RIGHT VENTRICULAR FUNCTION IN CHRONIC BRONCHITIS AND EMPHYSEMA

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FORMAL DECLARATION

I declare that I have written the dissertation presented to the University of Glasgow for the degree of Doctor of Medicine; that it is based upon my own observation and that, except as indicated in the thesis, the data was collected, analysed and interpreted by me.

W MACNEE

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Abreviations and units used in this thesis:

Abbreviation		Units
CaO_2, CVO_2	Arterial and mixed venous oxygen contents	ml/100 ml
CI	Cardiac index	litres/min/m^2
COD	Coefficient of oxygen delivery	
EF	Ejection fraction	
$FEV_{1.0}$	Forced expiratory volume in 1 second	litres
FVC	Forced expiratory volume	litres
HR	Heart rate	beats/minute
H+	Hydrogen ion concentration	nmol/litre
LV	Left ventricle	
LVEF	Left ventricular ejection fraction	
MBP	Mean systemic blood pressure	mmHg
MPAP	Mean pulmonary arterial pressure	mmHg
$PaCO_2$	Arterial carbon dioxide tension	kilopascals
PaO_2	Arterial oxygen tension	kilopascals
PCW	Pulmonary capillary wedge pressure	mmHg
P/V	Pressure volume ratio	
RAP	Right atrial pressure	mmHg
RV	Right ventricle	
RV_{EDVI}	Right ventricular end-diastolic volume index	ml/m^2

RV_{EDP}	Right ventricular end-diastolic pressure	mmHg
RVEF	Right ventricular ejection fraction	
RV_{ESVI}	Right ventricular end-systolic volume index	ml/m^2
RVSP	Right ventricular peak systolic pressure	mmHg
RV_{SWI}	Right ventricular stroke work index	$g.m/m^2$
SaO_2	Arterial oxygen saturation	%
SDO_2	Systemic oxygen delivery	$ml/min/m^2$
SVI	Stroke volume index	ml/m^2
SVR	Systemic vascular resistance	$dynes.s.cm^{-5}$
TPVR, PVR	Total pulmonary vascular resistance	$dynes.s.cm^{-5}$

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A reproducible method of measuring right ventricular ejection fraction was devised using the technique of equilibrium radionuclide ventriculography. In an assessment of ventricular function, in a population of 100 patients with chronic bronchitis and emphysema, the right ventricular ejection fraction was, on average, lower than in normal subjects, but was still relatively well preserved in most, as was the left ventricular ejection fraction. However, the range of values of ejection fractions in patients with chronic bronchitis and emphysema was wide, and low values occurred mainly in patients with oedema, indicative of decompensated pulmonary heart disease. The right ventricular ejection fraction was lower in those patients with lower arterial oxygen and higher carbon dioxide tensions, but was not related to the level of simultaneous measurements of pulmonary arterial pressure. Right ventricular ejection fraction was, however, related to right ventricular afterload as measured by the pulmonary vascular resistance.

Occult right ventricular dysfunction could be demonstrated during exercise in patients with chronic bronchitis and emphysema. The change in right ventricular ejection fraction was related to the fall in oxygen saturation which occurred in such patients during exercise.

In 20 patients with chronic bronchitis and emphysema and pulmonary hypertension, the right ventricular end-systolic pressure/volume relation was calculated from combined measurements of right ventricular pressure, ejection fraction and cardiac output, in order to assess right ventricular contractility. Analysis of the pressure/volume relation indicated normal or enhanced right

ventricular contractility in these patients, despite the presence of pulmonary hypertension. The right ventricular end-systolic pressure/volume ratio was unchanged when right ventricular systolic pressure was reduced by an infusion of sodium nitroprusside.

Oxygen (3 litres/minute, nasal prongs) both when given acutely and over a period of 6 months (15 hours/24 hour day) to patients with chronic respiratory failure reduced pulmonary arterial pressure, but did not result in any change in right ventricular ejection fraction, nor in right ventricular contractility as assessed by the pressure/volume relation. From these results there was little to suggest that the effect of domiciliary oxygen in improving survival in patients with respiratory failure was mediated through a direct effect on the right ventricle. However, oxygen did improve right ventricular function during exercise in such patients although the mechanism remains obscure.

The beta-agonist Pirbuterol produced pulmonary vasodilatation in patients with hypoxic chronic bronchitis and emphysema. Moreover, the right ventricular end-systolic pressure/volume ratio increased, suggesting that this drug had an additional inotropic effect.

In order to determine if patients with acutely decompensated pulmonary heart disease truly had `heart failure', haemodynamic measurements were made in 6 patients with respiratory failure and pulmonary hypertension, who presented acutely with oedema. Measurements of right ventricular ejection fraction and analysis of the right ventricular end-systolic pressure/volume relation, suggested that right ventricular contractility was depressed. However, right ventricular function, as measured by the cardiac index

of stroke work index, was "normal as a result of an adaptive mechanism involving large increases in right ventricular end-diastolic volume, as predicted by Starling's Law. In those patients who presented with oedema, these haemodynamic changes did not seem to result from an increase in pulmonary arterial pressure. Moreover, the relief of hypoxaemia by breathing oxygen had no consistent effect on right ventricular performance, despite a small reduction in pulmonary arterial pressure.

The measurement of right ventricular ejection fraction in patients with chronic bronchitis and emphysema when measured in isolation, may give little information as to the cause of right ventricular dysfunction in such patients, but when combined with haemodynamic measurements obtained during right heart catheterisation, allows assessment of the right ventricular pressure/volume relation. This measurement is useful in assessing the mechanism of right ventricular dysfunction and in measuring the effects of therapeutic interventions in patients with pulmonary heart disease.

Chronic bronchitis and emphysema is a common disease. A survey of 18,000 male civil servants in London revealed that 10% had symptoms suggestive of chronic bronchitis, although few had a reduction in their ventilatory capacity (270). In the UK this condition is estimated to account for 10% of all days lost from work due to sickness, more than any other single disease entity (254), and in Scotland results in 46.5 deaths/100,000 of the population (269).

In some patients the condition will progress leading to chronic hypoxaemia, with or without hypercapnia. Once chronic hypoxaemia has developed such patients are at risk of developing `cor pulmonale' or `pulmonary heart disease'. The classical view of the development of cor pulmonale is that hypoxia results in pulmonary vasoconstriction, leading to pulmonary hypertension (113). It is proposed that the consequence of this increased pressure load is the development of right ventricular hypertrophy or cor pulmonale (361) with eventually clinical signs of right ventricular failure, often occurring during an exacerbation of chronic bronchitis and emphysema. However, whether the clinical syndrome of oedema in association with cor pulmonale is due to true right ventricular failure remains controversial (276). Whatever the events are which lead to cor pulmonale, its presence results in a high mortality, only 45% of such patients surviving for 2 years, compared with a 69% survival at 2 years in those patients without cor pulmonale (271). Similarly, the presence of pulmonary hypertension in patients with chronic bronchitis and emphysema also worsens the survival (351).

Clearly a greater understanding of the effects of pulmonary

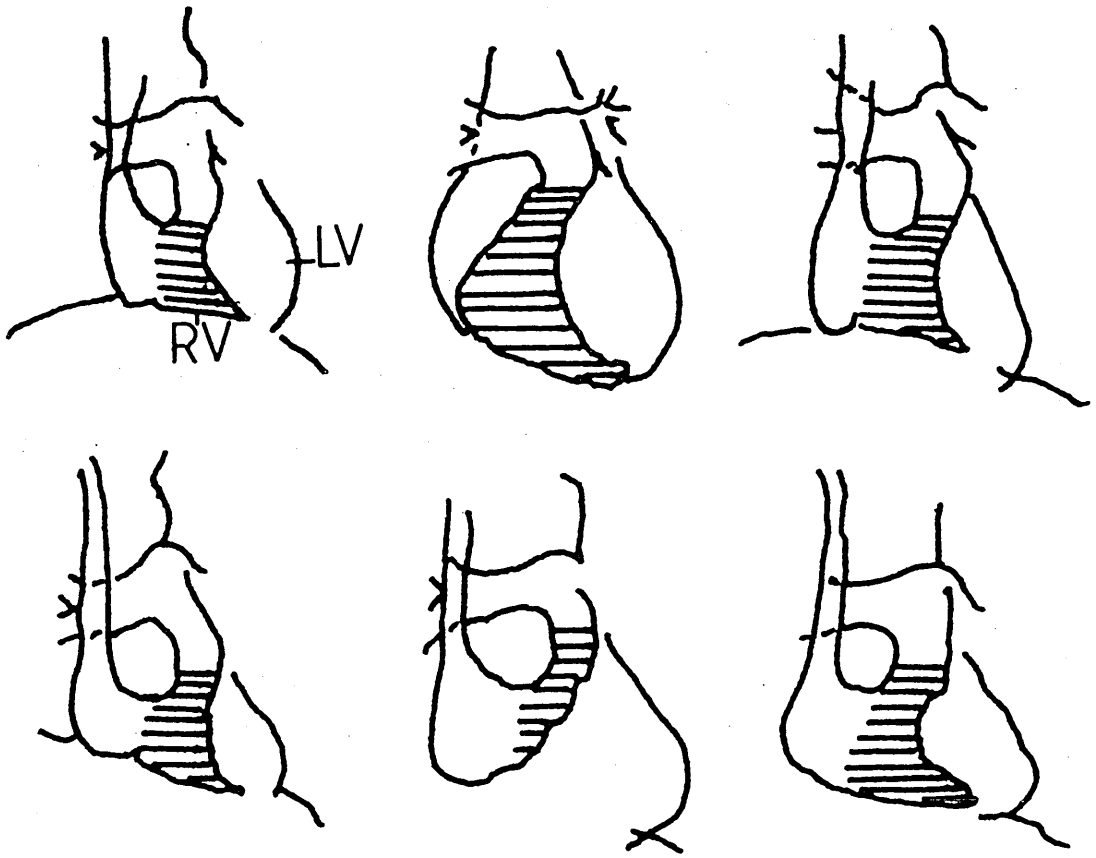


Figure 1 Traced outline of contrast angiographic studies in 6 normal subjects without evidence of cardiovascular disease. The right ventricle is shaded (after Arcilla R A et al [10]).

bronchitis and emphysema, particularly in determining whether true ventricular failure occurs in the syndrome of cor pulmonale, would lead to more rational treatment of this condition, which might reduce the mortality.

The assessment of right ventricular function, particularly measurement of its volume by contrast angiography (126) has previously been difficult, principally because of the variable and irregular shape of the right ventricle (figure 1). The introduction of radionuclide ventriculography (317) allows the measurement of ventricular ejection fractions, independent of the ventricular geometry. More detailed measurements of right ventricular mechanics can be made by combining simultaneous measurements of right ventricular ejection fraction and conventional pulmonary haemodynamics, measured during right heart catheterisation. These measurements allow a detailed analysis of the pressure/ volume relationships within the right ventricle.

The purpose of this dissertation is to assess in detail, the function of the right ventricle in patients with chronic bronchitis and emphysema. The initial studies were made to develop a reproducible method of measuring right ventricular ejection fraction (RVEF), using the technique of radionuclide ventriculography. Having established a reliable and reproducible method of measuring RVEF, it could be applied to assess right ventricular function in a population of patients with chronic bronchitis and emphysema, comparing the results with those in normal subjects. The measurements of both right and left ventricular ejection fractions (LVEF) could then be correlated with the clinical parameters of the disease in such patients.

Simultaneous measurements of right ventricular haemodynamics, measured during right heart catheterisation, and radionuclide right ventricular ejection fractions allow, as will be seen later, right ventricular volume to be derived and thus the right ventricular pressure/volume relationship can be measured. In this way the effects of pulmonary hypertension on right ventricular mechanics and contractility can be studied in patients with chronic bronchitis and emphysema. In addition, the effects on right ventricular function of therapeutic interventions which might reduce the pulmonary arterial pressure, such as vasodilators or oxygen, can also be studied in patients with cor pulmonale with and without the clinical signs of `right ventricular failure'.

From these studies I hope to answer the following questions:

1. Is right or left ventricular function impaired in patients with chronic bronchitis and emphysema?

2. How does right ventricular function relate to the clinical parameters of disease in such patients?

3. How does the presence of pulmonary hypertension affect right ventricular function in patients with chronic bronchitis and emphysema?

4. What are the effects of reducing pulmonary arterial pressure on right ventricular function in patients with pulmonary hypertension?

pulmonary hypertension and clinical signs of right ventricular failure?

Historical review

Each of the organs of the human body is supplied by a specialised circulation. However, the blood supply to the lungs is unique, since it is in series with the systemic circulation, and therefore receives all of the cardiac output. The large pulmonary arteries were known to Herophilus of Alexandria in the fourth century BC (179). Several centuries later Galen (138-201 AD) proposed that the function of the pulmonary circulation was to supply nutrients to the lungs. According to Galen blood was manufactured in the liver, passed to the right ventricle and hence to the lungs. The blood then entered the left ventricle through interventricular pores and was distributed from there, throughout the body, to be consumed in the tissues (179). It was presumed that the lungs delivered air via the pulmonary veins to the left ventricle, where it became the `vital spirit'. The left ventricle then acted as a furnace to supply heat to the rest of the body. The exhaust fumes from this furnace being conducted away, through the mitral valve, by way of the pulmonary veins to the lungs to be exhaled.

Blood was originally thought to ebb and flow, and it was not until the Renaissance that the concept of the circulation of blood was perceived. William Harvey (1578-1667), who was a medical student in Padua, realised that the circulation was not simply a generator of `vital spirits' (69). He estimated that the cardiac output was too great to simply allow a one way flow. In his classic work De Motu Cordis (146) he states "It is manifest that more blood is continually

can furnish, or is possible to be contained in the veins". Harvey first introduced the idea of the pulmonary circulation as a bridge between the two ventricles (145). However, it was not until a few years after Harvey's death that Malpighi provided proof of the continuity between the circulations, by visualising, in a frog lung, the passage of blood from the pulmonary artery to the pulmonary veins through what he called `porosities' (211).

Following the discovery of oxygen, by Priestley (1733-1804), it was Lavoisier (1747-1794) (68) who proved that oxygen was the essential constituent of air which was necessary to support life, thus introducing the concept of the lungs as an organ of gas exchange.

The first quantitative measurements of blood pressure were made by Stephen Hales (1677-1761) (65). Moreover, by pouring wax into the ventricles of dogs and measuring the volume of water displaced by the subsequent ventricular cast, Hales was able to estimate the stroke volume. By calculating the product of the stroke volume and the heart rate, he made the first measurements of cardiac output. In addition, although he was not able to measure the pulmonary arterial pressure, he deduced that the pulmonary vascular resistance was lower than the systemic vascular resistance, because the walls of the right ventricle were thinner than that of the left ventricle (65).

It was in Carl Ludwig`s laboratory in the 1850s that practical methods of measuring pulmonary vascular blood flow and pressure were developed (32). Adolph Fick (1829-1901), a student of Ludwig`s, derived the theoretical basis, in dogs, for the measurement of cardiac output: the total oxygen uptake per minute divided by the

through the lungs (138). Direct measurements of pulmonary arterial pressure are attributed to August Chauveau (1827-1917) and Etienne Jules Morey (1830-1904) who passed a double lumen catheter by way of the jugular vein to the pulmonary artery of a conscious horse. Both right ventricular and pulmonary arterial pressures could then be measured using an air filled manometer and recorded on a polygraph, which was also invented by Morey (138). Later Forsman (1929) demonstrated on himself, that a catheter could be passed to the right heart from a peripheral vein (119). The systematic investigation of pulmonary haemodynamics in man, however, began in 1941 with the catheterisation of the right atrium by Cournand (67) and five years later with the catheterisation of the pulmonary artery in normal man and in patients with chronic lung diseases (35).

STRUCTURE AND FUNCTION OF THE HUMAN PULMONARY CIRCULATION

The normal pulmonary circulation (110, 131, 140)

The pulmonary circulation and lungs form part of a complex system to enable external respiration to occur. As such the pulmonary circulation exists to perfuse , rather than nourish the lungs. In contrast with the systemic circulation, where the arterioles have a coat of circular smooth muscle, and are the vessels which contribute most to the systemic vascular resistance, the low pressure pulmonary circulation does not have an anatomical counterpart of the systemic arteriole. The absence of precapillary muscularised arterioles in the pulmonary circulation, means that other small vessels contribute appreciably to the driving pressure, which is represented by the difference in pressure between the pulmonary arteries and veins. Moreover, the small pulmonary vessels can respond passively to

as a reservoir for blood.

The pulmonary arteries themselves subdivide into terminal branches which have a wider bore and thinner wall than the corresponding systemic arteries. The structure of the wall of the large pulmonary arteries, which consists of smooth muscle inserting into short elastic fibres, appears to be designed to allow distensibility of the vessel, rather than active constriction or dilatation (148). However, the early animal work of Von Euler (96, 97) demonstrated that the potential exists for large pulmonary arteries to constrict and increase the pulmonary vascular resistance. Vessels which can actively change calibre need to have smooth muscle in their walls. Thus the small muscular pulmonary arteries appear to be the major site of changes in resistance in response to changes in pulmonary vasomotor tone. The presence of medial thickening in these small arteries would potentiate any active constriction and lessen the ability of the vessels to undergo passive distension. Thus, under these conditions, the vessels would contribute more to the resistance to blood flow (58).

The pulmonary capillary network appears to have neither contractile cells nor smooth muscle in its walls. It is therefore unlikely that the capillaries contract actively, but they may be more apt to be reduced in size passively as a result of extrinsic forces, such as swelling of the endothelial cells, perivascular transudates (85), raised alveolar pressures (280), or by changes in intrathoracic pressure (329). The pulmonary capillaries are suspended in the walls of the alveoli allowing the entire right ventricular output to take part in gas exchange. It is estimated that the pulmonary

of 50-70m^2 and increases further , to 90m^2, at 75% of the total lung capacity (345). The enormous expanse of the alveolar capillary surface in the normal subject can increase further during activity, without changing the balance between alveolar ventilation and pulmonary capillary perfusion, even during strenuous exercise (17).

Since the pulmonary circulation must accommodate the total cardiac output, a perfusion pressure of only 10 mmHg is required to distribute the cardiac output within the lungs at rest. The pulmonary circulation is therefore a low resistance system, with a low basal tone, since vasodilators which reduce systemic vascular pressures have little or no effect on the normal resting pulmonary arterial pressure (185, 236, 258, 335, 346). The normal pulmonary vascular bed therefore offers less than one-tenth of the resistance to flow of the systemic circulation. Thus , although factors such as gravity, lung inflation, neural stimulation, and local vasoactive substances affect the pulmonary circulation, they appear to have less of a physiological role in modifying pulmonary vascular resistance, which is affected much more by the local alveolar oxygen tension (109).

Thus the vascular resistance in the pulmonary circulation is dependent on the cross-sectional area of the small muscular arteries and the arterioles. However, it is also dependent on a number of other variables, such as the blood viscosity, the total mass of lung tissue (ie, resistance is higher in infants than in adults) and the extra-mural compression of vessels (eg, perivascular oedema). The distensibility of the normal pulmonary vascular bed means that the cross-sectional area of the bed varies directly with both the

transmural pressure and the flow, and thus pulmonary vascular resistance decreases passively, with increases in flow (57). Consideration of the Poiseuille equation:

$$R = P/Q = 8Ml/\pi r^4$$

(R = resistance; P = pressure drop; Q = flow; M = viscosity of fluid; l = length of the vessel; r = radius of the vessel)

shows that small changes in the vessel radius can have a large effect on resistance. A change in calibre may, of course, not only arise from a change in the diameter of the vessels, but also from a change in the number of parallel paths which are being perfused, ie, recruitment of previously under-perfused vessels (194). As an illustration of this, acute changes in flow, such as occur during balloon occlusion of a single pulmonary artery are associated, in the supine position, with an increase in pulmonary arterial pressure so that the pulmonary vascular resistance remains unchanged (299). However, in the upright position, the blood vessels are usually in a partial or completely collapsed state, and these vessels may expand in response to an increased flow resulting in a reduction in vascular resistance (142). Thus changes in pulmonary vascular resistance do not necessarily accurately reflect active changes in vascular calibre, unless all of the other passive mechanisms affecting vessel calibre are taken into account. This has led to the use of pulmonary arterial flow curves and pulmonary vascular flow resistance curves to detect active changes in pulmonary vascular calibre (109).

During supine exercise in normal man (292) the pulmonary arterial pressure increases by 3-5 mmHg. The increase in systolic pressure

the exercise, pulmonary arterial pressure often falls below the control resting values (81, 305). The pulmonary vascular resistance either remains unchanged (46) or falls during moderate supine exercise (277, 137), most probably by passive dilatation of the vessels. With severe exercise, where the cardiac output is tripled, the pulmonary vascular resistance becomes constant (192).

