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# Does right ventricular function predict survival in patients with chronic obstructive lung disease?

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ABSTRACT Non-invasive measurements of the right ventricular ejection fraction by radionuclide ventriculography were made in 115 patients with chronic obstructive lung disease. Survival was assessed over a mean period of 918 days. The right ventricular ejection fraction was reasonably normal in most patients (mean 0·42, range 0·10–0·66) but was lower in those with peripheral oedema, indicating cor pulmonale (mean 0·31 (SD 0·07); $p < 0·0001$). Right ventricular ejection fraction was related to survival, but the relationship was weak ($p = 0·03$) by comparison with the association between the arterial oxygen and carbon dioxide tensions and survival (both $p < 0·0001$). It is concluded that, although right ventricular function is predictive of survival in patients with chronic obstructive lung disease, it is probably a reflection of severity of disease and does not directly affect the prognosis.

## Introduction

The long term complications of chronic obstructive pulmonary disease are ventilatory failure and cor pulmonale due to pulmonary hypertension. Measurements of airflow limitation, such as forced expiratory volume in one second ($FEV_1$), are predictive of survival in such patients.[1–5] The development of pulmonary hypertension or the presence of clinical evidence of cor pulmonale also indicates a poor prognosis.[6 7] Measurement of pulmonary arterial pressure, however, is an invasive procedure and is performed much less often than spirometry.

We have shown that right ventricular performance, as assessed by radionuclide measurement of the right ventricular ejection fraction, is relatively well preserved in patients with chronic obstructive lung disease by comparison with normal subjects, except in those with the clinical syndrome of cor pulmonale.[8] In patients with chronic obstructive lung disease there is also a weak relationship between arterial oxygen tension and right ventricular ejection fraction.[8] In a preliminary study we found a relation between right ventricular ejection fraction and total pulmonary vascular resistance but not pulmonary artery pressure,[9] in contrast with the findings of other studies.[10 11]

Right ventricular ejection fraction is a non-invasive measure of global right ventricular performance, as it depends on right ventricular preload, afterload, and contractility.[12] Its value as a predictor of survival in patients with chronic obstructive lung disease has not been evaluated previously. We have examined the survival of a group of patients with chronic obstructive lung disease and compared right ventricular ejection fraction with other measures of disease severity as predictors of survival.

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## Methods

We studied patients with a diagnosis of chronic obstructive lung disease attending clinics in the department of respiratory medicine. The diagnosis of chronic obstructive lung disease was based on the presence of a history of chronic sputum production for three months a year for two consecutive years, a history of cigarette smoking, and the presence of largely irreversible airflow limitation ($FEV_1$/forced vital capacity (FVC) < 70%, and < 15% change in $FEV_1$ or FVC in response to two puffs of a $\beta_2$ agonist from a pressurised inhaler). Patients were selected to include a wide spectrum of disability.

$FEV_1$ and FVC were measured with a bellows spirometer (Vitalograph, Buckingham, England), the best of three measurements being used. Arterial oxygen tension ($Pa_{O_2}$) and arterial carbon dioxide tension ($Pa_{CO_2}$) were measured, with the patient at rest and breathing room air, by an ABL330 blood gas

analyser (Radiometer, Copenhagen, Denmark). Patients receiving controlled oxygen therapy had the treatment interrupted for at least half an hour before the arterial blood gas sample was withdrawn. Spirometric indices and blood gas tensions were measured within 30 minutes of the measurement of the right ventricular ejection fraction.

The right ventricular ejection fraction was measured by multiple gated equilibrium radionuclide ventriculography as described previously.[13] In brief, human serum albumin, labelled with 750 MBq technetium-99m, was injected into a peripheral vein. Five minutes later, when the radiotracer had equilibrated within the blood pool, the patient lay beneath a Searle large field of view gamma camera, placed in a 30° left anterior oblique position with 10° caudal tilt to obtain the best separation between the right and the left ventricle. Radioactive counts were recorded from 500 sequential cardiac cycles in frame mode and the images displayed in movie format. Regions of interest were drawn around the right and left ventricles. Radioactive counts within a region of interest are proportional to blood volume, so that after correction for background and right atrial counts[13]

$$\text{ejection fraction} = \frac{EDC - ESC}{EDC},$$

where EDC and ESC are the end diastolic and end systolic counts. Normal subjects in our hands have a mean (SD) right ventricular ejection fraction of 0·58 (0·09) with this technique,[14] giving a lower limit of normal for the right ventricular ejection fraction at rest of 0·40 (2 SD below the mean).

