Improved Radionuclide Method for Assessment of Pulmonary Artery Pressure in COPD*

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An improved method of noninvasive assessment of pulmonary arterial pressure is presented. The already existing radionuclide method for assessment of pulmonary arterial pressure based on right ventricular ejection fraction, although having a relatively good positive predictive accuracy (75 percent), lacks in specificity and correlates only weakly with pulmonary arterial pressure, \( r = .66 \). In the present study a diastolic index of the ventricular performance (right atrial early diastolic emptying rate) was used to improve the predictive value of the right ventricular ejection fraction. Phase image analysis was used to differentiate the right atrium from the rest of the cardiac structures, and right atrial emptying rate was calculated after time activity curves were generated. A reasonably good correlation was found between right atrial emptying rate and pulmonary arterial pressure, \( r = .75 \). This diastolic index, however, was limited in its ability to detect patients with COPD and normal pulmonary arterial pressure (negative predictive value 62 percent). In order to improve the predictive value of right ventricular ejection fraction, having low specificity (33 percent) but high sensitivity (93 percent), a score index was constructed, combining right ventricular ejection fraction with right atrial emptying rate (having high specificity 100 percent, but modest sensitivity 78 percent). Score index proved to be an excellent indicator of pulmonary arterial hypertension (positive predictive value 93 percent, negative predictive value 100 percent).

Pulmonary artery hypertension frequently complicates chronic obstructive pulmonary disease (COPD) and is the main cause in the development of right ventricular hypertrophy, progressive myocardial damage, and finally, overt right ventricular failure. A noninvasive technique would enable early diagnosis of pulmonary arterial hypertension in patients with COPD and may provide a screening and a follow-up method. Echocardiographic assessment of right ventricular function and pulmonary arterial hypertension is limited by the geometric complexity of the right ventricle and by the poor visualization of the right cardiac structures in most patients with chronic obstructive pulmonary disease. The radionuclide technique is independent of the anatomic structure of the right ventricle and permits an adequate imaging of the right heart structures in all patients. Therefore, most investigators use this technique for evaluation of right ventricular function in COPD. Brent et al. using the first pass radionuclide angiography technique, proposed the right ventricular ejection fraction as a noninvasive predictor of pulmonary arterial hypertension in COPD. However, the low specificity of their method imposed some limitations regarding the clinical usefulness of this index. As it is well known, in patients with sustained pulmonary hypertension with right ventricular hypertrophy, a consequent reduction in right ventricular compliance occurs. Measurement of right atrial diastolic emptying rate, as a diastolic index, combined with measurement of right ventricular ejection fraction, as a systolic index, may prove to be a better estimate of the pulmonary hypertension than the right ventricular ejection fraction alone.

In the present study, right atrial early diastolic emptying rate and right ventricular ejection fraction were measured by gated radionuclide ventriculography and a combined score index for noninvasive assessment of pulmonary artery pressure was derived. The predictive value of this index for the presence of pulmonary hypertension (PAH) in patients with COPD was evaluated in this study.

**Methods**

**Patient Population**

A prospective study was done involving 23 patients, 17 men and six women, aged 44 to 87 years, consecutively admitted to the pulmonary disease clinic with mild to severe COPD, diagnosed according to the established criteria. The patients studied had at least three years of follow-up and were in a stable and compensated state at the time of the study. Patients with clinically overt tricuspid insufficiency or severe right heart failure were excluded from the study. Also, four patients (three men and one woman) were excluded because refusal of catheterization (two patients) and the inability to differentiate the right atrial structure from the rest of the heart in the

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radionuclide study (two patients). None of the patients had systemic hypertension, valvular heart disease, ischemic heart disease, or primary myocardial disease. The ECG criteria of right ventricular hypertrophy (R/S ratio = 1 with an R wave of 5 mm or greater) were not met by any of the patients. However, ECG changes suggestive of right ventricular hypertrophy\(^8\) (incomplete right bundle branch block and right axis deviation) were found in five patients. As it is well known, right ventricular hypertrophy ECG signs are obscured by positional changes and increased lung volume.