As discussed above it is difficult, in a normal subject, to increase pressures in the pulmonary circulation more than a few mmHg. Although a large number of both humoral and neural factors can be shown to affect pulmonary vasomotor activity (74), at present there is little evidence to indicate that, under normal circumstances, these factors are critical in maintaining normal pulmonary vascular function. However, in disease states, the pulmonary vascular bed can undergo profound changes in vasomotor tone. It might be supposed, in the development of pulmonary hypertension, that reduction in the extent of the pulmonary vascular bed would be more important than humoral or neural pressor mechanisms. This is of course of practical importance, since diseases such as emphysema may destroy large areas of the pulmonary capillary bed. However, it is generally believed that the physical loss of vessels contributes significantly to the development of pulmonary hypertension only when the reduction in vessels is extreme, such as in multiple pulmonary emboli, aplasia, or extensive excision of lung tissue (3, 130, 202). Support for this view comes from experiments in dogs, where more than two-thirds of the pulmonary vasculature has to be ablated before pulmonary hypertension develops (192). In addition, in patients with pulmonary emphysema where alveolar vessels are widely destroyed, resting pulmonary arterial hypertension occurs only late in the

In the early 1940s the mechanism of the development of pulmonary hypertension, in what was then called 'chronic emphysema', was stated to be from lung destruction, and was thought to be irreversible (102). However, in 1946 Von Euler and Liljestrand (96) first proposed, from experiments in the cat, that acute hypoxia produced pulmonary vasoconstriction. Morley et al (1947) (238) were the first to describe hypoxic vasoconstriction in normal subjects. There followed several other studies showing that, in normal subjects, when the inspired oxygen concentration falls below 15%, pulmonary arterial pressure rises, with no change, or a slight increase in the cardiac output and the pulmonary capillary wedge pressure so that pulmonary vascular resistance rises under these conditions (84, 107, 108, 112, 354). The mechanism of this rise in pulmonary arterial pressure in response to hypoxia remains unclear (112, 202). However, it seems likely that the site of the hypoxic vasoconstriction is in the small pulmonary arterioles, that it does not depend upon innervation of the lungs, and may act through the release of an as yet unspecified mediator, or as a result of the direct action of hypoxia on the pulmonary vessels (112, 127, 174). When normal subjects, who are resident at sea level, breathe oxygen heart rates falls, cardiac output changes little, and there is a trivial fall in pulmonary arterial pressure (18, 119).

The pulmonary circulation in chronic bronchitis and emphysema

Early studies of pulmonary haemodynamics in patients with 'chronic emphysema' indicated that pulmonary arterial pressure may be normal or slightly elevated when measured at rest (37, 143, 162, 243) and may rise to an abnormally high level during exercise (153, 277),

pulmonary arterial pressure - the increase being greater in subjects over the age of 50 years (81, 91, 153, 277). This greater rise in pulmonary arterial pressure during exercise in patients with chronic lung diseases was considered to be due to the inability of the reduced pulmonary vascular bed, in such patients, to expand to accommodate the increased cardiac output, as can occur in the normal pulmonary circulation (79). However, it is now known that in the development of pulmonary arterial hypertension, several factors must be considered (table 1).

FACTORS CONTRIBUTING TO THE DEVELOPMENT OF PULMONARY HYPERTENSION

Destruction of the pulmonary vascular bed

As discussed above, decrease in the anatomical extent of the pulmonary vascular bed does not appear to have a major role in the development of pulmonary hypertension. Since the quantification of pulmonary emphysema in life is difficult (331) studies where a comparison has been made between the 'emphysematous' and the 'bronchitic' patients are open to question. However, these studies seem to indicate that pulmonary arterial pressure is raised in the 'bronchitic' and normal in the 'emphysematous' patients (243, 347), when measured at rest, despite the fact that emphysema produces a greater destruction of the vascular bed. In addition, it appears from post mortem studies that there is no correlation between right ventricular hypertrophy and the total alveolar surface area, which is reduced in emphysema (140).

The evidence that breathing gases of low inspired oxygen concentrations produces an increase in pulmonary arterial pressure in normal man has been discussed previously (112). The rise in pulmonary arterial pressure is proportional to the fall in SaO_2 (122). In patients with chronic bronchitis and emphysema the correlation between pulmonary arterial pressure and SaO_2 was first reported by Harvey et al (143), and has been subsequently confirmed by many other authors (37, 88, 93, 103, 120, 122, 159, 229, 243, 355, 356, 365). Most recently data from a large European multicentre study of almost 1,000 patients suffering from common chronic lung diseases (595 of whom had chronic bronchitis and emphysema), showed a highly significant correlation in such patients between pulmonary arterial pressure and SaO_2 or PaO_2 (34). This relationship does not constitute proof that chronic hypoxia is the only cause of pulmonary hypertension in patients with chronic bronchitis and emphysema. However, as has been stated earlier, acute hypoxia produces pulmonary vasoconstriction in normal subjects and in patients with chronic bronchitis and emphysema (52, 84, 108).

A positive correlation also exists between the arterial PCO_2 and the pulmonary arterial pressure (2, 143, 159, 299). However, in studies where increasing concentrations of inspired carbon dioxide were given to patients with chronic bronchitis and emphysema, although the pulmonary arterial pressure rose, carbon dioxide may not have produced vasoconstriction directly, since cardiac output also increased (108, 183, 281). Moreover, in only one of these studies did pulmonary vascular resistance increase significantly in response to breathing hypercapnic gas mixtures (183). Thus the pulmonary vasoconstrictor effect of carbon dioxide in patients with chronic

has been suggested that part of the effect of the $PaCO_2$ on pulmonary arterial pressure may be as a result of changes in lung mechanics produced by the hyperventilation induced by the rise in $PaCO_2$ (141). There is also some data which suggests that an increase in the alveolar PCO_2 potentiates hypoxic vasoconstriction (87).

The influence of arterial hydrogen ion concentration on the pulmonary circulation

Although a positive correlation has been shown between the arterial hydrogen ion concentration and the pulmonary arterial pressure, the induction of changes in arterial hydrogen ion concentration in patients with chronic bronchitis and emphysema has been shown to have equivocal effects on pulmonary arterial pressure (2, 94, 144, 160). In normal subjects intravenous infusion of sodium bicarbonate, so as to increase the pH to 7.5, had no effect on the pulmonary arterial pressure or cardiac output (28), whereas in patients with chronic bronchitis and emphysema, intravenous infusion of sodium bicarbonate or TRIS buffer produced no significant change in pulmonary arterial pressure but did produce a substantial increase in cardiac output, suggesting that pulmonary vasodilatation had occurred (94).

However, in view of the curvilinear relationship between pressure and flow in the pulmonary circulation in patients with chronic bronchitis and emphysema changes in pressure and flow should be interpreted with caution. Similar inconsistent effects on the pulmonary circulation have been reported when attempts were made to increase the hydrogen ion concentration in patients with chronic bronchitis and emphysema, by the intravenous infusion of hydrochloric acid (144, 160). Indeed when the arterial pH was decreased over a period of 5-7 days by

and emphysema, no consistent change in the pulmonary arterial resistance occurred. However, there does appear to be some synergism between hypoxia and acidaemia in their pulmonary vasoconstrictor effect in patients with chronic bronchitis and emphysema, such that for a given SaO_2 mean pulmonary arterial pressure is higher at higher levels of arterial hydrogen ion concentration (94). Thus when there is marked desaturation the pulmonary arterial pressure is more sensitive to changes in hydrogen ion concentration than at lesser degrees of desaturation. These studies take no account however of the extent to which changes in extra-cellular pH affect the intra-cellular pH of the smooth muscle of the pulmonary vessels.

Alterations in pulmonary mechanics

Changes in airway resistance have an important effect on gas exchange in patients with chronic bronchitis and emphysema. Since correlations have been shown between the PaO_2, $PaCO_2$, hydrogen ion concentration and the pulmonary arterial pressure, it is not surprising that a correlation has also been shown between pulmonary arterial pressure and FEV_1 in such patients (141). Changes in airway resistance may augment pulmonary vascular resistance in patients with chronic bronchitis and emphysema by an effect on alveolar pressure. Harris et al (141) showed in normal man, that the relationship between pressure and flow in the pulmonary circulation, when alveolar pressure is normal, is rectilinear. However, when the alveolar pressure is increased (by increasing the gas pressure at the mouth) the pressure flow relationship in the pulmonary circulation initially becomes steeper and the relationship is now a curved one, the pressure no longer increasing in proportion

increased alveolar pressure causing compression of the resistance vessels of the lungs. Thus if alveolar pressure is increased in normal subjects the relationship between pressure and flow in the pulmonary circulation resembles the relationship which exists between pressure and flow in bronchitic patients during normal tidal breathing (141).

The influence of the airways resistance on the pulmonary arterial pressure may be important in patients with chronic bronchitis and emphysema during episodes of hyperventilation. In contrast to normal subjects, where hyperventilation produces no effect on the pulmonary circulation, hyperventilation in patients with severe chronic bronchitis and emphysema causes an increase in both pulmonary arterial pressure and wedge pressures, without changing cardiac output, so that the resulting increase in pulmonary vascular resistance can be interpreted to be as a result of a reduction in calibre of the vessels (141). Conflicting results have been reported in less severely disabled patients with chronic bronchitis and emphysema, where hyperventilation did not change the pulmonary vascular resistance (198). It has also been shown that the amplitude of the respiratory swing of the pulmonary arterial pressure, when patients with chronic bronchitis and emphysema perform exercise (which is related to changes in intrathoracic pressures), correlates with the pulmonary arterial pressure (348).

Increased cardiac output

The increase in cardiac output which occurs during exercise, for example, can be accommodated in the normal pulmonary circulation because of its distensibility, without producing large changes in

increase by a factor of 2.5 to produce any significant increase in the pulmonary arterial pressure in the normal vascular bed (140). In contrast, in patients with chronic bronchitis and emphysema, where the vascular bed may be restricted, small increases in flow, even those occurring during mild exercise, may produce significant increases in pulmonary arterial pressure (278).

The effect of blood volume

Abraham et al (5) studied the effects of expansion of the blood volume on the pulmonary arterial pressure, in patients with chronic bronchitis and emphysema. Hypoxia resulted in a rise in the pulmonary arterial pressure and only a small increase in the cardiac index and thus an increase in the pulmonary vascular resistance, in these patients. Albumen infusion increased both the pulmonary arterial pressure with a greater increase in the cardiac index, producing a fall in the pulmonary vascular resistance. Breathing hypoxic gas mixtures, after the infusion of albumen, blunted the hypoxic vasoconstrictor effect, perhaps because the infusion of albumen increased pulmonary arterial transmural pressure, thus diminishing the vasoconstrictor effect of hypoxia (5).

The results of this study (5) do not support the hypothesis that an increase in blood volume is a major factor in the development of pulmonary hypertension. Moreover, during the recovery phase in patients with acute respiratory failure, the pulmonary arterial pressure starts to fall without any corresponding changes in the plasma volume and there is no significant correlation between the pulmonary arterial pressure and the plasma or total blood volume in such patients (6).

The effect of blood viscosity

Patients with chronic bronchitis and emphysema who become hypoxic, develop secondary polycythaemia (32) which increases the viscosity of the blood. In theory since viscosity is a factor in the Poiseuille equation, then viscosity may have a role in the development of pulmonary arterial hypertension. The effects of reducing packed cell or blood volume and thus the plasma viscosity in patients with chronic bronchitis and emphysema have been studied by Segal and Bishop (305). Reducing the blood volume produced a small fall in pulmonary arterial pressure without change in cardiac output. Thus pulmonary vascular resistance fell slightly. This study suggests that blood viscosity at least contributes to the development of pulmonary arterial hypertension.

The effect of pulmonary venous pressure

Although a raised pulmonary venous pressure produces an equal rise in pulmonary arterial pressure in patients with mitral valve disease or chronic left ventricular failure, it does not appear to have a role in the development of pulmonary arterial hypertension in patients with chronic bronchitis and emphysema, unless these other conditions are present concomitantly.

In the preceding section I have discussed the various factors which have an influence on the development of pulmonary arterial hypertension in patients with chronic bronchitis and emphysema. Hypoxia, either directly, or indirectly via a mediator, appears to be the most important factor (109, 110, 112, 131, 140, 222). I will now consider the consequences of pulmonary arterial hypertension in patients with chronic bronchitis and emphysema, how it progresses,

THE EFFECTS OF PULMONARY HYPERTENSION IN CHRONIC BRONCHITIS AND EMPHYSEMA

In this dissertation I have used the terms chronic bronchitis and emphysema synonymously, as both conditions usually co-exist pathologically (330). Most patients, however, lie in clinical, physiological and pathological terms in the middle of a spectrum of disease. Those with predominant chronic bronchitis or predominant emphysema are in the minority and lie at either end of the spectrum (54, 56, 232). A simplistic distinction of chronic bronchitis from emphysema was first attributed to Dornhorst (82) who coined the phrases `pink puffer' and `blue bloater'. The `pink puffer' is thought to have predominant emphysema, with relatively normal arterial blood gas tensions. The development of pulmonary hypertension or right heart failure occurs late in the course of the disease. In contrast, the `blue bloater' is considered to have predominantly chronic bronchitis, have hypoxia and hypercapnia and develops pulmonary hypertension early in the course of the disease, resulting in repeated episodes of `right heart failure', often during acute episodes of respiratory failure. Thus not all patients with chronic bronchitis and emphysema inexorably pursue the road to `right heart failure'. In those who develop hypoxia, pulmonary arterial pressure increases (106). Hypoxaemia tends to occur earlier in the `blue bloater' and the prognosis in these patients seems to be worse (41). Burrows et al (57) in evaluating the pulmonary haemodynamics in 50 patients with stable `chronic airways obstruction', found that those with elevated pulmonary vascular resistance had two patterns of cardiovascular dysfunction. Some had relatively normal arterial

pulmonary arterial pressure. These patients were considered to have predominantly the `emphysematous type of lung disease'. Those with more severe blood gas abnormalities had a more `bronchitic type' of disease, and had normal or elevated cardiac outputs and more severe pulmonary hypertension. However, as with all such studies, the division of patients into `emphysematous' or `bronchitic' groups is imprecise, since the diagnosis of emphysema is a pathological one, and is difficult in life (330, 331).

What is the natural history of pulmonary hypertension in patients with chronic bronchitis and emphysema? Numerous studies have shown that when patients with chronic bronchitis and emphysema develop an elevated pulmonary arterial pressure, this pulmonary hypertension progresses slowly (41, 117, 288, 297, 349, 350). Weitzenblum et al (350) studied the changes in pulmonary arterial pressure in a group of patients with chronic obstructive pulmonary diseases, (mainly chronic bronchitis), over an average of 5 years, and found that pulmonary arterial pressure increased by an average of only 3 mmHg/year. The mean increase in pulmonary arterial pressure was greater than 5 mmHg in only 33% of these patients over this period. Those whose pulmonary arterial pressure worsened tended to have lower PaO_2 and higher $PaCO_2$ eventually than those patients without worsening haemodynamics. Similarly Boushy and North (41) reported a mean increase in pulmonary arterial pressure of only 7% in 136 patients with chronic obstructive pulmonary diseases , studied before and after an average interval of 25 months. This change in pulmonary arterial pressure was associated with an increase in cardiac output of 6%. In contrast, Schrijen et al (297) found no significant deterioration in pulmonary haemodynamics in a group of

period of 3 years, even in those with elevated pulmonary arterial pressure when first measured. However, in this study (297) 30% of patients had a fall in systemic arterial pressure with time. Schrijen suggested that this was as a result of the peripheral vasodilatory effects of hypercapnia.

Despite the slow progression of pulmonary arterial hypertension in patients with chronic bronchitis and emphysema, its presence results in a poor prognosis. Weitzenblum et al (351) showed that patients with a normal pulmonary arterial pressure (< 20 mmHg) had a 4 year survival of 72% compared with a 49% 4 year survival in those whose pulmonary arterial pressure was elevated (3). The prognostic value of pulmonary arterial pressure has been confirmed by others (217). Burrows et al (57), in a longitudinal 7 year study of 50 patients with chronic airways obstruction, showed that the level of pulmonary vascular resistance correlated best with survival, with none of the patients whose pulmonary vascular resistance exceeded 550 dynes.sec.cm^{-5} surviving for more than 3 years. However, in one study of patients whose pulmonary arterial pressure was only minimally raised (mean PAP 20-29 mmHg at rest), although there was a 25% mortality within 3 years, a similar percentage were alive after 10 years (257). This conflicting data may relate to the duration of the pulmonary hypertension in an individual patient. However, it is clear that some patients tolerate increases in pulmonary arterial pressure remarkably well.

The presence of pulmonary arterial hypertension in patients with chronic bronchitis and emphysema usually attracts clinical attention when it causes the clinical syndrome of `cor pulmonale'or pulmonary

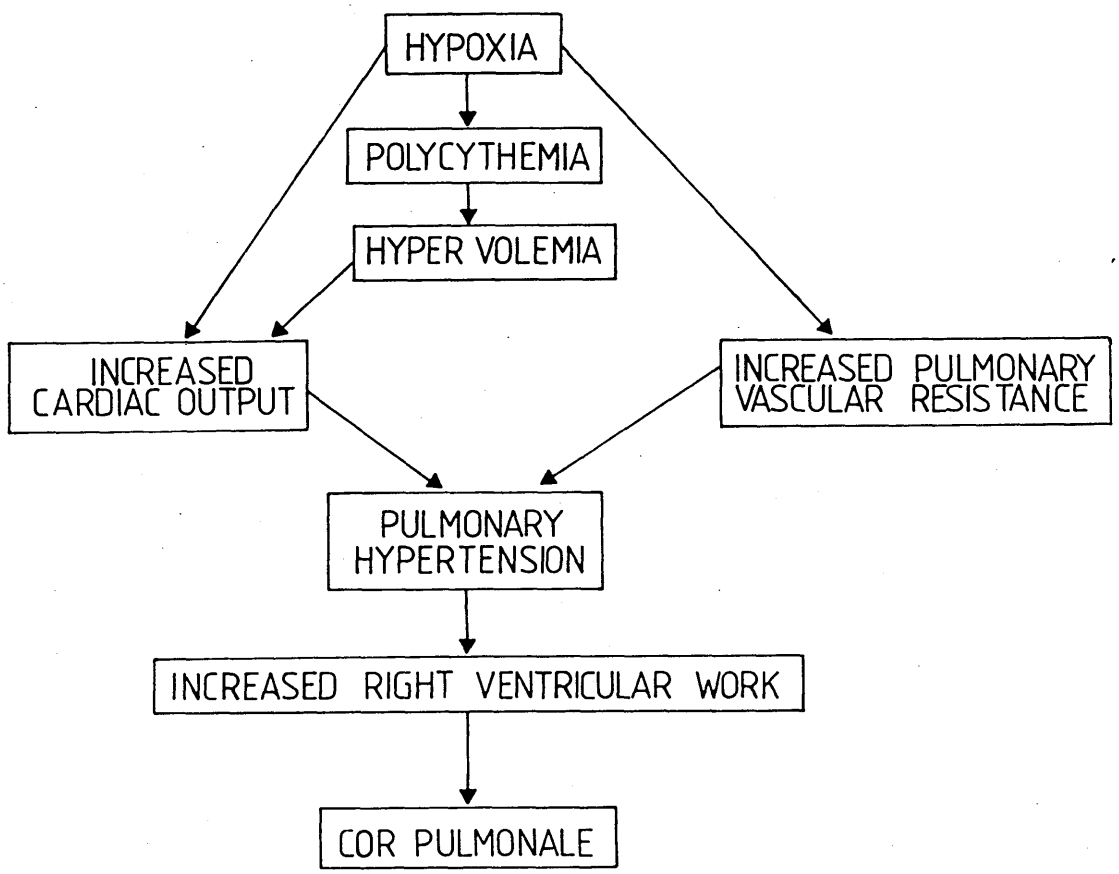


Figure 2 The sequence of events in the development of cor pulmonale

radiological and electrocardiographic evidence of right ventricular hypertrophy, often in association with peripheral oedema and raised jugular venous pressure (103, 104, 113). The current wisdom (figure 2) suggests that in patients with chronic bronchitis and emphysema, hypoxia, in association with the other factors discussed previously results in pulmonary hypertension, which in turn leads to increased right ventricular work and cor pulmonale (103, 104, 113, 202, 328). However, no standard definition of cor pulmonale or pulmonary heart disease has been universally accepted. To some it indicates merely the presence of pulmonary hypertension, to others associated oedema and to yet others the presence of right ventricular hypertrophy. The difficulties of definition were highlighted by the WHO who defined chronic cor pulmonale as `right ventricular hypertrophy resulting from disorders that affect either the structure or function of the lungs' (361). Thus accurate diagnosis of cor pulmonale requires pathological confirmation, since right ventricular enlargement may be difficult to diagnose in life either clinically or radiologically (155, 202, 278).

Pathological changes of pulmonary hypertension

As a result of pulmonary hypertension, longitudinal muscle may develop in the intima of the muscular pulmonary arteries, and in pulmonary arterioles (140). This change in the intima may also result from repeated stretching of the arteries particularly around emphysematous bullae, as it does occur in some cases of bullous disease without pulmonary hypertension (154). In addition the pulmonary arterioles may become muscularised (147), in contrast to the muscular pulmonary arteries which do not undergo any significant medial hypertrophy (154). These findings in patients with chronic

pulmonary vascular disease produced by primary pulmonary hypertension or left atrial hypertension which produces marked medial hypertrophy (59). The muscularisation of the pulmonary arterioles relates closely to the development of right ventricular hypertrophy in bronchitic patients (86).

Measurements of right ventricular thickness can be inaccurate and misleading in determining the size of the right ventricle (233). It appears to be more accurate to weigh the right ventricle by the standard method of Fulton et al (124). In this method the right ventricle is dissected free and the septum and left ventricle are weighed together. Measurements can then be made of the right ventricular weight or the ratio of the right ventricular weight to that of the left ventricle plus the interventricular septum. It has also been suggested that measurements of the myocardial fibre diameter is a better indicator of right ventricular hypertrophy (166).

Although initial studies suggested a relationship between 'chronic emphysema' and right ventricular hypertrophy and failure (298), later studies have all shown no relationship between the anatomical extent of the emphysema and the weight of the right ventricle (70, 86, 229, 233). In fact, severe emphysema involving 80% of the lung can be present with a normal right ventricular weight, but 45% emphysema with evidence of associated chronic bronchitis can result in right ventricular hypertrophy (86). In one study when the ECG showed right ventricular hypertrophy 25% of cases did not show hypertrophy of the right ventricle at post mortem (340). Thus factors other than an increase in right ventricular mass can produce right

contrast, have shown that ECG changes of right ventricular hypertrophy in life do correlate with the pathological estimation of right ventricular hypertrophy at autopsy (71, 233).

