Right Ventricular Function at Rest and During Exercise in Chronic Obstructive Pulmonary Disease

Comparison of Two Radionuclide Techniques

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Right ventricular function was assessed in 24 patients with COPD, at rest and during submaximal exercise, using both technetium-99m (99mTc) blood-pool and krypton-81m (81mKr) equilibrium ventriculography. Technetium-99m right ventricular ejection fraction (RVEF) at rest was lower than 81mKr RVEF (0.39 ± 0.12 and 0.54 ± 0.08, respectively; p < 0.001). During submaximal exercise, there was no increase in RVEF using either imaging technique. This observation contrasted with an increase in RVEF in a group of age-comparable normal subjects during modest submaximal exercise. An inability to obtain spatial separation of right heart structures using 99mTc imaging leads to a value for RVEF that is consistently lower than that measured using 81mKr ventriculography. Resting RVEF is well preserved at rest in most patients with COPD. In contrast to normal subjects, many show an inability to augment right ventricular function during exercise that may contribute to the reduced exercise capacity observed in these patients. 

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Patients with advanced COPD frequently develop pulmonary hypertension. Chronic alveolar hypoxia leads to structural changes in the pulmonary vasculature and a rise in pulmonary vascular resistance and hence pulmonary artery pressure. This predisposes to pulmonary heart disease, defined as hypertrophy of the right ventricle resulting from diseases primarily affecting the structure and/or function of the lungs.

Right ventricular ejection fraction (RVEF) is an index of global right ventricular function, which is dependent on preload, contractility, and afterload. In patients with COPD, an inverse relationship has been reported between RVEF and both pulmonary artery pressure and pulmonary vascular resistance index, suggesting that afterload is an important determinant of RVEF. Using a first-pass radionuclide technique, it has been suggested that many patients with longstanding COPD have a reduced RVEF at rest, particularly if there is evidence of pulmonary heart disease. Studies using technetium-99m (99mTc) blood-pool ventriculography have also reported that RVEF is often low in COPD. However, in one of these studies, a high proportion of patients with pulmonary heart disease without fluid retention at the time of study had a relatively well-preserved resting RVEF.

During exercise, patients with pulmonary heart disease have a disproportionate rise in pulmonary artery pressure compared to the increase in cardiac output and Matthay et al. using 99mTc first-pass radionuclide ventriculography, found that the rise in RVEF on exercise was frequently impaired, even if resting ejection fraction was normal.

While different results from some of these studies may reflect patient selection, methodologic differences in the assessment of cardiac function may also contribute. In particular, equilibrium 99mTc blood-pool ventriculographic imaging is performed in the left anterior oblique projection to avoid superimposition of left heart structures on the right ventricle. In this projection, there is substantial overlap of right atrium and right ventricle throughout the cardiac cycle. When right ventricular afterload is elevated, such as in pulmonary heart disease, considerable reservations have been expressed about the interpretation of RVEF using this method.

Krypton-81m (81mKr), an inert gas radionuclide, has properties that make it an ideal agent for the evaluation of right ventricular function. Krypton-81m in solution is infused intravenously, and after passage through the right side of the heart, enters the pulmonary circulation where, because of its insolvency, itdiffuses rapidly across the alveolar membrane and is exhaled. Imaging of the right side of the heart in isolation allows the right anterior oblique projection to be employed and results in better spatial separation of right heart structures.

In view of the variable results from previous studies, we compared RVEF derived using 99mTc blood-pool imaging to...
ventriculography with that using $^{81m}$Kr equilibrium ventriculography at rest and during exercise. Results from patients with COPD were compared with those from a group of normal subjects of similar age studied using $^{81m}$Kr equilibrium ventriculography alone.

**METHODS**

**Patients**

The study group consisted of 24 patients (age 52 to 73 years) with COPD, with a range of airflow limitation from mild to severe. The diagnosis of COPD was based on a characteristic history and a largely irreversible airflow limitation (FEV/FVC ratio less than 70 percent and less than 20 percent change in FEV, following nebulized salbutamol). Patients were excluded from the study if they were any history of hypertensive, ischemic, or valvular heart disease. All patients were being treated with inhaled bronchodilator therapy, and many were receiving oral methylxanthines and oral and/or inhaled steroids. No patient was taking any medication likely to depress myocardial function, but seven were receiving diuretic therapy to control fluid retention considered to be related to decompensated pulmonary heart disease (cor pulmonale).

