

Acute Hyperinflation Studies

Five of the normal individuals served as subjects to test the effects of acute hyperinflation on externally recorded STI. Hyperinflation was accomplished by obstructing the expiratory side of a two-way Hans Rudolph valve attached to a mouthpiece for a five-minute period. The FRC was measured pre and post hyperinflation in a constant volume body plethysmograph.\textsuperscript{a} The maneuver was repeated in a semirecumbent position while measurement of the STI as described above was made both pre and post hyperinflation.

Results

Twenty-eight male patients with clinically stable COPD were selected for study. Patients ranged in age from 35 to 67 years.

The patients were divided into three groups (I, II, III) based on increasingly severe airways obstruction on the basis of the percent predicted forced expired volume in one second (FEV\textsubscript{1}–PP). Group I consisted of eight persons whose FEV\textsubscript{1}–PP ranged from 76–90%. Group II consisted of ten patients with an FEV\textsubscript{1}–PP between 51–75%; and group III consisted of ten patients with an FEV\textsubscript{1}–PP between 26–50%. The results of the pulmonary function studies for each group are listed in table 1. It should be noted that none of the patients had a forced expired volume in one second (FEV\textsubscript{1}) of less than 1,000 cc, and the mean FEV\textsubscript{1} for the most severely obstructed group (group III) was 1,380 cc. The results of blood gas analysis were available in 22 of the 28 patients, including all of the ten patients in group III. The arterial pO\textsubscript{2} was 60 mm Hg or greater in all patients and none of the patients were hypercapnic.

The results of the measurements of systolic time intervals are listed in table 2. The values for the control subjects are similar to those previously published.\textsuperscript{4, 9} There are no significant differences in PEP\textsubscript{1}, LVET\textsubscript{1}, and PEP/LVET between the control subjects and patients in groups I and II. There is a significant difference in PEP\textsubscript{1} (P < 0.01) and LVET\textsubscript{1} (P < 0.05) between the control subjects and the patients in group III. In figure 1, the PEP/LVET ratio for each group is depicted. There is a highly significant difference (P < 0.001) in PEP/LVET between the control subjects and the patients in group III. The individual values for the PEP/LVET for the patients in each group are depicted in figure 2. Three of the eight patients in group I, four of the ten patients in Group II and eight of the ten patients in group III had a PEP/LVET ratio greater than two standard deviations above the mean of the control subjects (95% confidence limits). Although no statistical difference in the mean PEP/LVET existed between the control

### Table 1

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>FEV\textsubscript{1} (cc)</th>
<th>FEV\textsubscript{1}/FVC (%)</th>
<th>VC-PP*</th>
<th>RV-PP</th>
<th>TLC-PP</th>
<th>PaO\textsubscript{2} (mm Hg)</th>
<th>PaCO\textsubscript{2} (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>49.8\textsuperscript{+}</td>
<td>2910</td>
<td>64</td>
<td>99</td>
<td>144</td>
<td>110</td>
<td>77</td>
<td>33</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53.4</td>
<td>2225</td>
<td>59</td>
<td>88</td>
<td>141</td>
<td>102</td>
<td>72</td>
<td>32</td>
</tr>
<tr>
<td>Group III</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>56.3</td>
<td>1380</td>
<td>46</td>
<td>68</td>
<td>246</td>
<td>117</td>
<td>72</td>
<td>34</td>
</tr>
</tbody>
</table>

\*Mean value.
\textsuperscript{†}Range.

**Abbreviations:** FEV\textsubscript{1} = forced expired volume in one second; FVC = forced vital capacity; VC = vital capacity; PP = percent predicted; RV = residual volume; TLC = total lung capacity; PaO\textsubscript{2} = arterial oxygen tension; PaCO\textsubscript{2} = arterial carbon dioxide tension.
subjects and groups I and II, there were clearly patients in both groups who had abnormal values. No relationship could be established between resting PaO₂ and the presence of abnormal STI.

The five normal individuals who underwent acute hyperinflation all demonstrated a post obstruction functional residual capacity of at least 140% of their control value. There was no significant change in the STI after hyperinflation in any of the subjects.

Discussion

Traditionally chronic lung disease has been considered to affect only the right ventricle. Since early postmortem studies demonstrated the presence of left ventricular hypertrophy in a significant percentage of patients dying with COPD, the relationship between COPD and left ventricular function has been controversial. Until recently there has been little convincing evidence of left ventricular dysfunction in patients with COPD. Although elevation of the left ventricular end-diastolic pressure has been demonstrated in an occasional patient with COPD, this parameter of left ventricular function has been normal in the great majority of patients studied to date.

Three groups have performed more sensitive studies of left ventricular function in patients with COPD by constructing left ventricular function curves using variations of the technique originally described by Ross and Braunwald. Although Williams et al. and Khaja and Parker concluded that their studies failed to demonstrate left ventricular dysfunction, careful analysis of their reports suggests an alternate interpretation of their data is possible. Inspection of the left ventricular function curves published by Williams et al. reveals that many of their patients with pulmonary hypertension actually had curves similar to Ross and Braunwald’s abnormal group II and III patients. Similarly in the study of Khaja and Parker, patients with resting pulmonary hypertension had abnormal left ventricular function curves. Khaja and Parker also demonstrated in these patients an inability of the right ventricle to increase stroke volume in response to stress and concluded that this abnormality was primarily responsible for the abnormal left ventricular curves. Nevertheless the slope of the left ventricular function curves still demonstrated that the rise in left ventricular end-diastolic pressure which did occur was inappropriate for the increase in left ventricular stroke work that was observed. Baum et al. clearly demonstrated abnormal left ventricular function curves in 14 of the 15 patients with COPD they studied. In addition, they documented an increase in left ventricular wall thickness and/or diastolic chamber size in nine of the ten patients in whom these measurements were made.

