Clinicopathological correlations in cor pulmonale

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Abstract

Background The relation between pulmonary disease and physiological abnormality in patients with hypoxic cor pulmonale is controversial and the association between arterial hypoxaemia and right ventricular hypertrophy has been challenged. To address these problems matched patients treated with and without domiciliary oxygen were studied.

Methods Necropsy data were obtained on 19 patients (14 male), 10 of whom had been treated with domiciliary oxygen. Pulmonary artery pressure and total pulmonary vascular resistance as well as blood gas tensions during the breathing of air and oxygen were available for the six months before death. Formalin fixed lung slices were assessed for panacinar and centriacinar emphysema. Right and left ventricular weights were measured and their ratio (LV&S/RV) was used as an index of right ventricular hypertrophy. Carotid body weights were available in 14 cases.

Results Fourteen patients died of respiratory failure and antemortem thrombus was found in the pulmonary arteries of eight cases. Physiological measurements were unrelated to the degree of macroscopic emphysema, pulmonary hypertension, or daytime blood gas tensions. When allowance was made for the higher "ambient" arterial oxygen tension (PaO_2) of those who had oxygen, PaO_2 was correlated with LV&S/RV ($r = 0.79$), absolute right ventricular weight ($r = -0.53$), and carotid body weight ($r = 0.68$).

Conclusions These data show that in hypoxic cor pulmonale in vivo physiological disturbances are poor indicators of the underlying disease process. The relation of "ambient" PaO_2 to right ventricular hypertrophy and carotid body weight suggests that domiciliary oxygen therapy might lead to regression of such established disease.

life are more indirect.^{4,5} Recent studies where blood gas data were available have focused on pulmonary vascular remodelling and airway pathology.^{6,7} Right ventricular weight was not related to the blood gas tensions during the breathing of air,⁷ but no account was taken of the higher arterial oxygen tension (PaO_2) in those treated with domiciliary oxygen.

Using data derived from the Medical Research Council trial of domiciliary oxygen therapy,⁸ we wished to determine whether any form of macroscopic pulmonary lesions predominated in these "blue and bloated" patients and what effect, if any, the use of domiciliary oxygen had had on their degree of ventricular hypertrophy and on the size of their carotid bodies, which are known to enlarge during the course of chronic hypoxia.⁹

Methods

We obtained necropsies in 19 patients (14 men) with severe airways obstruction, persistent arterial hypoxaemia, and hypercapnia (table 1), all of whom had at least one documented clinical episode of right ventricular failure with fluid overload during an exacerbation of chronic obstructive lung disease and who had severe obstructive bronchitis (in the Medical Research Council questionnaire dyspnoea grade 4 or more).¹⁰ Each had participated in a prospective study of long term domiciliary oxygen treatment, reported elsewhere,⁸ from which patients with known ischaemic heart disease and hypertension were excluded. These 19 were the only patients for whom permission for necropsy was granted out of the 50 screened for this study and followed up to death. Their clinical features and physiological measurements were representative of this larger group at the time when treatment was allocated.

All had attended the outpatients department at two monthly intervals for clinical assessment, spirometry, analysis of blood gas tensions while breathing air and also 2 litres of oxygen in those so treated, and determination of the venous carboxyhaemoglobin concentration to check on current smoking habits. Data were analysed retrospectively from the last six months of life for periods of clinical stability. At the annual inpatient assessment full lung volumes were measured by the helium dilution technique, but too few patients were able to complete the gas transfer factor test for inclusion in this report. A right heart catheterisation was performed and pulmonary artery

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The relation between in vivo physiological measurements and the postmortem findings in chronic obstructive lung disease remains controversial.¹⁻³ The mechanical properties of the lungs have been carefully studied during and after life³ but data on the severity of emphysema and the blood gas tensions during

Table 1 Clinical characteristics (mean (SD)) of control and oxygen treated patients when stable before death

Patients	Age (y)	FEV ₁ (l)	FVC (l)	TLC (% pred)	PaO ₂ (kPa)		PaCO ₂ (kPa)		PAP (kPa)	TPVR (dyn.cm.s ⁻⁵)
					Air	O ₂	Air	O ₂		
Control (n = 9)	60.2 (5.2)	0.58 (0.2)	1.46 (0.4)	112 (22)	6.9 (0.96)	10.7 (1.7)	7.1 (1.2)	8.8 (1.4)	3.9 (0.8)	493 (279)
Oxygen treated (n = 10)	60.7 (3.2)	0.56 (0.2)	1.63 (0.4)	114 (20)	7.0 (0.57)	10.5 (1.7)	7.6 (1.1)	8.6 (1.5)	4.2 (1.36)	537 (252)