It appears important, therefore, to be able to distinguish those patients with chronic bronchitis and emphysema who have pulmonary hypertension alone, from those with `cor pulmonale' as defined by the WHO (361), as an enlargement of the right ventricle in response to the increase in pulmonary arterial pressure. A distinction should also be made between those with `cor pulmonale', and those with, in addition, evidence of right ventricular failure, which is seen as the eventual consequence of cor pulmonale (322). These distinctions can be difficult to define clinically, since pulmonary hypertension and right ventricular enlargement often do not present with classical clinical, radiographic or electrocardiographic signs (222, 252). In addition, the presence of peripheral oedema in patients with cor pulmonale may not represent clinical evidence of true right ventricular muscle failure (276). In future discussions in this thesis I will use the term cor pulmonale as being right ventricular enlargement consequent on pulmonary hypertension and acute cor pulmonale as being an acute increase in pulmonary arterial pressure resulting in acute right heart strain or overload, usually as a result of a massive pulmonary embolism (165). The terms cor pulmonale with right heart failure or decompensated pulmonary heart disease will be used when there is clinical evidence of peripheral oedema for which no cause, other than cor pulmonale, can be found. Such patients may or may not have engorged jugular veins which are often difficult to detect clinically in patients with airflow limitation.

Incidence of cor pulmonale or pulmonary heart disease

Cor pulmonale is considered to be a relatively common type of heart disease (113, 361) and is commonly associated in the UK, and the USA, with chronic bronchitis and emphysema (272). Recent figures indicating the incidence and prevalence of this condition are lacking, perhaps because of the difficulty in defining the condition clinically. In the UK at autopsy, 40% of patients with chronic bronchitis and emphysema show pathological evidence of cor pulmonale (149) and cor pulmonale accounts for 30-40% of cases in the UK (319, 355), and 10-30% of cases in the USA (165), admitted to hospital with a diagnosis of congestive cardiac failure.

Right ventricular function in chronic bronchitis and emphysema

Since hypoxia produces pulmonary vasoconstriction (112), and since the degree of hypoxia in patients with chronic bronchitis and emphysema has been shown to correlate with the level of the pulmonary arterial pressure in such patients (34), it seems reasonable to compare the effects on the right ventricle of chronic elevations in pulmonary arterial pressure, with the effects of systemic hypertension on the left ventricle (202). A further increase in pulmonary arterial pressure, which occurs during periods of acute exacerbations of bronchitis (often precipitated by a respiratory infection) (6), should then lead to right ventricular overload and the features of right heart failure (143, 319).

Before birth both right and left ventricles appear to have the same pumping action. The differences which exist between the two ventricles in adulthood have been attributed to the different flow-resistance conditions in the two circulations (45, 191). The right

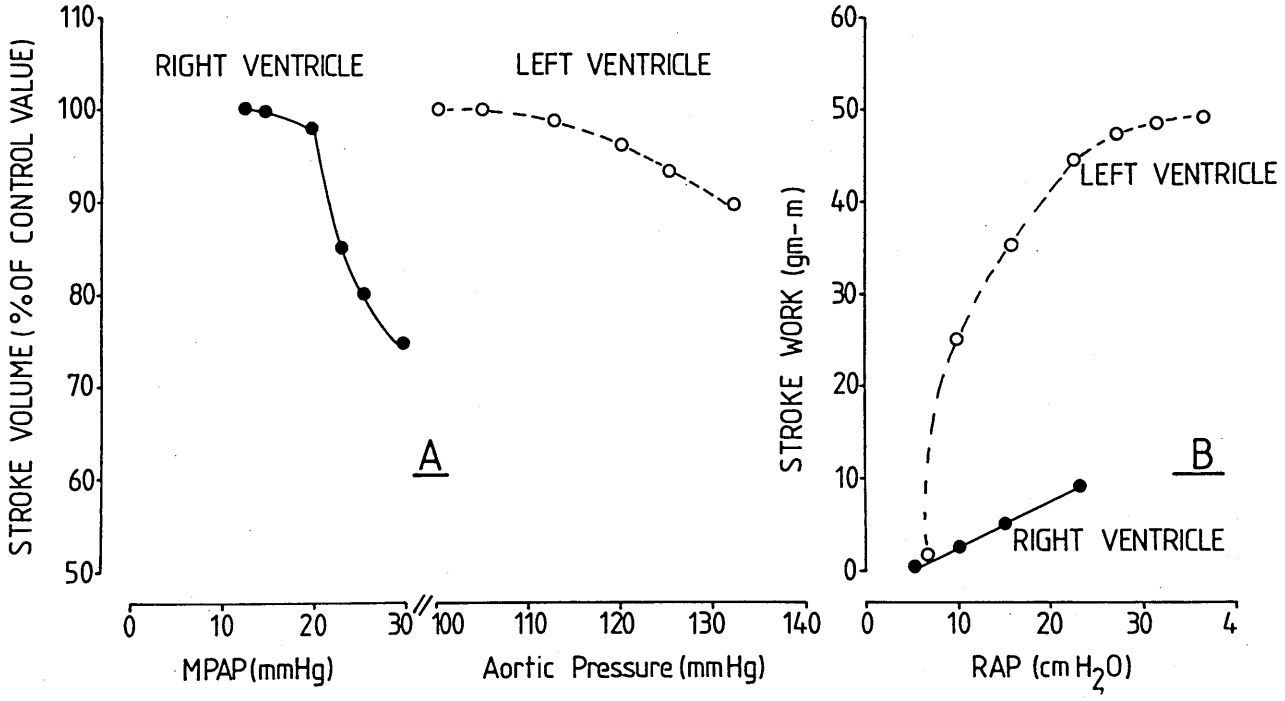


Figure 3 The effects of increasing afterload (A) and pre-load (B) on the right and left ventricles in the dog. Stroke volume decreases rapidly when afterload is increased in the right ventricle, in contrast to the left ventricle, which maintains stroke volume reasonably well against an augmented afterload (A).
In contrast, the stroke work of the left ventricle increases dramatically when pre-load is increased, which is not the case with the right ventricle (B) (after McFadden E R and Braunwald) [202].

series with the low pressure pulmonary circulation. This is in contrast to the concentric contraction of the left ventricle, which works in a high pressure system. The normal thin walled right ventricle is therefore more compliant, and is capable of distending. Its geometric configuration is thought to be most suited to ejecting large volumes of blood with minimal myocardial shortening. It can therefore cope with considerable variations in the systemic venous return, without producing large changes in filling pressures (115, 191). However, it is thought that the right ventricle is less able to adapt to the development of high intra-cavity pressures (1, 294). In contrast the left ventricle, has the ability to cope with increases in pressure load. The response of the right ventricle to progressive increases in afterload has been sparsely studied and most of the evidence for the difference in the response of the ventricles to changes in pressure and volume have come from animal data (1, 191, 294). Figure 3 illustrates changes in stroke volume plotted as a function of various increases in ventricular afterload, produced by actively constricting the main pulmonary artery or aorta in dogs. For the right ventricle, even small increases in pulmonary arterial pressure result in a rapid decrease in stroke volume, whereas the left ventricle maintains its stroke volume relatively well despite increases in systemic arterial pressure. However, increasing ventricular pre-load or filling pressure fourfold (from 5 to 20 mmHg) (figure 3) by volume infusions into the atria - again in dogs, produced an increase in left ventricular work five times that of the right ventricle.

Thus a chronic increase in pressure load should lead to changes in the configuration, mass and function of the right ventricle. The

found in patients with chronic bronchitis and emphysema produce these changes, is unknown. It is known, however, that acute constriction of the pulmonary artery in dogs produces no change in right ventricular pressure or cardiac output until the lumen of the pulmonary artery is constricted by more than 50% (324). Animal studies suggest that the ability of the right ventricle to compensate as the pulmonary artery is constricted is determined by (1) the increase force of contraction as the right ventricle distends; (2) the adequacy of the coronary circulation; (3) the circulatory neurohumoral reflexes, which increase the force of contraction; (4) the blood volume which can augment right ventricular end-diastolic pressure (134).

In patients with pulmonary hypertension as a result of mitral valve disease, right ventricular dilatation and failure occurs when the right ventricular systolic pressure reaches 60-80 mmHg. The level of right ventricular outflow tract obstruction which produces these changes can be increased or reduced by increasing or decreasing right coronary artery blood flow (50). Although banding of the pulmonary arteries in the cat produces a 2-3 fold increase in right ventricular weight, it is very unlikely that such rapid changes occur in man. Furthermore, the levels of pulmonary hypertension in bronchitic patients seldom reach the systemic levels needed to produce the acute changes which may occur in patients with multiple pulmonary emboli or primary pulmonary hypertension (339).

Thus in summary patients with relatively mild obstructive airways disease, without severe hypoxaemia or hypercapnia, have normal or low cardiac output, the latter occurring late in the course of the

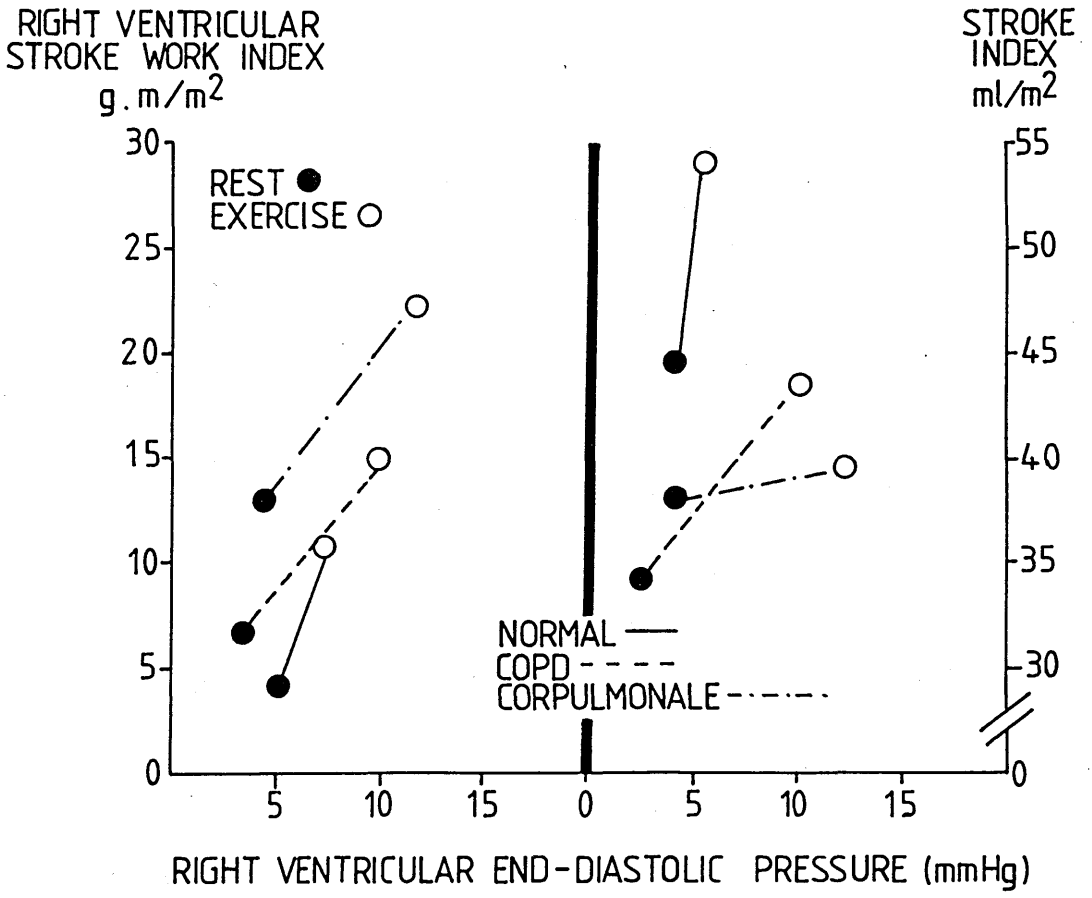


Figure 4 Right ventricular stroke work index is highest in those patients with cor pulmonale both at rest and during exercise. When stroke index (right) is related to the right ventricular end-diastolic pressure, patients with cor pulmonale do not have a normal increase in stroke index during exercise, suggesting depressed right ventricular function. However, right ventricular stroke work index increases during exercise in all 3 groups (left), those with COPD and cor pulmonale operating on an extension of the normal right ventricular function curve, at the expense of an increase in right ventricular end-diastolic pressure (after Khaja et al [181]).

303, 338, 355, 356, 365). Right atrial pressures and right ventricular end-diastolic pressures are normal. Pulmonary arterial pressure is only slightly elevated but is inappropriately high for the level of cardiac output. Pulmonary vascular resistance is normal or only slightly elevated when at rest. When exercising pulmonary arterial pressure rises to abnormal levels (54, 252). However, as in normal subjects, the increase in cardiac output during exercise is normal relative to the increase in oxygen consumption (49, 181, 356). Right ventricular end-diastolic pressure also rises to abnormal levels on exercise (181). Right ventricular stroke work is normal at rest in these patients and rises on exercise (181). The increase in heart rate and stroke volume on exercise is similar to the changes which occur in normal subjects. However, the right ventricular stroke work index (which relates the stroke index to the pressure difference between right ventricular end diastolic-pressure and pulmonary arterial pressure) (figure 4) is higher in these patients due to an increase in pressure work against a higher pulmonary arterial pressure. However, if the right ventricular stroke work index is plotted against the right ventricular end-diastolic pressure, it appears that these patients operate on an extension of the normal right ventricular function curve (181). These findings are in keeping with the Starling mechanism such that the small increases in right ventricular end-diastolic pressure which occur on exercise, produce a large increase in right ventricular stroke work index. These changes in right ventricular haemodynamics may not be associated with clinical or electrocardiographic evidence of right ventricular hypertrophy in such patients (57).

As the airflow limitation and arterial blood gas abnormalities in

at the stage when chronic hypoxaemia develops, often but by no means always, in association with chronic hypercapnia, pulmonary hypertension is present at rest and worsens with exercise (49, 170, 181, 338, 356). However, at rest right ventricular end-diastolic pressure is normal (181) even in those patients with past episodes of right heart failure or clinical evidence of right ventricular enlargement. Right ventricular end diastolic-pressure is, however, elevated in the majority of such patients during exercise. The presence of normal right ventricular end-diastolic pressures in these patients, at rest, is at least presumptive evidence of normal right ventricular end-diastolic volume (49).

Right ventricular function in patients with decompensated pulmonary heart disease

Relatively few haemodynamic studies have been made in patients with chronic bronchitis and emphysema who have had episodes of 'right heart failure' either at the time of study or in the past (37, 57, 184, 243, 356). Such patients have a lower arterial oxygen saturation or tension, and a higher pulmonary arterial pressure and pulmonary vascular resistance, when at rest than those without previous evidence of cardiac failure (356). Some, but not all of these patients desaturate during exercise when breathing air, and exercise also produces an increase in pulmonary arterial pressure resulting in an increase in pulmonary vascular resistance (57, 181, 356). In the few studies where right ventricular function has been measured (27, 170, 181), right ventricular end-diastolic and right atrial pressures are often elevated,. However right ventricular stroke work index is well maintained. Moreover, in those patients

failure, right ventricular stroke work index responds normally to the increase in pressure work which occurs on exercise (figure 4). However, the right ventricular stroke index does not change significantly during exercise in those patients with right ventricular failure despite similar increases in heart rate (181). These changes produce a further increase in filling pressures.

There does not seem to be strong evidence, from the few studies available, that the right ventricle truly fails in cor pulmonale even when there is right ventricular enlargement or oedema (49, 113, 276). From the few studies of patients with cor pulmonale who have oedema, there is circumstantial evidence from right ventricular pressure measurements and cardiac output, that the right ventricle, with its smaller muscle mass, adapts to a high pulmonary vascular resistance by increasing its fibre length (increased diastolic volume) at the expense of a rise in end-diastolic pressure as would be predicted from Starling `s law of the heart (175). Clearly it is important to differentiate the failure of the ventricle to perform as a pump, from the failure of the heart muscle to perform as contractile tissue. It is possible that the right heart, faced with an excessive volume load or pressure load in `cor pulmonale' may be failing in a clinical sense, yet the contractility of right ventricular muscle is well maintained, however, its efforts are wasted by the excessive tension requirements of the ventricle as a whole. Thus a clearer understanding of right ventricular performance in patients with cor pulmonale would be important in determining rational treatment for this condition. The major purpose of this thesis is therefore to explore in more detail the right ventricular performance in patients with chronic bronchitis and emphysema.

RADIONUCLIDE ASSESSMENT OF VENTRICULAR FUNCTION

INTRODUCTION

Until recently ventricular performance could only be accurately assessed by cardiac catheterisation and contrast ventriculography. Although right heart catheterisation probably involves less risk of complications than the arterial puncture required for left heart catheterisation, complications occur overall , in one quarter of cases, but are serious in only 4% (42). The injection of hypertonic contrast media is also not without risk and, because of the marked variability of the normal right ventricular shape and configuration (83), quantitative measurements of right ventricular volumes and of right ventricular ejection fractions using contrast ventriculography, are extremely difficult to obtain. This invasive technique is therefore less suitable when repeated measurements are required to study the effects of therapeutic interventions, or to study ventricular function in large populations. Many other methods have been used to assess right ventricular performance, in particular to detect right ventricular enlargement, which is a prerequisite for the diagnosis of cor pulmonale. These include ECG/vectorcardiography (237), echocardiography (7) and thallium myocardial scintigraphy (182). No one method has been shown to predict right ventricular hypertrophy reliably. Measurements of right ventricular function, from M-mode or two dimensional echocardiography are also limited, due to the difficulty in obtaining satisfactory images, particularly in patients with chronic bronchitis and emphysema (352).

Radionuclide ventriculography has proved to be an accurate,

global, and regional function (318). However, its use in assessing right ventricular function, particularly in patients with chronic bronchitis and emphysema, has not been fully defined.

Historical background

Following the discovery of radioactive isotopes by Becquerel, in 1896, radioactive materials were first used in assessing cardiovascular performance by Blumgart and Weiss (1927) (36). They used radium 226 to generate radon gas and subsequently its decay product radium C, which they injected intravenously , as an aqueous solution. Using a cloud chamber to detect activity, they were able to measure trans-pulmonary transit time as a measure of pulmonary blood volume. Twenty years later, using an artificial isotope (sodium 24) and more sophisticated radio-sensitive detectors, in the form of a Geiger counter, Prinzmetal was able to record right and left ventricular volume curves during the first transit of a radioactive isotope through the right and left ventricles - the so called first pass technique (265). The generation of time activity curves from the ventricles using this first pass technique was then used in the late 1950`s to estimate cardiac output and pulmonary transit time (205) derived from the principle of radiodilution based on the Stewart-Hamilton equation (136, 315). Using rectilinear scanners static images of the heart could be obtained, but with the later development of the modern scintillation gamma camera and the development of tracers labelled with radionuclides, dynamic images of the heart were possible.

Three elements are required for radionuclide ventriculography: (1) a radioactive tracer, (2) a gamma camera, (3) a system for handling and

Radioactive tracers

The availability of radioactive substances for use as tracers was initially restricted to radium and its products. Blumgart and Weiss (36) initially used the ionic form of radium C or bismuth 214 which, although it has a short half life of 20 minutes, emits alpha, beta and gamma rays which result in a substantial radiation burden to the patient. Modern radionuclides, in contrast, emit only gamma photons or x-rays of sufficient energy to pass through the overlying tissues and thus be detected, without themselves producing substantial accompanying radiation, which is produced as a result of deposition of some of the photon energy in the tissues through which it traverses. Moreover, the half life of a radionuclide should be sufficiently long to allow measurements to be repeated over a period of hours but not long enough to produce an excessive radiation burden to the patient. In radionuclide ventriculography the radionuclide should be distributed and equilibrate in the blood pool, and must therefore be bound to a vector which determines its bio-distribution - the radionuclide and the vector together constituting a radiotracer.

The radioisotope which has the most suitable physical properties for use in nuclear cardiology is technetium^{99m}. It was originally made in 1937 by bombarding its parent element Molybdenum with neutrons in a cyclotron (260) and was, in fact, the first artifically produced element. Later, in the 1960's, a practical generator system became available to separate technetium^{99m} from Molybdenum^{99m} (275). Technetium^{99m} has a half life of 6 hours. During its decay it emits a single photon of 140 KeV. Where repeated studies are required it

vitro) or, more easily, to albumin, using a kit preparation (139). The tracer Tch^{99m} labelled human serum albumin (HSA) can therefore be injected as a bolus intravenously and data can be acquired during the 'first pass' of radioactivity through the cardiac chambers, stopping the acquisition of data before the radioactivity reaches the lung fields. Alternatively, after a suitable time the radiopharamaceutical (radiotracer) mixes evenly within the blood pool (equilibration) and thereafter the acquisition of data can be commenced, and repeated if required, with adequate radioactive counts obtainable over approximately 3 hours. The radiation dose delivered to a subject, after an injection of Tch^{99m} HSA has been estimated to be 16 mRADS/mCi injected (1mCi = 37 MBq). If on average for a radionuclide ventriculogram one injects 20-30 mCi then the radiation dose is 320-480 mRADs (30).

The gamma camera

In order to measure cardiac function the radiotracer must be distributed in the heart in proportion to the function under investigation. Thereafter the nucleus of the radionuclide must rearrange itself to a more stable state by emitting a photon with sufficient energy to traverse the chest wall. The path of this photon must allow it to pass through a hole in the collimator, attached to the face of the camera and finally the photon must interact in a radiation detector to produce a signal, which permits localisation of this interaction.