None of the patients studied had clinical or electrocardiographic evidence of systemic hypertension, ischaemia, or valvular heart disease. Cor pulmonale was defined in clinical terms as the presence of peripheral oedema in association with chronic obstructive lung disease for which no other cause could be found. Although none of the patients was studied during an exacerbation of their chronic obstructive lung disease some patients had oedema when studied. The patients were therefore classified into three groups: (*a*) no previous clinical evidence of cor pulmonale; (*b*) past history of cor pumonale, but no oedema at the time of study; (*c*) oedema present at the time of study.

Table 1 *Spirometric and blood gas values and ejection fraction data in 115 patients with chronic obstructive lung disease*

| *Variable* | *Mean* | *SD* | *Range* |
|---|---|---|---|
| $FEV_1$ (l) | 0·79 | 0·48 | 0·2 - 3·7 |
| FVC (l) | 2·11 | 0·84 | 0·45- 4·7 |
| $Pao_2$ (kPa) | 7·34 | 1·16 | 4·3 -12·0 |
| $Paco_2$ (kPa) | 6·45 | 1·31 | 4·2 -10·4 |
| RVEF | 0·41 | 0·11 | 0·10- 0·66 |
| LVEF | 0·51 | 0·12 | 0·24- 0·80 |

$FEV_1$—one second forced expiratory volume; FVC—forced vital capacity; $Pao_2$, $Paco_2$—arterial oxygen and carbon dioxide tension; RVEF, LVEF—right and left ventricular ejection fraction.

Informed consent was obtained before the measurement of right ventricular ejection fraction and the study had the approval of our local ethical committee.

After the initial assessment patients were reviewed regularly in the outpatient clinic, and the outcome in relation to variables of possible prognostic importance was assessed by means of Cox's survival model.[15] Comparisons of mean levels between pairs from the three groups of patients were made by Welch's test after overall differences had been established.

## Results

The 115 patients (75 male, 40 female) who were studied had a mean age of 61 (range 39–81) years. All patients were followed until death or until 1 January 1987, whichever was the earlier. No patient was lost to follow up. The mean follow up period was 918 (SD 643) days. Patients had a wide range of $FEV_1$ and arterial blood gas tensions (table 1). Forty three patients were receiving long term domiciliary oxygen. Twenty three patients had oedema at the time of study, 49 a past history of oedema attributed to cor pulmonale, and 43 no clinical evidence of cor pulmonale at any time. Patients with oedema at the time of study had

Table 2 *Pulmonary function and right ventricular ejection fraction (RVEF) values (mean (SD)) in patients with no oedema, oedema in the past, or oedema at time of study*

| | *No oedema (group 1) (n = 43)* | *Past oedema (group 2) (n = 49)* | *Present oedema (group 3) (n = 23)* | *Significance* | |
|---|---|---|---|---|---|
| | | | | *1 v 2 or 3* | *2 v 3* |
| $Pao_2$ (kPa) | 8·4 (1·5) | 7·0 (1·2) | 6·0 (1·0) | <0·0001 | <0·001 |
| $Paco_2$ (kPa) | 5·8 (0·8) | 6·5 (1·3) | 7·6 (1·4) | <0·01 | <0·01 |
| $FEV_1$ (l) | 0·98 (0·63) | 0·67 (0·35) | 0·69 (0·28) | <0·01 | NS |
| FVC (l) | 2·37 (0·93) | 2·02 (0·81) | 1·82 (0·60) | <0·05 | NS |
| RVEF | 0·46 (0·11) | 0·42 (0·10) | 0·31 (0·70) | <0·05 | <0·0001 |

Abbreviations as in table 1.