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; TLC—total lung capacity; PaO₂—arterial oxygen tension; PaCO₂—arterial carbon dioxide tension; PAP—mean pulmonary artery pressure; TPVR—total pulmonary vascular resistance.

pressures were measured with the patients semi-recumbent; cardiac output was measured by the indicator dye dilution technique. The total pulmonary vascular resistance (TPVR) was calculated by using the formula

$$\text{TPVR} = \frac{\text{mean pulmonary artery pressure (mm Hg)}}{\text{cardiac output (l/min)}} \times 80 \text{ dyn.cm.s}^{-5}$$

Arterial blood gas tensions were measured with an IL232 blood gas analyser (Instrumentation Laboratories) and carboxyhaemoglobin with an IL213 CO oximeter. In relating blood gas tension data to physiological and pathological variables we have used the values for arterial oxygen and carbon dioxide tension during the breathing of air and the "ambient" blood gas tensions. These latter were derived by using the gas tensions measured while the patient was breathing oxygen in the 10 individuals who had been treated in this way during the last six months of life—gas tensions during the breathing of air being retained, however, for the control subjects. In this way we hoped to obtain a better guide to the arterial oxygen tensions these patients had when clinically stable.

Ten of our patients (two female) had received domiciliary oxygen for more than six months (seven months to five years) and nine control patients had not received this treatment. Oxygen treated patients had received 2–3 l/min via nasal prongs for 15 hours or more per 24 hours, sufficient to maintain their PaO₂ above 8.0 kPa by day as previously described.⁸ Oxygen usage was confirmed by regular unannounced home visits and review of the chemists' oxygen dispensing records. Routine drug treatment did not differ between the groups, all receiving oral diuretics and intermittent courses of antibiotics for infective exacerbations, and nine patients (five of them controls) taking oral digoxin as well.

In all 19 patients a full necropsy was performed. One lung was inflated and fixed with

10% formalin via the airways at an inflation pressure of 20 cm H₂O. The heart was carefully stripped of fat and the right ventricle dissected away from the left ventricle and intra-ventricular septum (LV&S) to be weighed separately. We related the right ventricular weight to that of the left ventricle and septum, as described by Fulton *et al.*¹¹ The carotid bifurcations were fixed at necropsy in 14 cases. The pulmonary vascular tree was inspected and the site of any antemortem thromboembolism noted. From midsagittal whole lung sections the percentage of the total area occupied by panacinar emphysema was visually assessed by two experienced pathologists (RH, DL) and centriacinar lesions were counted individually.^{12,13}

All investigations during life were approved by the hospital ethical committee.

Data are expressed as means with standard deviations in parentheses or ranges as appropriate. Statistical comparisons between groups used the unpaired Student's *t* test with a correction for multiple comparisons¹⁴ and correlations were obtained by the least squares regression method.

Results

There were no significant differences in the severity of airflow limitation, resting arterial hypoxaemia, or pulmonary vascular resistance between the treated and the control patients (table 1). Most patients died from respiratory failure, in some cases suddenly at home; but three patients died from carcinomatosis, two of them (one in each treatment group) having bronchial carcinomas, and an oxygen treated patient who died from respiratory failure was also found to have a small bronchial carcinoma at necropsy (see below). In addition, one patient committed suicide and one developed intestinal obstruction due to adhesions.

Table 2 Pathophysiological data (means with ranges) for control and oxygen treated patients

Patients	Emphysema Panacinar (%)	Centriacinar (No of lesions)	Weight (g) of		LV&S/RV	Carotid body weight (mg)
			RV	LV		
Control (n = 9)	24.9 (10–45)	92.4 (25–223)	110.5 (32)	149 (32)	1.35 (0.22)	107 (48)
Oxygen treated (n = 10)	25.2 (0–76)	133.7 (0–288)	95.7 (37)	167 (32)	1.87 (0.44)	82 (30)

RV—right ventricle; LV—left ventricle; LV&S/RV—ratio of weight of left ventricle and septum to weight of right ventricle.