The scintillation camera is the standard device in nuclear medicine for imaging the heart. This instrument is equally sensitive to radiation across its field of view, and is capable of localising the

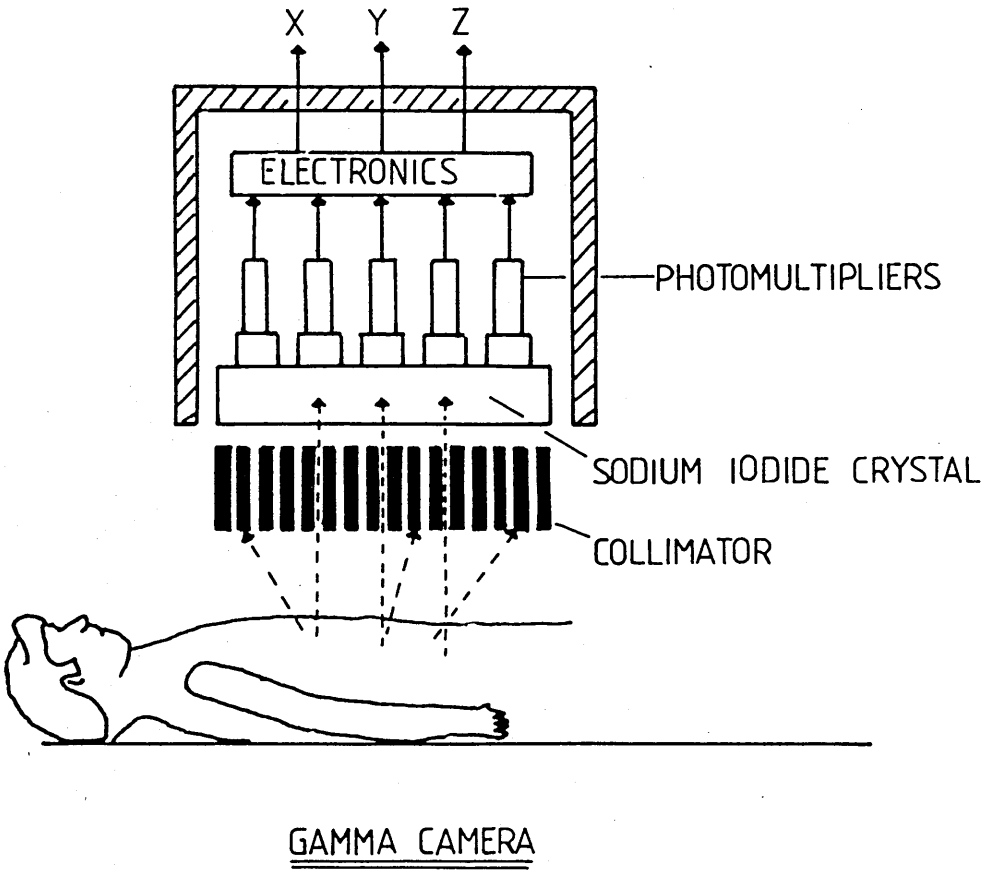


Figure 5 Schematic diagram of a gamma camera

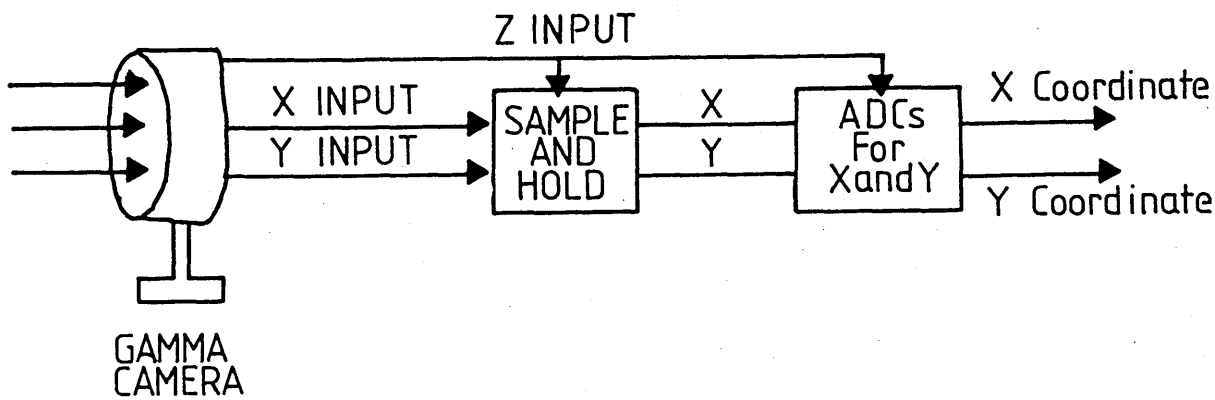


Figure 6 Diagramatic representation of the gamma camera/computer interface. ADCs = analogue to digital converters.

crystal of the detector. Two common scintillation devices are in use:

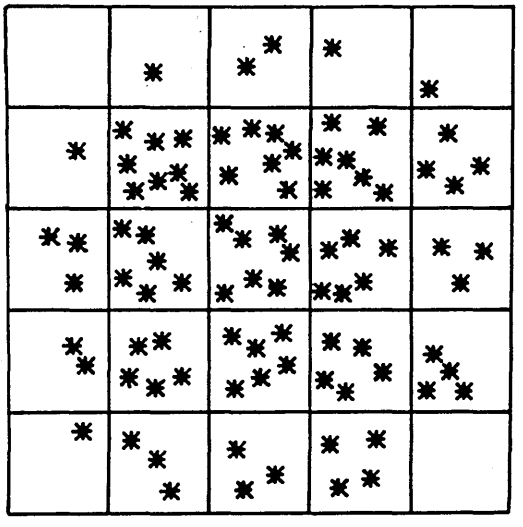
The single crystal camera (figure 5)

The interaction of a gamma photon on a sodium iodide crystal produces a flash of light (scintillation). The scintillation is brightest at the site of the interaction but light is also propagated throughout the crystal. A number of photo multiplier tubes are used to view the crystal and each detects a fraction of the light output from the scintillation. The gamma interaction can be localised by comparing the intensity of light observed by each tube (9).

The multicrystal camera

This device uses an array of discrete sodium iodide crystals which are viewed by a number of photomultiplier tubes. This arrangement allows a higher speed of processing and a higher count rate than the single crystal camera. However, the single crystal camera has a higher resolution than the multicrystal camera.

The addition of a lead collimator (figure 5) in front of the camera assembly results in gamma photons, other than those which are emitted parallel to the axis of the collimator holes, to be screened out, thus producing a one to one correspondence between the point of emission from the patient and the image. The X and Y position of light flashes detected by the camera crystal are indicated by the output X and Y (figure 6) and are used to control the horizontal and vertical deflection amplifiers of a cathode ray oscilliscope. When a light flash falls within the appropriate energy range, the signal Z is generated. The outputs from the camera are then fed into an



A

0	1	2	1	1
1	8	7	8	4
3	6	7	6	3
2	5	6	5	4
1	3	3	4	0

B

Figure 7 Creation of a digital image (B) from the scintillations produced as gamma photons strike the crystal (A).

system. When the signal Z is detected, the outputs of the X and Y signals are sampled, held at a constant voltage, and converted to a digital representation. Thus events which are within the desired energy window can be converted by the ADC's to digital form and can be processed by the computer.

The coordinates of the gamma photon scintillation on the camera crystal are processed according to the mode of acquisition, either frame mode or list mode. Frame mode is the more common form of acquisition and is simply a process of creation of a digital image as the counts strike the face of the crystal. This process can be illustrated by considering the face of the camera as if partitioned by a wire mesh (figure 7). The number of scintillations produced as gamma photons strike the crystal (A), within each square, will have the corresponding digital value (B). In practice, the camera field is divided into finer partitions using larger matrix sizes and thus the net effect is to produce a small light dot on the cathode ray tube for each gamma ray detected, in the same relative position as it occurred within the subject.

In contrast, list mode acquisition results in transfer of the X and Y coordinates of the scintillation directly on to the computer memory without initially producing an image. The data can thereafter be converted into a digital matrix after the acquisition has been completed. The advantage of frame mode acquisition is that the images are available immediately after acquisition and therefore less computer time and storage space are required (15).

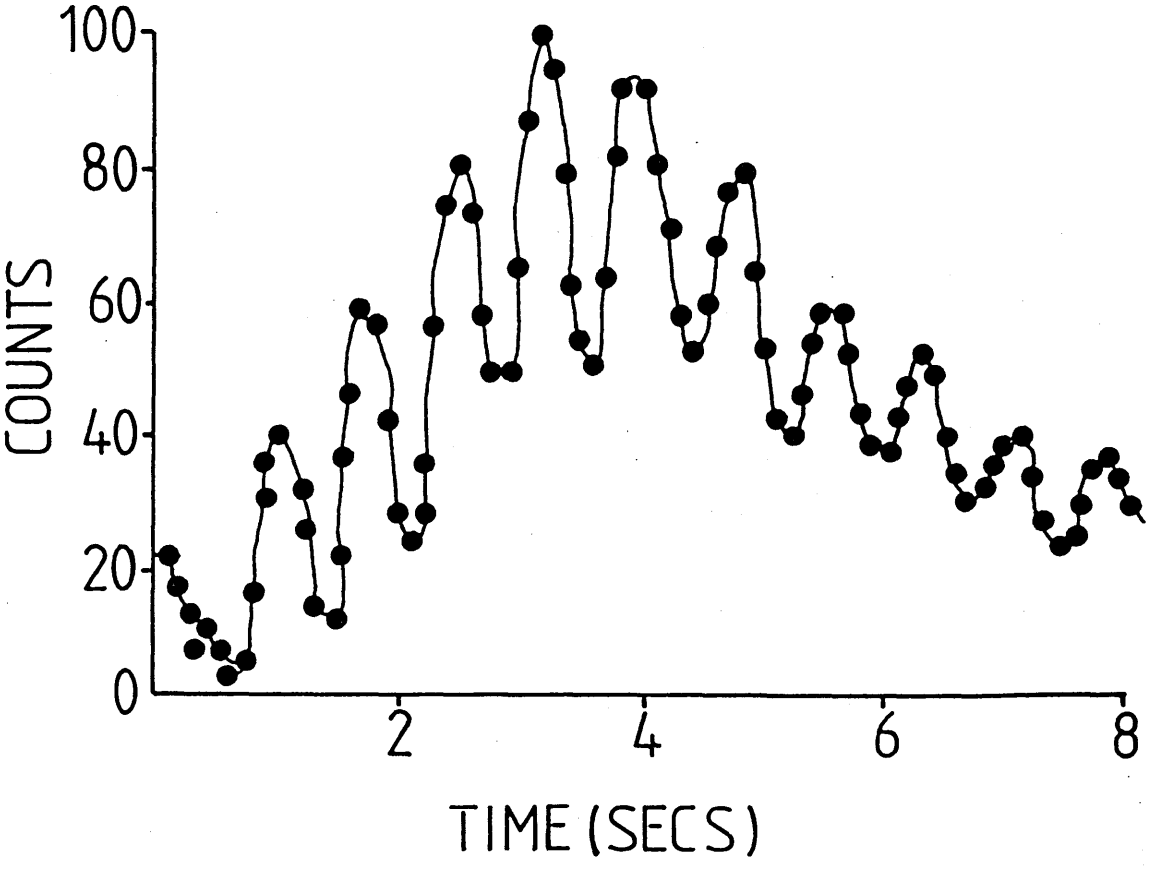


Figure 8 Time activity curve from a region of interest around the left ventricle during the first passage of a radionuclide bolus through the left ventricle. The systolic troughs and diastolic peaks of radioactivity are shown.

The first pass method

In cardiovascular nuclear imaging several heart beats will be needed before sufficient photons have been accumulated in the camera and computer to accurately assess cardiac function. The measurement of ejection fraction by radionuclide techniques originates from the work of Kriss et al in 1966 (190), who first used a gamma camera connected to a digital computer to visualise the initial passage or `first pass' of radionuclide labelled-tracers through the central circulation and were able to photograph the events. Later Van Dyke and colleagues were the first to quantify left ventricular function using the first pass technique (338). Accurate measurements of left ventricular ejection fraction, during the first passage of a peripheral intravenous injection of a radionuclide bolus, were made by frequent sampling of the fluctuations in activity during several cardiac cycles. Time activity curves, with high temporal resolution, can thus be generated from the left ventricle made up of a series of oscillations, the peaks and troughs of activity corresponding to the end-systolic (ES) and end-diastolic (ED) activity respectively (figure 8). The difference between the ED and ES activity corresponds to the stroke volume. Measurement of left ventricular ejection fraction from an analysis of these time activity curves, generated from the first pass technique, have been shown to correlate well with measurements made by biplane contrast angiography (295).

Background activity

In the analysis of left ventricular ejection fraction by the first pass technique, an appropriate correction must be made for background

In order to correct for the background contributions to the ventricular time activity curve, two regions of interest (ROI) should be drawn; the first around the left ventricle and the second to account for the background counts. The best area for background correction has been found empirically to be a horseshoe area around the lateral and inferior borders of the left ventricular ROI. Thus two simultaneous time activity curves can be generated from these two regions. The activity curve from the background region can then be digitally smoothed to minimise statistical noise. Thereafter the contribution of background radioactive counts to the left ventricular ROI can be calculated by multiplying the background radioactivity by the ratio of the ventricular to background areas to 'normalise' to an area equal to that of the ventricular area. Since the radioactivity from each selected area is proportional to the ventricular volume, the average systolic and diastolic volumes for the three beats at the peak of the radioactive dilution curve (figure 8) (if there is adequate mixing) can be used to calculate the ejection fraction (EF):

$$EF = \frac{\text{End-systolic counts} - \text{end-systolic counts}}{\text{End-diastolic counts} - \text{background counts}}$$

An accurate assessment of background activity is therefore essential to avoid under-estimation of the ejection fraction (245).

The first pass method has several advantages. It allows both temporal and spacial separation between the right and left ventricles (267). This is particularly important in accurately determining the

acquisition time is required (20-30 seconds). When studying the right ventricle in isolation the acquisition of data can be stopped before the bolus of radiotracer enters the lungs, thus reducing the background counts.

However, there are certain disadvantages of the first pass technique. Only a single measurement of ejection fraction can be made following each injection of radiotracer. Repeated injections must therefore be limited to two or three in the same day because of the cumulative radiation burden. Thus haemodynamic changes following therapeutic interventions are difficult to study using this technique. Before the injection of the radionuclide bolus the camera must be in a good position to record the events during the first passage of radioactivity, since it is impossible to readjust the position of the gamma camera during the course of the examination. It is also important to obtain a good bolus of radiotracer, in order to achieve acceptable radioactive counts and this may be difficult in, for example, severe pulmonary hypertension or severe tricuspid regurgitation. The assumption that radioactive counts are proportional to volume demands that there is adequate mixing of the radiotracer in the blood within the cardiac chamber (88). Even with an adequate bolus injection, count rate limitations make the first pass technique less suited to conventional gamma cameras and a multicrystal scintillation camera with high count rate capabilities is often required to obtain statistically reliable data (23).

Despite these limitations, quantitative first pass radionuclide ventriculography has become a useful technique for non-invasive assessment of left ventricular performance in man (245). Until

assessment of right ventricular performance using radionuclides. Several authors have now also published results of measurement of right ventricular ejection fraction using the first pass technique in patients with chronic bronchitis and emphysema (23, 24, 307, 309, 364). Angiographic determinations of right ventricular volumes are difficult, and may be unreliable (126). However, correlation between right ventricular ejection fraction measured by first pass radionuclide and contrast angiography has been made in one previous study of patients with ischaemic heart disease (312).

Gated cardiac studies

Strauss et al (317) first described a technique which allowed serial evaluation of left ventricular performance. This technique uses electrocardiographic gating mechanisms to trigger repeated acquisition of data at end-systole and end-diastole after the injection of a radiotracer has completely equilibrated in the blood pool. Radioactive counts from 200-500 heart beats can be summated permitting ejection fraction to be measured. Thus following a bolus injection of radiotracer, measurements of ejection fraction can be made during the first passage of radioactivity, and thereafter the radiotracer can be allowed to equilibrate for a gated equilibrium blood pool study. The electrocardiogram lead with the most prominent R and T waves is usually most suitable for gating. The technique of gating involves an electronic switch which determines the interval during which the events are recorded by the scintillation camera. The onset of the recording period is fixed by a delay control which regulates the time between the triggering signal (R wave) and the opening of the electronic 'gate'. The time thereafter during which an image is recorded is determined by a

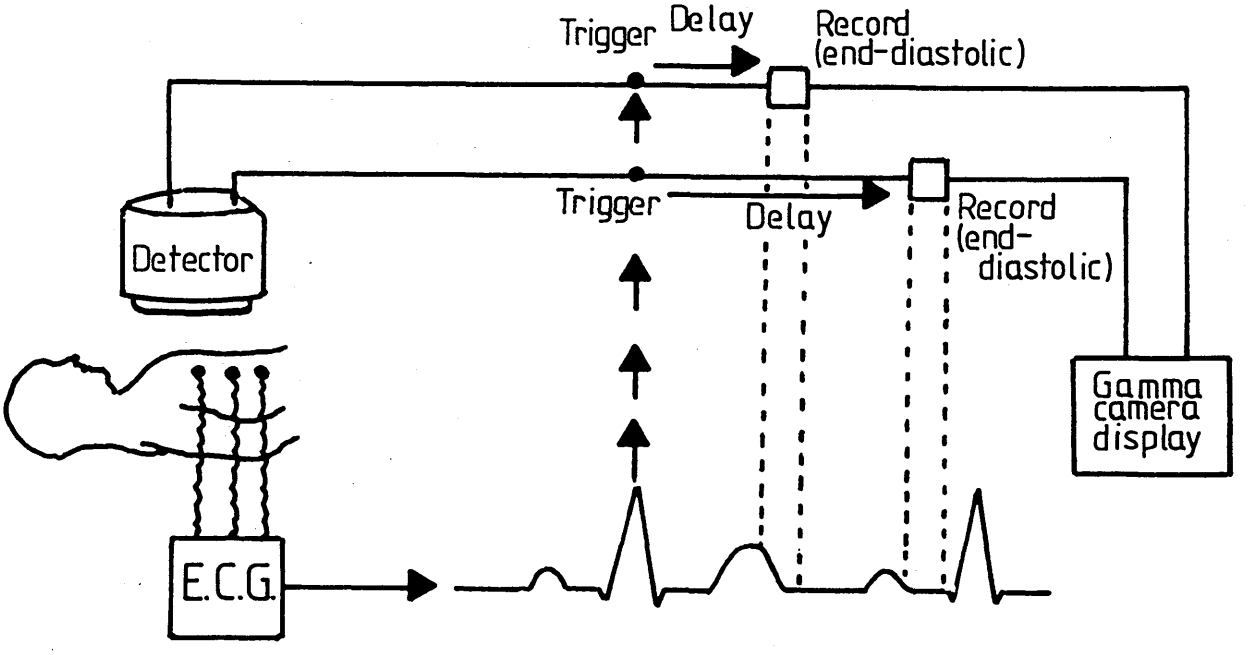


Figure 9 Diagramatic representation of the electrocardiographic gating system of the gamma camera. The R wave of the electrocardiogram triggers the gating circuit, which is followed by a delay interval. After this interval the gate is opened and the gamma camera accepts data during the record interval. Data is thus acquired and accumulated during a record interval at end-diastole and end-systole (after Strauss et al 1971 [317]).

viz the last 40 milliseconds after the R wave and during the 60 milliseconds before the next R wave, counts can be accumulated over 200-500 beats and an image of the mean appearance of the heart at both end-systole and end-diastole can be achieved (figure 9) (317). The data can then be stored on magnetic disc or tape for subsequent analysis of end-diastolic and end-systolic left ventricular volumes calculated from long axis and area measurements with subsequent calculation of left ventricular ejection fraction.