All patients gave written informed consent and the study was approved by the Southampton and South-West Hampshire Joint Ethics Sub-Committee and by the Administration of Radioactive Substances Advisory Committee, Department of Health, London.

**Methods**

All patients received their usual oral medication on the morning of the study, but bronchodilator therapy was withheld for a period of 4 h before attending the hospital. Spirometry was performed with the patient seated 10 min following nebulized salbutamol (2.5 mg). Spirometric lung volumes (FEV, and FVC) were the best of three measurements and were expressed as a percentage of predicted values. Arterial oxygen and carbon dioxide tension (PaO$_2$ and PCO$_2$) were measured at rest with the patient breathing room air (Radiometer ABL 3).

In random order, patients underwent imaging in the seated position at rest using both $^{99m}$Tc blood-pool ventriculography and $^{81m}$Kr equilibrium ventriculography. This was immediately followed by imaging during seated submaximal exercise using an electronically braked bicycle ergometer (Siemens). The level of exercise (10 to 50 W) was previously defined for each patient so that sustained exercise could be maintained for the 5 to 7 min required for image acquisition. Imaging was commenced as soon as a stable heart rate was achieved, usually after 2 min. After imaging using one radionuclide technique, at least 30 min of rest was allowed for recovery before commencing imaging using the other technique. Imaging was repeated at rest and at the same level of submaximal exercise.

Mean heart rate was derived from the total ECG cardiac cycle count divided by the duration of imaging in minutes. Systolic and diastolic blood pressures were monitored at 2-min intervals at rest and during submaximal exercise using an automatic sphygmomanometer (Datascope Accutorr 1A). Capillary oxygen saturation was monitored throughout the study using a transcutaneous pulse oximeter (Ohmeda Biox 3700).

The reproducibility of imaging using $^{81m}$Kr equilibrium ventriculography was assessed in eight patients. After an interval of 1 h, with both patient and collimator repositioned, imaging was repeated at rest (short-term reproducibility). Patients were also restudied at rest at a mean interval of 23 weeks (range, 18 to 31 weeks) (long-term reproducibility).

A control group of eight normal subjects (age range, 46 to 63 years), without evidence of cardiorespiratory disease, were studied using $^{81m}$Kr equilibrium ventriculography alone. Imaging was performed at rest and during submaximal exercise at 50 W immediately followed by 100 W.

**Radionuclide Imaging Techniques**

$^{99m}$Tc Blood-Pool Ventriculography: Imaging was performed after in vivo red blood cell labelling with $^{99m}$Tc pyrophosphate (800 MBq). Sixteen ECG-gated frames were acquired over 5 min at rest and during submaximal exercise using a gamma camera fitted with a general purpose low-energy parallel-hole collimator. Imaging was performed in the 30° to 70° left anterior oblique projection sought to achieve optimal separation of left and right ventricles. In addition, a 10° caudal tilt of the collimator was used to reduce the overlay of right atrium and right ventricle.

$^{81m}$Kr Equilibrium Ventriculography: The technique of right heart $^{81m}$Kr equilibrium ventriculography has been described in detail previously. The $^{81m}$Kr was continuously eluted in 5 percent dextrose from a rubidium-81m generator (MRC Cyclotron Unit, Hammersmith Hospital, London) and infused into a median antecubital fossa vein. Sixteen ECG-gated frames were acquired over 5 to 7 min at rest and during submaximal exercise in the 20° right anterior oblique projection that gives reliable separation of right atrium and right ventricle.

**Radionuclide Imaging Analysis**

$^{99m}$Tc Blood-Pool Ventriculography: The $^{99m}$Tc blood-pool study was analyzed to derive both RVEF and left ventricular ejection fraction (LVEF).

A method of analysis similar to that described by Xue et al. was used in the calculation of RVEF from the $^{99m}$Tc blood-pool images. End-diastolic and end-systolic regions were visually identified from the dynamic 16-frame study after spatial smoothing. Separate end-diastolic and end-systolic regions of interest were manually defined on the appropriate frames. The pulmonary valve plane was defined as the junction of contracting and noncontracting segments of the right ventricular outflow tract. Regions of interest were upgraded using Fourier phase and amplitude images and particular care was taken to exclude right atrial counts from the end-systolic region of interest using the phase image. In addition, subtraction of the end-systolic frame from the frame immediately preceding it was sometimes helpful in identifying counts that were atrial in origin (ie, atrial counts would be increasing and appear negative on the subtracted image). A left paraventricular region of interest defined on the end-systolic frame was used to correct for background activity. Counts from the background region of interest were normalized to the areas of the end-diastolic and end-systolic regions and background corrected end-diastolic and end-systolic counts were used to calculate RVEF from the expression:

$$\text{Ejection fraction} = \left( \frac{\text{EDC} - \text{ESC}}{\text{EDC}} \right) \times 100,$$

where EDC = background corrected end-diastolic counts and ESC = background corrected end-systolic counts.