Figure 1 Relation between right ventricular hypertrophy and arterial oxygen tension (P_{aO_2}) (A) during the breathing of air and (B) corrected for the higher P_{aO_2} of the patients treated with domiciliary oxygen (P_{aO_2} "ambient"). LV&S/RV—ratio of weight of left ventricle and septum to weight of right ventricle.

Antemortem thrombus was occluding one or more segmented pulmonary arteries in eight cases, with extension to the main pulmonary artery in two of these cases, where aneurysmal dilatation was present. One of these patients had a coexisting, non-adjacent bronchial tumour but the other died from respiratory death causes.

The severity of panacinar and centriacinar emphysema varied considerably despite the uniformity of the antemortem physiological measurements (table 2). There was no relation between either the resting blood gas tensions during the breathing of air, spirometric values, or vascular resistance measurements and any macroscopic measure of lung parenchymal damage. A weak correlation ($r = 0.46$, $p < 0.05$) was found between the percentage of panacinar emphysema and the total lung capacity (% predicted) as measured by helium dilution. No relation was seen between the number of centriacinar lesions and the total lung capacity and neither measure of macroscopic emphysema was correlated with ventricular weights.

The weight of the right ventricle was generally increased (upper limit of normal 70 g,

patients 103 (SD 35)g)—more so, proportionately, than that of the left ventricle (upper limit of normal 200 g, patients 159 (32) g). This was reflected by a reduction in the LV&S/RV ratio to 1.63 (0.44) (lower limit of normal 2.1). There was no relation between the absolute ventricular weights or their ratio and the arterial blood gas tensions during the breathing of air. When the "ambient" P_{aO_2} of the patients was substituted, however, both the absolute weight of the right ventricle and the LV&S/RV ratio were significantly related to the oxygen tension (fig 1). Neither the arterial carbon dioxide tension (during the breathing of air or corrected for oxygen use) nor the resting pulmonary vascular resistance was related to any pathological index of ventricular hypertrophy. There were no clinical or pathological differences between the eight patients known from their carbohaemoglobin concentration to have continued smoking and the 11 who were non-smokers during the follow up period.

Carotid body weights were increased (normal range up to 30 mg, patients 94.5 (40) mg). In our patients carotid body weight was unrelated to arterial oxygen tensions during the breathing of air but substitution of the "ambient" oxygen tension yielded a closer correlation ($r = 0.68$, $p < 0.01$) (fig 2). Carotid body weight was not related to any index of ventricular hypertrophy or to the severity of emphysema, nor did the smokers show a preponderance of carotid body enlargement (mean carotid body weight 96.0 (56) mg in smokers, and 93.0 (28) mg in non-smokers).

Discussion

Several studies have compared the antemortem physiological measurements with postmortem appearances in patients with chronic obstructive lung disease,^{1-7,15} but they have usually considered patients with a wider range of physiological abnormality and used measurements made some time before death. Recently data from two large series of carefully monitored patients have become available.^{5-7,16} The patients in the intermittent positive pressure breathing trial,¹⁷ however, were not uniformly hypoxaemic and had not had episodes of ankle swelling, whereas the nocturnal oxygen therapy trial¹⁸ included many normocapnic patients. Our study examined patients with closely defined clinical and physiological abnormalities and considered measurements made within two months of their final illness or, in the case of total pulmonary vascular resistance and lung volumes, within nine months.

In the study of Burrows *et al*² a relationship was found between the presence of macroscopic emphysema and a "pink and puffing" emphysematous clinical type (type A). This classification was based on several clinical and radiographic criteria, only one of which was clinical right ventricular failure. When data from the nocturnal oxygen therapy trial were analysed in this way⁷ there was no difference in the amount of macroscopic emphysema or the

Figure 2 Relation between carotid body weight and arterial oxygen tension (P_{aO_2}) corrected for the higher oxygen tensions of the patients treated with domiciliary oxygen (P_{aO_2} "ambient") in 14 patients with hypoxic cor pulmonale.

mean linear intercept data between type A and type B ("blue and bloated") patients, and our data support this finding.