Multiple gated acquisition

By gating picture frame images from short time intervals distributed throughout the cardiac cycle (multiple gated acquisition), images can be summated from 500 sequential heart beats and viewed in a movie format (245). The gated image is created by recording the X and Y coordinates of all the gamma photon scintillations occurring in each 20 millisecond interval after the R wave marker. All the scintillation data from 500 heart beats are then sorted and accumulated into the appropriate 20 millisecond frames, resulting in a ventricular curve with its temporal relationship to the electrocardiogram (figure 10). The first 20 millisecond accumulation of data, triggered by the upstroke of the R wave, thus produces the first frame which represents end-diastole. Since radioactive counts are proportional to volume (if complete mixing of the radiotracer has occurred in the blood pool), the ejection fraction can be calculated, after suitable correction for non-cardiac background activity. Empirically, for the left ventricle when the gamma camera is placed in the normal 30^{o} left anterior oblique position for imaging, a background area is chosen from the inferolateral wall of the left ventricular outline (figure 10) the

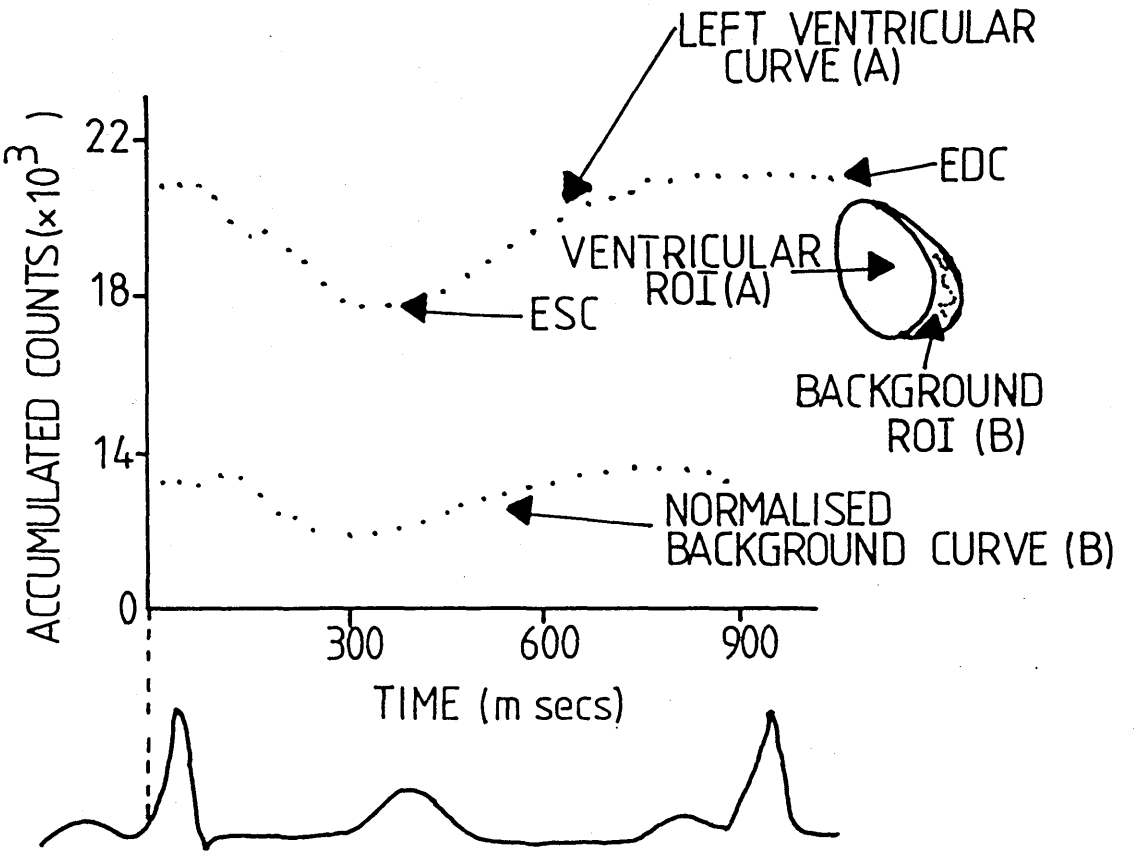


Figure 10 Cumulative time activity curves from the left ventricular (A) and background regions of interest (ROI). Since radioactive counts are proportional to volume, the ejection fraction is the difference between the end-diastolic (EDC) and end-systolic counts (ESC) divided by the EDC minus the normalised background counts.

technique, normalised to an area equal to that of the left ventricle (245).

This technique has several advantages:

1. Most gamma cameras single or multiple crystal can be used for this method with minimal additional instrumentation.
2. Repeated studies can be performed with ease and with no further radiation burden. The camera can be adjusted between periods of data acquisition and thus the effects of therapeutic interventions can be easily studied.
3. Multiple scans can be recorded over 3 hours without loss of tracer into the intra-vascular space, provided a high quality electrolytically labelled human serum albumin is used.
4. Since data is acquired over numerous beats the radioactive count statistics are more reliable than with the first pass technique.
5. A bolus injection is unnecessary.

The disadvantages are:

1. The routine position for imaging - the left anterior oblique position - may not produce adequate separation between the right and left ventricles.
2. This technique produces best results where the cardiac rhythm is regular, although it is possible to utilise computer programmes to eliminate data collected from ectopic beats.
3. The relatively lengthy acquisition time may result in problems of haemodynamic stability, particularly in obtaining adequate data during maximal exercise.

Left ventricular performance

The measurement of left ventricular ejection fraction from either first pass or gated equilibrium radionuclide ventriculography, is now standard in all nuclear medicine departments. As discussed previously, several studies have confirmed a good correlation between left ventricular ejection fraction (LVEF), measured by contrast or radionuclide ventriculography and this has been confirmed in our own laboratory (245). There is also a good correlation between the first pass and equilibrium techniques both at rest and on exercise and both techniques have a variability of only 4% when measured on separate occasions (216).

Right ventricular performance

As discussed previously the use of contrast angiography to visualise the right ventricle and measure its volume is difficult and tedious because of the wide variability of the right ventricular geometry (10, 126, 268). Radionuclide ventriculography to some extent avoids this problem, particularly when the first pass technique is used since measurement of right ventricular ejection fraction (RVEF) can be made from the time activity curve, and therefore variations in the geometric configuration of the ventricle become less important. Most previous studies of right ventricular performance have used the first pass, rather than the gated equilibrium technique, which appeared more suitable for studying right ventricular function. Both techniques have advantages and disadvantages. The principal disadvantage of the first pass technique, namely the difficulty in performing repeated measurements and the short acquisition time, results in low counts and statistical uncertainty in the calculation

attractive. As discussed in the preceding section, the equilibrium technique is the standard method of measurement of left ventricular ejection fraction, but until recently it has not been used to measure right ventricular performance because of a number of problems.

The first pass technique uses a right anterior oblique projection to separate the right atrium from the right ventricle (23) and counts from the overlapping left ventricle can be prevented by detecting the bolus of radiotracer only as it passes through the right side of the heart, stopping the acquisition before it reaches the left ventricle. Whereas, to separate the right and left ventricles with the equilibrium method, a left anterior oblique projection must be used. Until recently it was thought that this projection could not be used for the determination of RVEF because of the contribution of the right atrium. Recently, Maddahi and colleagues (209) suggested that this difficulty could be overcome by assigning separate regions of interest to the right ventricle at end-diastole and end-systole. However, in this study of normal subjects and patients with ischaemic heart disease, in whom the majority had normal RVEF, the authors admitted that in its present form the technique was subjective, and required a considerable experience for accurate assignment of a right ventricular region of interest. However, for the purpose of this thesis the equilibrium technique was deemed to be more suitable because of the ability to repeat measurements in intervention studies. To achieve an accurate and reproducible method of measuring RVEF by the gated equilibrium technique, particularly in patients with chronic bronchitis and emphysema, there appeared to be several major problems:

1. The right ventricle has an extremely irregular shape that varies from patient to patient, making the assignment of an accurate right ventricular region of interest more difficult.
2. The contribution from the right atrium to the counts in the right ventricular region of interest will vary depending on the atrial size.
3. A deformed or poorly contracting right ventricle may worsen the separation between the right and left ventricles.
4. The contribution from background counts is higher with the equilibrium than with the first pass technique, and comes from all of the structures around the right ventricle. The most suitable site for a background correction remained uncertain.

A standardised and reproducible technique for assessing right ventricular performance, both in normal subjects and in patients had therefore to be developed before applying this technique to populations of patients or using it in intervention studies.

RIGHT VENTRICULAR PERFORMANCE ASSESSED BY FIRST PASS AND EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY

Patients

A comparison of measurements of right ventricular ejection fraction (RVEF) by both first pass and gated equilibrium methods was made in 43 patients (364). Eleven of these patients had atypical chest pain and had a normal left ventricular ejection fraction both at rest and on exercise. Their subsequent follow up suggested that their chest pain was musculoskeletal in origin and because of this they were, for the purpose of this study, deemed to be normal subjects. Fifteen patients had ischaemic heart disease documented by history and/or electrocardiographic findings. Seven of these patients had evidence of previous myocardial infarction. The remaining 17 patients had chronic bronchitis and emphysema with severe airflow limitation (FEV_1 0.70 $\pm$ SD 0.32 l, FVC 2.35 $\pm$ 0.70 l). These different groups of patients were chosen so that a wide range of values of both RVEF and LVEF could be measured.

Radionuclide methods

The patients lay supine beneath a Searle LEM gamma camera equipped with a high sensitivity parallel-hole collimator (figure 11). An intravenous infusion of 5% dextrose was given via a large peripheral vein. Through the IV line a bolus injection of 740 MBq (20 mCi) of technetium^{99m} labelled human serum albumin (HSA) was given rapidly, followed by a bolus of 5% dextrose squeezed from the reservoir of the IV giving set. This technique was used to obtain an adequate bolus injection. The gamma camera was positioned in a 10^{o} right anterior

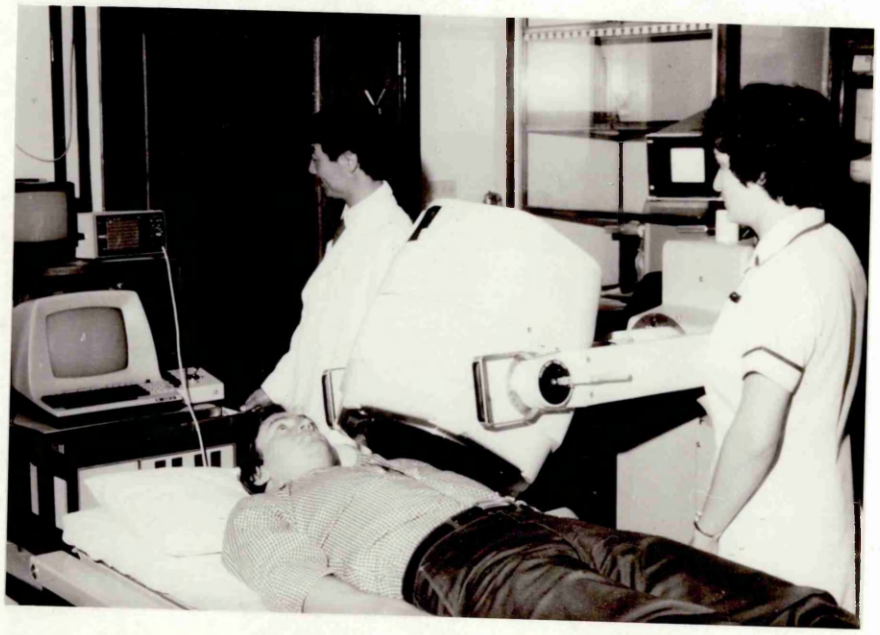


Figure 11 Patient lying supine beneath the gamma camera positioned in the 30^{o} left anterior oblique position.

images were gated from the R wave of the patient's electrocardiogram, and collected in frame mode on a Cromemco (System 3) microcomputer. For the first pass technique data acquisition was started immediately after the bolus was injected and terminated once the activity, viewed on the gamma camera's persistence monitor, was seen to be in the lungs. Thus the first pass technique was modified to include a gated system and in this way approximately 10 cardiac cycles were recorded (205).

For a period of 5 minutes following the bolus injection, the radiotracer was allowed to equilibrate in the blood pool. The position of the gamma camera was then changed to a 20 - 30^{o} left anterior oblique projection with a 20^{o} caudal tilt for the equilibrium study (figure 11). Gated images were then acquired from 500 sequential heart beats, as previously described, for the assessment of left and ventricular function (216, 245). Images from the composite cardiac cycle were then displayed from both first pass and equilibrium studies in 'movie' format on a TV monitor.

Analysis of right ventricular ejection fraction

First pass study

From the movie image and the time activity curves from the right ventricular region of interest (ROI), the end-diastolic and end-systolic images were identified (figure 12). Using a light pen regions of interest were drawn around both of these images and the radioactive counts within these regions could be obtained. These end-diastolic and end-systolic counts were corrected for background counts by drawing separate background ROI's along the inferior margin of the right ventricular ROI at the appropriate phases of the cardiac

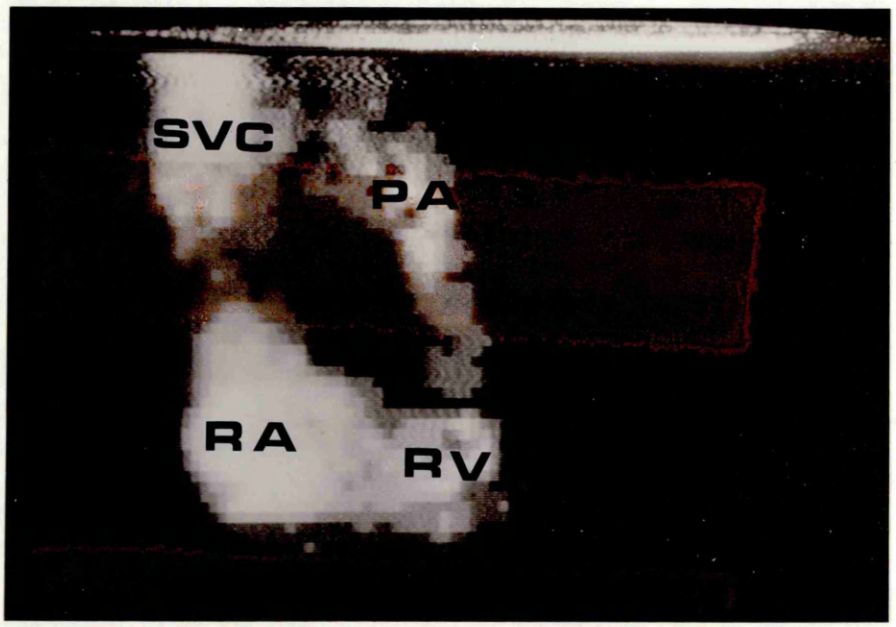


Figure 12 The end-systolic frame of a first pass radionuclide ventriculogram. Data acquired in the right anterior oblique position.
RA = right atrium, RV = right ventricle, SVC = superior vena cava, PA = pulmonary artery.

cycle, and scaling the counts obtained within these background ROI's to an area equal to that of the corresponding right ventricular region (205). RVEF was calculated from the equation:

$$RVEF = \frac{EDC - ESC}{EDC}$$

where EDC and ESC are background corrected counts at end-diastole and end-systole respectively.

Equilibrium study

Minor adjustments of the position of the gamma camera were required in each individual patient to obtain good separation between the right and left ventricles and this could be done by assessing the image produced on the persistence monitor of the gamma camera. With experience less than 2% of all studies could not be analysed satisfactorily because of the overlap of the cardiac chambers, which persisted despite repeated adjustments of the projection of the gamma camera. In the vast majority of cases therefore, inspection of the movie image demonstrated good separation between the right and left ventricles (figure 13). However, during ventricular systole the right atrium enroached on the right ventricular end-diastolic ROI. Thus the use of a fixed ROI, as previously described in the analysis of LVEF would be inappropriate since a contribution from the right atrium, which would be variable depending on its size, would result in a significant underestimation of the RVEF. It will be apreciated that accurate edge detection is essential in obtaining an accurate ventricular ROI. In radio-isotope studies the presence of isotope in cardiac and non-cardiac structures, which may overlap the ventricular ROI may interfere with edge detection, particularly during the equilibrium technique where, in contrast to the first pass technique, there is no temporal separation of the isotope in the left

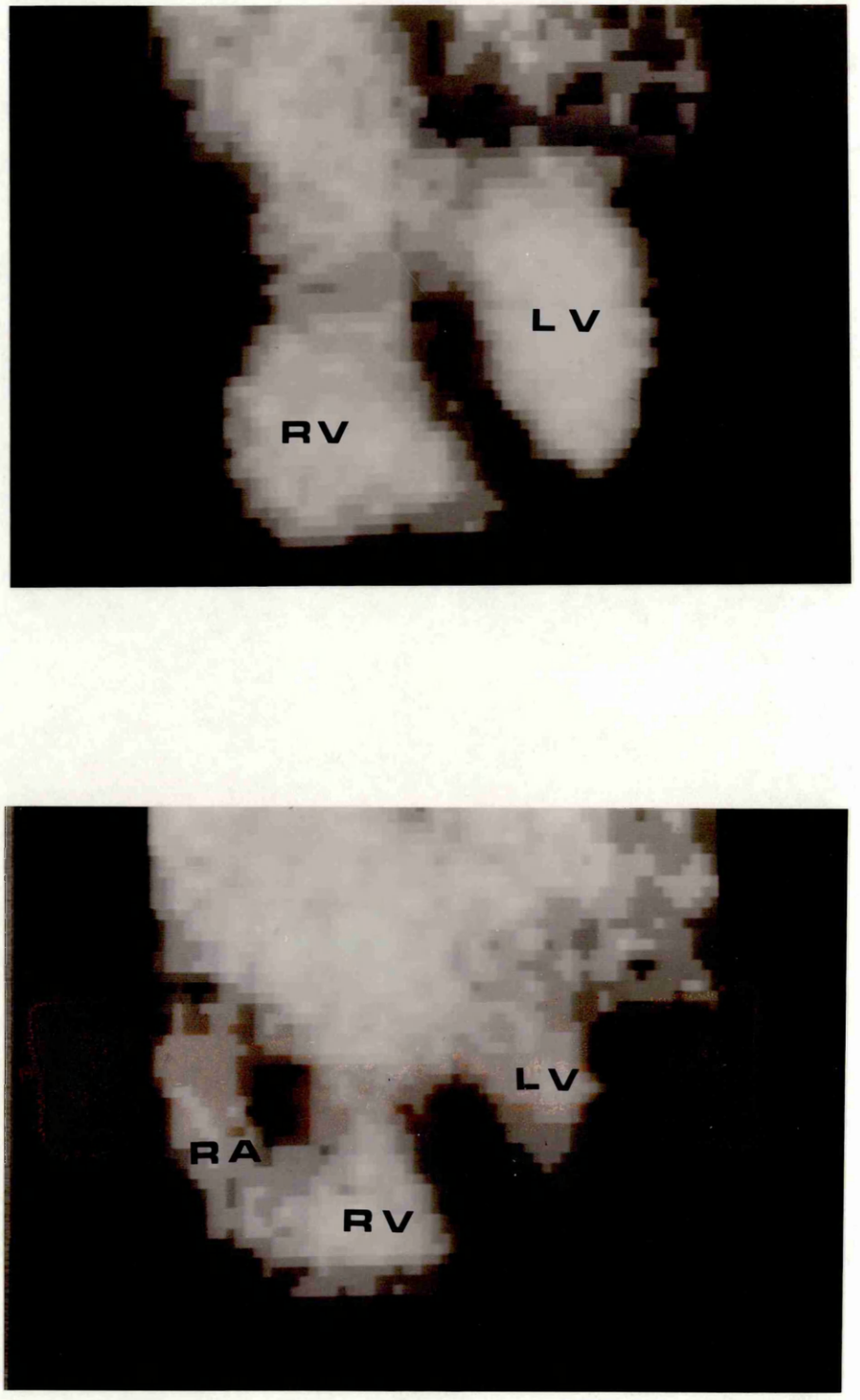


Figure 13 The end-diastolic (A) and end-systolic (B) frames of a gated equilibrium radionuclide ventriculogram. Data acquired in the 30° left anterior oblique position. The right and left ventricles are separated by the interventricular septum. The right atrium is also shown in the end-systolic frame (B).

and right ventricles. A form of threshold analysis is used in our laboratory to help to detect the ventricular edges, which places the ventricular edge where a specified change in counts occurs. In addition to careful positioning of the gamma camera, so as to achieve separation between the cardiac chambers, and inspection of the movie image, three specific computer programmes were used to assist in identifying the right ventricular end-diastolic and end-systolic images.

1. A movie sequence could be used which subtracted counts in frame n from frame n - 1 and so on throughout the cardiac cycle. This resulted in a movie image with maximum contrast between the ventricles and atria by identifying the different phases of emptying and filling of these chambers (78).
2. A further computer programme was used based on a Fourier transformation of the ventriculogram (83). This technique is particularly useful for delineating the right ventricular outflow tract, which was difficult to identify by any other method (figure 14).
3. A third programme was based on the logarithm of variance between each pixel and the surrounding pixels. This technique allowed identification of a count gradient for each image and is a form of edge detection analysis which enabled delineation of the ventricular outline at end-systole and end-diastole.

In order to identify the right ventricular outline, it was often necessary to use a combination of these computer methods in addition to observation of the movie image.

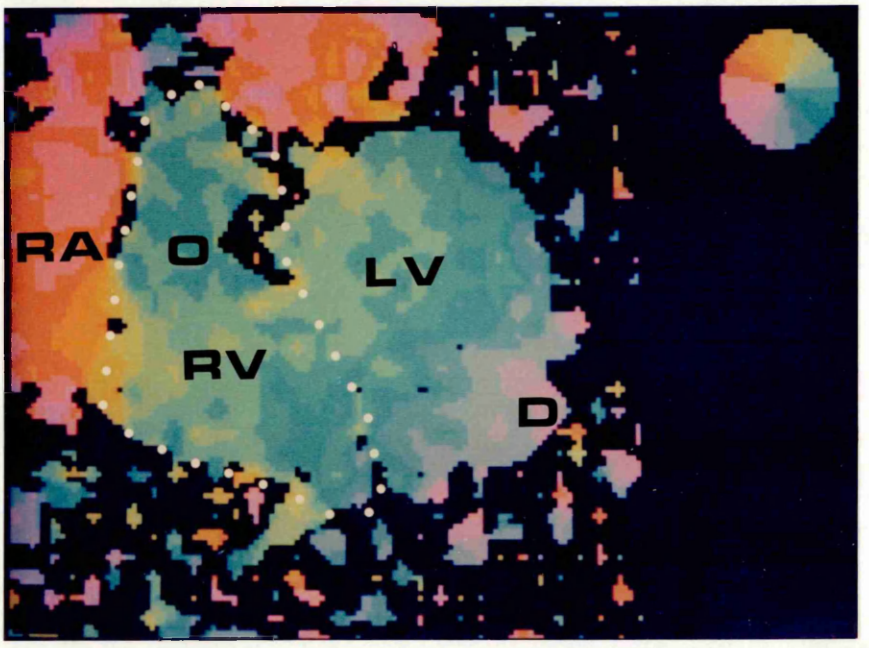


Figure 14 Phase image of a radionuclide ventriculogram. Regions of the image which are out of phase in the cardiac cycle are shown as opposing colours on the `colour clock'. Thus a contrast is achieved between the right atrium (RA) and the right ventricle (RV). A dyskinetic area (D) is also shown at the apex of the left ventricle (LV). This technique also allows delineation of the right ventricular outflow tract (O).