The majority of the patients (20 patients) had P wave axis of +90°, highly suggestive of chronic obstructive lung disease.\(^3\) Baseline pulmonary function and arterial blood gas values were obtained from all patients at the time of the right heart catheterization (Table 1). Administration of all drugs was discontinued at least 48 hours before the study. These included methyl xanthines, beta-receptor agonists, corticosteroids, diuretics, digoxin, and vasodilators. All patients underwent right heart catheterization with a balloon tipped thermodilution pulmonary catheter passed through the femoral vein to the pulmonary artery. Gated radionuclide ventriculography was performed within 48 hours after the catheterization. No oxygen was administered to the patients during this period. All patients signed an informed consent form.

**Radionuclide Technique**

The scintigraphic technique was described in a previous report and is briefly summarized.\(^7\)

All patients underwent resting gated blood pool scintigraphy using in vivo labelled red blood cells with 20 mCi of \(^{99m}\)Tc, a standard field-of-view camera, and a low energy medium resolution parallel hole collimator. The camera was interfaced with a dedicated minicomputer system, and data were collected in 45° left anterior oblique with 15° caudal angulation. The cardiac cycle was divided into 20 equal frames, and 5 million counts were collected for each view, then displayed in cinematic mode. For analysis of data, time activity curves were generated from the left and right ventricles, and right ejection fraction was calculated.

In each study phase, image analysis was performed using the fundamental Fourier harmonic coefficients.\(^16\) The phase image was then displayed using a 16-color code. The atria were differentiated from the rest of the cardiac structure in all subjects. A region of interest was drawn, surrounding the atrial structure, with a manual electronic cursor delineating both atria, and atrial time activity curves were generated. Although the Fourier analysis cannot eliminate the overlap of various right heart structures, it can assist in resolution of the nonoverlapping atrial structures, thus enabling us to exclude nonatrial structures from the region of interest and obtain a time activity curve which reflects only changes in right atrial volume. It is reasonable to assume that even if a small part of the atrium were excluded, changes in relative volume would not be affected, the atrium being a homogeneous chamber in this respect. The early diastolic emptying rates were calculated by a linear fit. The rates were calculated and normalized for peak number of counts and expressed as percent emptying over the early diastolic period, according to the formula:

\[
P_{\text{end of early diastolic emptying}}(\text{NR}) = \frac{C_1 - C_2}{T_1 - T_2} \times 100
\]

where:

- \(C_1 = \text{number of counts at the end of right atrial early diastolic emptying}\)
- \(C_2 = \text{peak right atrial counts obtained at the end-systolic ventricular phase}\)
- \(T_1 = \text{end of early diastolic emptying of the right atrium detected by an abrupt change in the atrial emptying rate (17)}\)
- \(T_2 = \text{end of ventricular systole}\)

The results are expressed as percent emptying of the right atrium over the early diastolic period expressed in seconds (%sec).

The right atrial emptying rates were measured in the same person independently by two highly skilled nuclear medicine specialists, and the interobserver and intraobserver variability was calculated. Interobserver and intraobserver variability was 5 ± 1.2 percent and 0.9 ± 0.3 percent, respectively.

**Statistical Analysis**

Data are expressed as mean value ± SD. Comparisons between various groups of patients were performed using unpaired Student's t-tests. From the following equations, the following variables were derived:

- sensitivity(%) = true positive/true positive + false negative × 100
- specificity(%) = true negative/true negative + false positive × 100