While left ventricular dysfunction has been demonstrated in each of these studies, the pathogenesis of the left ventricular dysfunction is unclear since many of the patients had severe hypoxemia, hypercapnia, and had had episodes of right heart failure. We have attempted to clarify to some extent the relationship between left ventricular function and COPD by measuring STI in a highly selected group of patients with less severe COPD.

The measurement of STI is a noninvasive technique which has been demonstrated to be a reliable index of left ventricular function.** Internal measurements of PEP and LVET correlate closely with externally recorded PEP and LVET.** In addition, a highly

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>PEP/LVET</th>
<th>LVET (ms)</th>
<th>PEP/LVET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls I</td>
<td>133 ± 7</td>
<td>417 ± 13</td>
<td>34.5 ± 1.8</td>
</tr>
<tr>
<td>Group I</td>
<td>136 ± 8</td>
<td>413 ± 10</td>
<td>36.4 ± 3.1</td>
</tr>
<tr>
<td>Group II</td>
<td>132 ± 7</td>
<td>405 ± 10</td>
<td>36.4 ± 3.8</td>
</tr>
<tr>
<td>Group III</td>
<td>146 ± 14</td>
<td>402 ± 17</td>
<td>45.0 ± 7.7</td>
</tr>
</tbody>
</table>

Abbreviations: PEP = pre-ejection period index; LVET = left ventricular ejection time index.
significant correlation between the PEP/LVET ratio and the left ventricular ejection fraction as measured by angiography has been demonstrated in a variety of cardiac diseases.\textsuperscript{5} PEP prolongation, LVET shortening, and an increase in the PEP/LVET ratio is the characteristic pattern observed in patients with left ventricular dysfunction, provided the patients are in sinus rhythm and do not have conduction defects or valvular heart disease.\textsuperscript{6,6}

Our study demonstrates that prolongation of the PEP, shortening of the LVET, and an increase in the PEP/LVET ratio were present with increasing frequency in patients with increasingly severe COPD, despite the absence of both cardiac symptomatology and clinical evidence of cardiac dysfunction. There is a statistically significant difference in the PEP, and LVET\textsubscript{i} between the control subjects and the patients in group III and a highly significant difference in the PEP/LVET ratios between these two groups. While the difference in the mean PEP/LVET ratios between control subjects and the patients in groups I and II is not significant, three of the eight patients in group I and four of the ten patients in group II have ratios greater than 95% confidence limits for the control subjects. The abnormalities in the STI measurements observed in our group III patients are nearly identical to the abnormalities previously demonstrated in a group of clinically asymptomatic alcoholic patients with subclinical left ventricular dysfunction.\textsuperscript{9} These results demonstrate subclinical left ventricular dysfunction is present in patients with less severe COPD and is not related to hypoxemia, hypercapnia, or prior right ventricular failure.

There are three major points which can be raised as objections to our study. Firstly, the validity of STI measurements in patients with COPD have not been substantiated by direct physiologic measurements of cardiac hemodynamics. There is no reason to suspect that a significant difference from internally recorded indices of left ventricular function would exist, provided the external recordings are of adequate quality. In addition, the studies we performed in control subjects following acute hyperinflation showed no changes in STIs under these conditions.

Secondly, age matched controls were not used in our study. Previous studies have demonstrated STI change only slightly with aging, and then only in patients over 60 years of age.\textsuperscript{11,12} Only four of our patients were over 60. Three of the four had abnormal ratios and in two of the three the abnormalities were significantly greater than any change expected from aging alone. In addition our control values are nearly identical to normal values published by other authors who studied normal subjects with a wide range of ages.

Finally, it is conceivable that undiagnosed organic heart disease affecting the left ventricle was present in our patients. Cigarette smoking alone is considered to be a risk factor for coronary artery disease, and all of our patients were smokers and exsmokers. Consequently, one cannot completely exclude the possibility of undiagnosed coronary artery disease as an explanation for our findings. However, considering the criteria used for the selection of patients and that eight of the ten patients in group III had abnormal ratios, the authors feel it is improbable the results could be explained on this basis alone.

The pathogenesis of the left ventricular dysfunction demonstrated by systolic time intervals in this study is unknown. However, since the FEV\textsubscript{i}/PP has been previously demonstrated to be the parameter of airways obstruction which correlates best with resting pulmonary vascular resistance,\textsuperscript{13} it is possible to speculate that the left ventricle, in addition to the right ventricle, is adversely affected by the increased pulmonary vascular resistance present in patients with COPD. The results of biochemical and physiologic studies of the left ventricle in experimental cor pulmonale tend to support this concept.\textsuperscript{14-16}

Acknowledgments

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