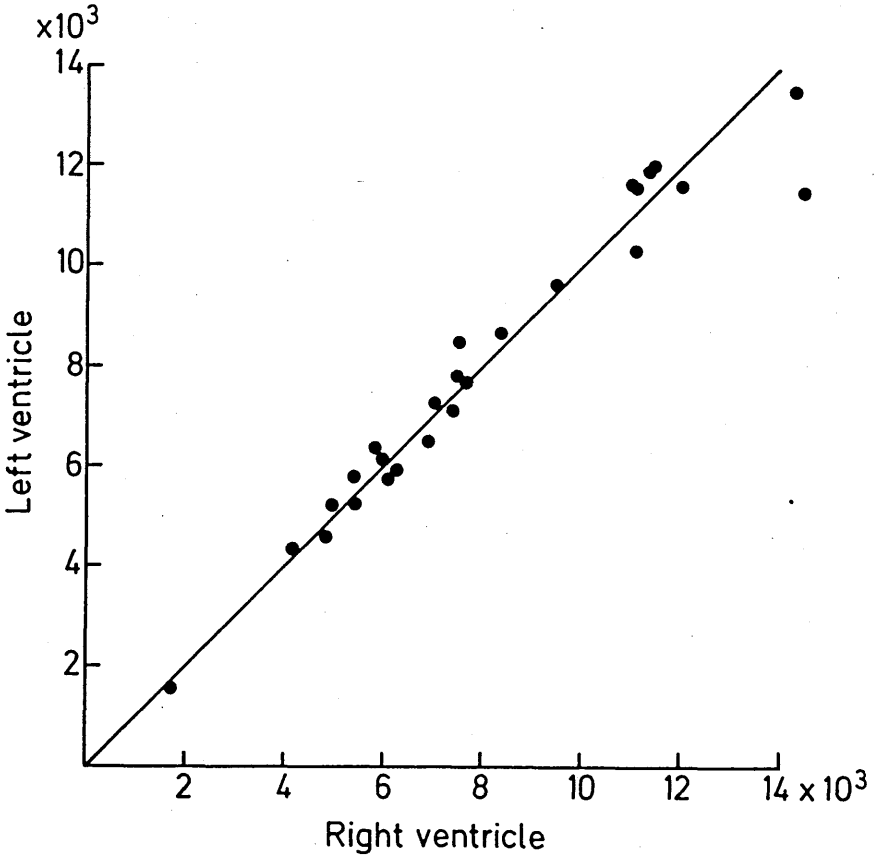


Figure 15 Comparison of the stroke counts for both ventricles when the background for the right ventricle was taken along the inferior paraventricular border of the right ventricle at end-diastole and end-systole. The line of identity is shown. The mean difference between the stroke counts from the two ventricles was 4.9%.

Background correction

The correction for background counts for the left ventricle has been derived empirically, but has been shown to produce calculated left ventricular ejection fractions which correlate with those measured by contrast angiography (242). Various areas around the right ventricular outline were chosen to identify a suitable region for background correction for the right ventricular counts. The stroke counts (EDC - ESC) should be the same for each ventricle. Thus, using the left ventricular stroke counts as a standard, the right ventricular stroke counts were calculated, corrected for the background counts obtained from various background areas. The best area for right ventricular background correction should produce equal stroke counts from both ventricles.

RESULTS

Background correction

Four possible background regions were compared in 20 patients: superior and inferior right and left paraventricular regions. The most consistent results were obtained when using a right paraventricular region along the inferior border of the right ventricular outline. By assigning separate background regions at end-diastole and end-systole in this area, then `normalising' the counts to the corresponding ventricular area, a background correction for the end-diastolic and end-systolic right ventricular counts could be obtained and could be substracted from the two different ventricular regions of interest. Thus the background corrected right ventricular stroke counts could be calculated and a comparison could be made with the corresponding left ventricular background corrected stroke counts. Using this inferior right paraventricular

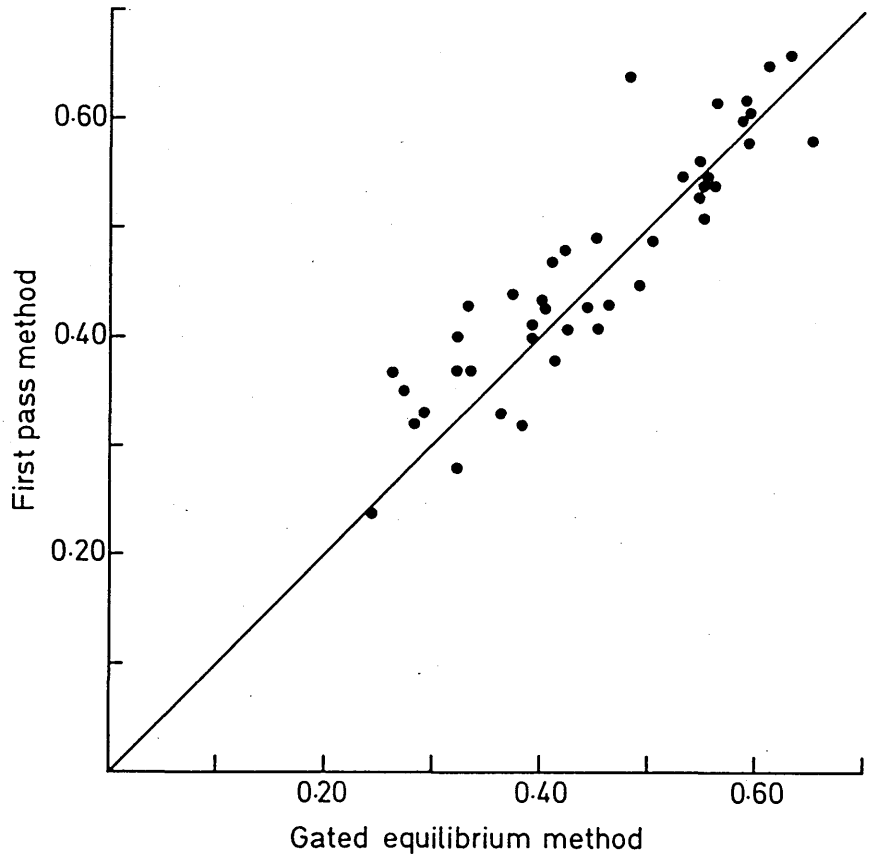


Figure 16 Comparison of the right ventricular ejection fraction (RVEF) by the first pass and equilibrium methods. The line of identity is shown. The mean difference in RVEF by the two methods was 0.04 ($n = 43$, $r = 0.91$, $p < 0.001$).

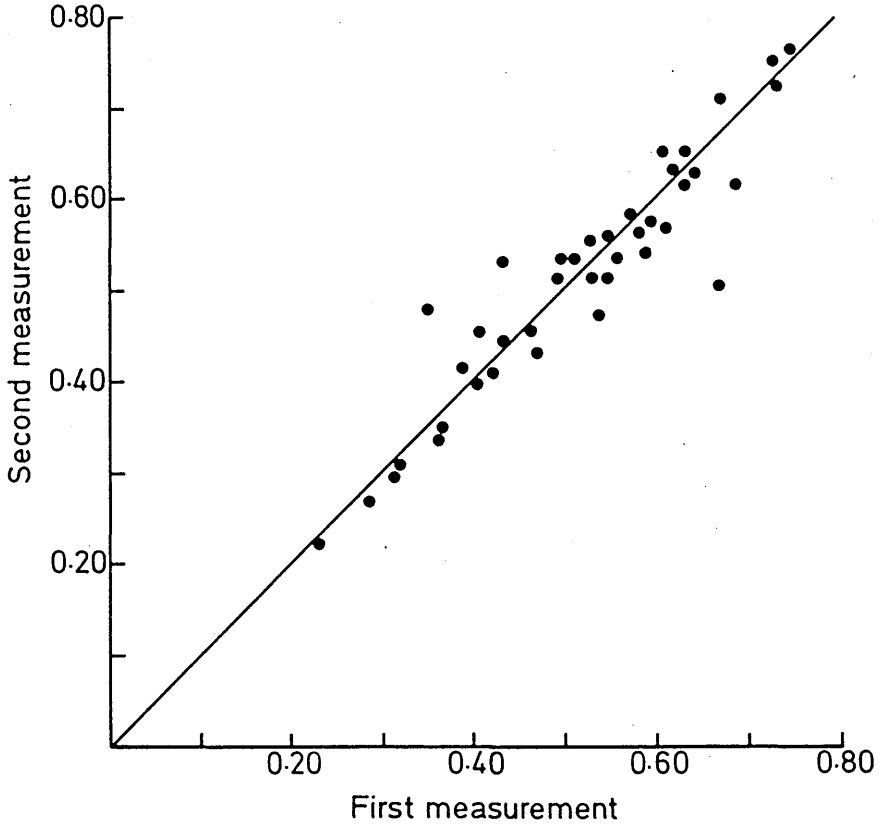


Figure 17 Repeat analysis of RVEF by the same observer in 40 equilibrium studies. The line of identity is shown. The mean intra-observer variation was 0.03.

area for background correction, the stroke counts from both ventricles were closely correlated (figure 15). The mean difference between the counts for the two ventricles in the 20 patients who were studied was only 4.9%.

Reproducibility

The values of RVEF measured by the first pass and equilibrium techniques were compared in 43 patients. An excellent correlation was achieved between the two methods ($r = 0.91$, $p < 0.001$) (figure 16). The mean difference in RVEF between the two methods was only 0.04.

To assess intra-observer variability 40 equilibrium studies were analysed on two separate occasions by the same observer. Intra-observer variation was only 0.03 (figure 17). Inter-observer variation was assessed by two observers who independently analysed 15 studies using the equilibrium technique. The inter-observer variation in RVEF was 0.04.

In 7 patients RVEF was measured using the equilibrium technique on two separate occasions 30 minutes apart, during which time the patient rested in a supine position. There was no significant difference in the mean between the two measurements (figure 18), the mean difference being only 0.02. The reproducibility of RVEF over a period of time was also assessed in one patient who lay at rest. RVEF remained unchanged when measured at 30 minute intervals over a period of two hours (figure 19).

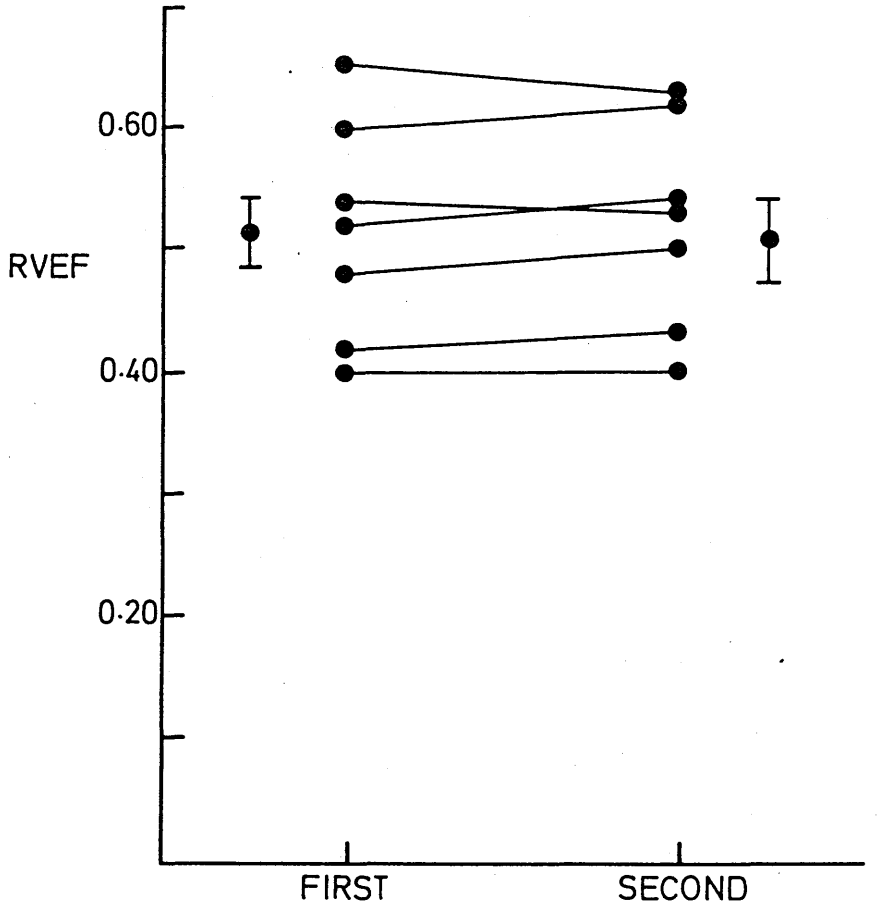


Figure 18 Repeat measurements of RVEF in 7 patients on two separate occasions 30 minutes apart. Mean values and standard errors are also shown. The mean difference between successive measurements was 0.02.

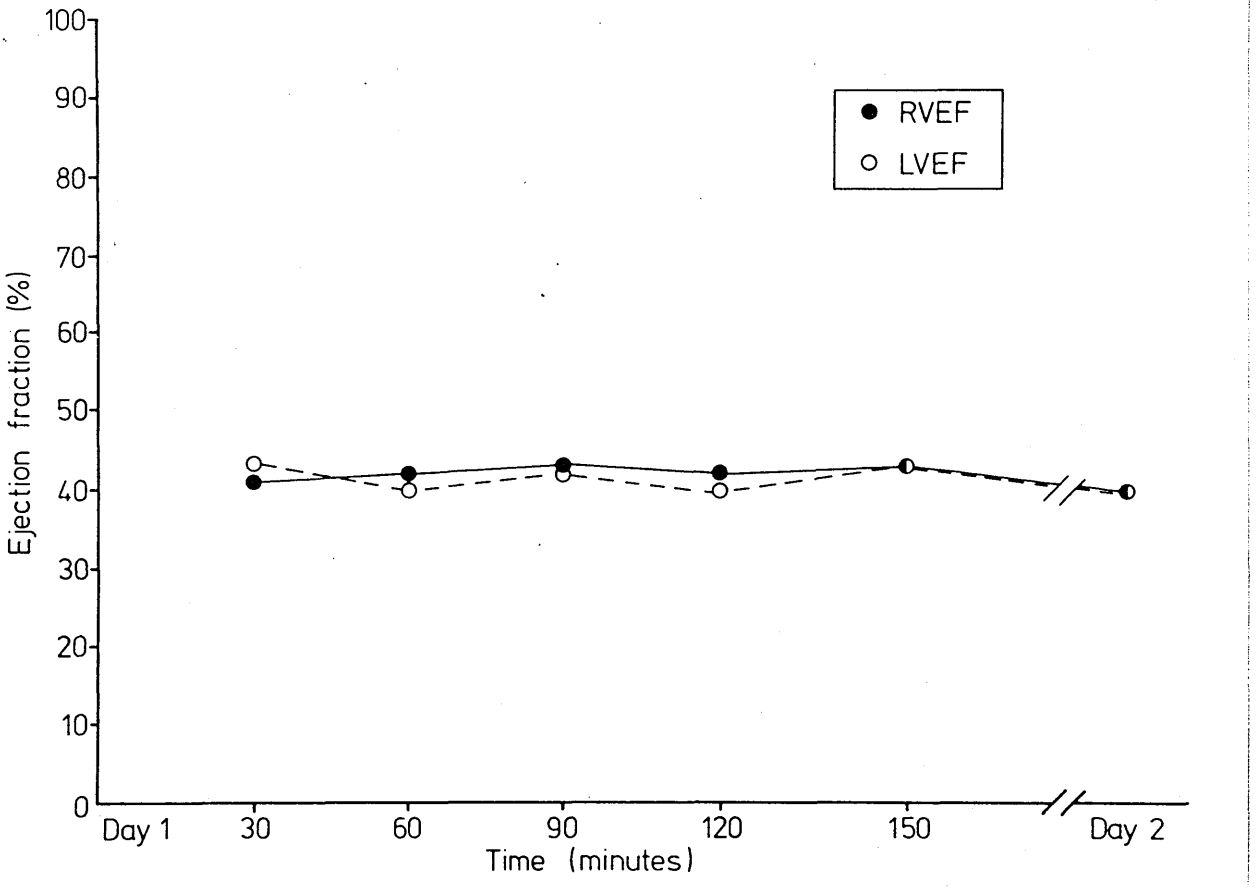


Figure 19 Repeat measurements of RVEF and LVEF in one subject at rest at 30 minute intervals over a period of two hours.

There are inherent difficulties in studying right ventricular function which must be considered.

The contraction of the right ventricle

Not only is the configuration of the right ventricle variable (287) but its contraction is complex and consists of three independent movements (287). Firstly, the trabeculae and papillary muscles displace the tricuspid valve downwards, towards the apex, which shortens the longitudinal axis of the chamber, but does not produce much effective ejection of blood. Secondly, the right ventricular free wall opposes the convex surface of the septum, producing the majority of the right ventricular ejection fraction. Thirdly, the circular fibres of the left ventricle contract and increase the curvature of the inter-ventricular septum. The mode of contraction of the right ventricle has been likened to a bellows. This complex action contrasts with the isometric, concentric contraction of the left ventricle. Thus although contrast angiographic studies have been performed in order to measure right ventricular volumes, the great variability in right ventricular shape and configuration has meant that no technique has found general acceptance (10, 100, 126, 268).

In all of these techniques, certain assumptions, to account for the three dimensional shape of the right ventricle, have to be made when measuring right ventricular volume. Although such measurements have been shown to correlate relatively well with the data derived from post mortem casts of the right ventricle, the reported normal ranges

of right ventricular volumes vary widely, and there have been no correlative studies in patients with cardiac or respiratory diseases (25). Radionuclide ventriculography has the advantage that since radioactive counts are proportional to volume, the right ventricular ejection fraction measured by this technique is independent of the right ventricular geometry. However, an appreciation of right ventricular contraction, as discussed above, must be considered when determining the limits of the right ventricular outline. Moreover, the variability in shape and more complex right ventricular contraction, make overlap of the cardiac chambers more likely, making the measurement of right ventricular ejection fraction by the equilibrium radionuclide technique more difficult.

Projection

In most patients, separation between the left and right ventricles can be achieved using a 20-30^{o} left anterior view. However, variable degrees of obliquity must be used in individual patients to obtain maximal separation of the ventricles (248). Failure to achieve separation between the ventricles makes accurate measurement of right ventricular ejection fraction impossible. With experience, however, this occurs infrequently.

The overlap between the right atrium and right ventricle presents a further problem in measuring right ventricular ejection fraction. As discussed previously, this can be solved by drawing two regions of interest around the right ventricle, the first at end-systole and the second at end-diastole. In addition, in a previous study (364), in order to check the effect of various projections on the degree of overlap between the ventricles and between the right atrium and right ventricle, a fixed human heart was filled with particles of an ion

exchange resin labelled with Tc^{99m}. The gamma camera was then placed in the right anterior, anterior; and 10^{o}, 20^{o}, 30^{o} and 40^{o} left anterior oblique projections. In each projection images were also obtained with the camera in a 10^{o}, 20^{o} and 30^{o} caudal tilt. The atrium was then filled with the Tc^{99m} labelled resin and the contribution of the right atrium to right ventricular counts was determined in the various projections. In this way the projection which produced the best separation between the ventricles was found to be a 20^{o} left anterior oblique projection with a 20^{o} caudal tilt. However, even in this projection the right atrial contribution to the right ventricular counts was around 30% and this may increase further in diseased hearts with right atrial enlargement. These results stress the importance of using two regions of interest in the calculation of right ventricular ejection fraction so as to eliminate the right atrial counts which encroach on the right ventricular region of interest during systole. As previously discussed, the use of phase image and edge detection techniques may be useful to obtain a more accurate estimation of the right ventricular outline, particularly the free right ventricular wall. The phase image is particularly useful in delineating the right ventricular outflow tract (figure 14) which has largely been ignored by other authors (156, 209, 239, 306). Thus a combination of techniques is necessary to obtain a reproducible right ventricular outline.

Background

As with the left ventricle, the area for background correction in the measurement of right ventricular ejection fraction has been chosen empirically. However, the validity of the chosen area for background correction was verified by the fact that the ratio between background corrected left and right ventricular stroke counts

approached unity.

I have not corroborated the values of RVEF measured by the equilibrium technique with measurements using contrast angiography because no standardised technique is available for the measurement of RVEF by contrast angiography. Quoted normal values for RVEF using contrast angiography have varied in the literature (10, 100, 126, 268). Gentzler et al (126) found a mean RVEF, using angiographic techniques, of 0.50 $\pm$ 0.16 in 8 normal subjects, whereas Ferlinz et al (100) quotes a mean RVEF of 0.66 $\pm$ 0.12 in 9 normal subjects. Only one study has correlated radionuclide scintigraphic measurements of RVEF with those obtained by contrast angiography (312). In this study the mean RVEF for 14 normal subjects was 0.57 $\pm$ 0.06, similar to the range of values obtained in this study. A good correlation was obtained between RVEF measured by contrast angiography and first pass radionuclide ventriculography (r = 0.80). No similar data has been published in patients with chronic bronchitis and emphysema.

Thus since there is no standard method of measuring right ventricular volumes by contrast angiography the results of measurements of right ventricular ejection fraction by the equilibrium radionuclide technique have been compared with those measured by the first pass technique and a good correlation between the two was achieved. Previous studies (156, 209, 239, 306, 360) have also shown good correlations between measurements of right ventricular ejection fraction made by first pass and equilibrium techniques.