Table 3 *Association of variables of possible prognostic value with survival*

| *Variable* | $\chi^{2*}$ | *p value* |
|---|---|---|
| $Pa_{O_2}$ | 17·6 | <0·0001 |
| $Pa_{CO_2}$ | 15·7 | <0·0001 |
| Cor pulmonale | 15·6 | 0·0001 |
| $FEV_1$ | 9·5 | 0·002 |
| $FEV_1$ (% predicted) | 5·7 | 0·02 |
| RVEF | 4·5 | 0·03 |
| FVC | 3·0 | 0·08 |
| FVC (% predicted) | 1·1 | 0·31 |
| LVEF | 0·7 | 0·40 |
| Sex | 0·7 | 0·41 |
| Age | 0·02 | 0·90 |

*Likelihood ratio test based on Cox survival models.
Abbreviations as in table 1.

lower values for $FEV_1$, FVC, right ventricular ejection fraction, and $Pa_{O_2}$ and a higher $Pa_{CO_2}$ than those with no history of oedema (table 2). There were no significant correlations between right ventricular ejection fraction and $Pa_{O_2}$, $FEV_1$, or FVC in the whole group of 115 patients or in any of the subgroups. There was a weak correlation between right ventricular ejection fraction and $Pa_{CO_2}$ ($r = -0{\cdot}25$, $p < 0{\cdot}01$; $n = 115$).

Fifty patients died during the follow up period. The possible prognostic variables showing a significant association with mortality in a univariate analysis were, in order of their importance, $Pa_{O_2}$, $Pa_{CO_2}$, presence or absence of cor pulmonale, $FEV_1$, and right ventricular ejection fraction (table 3). Figure 1 illustrates survival in relation to right ventricular ejection fraction. To allow for interrelationship between prognostic variables a multivariate analysis was carried out, a forward stepwise procedure being used in conjunction with the Cox survival model.[15] The method parallels closely the more familiar methods of multiple regression. After the most significant variable ($Pa_{O_2}$) had been entered into the model, none of the remaining variables improved the model significantly, although $Pa_{CO_2}$ ($p = 0{\cdot}06$) and cor pulmonale ($p = 0{\cdot}07$) were close to the conventional threshold of statistical significance. Right ventricular ejection fraction ($p = 0{\cdot}3$) and $FEV_1$% predicted ($p = 0{\cdot}4$) did not contribute after $Pa_{O_2}$ had been taken into account. In contrast, $Pa_{O_2}$ retained its significance after the other variables had been taken into account. With only $Pa_{O_2}$ in the model the estimated relative reduction in mortality rate was 36% for every unit increase in $Pa_{O_2}$ (95% confidence limits 20–48%).