In the calculation of left ventricular ejection fraction (LVEF), analysis was similar to that for calculation of RVEF with separate end-diastolic and end-systolic regions of interest manually defined on the appropriate frames and a left paraventricular region of interest defined on the end-diastolic frame adjacent to the end-systolic region to correct for background activity. Background corrected end-diastolic and end-systolic counts were used to calculate LVEF using the expression defined above.

$^{81m}$Kr Equilibrium Ventriculography: The analysis of the $^{81m}$Kr study was carried out as previously described and summarized below. End-diastolic and end-systolic frames were visually identified from the dynamic 16-frame study after spatial smoothing. Using a semiautomated edge-detection technique, separate right ventricular end-diastolic and end-systolic regions of interest were defined because of substantial movement of the tricuspid valve plane during the cardiac cycle. Where necessary, the right ventricular regions of interest were manually upgraded to redefine the valve planes or
Table 1—Demographic Data for 24 Patients with Chronic Obstructive Pulmonary Disease

<table>
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<tr>
<th>Patient Age-Sex</th>
<th>PHD</th>
<th>FEV₁ (% pred)</th>
<th>FVC (% pred)</th>
<th>FEV₁/FVC (%)</th>
<th>PaO₂ (kPa)</th>
<th>PaCO₂ (kPa)</th>
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<td>Mean</td>
<td>± SD</td>
<td>40.5</td>
<td>± 17.5</td>
<td>± 19.0</td>
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PHD = pulmonary heart disease.
exclude extraneous counts arising from radionuclide activity within lung. A background region of interest was defined laterally and inferiorly to the right ventricle on the end-systolic image adjacent to the end-systolic region. Background corrected end-diastolic and end-systolic counts were used to calculate RVEF using the expression defined above. Using this analytic technique, the intraobserver and interobserver reproducibility has coefficients of variation of 4.9 percent and 5.4 percent, respectively.

Statistics
All values are quoted as mean ± SD. A paired Student's t test was used to compare within-patient differences in RVEF derived using the two imaging techniques and differences in RVEF or LVEF at rest and during submaximal exercise. An unpaired Student's t test was applied to the comparison between patient groups and between patients and normal subjects. Linear regression analysis was used to determine the relationship between RVEF and FEV₁ or PaO₂ as indices of severity of chronic airflow limitation.

Results
The baseline demographic data for the 24 patients studied are shown in Table 1. Fourteen patients had clinical evidence of pulmonary heart disease, defined as the presence of right ventricular hypertrophy (parasternal heave) or ECG criteria (dominant R-wave in the precordial leads, "p" pulmonale, or right axis deviation). None of the patients had clinical evidence of decompensation at the time of study but ten gave a history of fluid retention (cor pulmonale) during acute exacerbation and seven of these receiving diuretic therapy.

RVEF at Rest
Mean RVEF at rest was 0.39 ± 0.12 using ⁹⁹ᵐTc blood-pool ventriculography and 0.54 ± 0.08 using ⁸¹ᵐKr equilibrium ventriculography (p<0.001). Technetium-99m blood-pool RVEF was consistently lower than ⁸¹ᵐKr equilibrium RVEF at rest (Fig 1). Technetium-99m blood-pool RVEF was lower than normal
published values in 12 patients (normal >0.40), 10 of whom had pulmonary heart disease. Only four patients, all of whom had pulmonary heart disease, had \(^{81m}Kr\) equilibrium RVEF at rest below the references range for healthy subjects studied in Southampton (normal >0.45; unpublished data). In the eight normal volunteers, mean \(^{81m}Kr\) equilibrium RVEF at rest was 0.58 ± 0.04, which was not significantly different from that in the patient group. In the patients, there was a relationship between resting \(^{99m}Tc\) blood-pool RVEF and severity of airflow limitation \((r = 0.68; p<0.001)\) but no such relationship for resting \(^{81m}Kr\) equilibrium RVEF.