Great variability exists in the literature concerning the methods used in calculating right ventricular ejection fraction by gated equilibrium radionuclide ventriculography (95, 151, 156, 187, 189,

193, 209, 239, 306, 310, 360). Most studies, including the technique described in this thesis, use a modification of the method described by Maddahi (209) where two regions of interest at end-diastole and end-systole are used in the analysis to avoid the overlap between the right atrium and right ventricle (193, 239, 310). Other authors make an attempt to correct the right atrial contribution within the right ventricular region of interest (151). In yet other studies a single region of interest around the right ventricle is used (306). In addition, however, images can be generated which register the changes in counts between end-diastole and end-systole in both the ventricle and the atrium. These stroke count images (stroke counts being proportional to stroke volume) from the right ventricle and right atrium can be superimposed resulting in a functional image which allows delineation of the ventricular and atrial borders (95, 156, 188, 189). Only a few studies have used phase analysis to delineate the right ventricular outflow tract (193, 364).

Conclusion

The measurement of right ventricular ejection fraction is by no means easy. However, the inaccuracies inherent in this measurement can be reduced. Accurate delineation of the right ventricular outline can only be achieved by the use of a combination of techniques as described above and may be technically impossible in a small proportion of patients. For the measurement of right ventricular ejection fraction the background correction, although derived empirically, can be checked by correlating right and left ventricular stroke counts.

In order to validate the measurement of right ventricular ejection

fraction there should be good correlation between ejection fraction measured by both first pass and equilibrium techniques. The reproducibility of the technique of measuring right ventricular ejection fraction should be confirmed by a low intra and inter-observer variability. Before embarking on studies of measurement of right ventricular ejection fraction in patients, the normal values for this measurement should be determined.

CHAPTER 4

RIGHT AND LEFT VENTRICULAR PERFORMANCE IN CHRONIC BRONCHITIS AND EMPHYSEMA ASSESSED BY RADIONUCLIDE VENTRICULOGRAPHY

INTRODUCTION

The last chapter dealt with the method used in measuring ventricular function by radionuclide ventriculography and its reproducibility when applied to normal subjects, patients with myocardial ischaemia and those with chronic bronchitis and emphysema. In this chapter I will present the results of measurements of right and left ventricular ejection fractions (RVEF, LVEF) in normal subjects and in a population of patients with chronic bronchitis and emphysema.

I have shown, in chapter 3, that gated equilibrium blood pool radionuclide ventriculography is an accurate and reproducible technique of measuring RVEF when compared with the first pass method. This technique can, in addition, be used to measure both RVEF and LVEF over a period of several hours following a single peripheral intravenous injection of a radiotracer, and is therefore a convenient method to study the effects on ventricular performance of physiological and therapeutic interventions (364). For these reasons, henceforth, all measurements of ventricular ejection fractions have been made by gated equilibrium ventriculography.

Ventricular function in normal subjects

Thirty subjects had measurements of RVEF and LVEF made by equilibrium radionuclide ventriculography (table 2), (26M: 4F, age 21-63; mean age 39.4 $\pm$ (SD) 12.5 years). These subjects were either normal

atypical chest pain (n = 18). None of the normal volunteers had any history or clinical evidence of pulmonary or cardiac diseases. All of the subjects had a normal chest radiograph and were studied only if their electrocardiograms and radionuclide LVEF were normal, both at rest and on exercise (reference values from previous studies for LVEF in our laboratory at rest = 0.57, SD 0.07; LVEF increases by 0.05 during supine exercise (77, 78). None of these control subjects were receiving respiratory or cardiovascular drugs at the time of study. Subsequent follow up of those subjects who presented with atypical chest pain, indicated that none had ischaemic heart disease or chronic bronchitis. Each subject had left and right ventricular ejection fractions measured when supine, at rest. In 10 subjects measurements were also made while the patients exercised supine, on a modified bicycle ergometer, at a fixed work load of 75 watts.

Right ventricular ejection fraction in normal subjects (table 2)

The mean RVEF in these 30 control subjects was 0.58 $\pm$ SD 0.09 (range 0.47 - 0.83) when at rest. From these results the lower limit of normal for RVEF (2 standard deviations below the mean) was 0.40 when measured at rest.

The mean RVEF in the subjects who exercised was 0.54 $\pm$ 0.06 (when measured at rest) not significantly different from the resting RVEF for the group as a whole. Mean RVEF in these subjects increased to 0.62 $\pm$ 0.06 ($p < 0.001$). Each subject increased their RVEF by at least 7% or an absolute increase of at least 0.04. Since the intra-observer variation in measuring RVEF by the equilibrium technique is 0.03, an absolute increase of $\geqslant$ 0.04 has been chosen as the normal

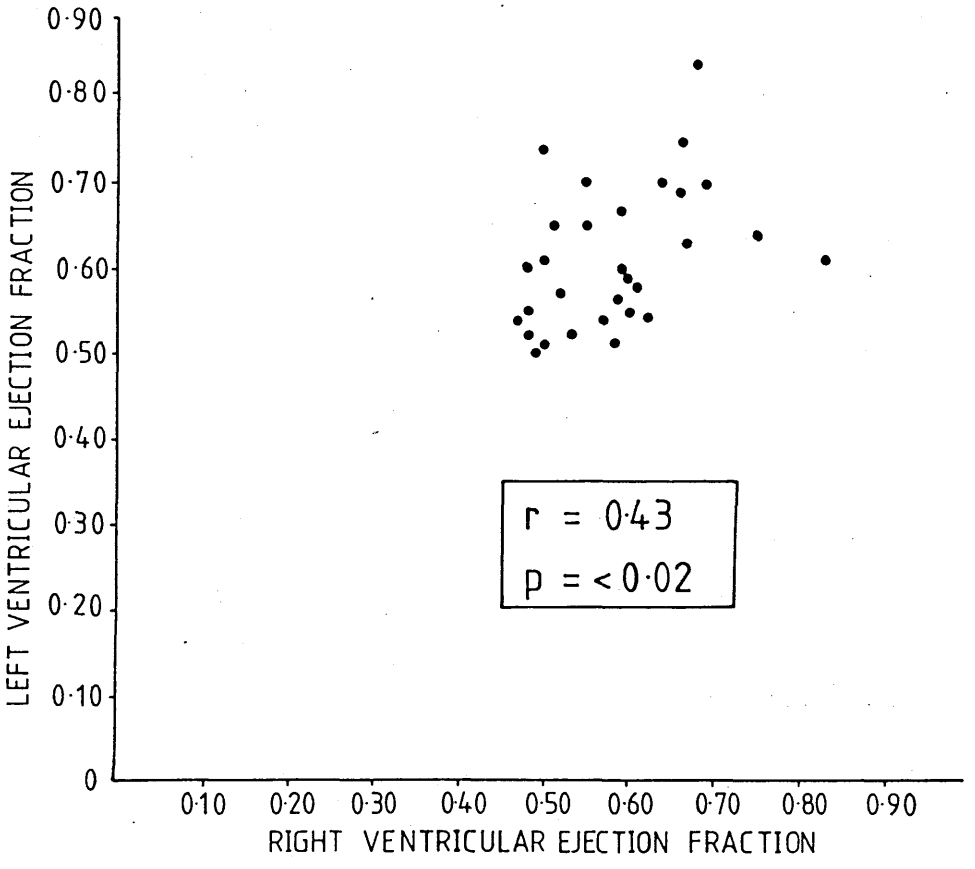


Figure 20 Relationship between right and left ventricular ejection fractions in 30 normal subjects.

Left ventricular ejection fraction in normal subjects

The resting LVEF in these 30 control subjects was 0.61 $\pm$ 0.08 (range 0.50 - 0.84). It is important to point out that these subjects had been selected because they had a normal LVEF when at rest. The mean LVEF when at rest in those patients who exercised was 0.58 $\pm$ 0.07, not significantly different from the mean value for the group as a whole, and increased to 0.69 $\pm$ 0.08 ($p < 0.001$) during exercise. Each patient had an increase in LVEF of at least 7% or an absolute increase of 0.05. From these and previous results (ref) the lower limit of the normal resting LVEF was taken as 0.45. In response to supine exercise the LVEF should increase by at least 0.05. There was no significant difference between the mean RVEF or LVEF for these 30 control subjects. In addition there was a significant correlation between the right and left ventricular ejection fractions in these 30 control subjects (figure 20).

VENTRICULAR FUNCTION IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

Methods and patients

Right and left ventricular ejection fractions were measured at rest by gated equilibrium radionuclide ventriculography in 100 patients with chronic bronchitis and emphysema. Sixty two males and 38 females were studied with a mean age of 62 years (range 41-80 years) (table 3). Ventilatory capacity and arterial blood gas values were measured while the patient breathed room air within 30 minutes of the radionuclide study. Only those patients who had largely irreversible airflow limitation were included in the study (ie

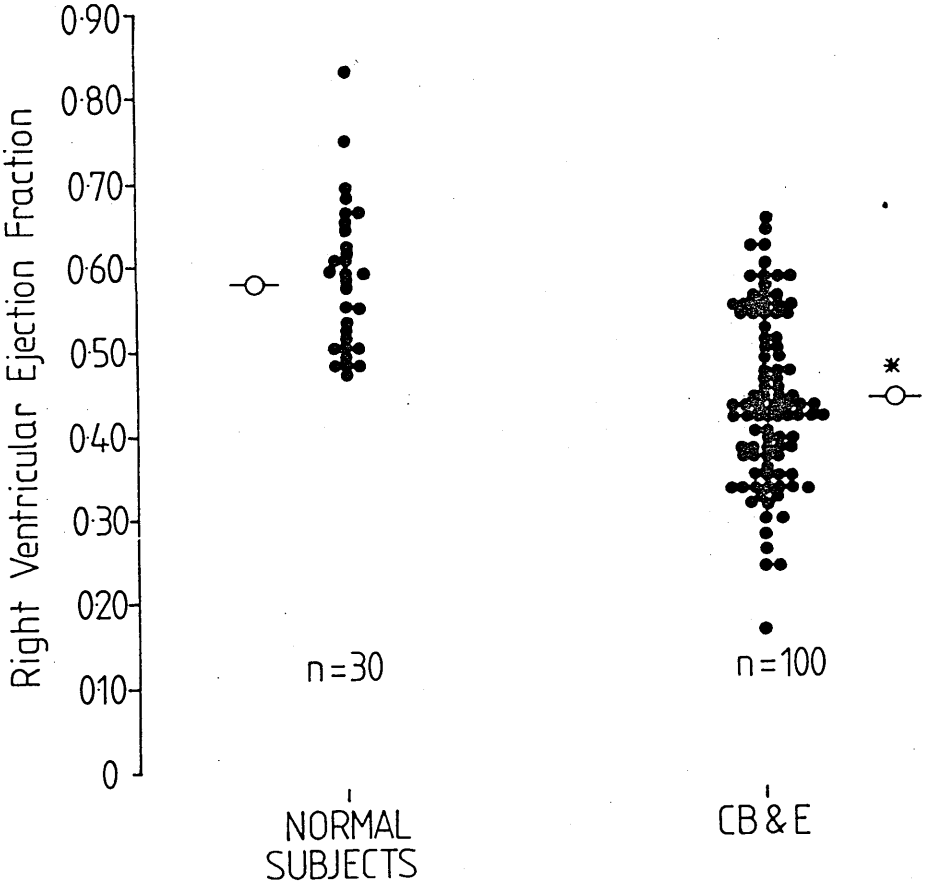


Figure 21 Individual values (●) of right ventricular ejection fractions (RVEF) in 30 normal subjects and 100 patients with chronic bronchitis and emphysema (CB&E). Although there is a wide range of values of RVEF in the patients with CB&E, the mean (-o-) RVEF is significantly lower than in normal subjects (* $p < 0.001$).

by a pressurised inhaler, measured within the preceding 6 months). None of the patients had a history, clinical or electrocardiographic findings to suggest ischaemic or valvular heart disease or systemic hypertension. In all patients current drug therapy was continued during the study but inhaled bronchodilators were discontinued four hours before measurement of FEV_1 and FVC. Patients were excluded if they were receiving domiciliary oxygen therapy (> 12 hours/day oxygen). Electrocardiograms were obtained, where possible, within 24 hours of the radionuclide study.

The patients were subdivided into three groups dependent on a history of peripheral oedema, documented by a doctor, for which no cause other than `right sided cardiac failure' could be found (tables 4a, b, c). On this basis 34 patients had no history or clinical evidence of oedema, 38 had episodes of oedema in the past and 28 had oedema present at the time of study.

In 50 of these patients (table 6) a Swan Ganz flow directed, balloon tipped catheter was placed in the pulmonary artery via a vein in the antecubital fossa or the femoral vein and simultaneous measurements of pulmonary arterial pressure (PAP) and RVEF were made. In a further subgroup of 20 of these patients cardiac output was measured by the thermodilution technique (Edwards laboratory) and total pulmonary vascular resistance could be calculated from the formula:

Total pulmonary vascular resistance

(dynes.s.cm^{-5}) =

$$\frac{\text{mean PAP (mmHg)} \times 80}{\text{cardiac output (l/min)}}$$

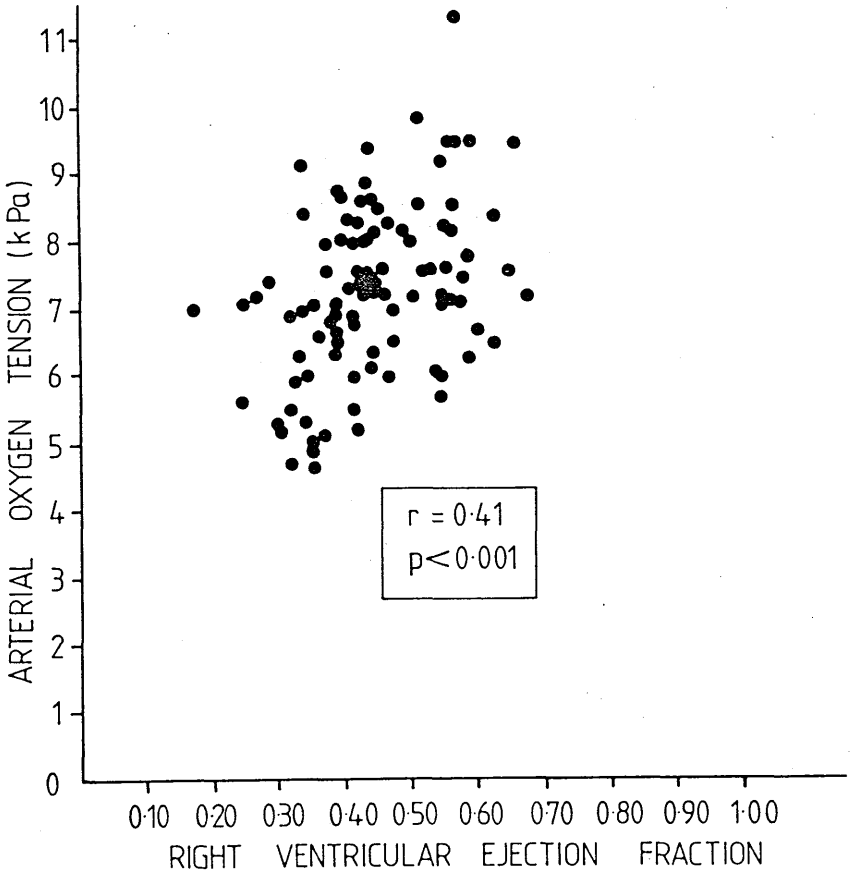


Figure 22 Relationship between right ventricular ejection fraction and arterial oxygen tension (measured when breathing air) in 100 patients with chronic bronchitis and emphysema.

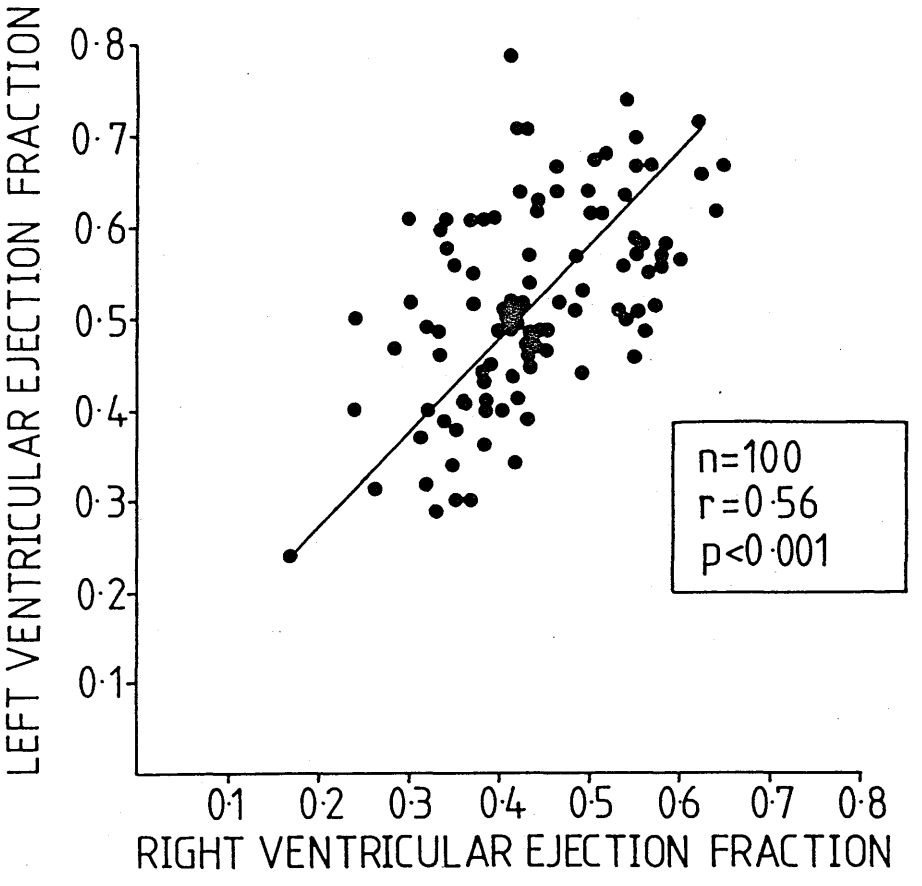


Figure 23 Relationship between simultaneous measurements of right and left ventricular ejection fractions in 100 patients with chronic bronchitis and emphysema.

In 25 patients RVEF and LVEF were measured at rest and during supine exercise at a workload of 50% of their maximum voluntary exercise tolerance (table 5a and b). In these patients ear oxygen saturation was measured continuously using a Hewlett Packard (47201A) ear oximeter.

RESULTS

The mean $FEV_{1.0}$ of the 100 patients with chronic bronchitis and emphysema was 0.75 $\pm$ 0.38 l, FVC 1.98 $\pm$ 0.8 l (table 3). These patients had a wide range of values of PaO_2 and $PaCO_2$, although most were hypoxic (mean PaO_2 7.3 kPa; range 4.7 - 11.3 kPa) and hypercapnic (mean $PaCO_2$ 6.4 kPa; range 4.2 - 10.8 kPa), with a mean arterial hydrogen ion activity of 43 $\pm$ 5 nmol/l (range 34 - 51 nmol/l).

Right ventricular ejection fraction

The mean RVEF measured at rest in these patients was 0.44 $\pm$ 0.10 which was significantly lower than the mean RVEF of the 30 control subjects (RVEF 0.58 $\pm$ 0.09; $p < 0.001$) (figure 21). However, there was a wide range of values of RVEF in these patients from 0.17 - 0.64. Thirty five of the 100 patients had a low RVEF (< 0.40) (figure 21, table 3).

There was a positive correlation between RVEF and PaO_2 ($r = 0.41$, $p < 0.001$) (figure 22) and a negative correlation between RVEF and $PaCO_2$ ($r = -0.34$, $p < 0.001$). Although both correlations were significant they did not indicate a close relationship between these variables. There were no significant correlations between RVEF and $FEV_{1.0}$ (r =

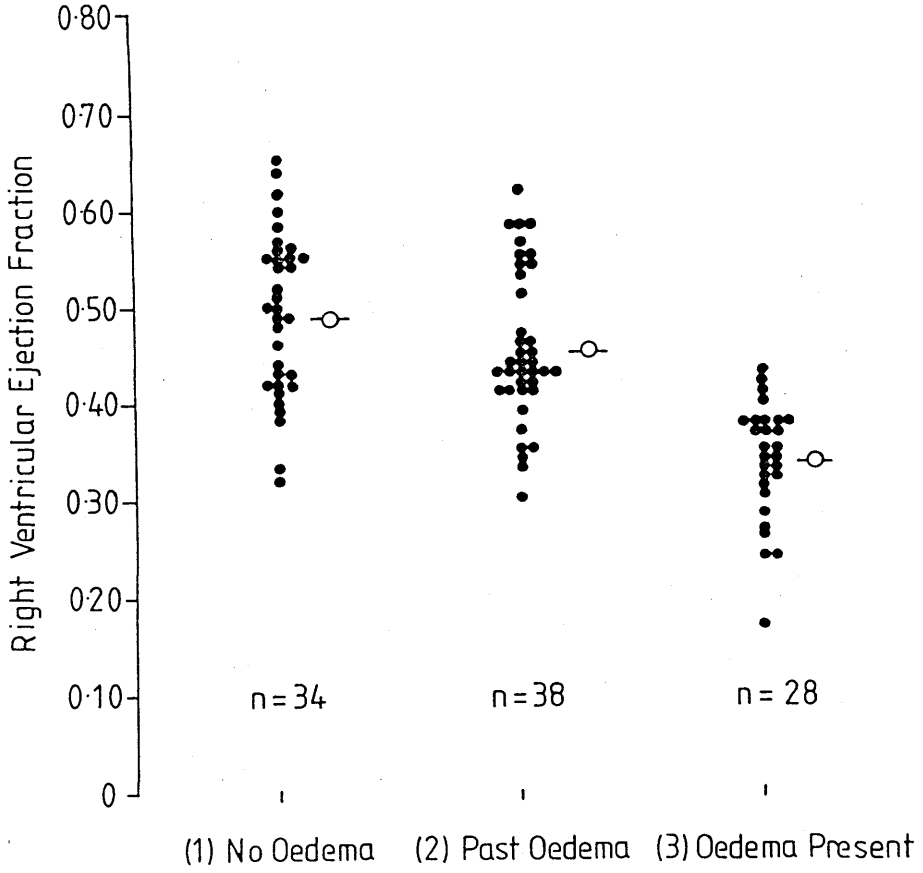


Figure 24 Right ventricular ejection fractions in patients with chronic bronchitis and emphysema with (1) no history of oedema, (2) past history of oedema, or (3) oedema when studied. Individual results (•) and mean values (-o-) are shown:

Statistical analysis
(1) vs (2) $p < 0.05$; (1) vs (3) $p < 0.001$; (2) vs (3) $p < 0.01$.