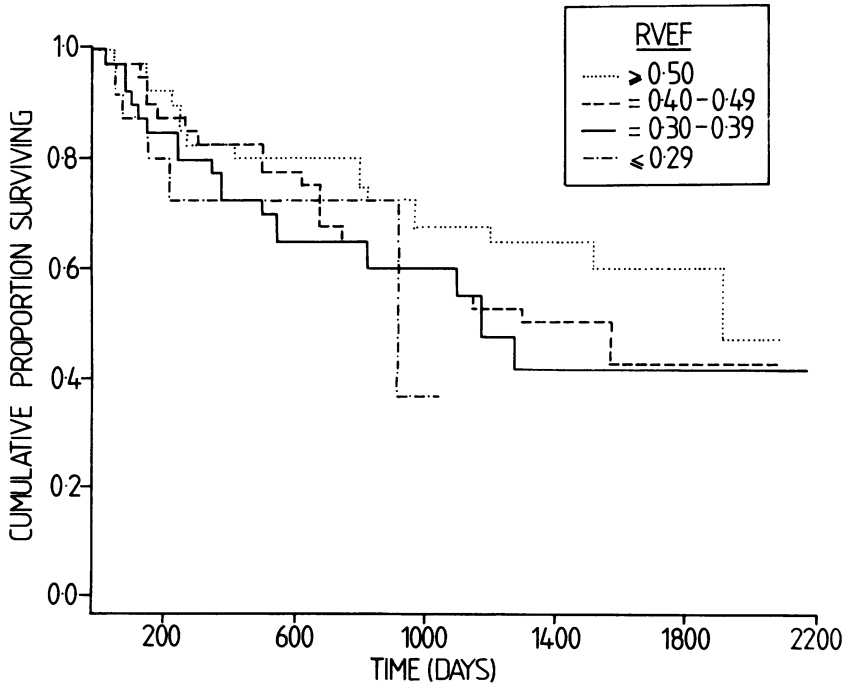


Fig 1 *Effect of right ventricular ejection fraction (RVEF) on survival in 115 patients with chronic obstructive lung disease. The numbers alive initially and at 500, 1000, and 1500 days were 28, 23, 19, and 14 for RVEF ≥ 0·5; 32, 25, 18, and 12 for RVEF 0·40–0·49; 37, 17, 11, and 5 for RVEF 0·30–0·39; 14, 6, 1, and 0 for RVEF ≤ 0·29.*

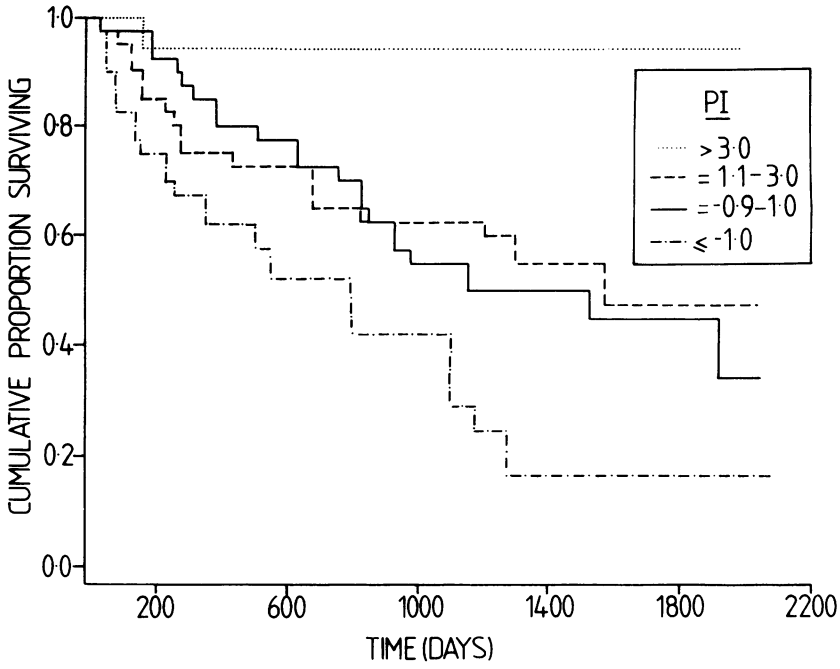


Fig 2 *Effect of blood gas tensions during the breathing of air on survival in 115 patients with chronic obstructive lung disease. The analysis is based on a prognostic index (PI) = arterial oxygen tension ($Pa_{O_2}$) − arterial carbon dioxide tension ($Pa_{CO_2}$) kPa. The numbers alive and under observation initially and at 500, 1000, and 1500 days were 23, 11, 9, and 7 for PI > 3·0; 32, 22, 19, and 12 for PI 1·1–3·0; 30, 24, 14, and 10 for PI −0·9–1·0; 26, 14, 7, and 2 for PI ⩽ − 1·0.*

When $Pa_{CO_2}$ was also entered into the model, none of the remaining variables was significant even at the 20% level of significance. With this model the coefficients for $Pa_{O_2}$ and $Pa_{CO_2}$ are almost identical but of opposite sign. This enables us to consider the value of $Pa_{O_2}$–$Pa_{CO_2}$ as a simple prognostic index. Survival curves for various values of this index are illustrated in figure 2. Similar results were obtained if patients receiving domiciliary oxygen were removed from the analysis.

## Discussion

This study has shown that radionuclide measurements of the right ventricular ejection fraction are related to survival in patients with chronic obstructive lung disease. The relationship is relatively weak, however, by comparison with the prognostic significance of the level of arterial oxygen and carbon dioxide tensions in such patients.