During analysis it became apparent that there was often considerable overlay of right atrium and right ventricle using \(^{99m}Tc\) blood-pool ventriculography. An experienced observer, blinded to the results of calculated RVEF, made a subjective assessment from the \(^{81m}Kr\) equilibrium ventriculographic images that the right atrium was unequivocally dilated in eight patients. The difference between the \(^{99m}Tc\) blood-pool RVEF and \(^{81m}Kr\) equilibrium RVEF was expressed as a proportion of \(^{81m}Kr\) equilibrium RVEF to determine the percentage “underestimate” of RVEF using \(^{99m}Tc\) blood-pool ventriculography. The mean percentage difference was -46.3 ± 12.3 percent when the right atrium was enlarged and -18.2 ± 14.4 percent when the right atrium was of normal size \((p<0.001)\) (Fig 2).

Mean \(^{81m}Kr\) equilibrium RVEF at rest was 0.51 ± 0.08 in patients with pulmonary heart disease and 0.59 ± 0.06 in patients without pulmonary heart disease \((p<0.01)\), although there was substantial overlap between the two groups.

Change in RVEF With Exercise

The level of sustainable submaximal exercise achieved by patients was limited by breathlessness or fatigue. The mean workload during exercise was 37.9 W (range, 10 to 50 W). Mean heart rate increased from 84.9 ± 10.3 bpm at rest to 107.1 ± 13.5 bpm during exercise. There was no difference in the resting heart rate or heart rate during exercise between the \(^{99m}Tc\) blood-pool and \(^{81m}Kr\) equilibrium study periods. Six patients exhibited capillary oxygen desaturation of greater than 5 percent during exercise; all of them had pulmonary heart disease.

Using \(^{99m}Tc\) blood-pool ventriculography, mean RVEF during exercise was 0.38 ± 0.09 and was unchanged from the value at rest (Fig 3). Using \(^{81m}Kr\) equilibrium ventriculography, mean RVEF during exercise was 0.55 ± 0.10 and was similarly unchanged from the value at rest (Fig 4); only five patients increased their RVEF by greater than 0.05; two of them had pulmonary heart disease. There was no relationship between the incremental increase in RVEF with exercise and either the severity of airflow limitation or the presence/absence of pulmonary heart disease.

In the eight normal subjects, mean RVEF increased from 0.58 ± 0.04 at rest to 0.61 ± 0.05 at 50 W \((p<0.001\) compared with value at rest) and 0.64 ± 0.05 at 100 W \((p<0.001\) compared with value both at rest and 50 W).

The mean increase in RVEF at 100 W was 0.07 (range, 0.05 to 0.09). Mean heart rate increased from

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**FIGURE 2.** Percentage difference in RVEF estimations using technetium-99m gated blood-pool and krypton-81m gated equilibrium ventriculography when the right atrium was enlarged and when of normal size \((^{99m}Tc\) GBP RVEF - \(^{81m}Kr\) GEQ RVEF)/\(^{81m}Kr\) GEQ RVEF; mean values and standard error bars are shown; \(* = p<0.001\).
increased to 0.65±0.09 during exercise (p<0.001) (Fig 5). Only four patients had a LVEF of less than 0.50 at rest, and in all but eight patients, the increase on exercise was greater than 0.05.

**Reproducibility of ⁸¹mKr Equilibrium Ventriculography**

When resting ⁸¹mKr equilibrium imaging was repeated after 1 h (short-term reproducibility), the mean difference in RVEF was −0.01 (range, −0.05 to +0.02), which was not significantly different from zero. When resting ⁸¹mKr equilibrium imaging was repeated at a mean interval of 23 weeks (long-term reproducibility), mean RVEF was not significantly different on the two occasions (0.52±0.06 and 0.55±0.07), but the mean absolute difference was 0.04 (range 0.01 to 0.10). Two of these patients showed a substantial increase in resting RVEF (0.09 and 0.10), which was associated with an improvement in arterial oxygen saturation.

**DISCUSSION**

Many recently published studies have used ⁹⁹mTc blood-pool ventriculography to assess right ventricular function in patients with COPD.⁵⁻⁷,¹⁶,¹⁷ Difficulties in obtaining spatial separation of the right atrium and right ventricle are well recognized, but some investigators have suggested that these can be overcome by using separate right ventricular regions of interest.¹³,¹⁴ Even using this technique, 30 percent of counts within the right ventricular regions of interest may arise from the right atrium.¹⁴

Our results are consistent with a substantial underestimate of RVEF using ⁹⁹mTc blood-pool ventriculography. This is particularly so in the presence of dilatation of the right atrium when spatial separation is likely to be even more difficult to achieve. Krypton-⁸¹m equilibrium ventriculography images the right heart in isolation with optimal spatial separation of right atrium and right ventricle using the right anterior oblique projection.¹² With this projection, RVEF derived from ⁸¹mKr equilibrium ventriculography correlates closely with that derived using first-pass techniques.¹¹,¹⁸ However, despite the large differences in resting RVEF recorded by the two methods, neither demonstrated any change during exercise.