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**Table 1—Clinical, Pulmonary Function and Hemodynamic Data**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Sex and Age (Yr)</th>
<th>FEV₁ (L)</th>
<th>FEV₁/PreD (%)</th>
<th>FEV₁/INVC (%)</th>
<th>FVC (L)</th>
<th>PO₂ (mm Hg)</th>
<th>PCO₂ (mm Hg)</th>
<th>PAP (S/D/M)</th>
<th>RVEF (%)</th>
<th>RAER Counts/s</th>
<th>Score (points)</th>
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</thead>
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<td>50</td>
<td>0.9</td>
<td>0.9</td>
<td>65</td>
<td>1.5</td>
<td>46</td>
<td>45</td>
<td>49/11/28</td>
<td>45</td>
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<td>7</td>
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<tr>
<td>2</td>
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<td>76</td>
<td>1.1</td>
<td>50</td>
<td>40</td>
<td>55/27/38</td>
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</tr>
<tr>
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<td>38</td>
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<td>85/21/56</td>
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<td>1.8</td>
<td>52</td>
<td>40</td>
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<td>1.8</td>
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<td>9</td>
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<td>41</td>
<td>2.1</td>
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<td>28/19/23</td>
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<td>78.41</td>
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<td>95/32/70</td>
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<td>1.6</td>
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<td>74/38/56</td>
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<td>0.9</td>
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<td>71</td>
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<td>41/10/29</td>
<td>38</td>
<td>45.00</td>
<td>7</td>
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<tr>
<td>15</td>
<td>F</td>
<td>44</td>
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<td>0.9</td>
<td>50</td>
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<td>0.9</td>
<td>56</td>
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<td>47</td>
<td>44</td>
<td>29/17/21</td>
<td>27</td>
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<td>54</td>
<td>40/6/22</td>
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<tr>
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<td>0.9</td>
<td>37</td>
<td>1.2</td>
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<td>33/10/21</td>
<td>36</td>
<td>71.40</td>
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<tr>
<td>MEAN</td>
<td></td>
<td>57.2</td>
<td>1.03</td>
<td>0.9</td>
<td>36</td>
<td>1.2</td>
<td>53</td>
<td>40.47</td>
<td>43/16/30</td>
<td>32.59</td>
<td>43.70</td>
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<tr>
<td>± SD</td>
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<td>12.1</td>
<td>0.3</td>
<td>12.57</td>
<td>8.76</td>
<td>21.9/15</td>
<td>11.1</td>
<td>23.30</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*FEV₁ = forced expiratory volume in 1 second; FVC, forced vital capacity; PAP, pulmonary artery pressure; RVEF, right ventricular ejection fraction; RAER, right atrial emptying rate; FEV₁/INVC = forced expiratory volume/inspiratory vital capacity; PO₂, arterial oxygen tension; PCO₂, arterial carbon dioxide tension; FEV₁/PreD, predicted forced expiratory volume.*
predictive accuracy of a positive test(%) = true positive/true positive + false positive × 100
predictive accuracy of a negative test(%) = true negative/true negative + false negative × 100.

Score Index

A numerical score index combining values from right ventricular ejection fraction and right atrial emptying rate was constructed (Table 2). The maximum points (5) were given for right ventricular ejection fraction above 50 percent and for right atrial emptying rate higher than 50 percent per second. For every 10 percent reduction in right ventricular ejection fraction or in right atrial emptying rate, one point was subtracted. The combined score ranged between 2 and 10: with scores of 8 to 10, patients were considered to have normal pulmonary artery pressure; with 5 to 7, mild to moderate, and patients with score below 4 were considered to have severe pulmonary arterial hypertension. Pulmonary arterial pressure was considered within normal limits when the systolic pressure was less than 30 mm Hg, mild to moderate between 31 to 70 mm Hg, and severe pulmonary hypertension was diagnosed when the systolic pulmonary arterial pressure was above 70 mm Hg.

RESULTS

In five patients, the pulmonary artery pressure was within normal limits, 24.2 ± 6.9/mm Hg, and 14 patients were considered to have pulmonary arterial hypertension (50 ± 20.4 mm Hg, p < 0.005). Mean pulmonary arterial oxygen pressure was 53 ± 12 mm Hg and PCO2 was 40.4 ± 8.7 mm Hg; FEV1 was 1.03 ± 0.3 L/s. No correlation was found between PO2, POC2, and FEV1 and pulmonary arterial pressure. The right ventricular ejection fraction was 38.7 ± 11 percent in patients with normal pulmonary arterial pressure, and 28.6 ± 9.5 percent in the patients with pulmonary arterial hypertension, p < 0.02. In the 14 patients with pulmonary arterial hypertension, the right atrial emptying rate was markedly depressed (26.2 ± 6.7 percent/s) when compared with the patients without pulmonary arterial hypertension (63.3 ± 22 percent/s, p < 0.005). A good correlation was found between right atrial emptying rate and pulmonary arterial pressure (r = 0.75, Fig 2). Right ventricular ejection fraction correlated weakly with pulmonary arterial pressure (r = 0.66, Fig 1). A very good correlation was found between the score index and pulmonary arterial pressure (r = 0.86, Fig 3, Table 3).