These data (table 2) support our findings in a smaller group of patients,[8] where the right ventricular ejection fraction remained relatively normal in patients with chronic obstructive lung disease in the presence of hypoxaemia and pulmonary hypertension, except when oedema, indicating decompensated cor pulmonale, was present. As in previous studies,[7] prognosis is worse in the presence of oedema due to cor pulmonale in patients with chronic obstructive lung disease. The prognostic significance of both cor pulmonale and right ventricular ejection fraction in this study was, however, outweighed by the influence of hypoxaemia and hypercapnia. These data support the hypothesis that poor right ventricular function in patients with chronic obstructive lung disease is a reflection of the severity of the disease and that right ventricular dysfunction and cor pulmonale per se do not influence survival in such patients. The same may be true of the influence of pulmonary artery pressure on survival in patients with chronic obstructive lung disease.[6] The correlation between pulmonary artery pressure and $Pa_{O_2}$ is well known.[16] Patients with chronic obstructive lung disease, however, usually have relatively mild pulmonary hypertension and very rarely does pulmonary artery pressure approach systemic levels. This is in contrast to patients with primary pulmonary hypertension,[17] where the substantially augmented right ventricular afterload leads

to right ventricular failure and a low cardiac output.

Several studies have shown that $Pa_{O_2}$ and $Pa_{CO_2}$ influence prognosis in patients with chronic obstructive lung disease[7 18-20] and rapidly progressive hypoxaemia has been shown to predict death.[21] Prognosis also relates to $FEV_1$,[1 2 22] rate of fall of $FEV_1$,[4] and the presence or absence of pulmonary hypertension[6] and oedema.[7 19] There is debate about whether pulmonary or right ventricular haemodynamics[6] or oxygen delivery to the tissues[20] is more important in predicting outcome in patients with chronic obstructive lung disease. The question is important since treatment in these patients has been directed towards the relief of hypoxia[23] and pulmonary vasodilatation.[24] Both long term oxygen trials[23 25] showed little change in pulmonary haemodynamics with oxygen therapy, although the slow progression of pulmonary hypertension expected in such patients[26] was prevented. Recent reports, however, suggest that the pulmonary haemodynamic response to oxygen therapy does relate to survival.[27 28]

There is clearly still difficulty in predicting which patients with chronic obstructive lung disease will respond to long term oxygen and controversy about whether the pulmonary haemodynamic response to oxygen relates to the improved survival obtained with this treatment.[20 27] Treatment with domiciliary oxygen did not correlate with survival in our patients and the results were similar whether or not patients having oxygen therapy were included in the analysis. This is not surprising as the study was not a controlled trial of long term oxygen; patients with and without oxygen were not matched and oxygen may have been given several years before entry into the study.

Morrison *et al*[29] suggested recently that measurement of the right ventricular ejection fraction reflects peripheral oxyen delivery in patients with hypoxic chronic obstructive lung disease and thus may be a means of determining, non-invasively, which patients might respond to long term oxygen therapy.[29] The relatively poor relationship between right ventricular ejection fraction and survival in our patients does not support this hypothesis. The strong relationship between $Pa_{O_2}$ and survival suggests that maintaining an adequate $Pa_{O_2}$ during continuous oxygen therapy might improve prognosis, though the mechanism by which oxygen influences survival is still unknown.

Thus, although right ventricular ejection fraction is related to survival in patients with chronic obstructive lung disease, its level may simply reflect the severity of hypoxaemia in such patients and ultimately the degree of airflow limitation. A low right ventricular ejection fraction in a patient with chronic obstructive lung disease presenting with oedema indicates that the oedema is due to cor pulmonale. Whether the presence of a low right ventricular ejection fraction in a patient with chronic obstructive lung disease who has never presented with oedema precedes the development of cor pulmonale is as yet unknown. Isolated measurements of $Pa_{O_2}$ or $Pa_{CO_2}$ in such patients are more likely to reflect prognosis than isolated measurements of the right ventricular ejection fraction.

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