The relation between hypoxaemia and pathological right ventricular hypertrophy is well documented in normal subjects at altitude and in patients with lung disease.¹⁹ The severity of hypoxaemia relates to the right ventricular weight in animal studies²⁰ but the relation between hypoxaemia and cor pulmonale in man has been challenged.⁶ This is based on detailed studies of the pulmonary vasculature of 10 patients, five treated with oxygen, who were investigated in a similar fashion to ours. Right ventricular weight, however, was available in only seven of these cases, and only two of these seven had been treated with domiciliary oxygen. Given the small numbers and less complete data on blood gas tensions, a type II error is possible in their report. In our study, when we allowed for the higher arterial oxygen tension of the oxygen treated patients the relation between hypoxaemia and right ventricular hypertrophy was significant. This was the case whether we used absolute right ventricular weight or the LV&S/RV ratio, which normalises for the difference in body size, as our index of ventricular hypertrophy, in contrast to the findings of Jamal *et al.*,⁷ who found this ratio to be unhelpful. This may reflect the selection of patients as we specifically excluded patients who might develop left ventricular hypertrophy. Thus only three of our 19 patients had left ventricular weights greater than 190 g. In contrast, hypercapnia, whether during the breathing of air or of oxygen, was not related to either index of ventricular hypertrophy, which may reflect the more restricted range of carbon dioxide tensions seen in our patients.

As our oxygen treated patients did not differ in the severity of their lung disease or in their initial physiological abnormalities from those not treated, and as they were allocated randomly to receive oxygen therapy, the differences in ventricular weights may reflect their better long term oxygenation. Similar data have been reported in studies on animals,^{21,22} where pulmonary vascular remodelling can be reversed by relative normoxia. The correction of the structural changes by normoxia is slower and may account for the failure of total pulmonary vascular resistance to rise in oxygen treated patients, unlike in the controls.⁸ The beneficial effect on cardiac muscle may not be mediated solely by changes in the pulmonary vasculature and could be explained by a direct effect on the heart. Cardiac muscle may increase in bulk during chronic hypoxia, as reported by others,^{23,24} and so we have used the LV&S/RV ratio in assessing right ventricular hypertrophy. The relief of hypoxia may reverse these changes independently of its effects on the pulmonary circulation.

Right ventricular hypertrophy was not related to total pulmonary vascular resistance or mean pulmonary artery pressure. Our measurements, however, were made at rest and underestimate the peak pulmonary vascular

resistance during exercise²⁵ or at night.²⁶ This failure to predict pathological change may explain the relatively poor prognostic value of resting pulmonary haemodynamic data in these patients.⁸ These observations are in keeping with those seen in the other patients in the Medical Research Council trial⁶ and in a larger group of patients with a wider range of severity of lung disease.²⁷

Carotid body enlargement occurs in chronic hypoxaemia²⁸ and has been reported in essential hypertension.²⁹ Where carotid body weights were available in our cases they exceeded the normal range in all but one of the patients. This patient had received domiciliary oxygen for over 18 months and had near normal arterial oxygen tensions during that time. There was a close relation between combined carotid body weight and the patient's "ambient" arterial oxygen tension, again implying that changes in carotid body weight may occur with oxygen treatment. The clinical significance of these findings is unclear but hypertrophy may be the result of chronic chemoreceptor activation, enhanced during periods of nocturnal hypoxaemia.³⁰

Antemortem thrombus has been noted in other series, with similar patients,¹ and was seen in almost half of our cases. Whether this played an important part in the final illness is difficult to assess as almost all tests for diagnosing thromboembolism in life are invalidated in patients such as these. Thrombi were equally distributed between treatment groups and their lack of relationship with the previous haemodynamic disturbance suggests that they were a late feature. None the less, the frequent occurrence of thrombus suggests that empirical anticoagulant treatment may be appropriate in some of these patients who do not respond to other measures.

In summary, we have found no evidence of a close relationship between the pattern of antemortem physiological disturbance and the presence of macroscopic emphysema in patients with hypoxic cor pulmonale. The carotid bodies were enlarged in these patients and antemortem thrombus was a frequent finding. Resting pulmonary vascular resistance was a poor guide to the presence of right ventricular hypertrophy but the arterial oxygen tension during the last year of life was closely related to ventricular size when allowance was made for the likely oxygen tension during this time. Whether these cardiac changes reflect parallel changes in the pulmonary vascular structure is not clear, but the data emphasise the beneficial effect of maintaining a relatively normal arterial oxygen tension in these patients.

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