Sensitivity, specificity, positive, and negative predictive accuracy of right ventricular ejection fraction, right atrial emptying rate, and score index were calculated (Table 3). The cutoff points between normal and abnormal values were obtained after ROC analysis. Thus, normal values for systolic pulmonary arterial pressure were considered 30 mm Hg, for right ventricu-

Table 2—The Score Index*

<table>
<thead>
<tr>
<th>RVEF (%)</th>
<th>Score (Points)</th>
<th>RAER (Counts/s)</th>
<th>Score (Points)</th>
<th>Total Score (Points)</th>
<th>PAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>5</td>
<td>≥50</td>
<td>5</td>
<td>10</td>
<td>Normal</td>
</tr>
<tr>
<td>40-50</td>
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<td>4</td>
<td>8</td>
<td>Normal</td>
</tr>
<tr>
<td>30-40</td>
<td>3</td>
<td>30-40</td>
<td>3</td>
<td>6</td>
<td>Moderate</td>
</tr>
<tr>
<td>20-30</td>
<td>2</td>
<td>20-30</td>
<td>2</td>
<td>4</td>
<td>Severe</td>
</tr>
<tr>
<td>≤20</td>
<td>1</td>
<td>≤20</td>
<td>1</td>
<td>2</td>
<td>Severe</td>
</tr>
</tbody>
</table>

* RVEF, right ventricular ejection fraction; RAER, right atrial emptying rate; PAP, pulmonary artery pressure.
ular ejection fraction 40 percent, for right atrial emptying higher than 50 percent/s, and normal score index 8 to 10. According to these criteria, we obtained a 92 percent sensitivity for right ventricular ejection fraction, but only 33 percent specificity (Fig 4). The specificity was markedly increased for right atrial emptying rate (100 percent), although the sensitivity decreased to 78 percent (Fig 4). Score had both strong sensitivity and specificity, with an excellent positive and negative predictive accuracy (93 percent and 100 percent, respectively, Fig 4).

The score index also proved to be a good predictor of the severity of the disease (Table 4), although the results should be interpreted with caution due to the small sample size.

**DISCUSSION**

Noninvasive detection of pulmonary hypertension has been attempted for several years, using a variety of techniques and observations. Several noninvasive methods have been proposed to assess pulmonary arterial hypertension in COPD, including chest roentgenography, echocardiography, radionuclide angiography, and others. With echocardiography, early pulmonary valve closure with midsystolic closure motion is commonly noted in the presence of severe pulmonary hypertension. However, evaluation of pulmonary arterial hypertension by echocardiographic technique based on visualization of the pulmonary valve closure is limited mainly to infants with congenital heart disease, and is practically inapplicable to adults with COPD, due to the poor quality and the inadequacy of the echocardiographic images. Bishop et al. in a large multicenter European study, used Po, PCO2, FEV1, and other pulmonary function parameters to predict the severity of pulmonary arterial hypertension. Mean pulmonary arterial pressure correlated weakly with Po2, and their results were not encouraging for using these parameters as noninvasive predictors of pulmonary arterial hypertension.

Our results confirm Bishop’s results, showing no correlation between Po2, PCO2, FEV1, and pulmonary arterial pressure. Recently, Brent et al. reported a correlation between right ventricular ejection fraction and pulmonary arterial hypertension, using radionuclide angiography. Although their method has some advantages compared with the previously mentioned methods, the correlation found between right ventricular ejection fraction and pulmonary arterial pressure was relatively modest, r = .74.

Although the sensitivity of right ventricular ejection fraction, right atrial emptying rate, and the score index in predicting pulmonary arterial hypertension in patients with COPD.
fraction was high in detecting pulmonary arterial hypertension (100 percent), specificity was only 55 percent (right ventricular ejection fraction considered normal ≥ 45 percent). Similar results were found in our study: right ventricular ejection fraction correlated weakly with pulmonary arterial pressure \( r = .66, \) Table 3, Fig 1) with a high sensitivity (92 percent) and a low specificity (33 percent, Table 3). The positive predictive accuracy for right ventricular ejection fraction was similar in both studies, 75 percent in our study compared to 79 percent in Brent's study. Thus, right ventricular ejection fraction seems to have some predictive value in both studies; however, the lack in specificity severely limits its applicability to every day clinical use. A possible explanation for the reduced specificity of right ventricular ejection fraction is the relative technical difficulty in obtaining adequate radionuclide imaging of the right ventricle due to the overlapping heart structures. Thus, the right ventricular ejection fraction is artificially reduced, accounting for the large number of false positive results, and consequently, for the low specificity of this method. In order to improve the predictive accuracy of the radionuclide method in the assessment of pulmonary arterial hypertension, we used the early diastolic right atrial emptying rate. Atrial emptying rate was shown to be a reliable indicator of decreased left ventricular compliance in hypertensive patients.19,30