It has been suggested that the thin-walled right ventricle is not well adapted to cope with an acute rise in afterload and that right ventricular systolic function is likely to be strongly afterload-dependent.¹⁹ It is less certain how the systolic function of the right ventricle is affected by chronic loading. The relationship between right ventricular systolic function and right ventricular afterload in COPD is disputed. Several studies have reported an inverse relationship between pulmonary artery pressure and RVEF using...
a variety of radionuclide techniques. However, others have shown no such relationship or only a weak relationship. The heterogeneous nature of patients studied combined with limitations of individual imaging techniques make comparisons among studies difficult. We have shown that resting RVEF is well preserved in the majority of patients even with clinical or electrocardiographic evidence of pulmonary heart disease. In support of this, Biernacki et al reported relatively normal contractility of the right ventricle in patients with COPD despite the presence of pulmonary hypertension. However, the use of Tc blood-pool ventriculography in this study has been criticized.

The relationship between RVEF and pulmonary artery pressure may be influenced by tricuspid valve regurgitation. The resultant “off-loading” of the right ventricle may give the impression of preservation of right ventricular systolic function. However, Morrison et al found that even in a group of patients without contrast angiographic tricuspid valve regurgitation, the relationship between RVEF and pulmonary artery pressure was not strong. Doppler echocardiography may be used noninvasively to establish the presence of tricuspid valve regurgitation, but technical difficulties often limit its application in patients with COPD.

Most of the patients with COPD did not increase RVEF during exercise, unlike the healthy volunteers. In the latter group, the absolute increase in RVEF was dependent on the level of submaximal exercise in healthy volunteers. Patients performed exercise at a level that was considered “near-maximal” and limited by breathlessness and fatigue; the same exercise workload in normal subjects could not be considered to represent a similar physiologic stress. However, exercise at 100 W resulted in a similar heart rate to that observed in patients and produced an absolute increase in RVEF of between 0.05 and 0.09. This is similar to the increase accepted as normal during exercise at unspecified workloads.

In patients with pulmonary heart disease, the ability to enhance right ventricular systolic performance during exercise is determined largely by the increase in pulmonary vascular resistance and thus right ventricular afterload. The reduced RVEF response to exercise in COPD probably reflects a normal physiologic response to altered afterload rather than evidence of inherent right ventricular myocardial dysfunction. Indeed, Olvey et al found that it could be restored by the administration of oxygen that reduces pulmonary artery pressure.

The majority of our patients had a normal resting LVEF consistent with published data. A possible explanation for the failure to augment exercise RVEF in the patients is that the physiologic stress was too low. However, most patients showed an increase in LVEF during exercise. Therefore, these results support previous observations that the exercise response of the right ventricle is impaired in patients with COPD.

The mechanisms responsible for the limitation of exercise capacity in patients with COPD are probably complex. Recently, Morrison proposed that impairment of right ventricular function may be a contributory factor. Exercise capacity in normal subjects is limited by their ability to increase cardiac output and hence oxygen delivery to the tissues, reflected by a fall in mixed venous oxygen saturation and widening of the arteriovenous oxygen content. Similar blood gas changes occur in patients with COPD although at lower levels of exercise and oxygen consumption. However, Spiro et al reported that in patients with COPD, cardiac output rises normally with increasing oxygen consumption and exercise workload. This was achieved by a more rapid rise in heart rate while stroke volume showed little increase. Impaired ventilatory mechanics and altered gas exchange are clearly major determinants of exercise capacity in patients with COPD, but the contribution of reduced right heart functional reserve has not been fully elucidated.

CONCLUSIONS

We have confirmed that dilatation of the right atrium in advanced COPD leads to a considerable underestimate of RVEF using Tc blood-pool ventriculography. Krypton-81m equilibrium ventriculographic imaging in the right anterior oblique projection minimizes overlap of right heart structures. This produces a higher and reproducible value for RVEF that may more accurately represent right ventricular systolic function. Using this method, resting RVEF is well preserved in most patients with advanced COPD, but many show an inability to augment right ventricular function during exercise. Impaired right ventricular function during exercise may contribute to the reduced exercise capacity observed in patients with COPD.

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