It is well known that prolonged pulmonary arterial hypertension induces right ventricular hypertrophy with a consequent reduction in right ventricular compliance.13 Therefore, one could use right atrial emptying rate as an indicator of long-standing pulmonary hypertension with right ventricular hypertrophy. As expected, a marked reduction in right atrial emptying rate was found in patients with pulmonary arterial hypertension, compared with patients with COPD but without pulmonary arterial hypertension (30.1 ± 10 vs 63.3 ± 22 percent/s, respectively, \( p < 0.001 \)). A reasonably good correlation was also found between right atrial emptying rate and pulmonary arterial pressure \( r = .75, \) Fig 2). However, no significant improvement in the negative predictive value of right atrial emptying rate was achieved when compared with right ventricular ejection fraction (0.66 vs 0.62 percent, respectively, Table 3).

Furthermore, the right atrial emptying rate was of limited value in patients with mild or no elevation of pulmonary arterial pressure (Fig 2). The positive predictive value improved for the moderate to severe hypertensive states (specificity 100 percent, Table 3, Fig 2). The right atrial emptying rate, although having a good correlation with pulmonary arterial pressure, is not accurate enough for clinical application (sensitivity and negative predictive accuracy being relatively modest—78 and 62 percent, respectively), so further improvement of the method seems essential.

The right atrial emptying rate depends mainly on the structural changes taking place in the right ventricle throughout the years, due to the long-standing pulmonary arterial hypertension, and is therefore a logical index of persistent pulmonary hypertension, having a high specificity for the disease. On the other hand, global right ventricular ejection fraction is highly sensitive to increased afterload (pulmonary arterial hypertension), but it is not specific enough, being influenced by preload and overlapping of the cardiac structures. By combining these two measurements, both specificity and sensitivity may be improved. Thus, a score index was created which gave the two measurements equal relative value (Table 2). Using the score index, a high correlation with pulmonary arterial pressure was obtained \( r = .86, \) Fig 3, Table 3), and a marked improvement in sensitivity and specificity was achieved (Table 3, Fig 4). The score index predicted not only the presence of pulmonary arterial hypertension, but it also estimated reasonably well the severity of the disease (Table 4). Thus, severe pulmonary arterial hypertension \( (\geq 70 \) mm Hg) was predicted by a score below 4 in 100 percent of the patients, and pulmonary arterial hypertension within normal limits was correctly predicted in four out of five patients (80 percent, Table 4).

In conclusion, the present study employed right atrial emptying rate as an indicator of pulmonary artery hypertension with a good correlation between the right atrial emptying rate and the presence of pulmonary arterial hypertension \( r = .75 \). By combining the two noninvasive measurements obtained during the same radionuclide study (right ventricular ejection fraction and right atrial emptying rate), an accurate, reliable method was developed for predicting pulmonary hypertension and its severity in patients with COPD. The excellent positive and negative accuracy obtained (93 percent and 100 percent, respectively) permits the use of the score index as a reliable predictor of the presence of pulmonary arterial hypertension in COPD.

Table 4—Predictive Value of Score Index in Assessing the Severity of Pulmonary Hypertension*

<table>
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<th>Score of 8-10</th>
<th>Score of 5-7</th>
<th>Score of 1-4</th>
</tr>
</thead>
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<tr>
<td>PAP 30 mm Hg</td>
<td>PAP 31-70 mm Hg</td>
<td>PAP 70 mm Hg</td>
</tr>
<tr>
<td>No. patients</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93%</td>
<td>85%</td>
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<tr>
<td>Positive predictive accuracy</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Negative predictive accuracy</td>
<td>93%</td>
<td>100%</td>
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*PAP pulmonary arterial pressure.