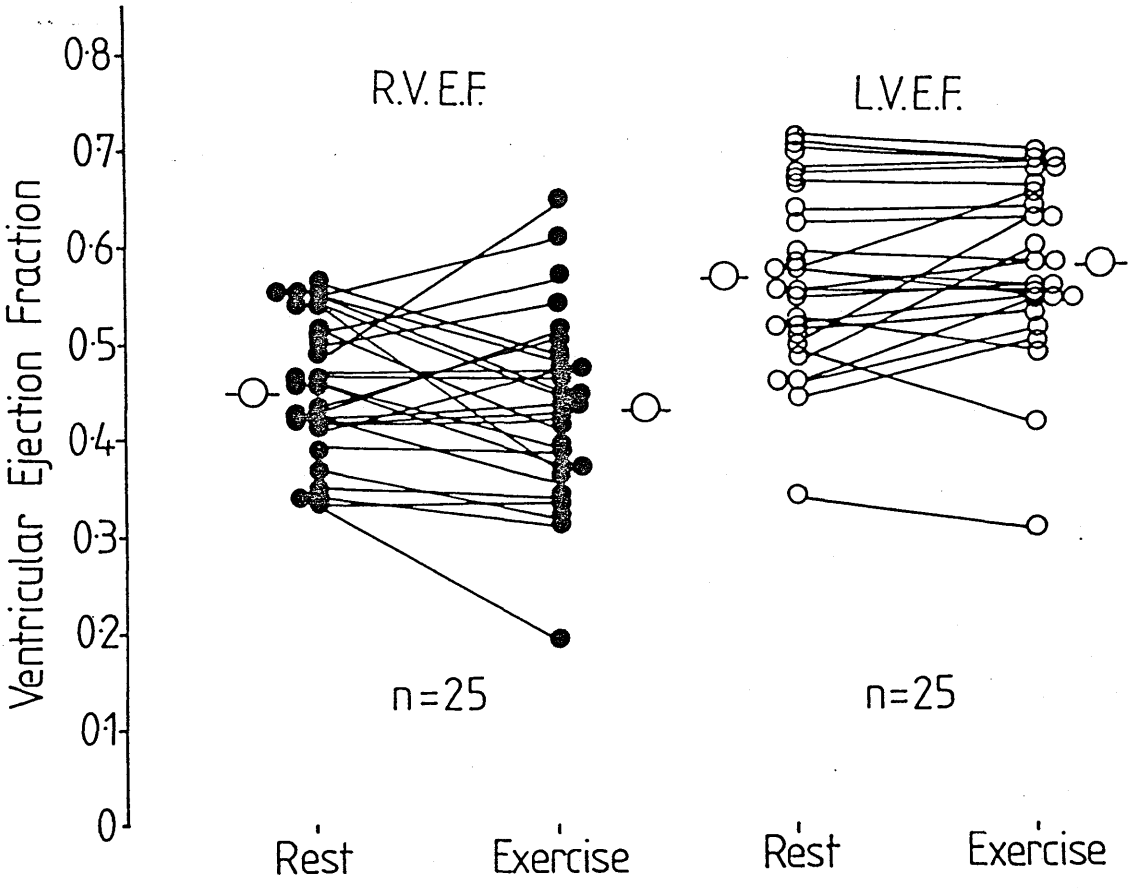


Figure 25 Right (•, RVEF) and left (o, LVEF) ventricular ejection fractions at rest and during supine exercise when breathing air in 25 patients with chronic bronchitis and emphysema. Mean values of RVEF and LVEF (-o-) did not change during exercise although the response to exercise was very variable.

correlation was also found between RVEF and LVEF in these patients ($r = 0.56$, $p < 0.001$) (figure 23).

When these 100 patients with chronic bronchitis and emphysema were subdivided into those with (table 4c) or without clinical evidence of oedema, either at the time of study (table 4a) or in the past (table 4b), those with oedema present at the time of study had a lower PaO_2 ($p < 0.001$), a higher $PaCO_2$ ($p < 0.01$), and a lower $FEV_{1.0}$ ($p < 0.01$) and FVC ($p < 0.01$) than those with no previous clinical evidence of oedema (table 4). The FEV_1, FVC, and $PaCO_2$ were similar but the PaO_2 was higher in those with oedema in the past, compared with those with oedema at the time of study. The mean RVEF in those patients who had oedema present at the time of study was 0.34 ± 0.06, which was significantly lower than either the mean RVEF for those with past evidence of oedema (mean RVEF 0.45 ± 0.08 $p < 0.01$), or those with no previous history of oedema (RVEF 0.49 ± 0.09, $p < 0.001$). There was a small but significant reduction in RVEF in those patients with a past history of oedema when compared to those with no previous oedema ($p < 0.05$) (figure 24). Only 4 of these 34 patients without previous history of oedema had a low RVEF compared with 24 of the 28 patients who had oedema present at the time of study.

The mean RVEF at rest in the 25 patients who exercised (table 5a) was 0.45 ± 0.07 (table 5b). This value did not change significantly during supine exercise ($RVEF_{exercise}$ 0.43 ± 0.10). However, the change in RVEF in response to exercise was very variable (figure 25). Seven of the 25 patients had a normal response to exercise, ie an absolute increase in RVEF of ≥ 0.04. None of the patients with a low RVEF had a normal increase in RVEF during exercise, but 12 of the

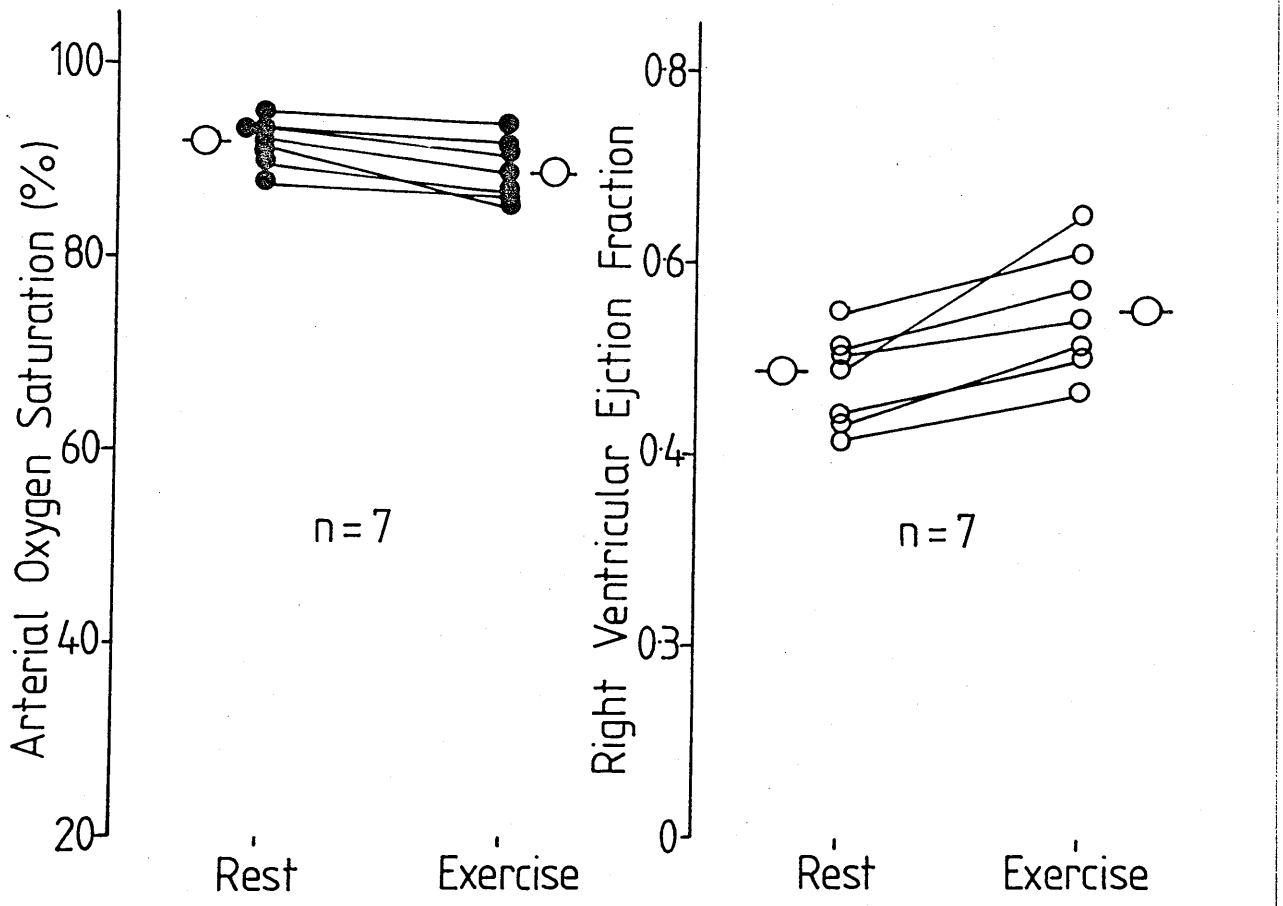


Figure 26A Arterial oxgyen saturation (SaO_2) and right ventricular ejection fractions (RVEF) at rest and during supine exercise, while breathing air, in 7 patients whose RVEF increased normally during exercise.

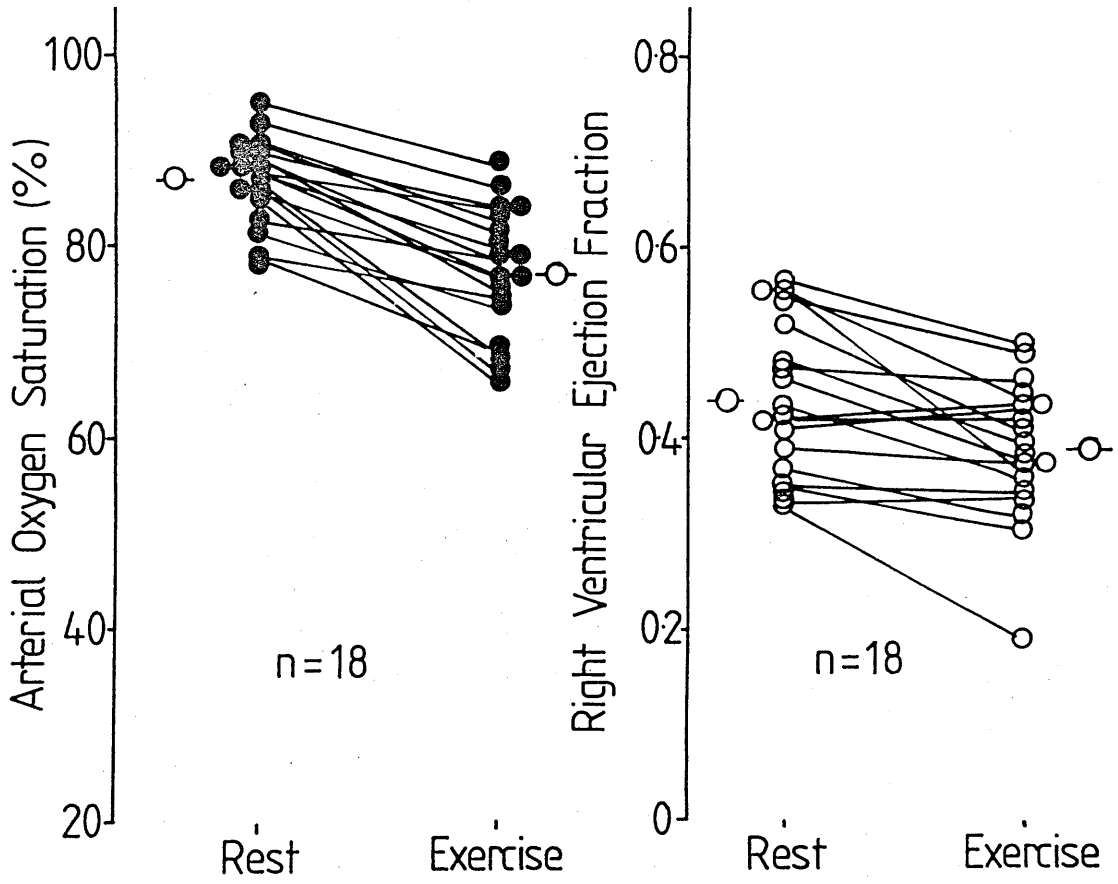


Figure 26B Arterial oxygen saturation (SaO_2) and right ventricular ejection fractions (RVEF) at rest and during supine exercise, while breathing air, in 18 patients whose RVEF did not increase normally during exercise, where the fall in SaO_2 was greater than in Figure 26A.

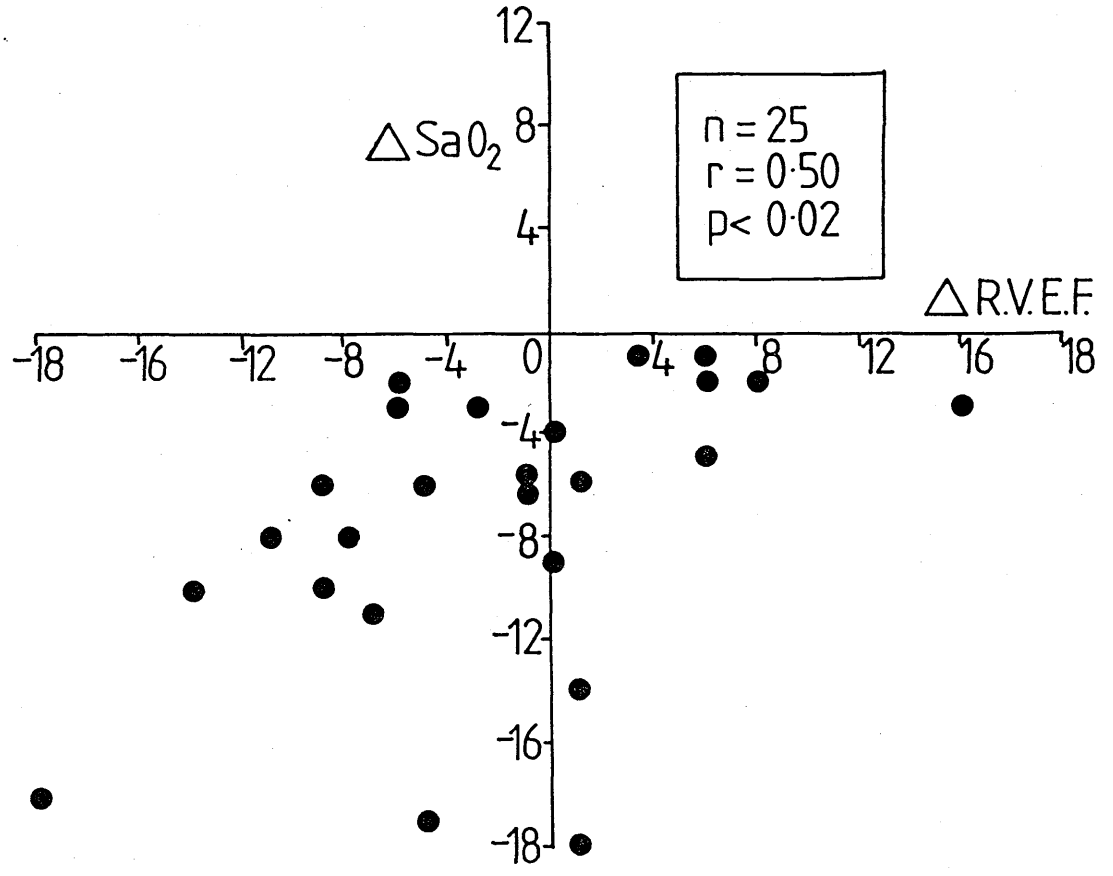


Figure 27 Relationship between the change in right ventricular ejection fraction (Δ RVEF), and the change in arterial oxygen saturation (ΔSaO_2) from rest to exercise while breathing air, in 25 patients with chronic bronchitis and emphysema.

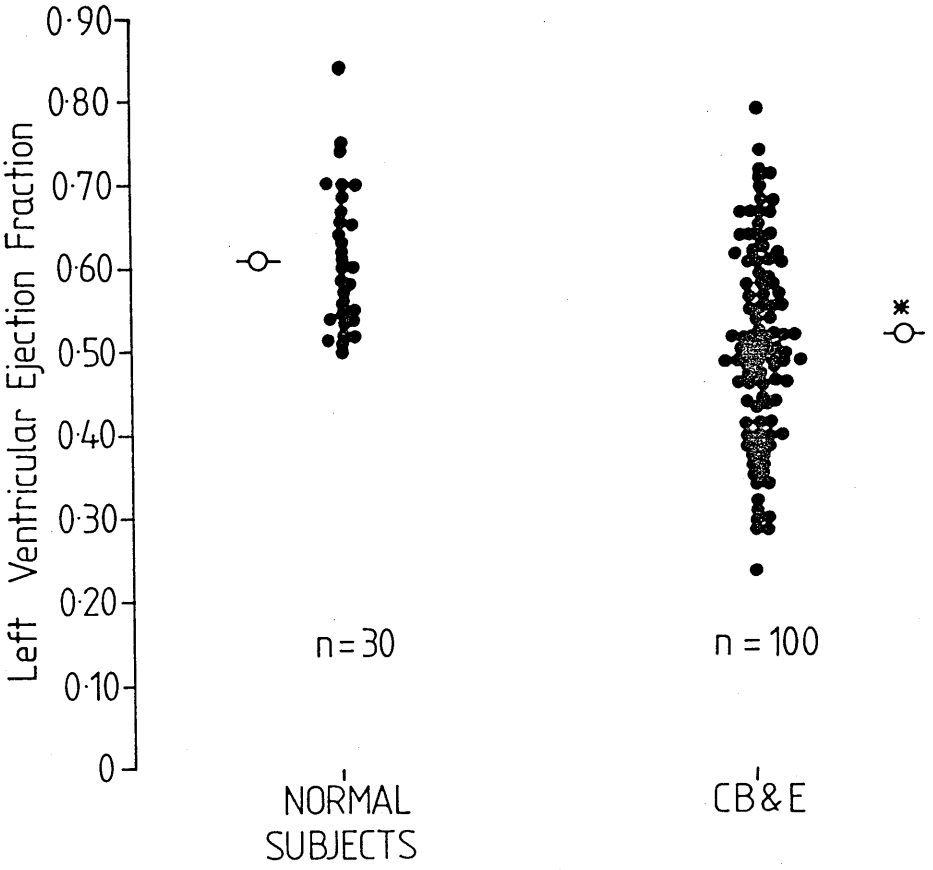


Figure 28 Individual values (•) of left ventricular ejection fractions (LVEF) in 30 normal subjects and 100 patients with chronic bronchitis and emphysema (CB&E). Although there is a wide range of values of LVEF in patients with CB&E, the mean (-o-) LVEF is significantly lower than in normal subjects (* $p < 0.001$).

increase in RVEF when exercising, and in 4 of these patients RVEF fell to an abnormally low value during exercise (table 5b).

During exercise all of these patients desaturated (table 5b). However, the change in oxygen saturation, as measured by the ear oximeter (SaO_2) was very variable and did not correlate with the initial oxygen saturation measured when at rest ($r = 0.30$, NS). The fall in SaO_2 was less in those patients who had an increase in RVEF of 0.04 during exercise, a normal response (figure 26A) compared with those whose RVEF did not increase by this amount or fell when exercising (figure 26B). A significant correlation was also found between the fall in saturation which occurred during exercise in these 25 patients and the corresponding change in right ventricular ejection fraction when exercising ($r = -0.5$, $p < 0.02$) (figure 27).

Left ventricular ejection fraction

The mean LVEF of the 100 patients with chronic bronchitis and emphysema, when measured at rest was 0.52 ± 0.11, which was significantly lower than the LVEF for the 30 normal subjects (0.61 ± 0.08, $p < 0.001$) (figure 28). However, the mean LVEF for these patients was still within the normal range. As with RVEF, the range of values of LVEF in these patients was wide from 0.29 to 0.79 (figure 28, table 3). Twenty three of the 100 patients had a low LVEF (< 0.45).

There were significant but weak correlations between LVEF and PaO_2 ($r = 0.40$, $p < 0.001$) and LVEF and $PaCO_2$ ($r = -0.26$, $p < 0.01$) but no significant correlations were found between LVEF and FEV_1 ($r = 0.05$, NS) or between LVEF and FVC ($r = -0.03$ NS). LVEF was significantly

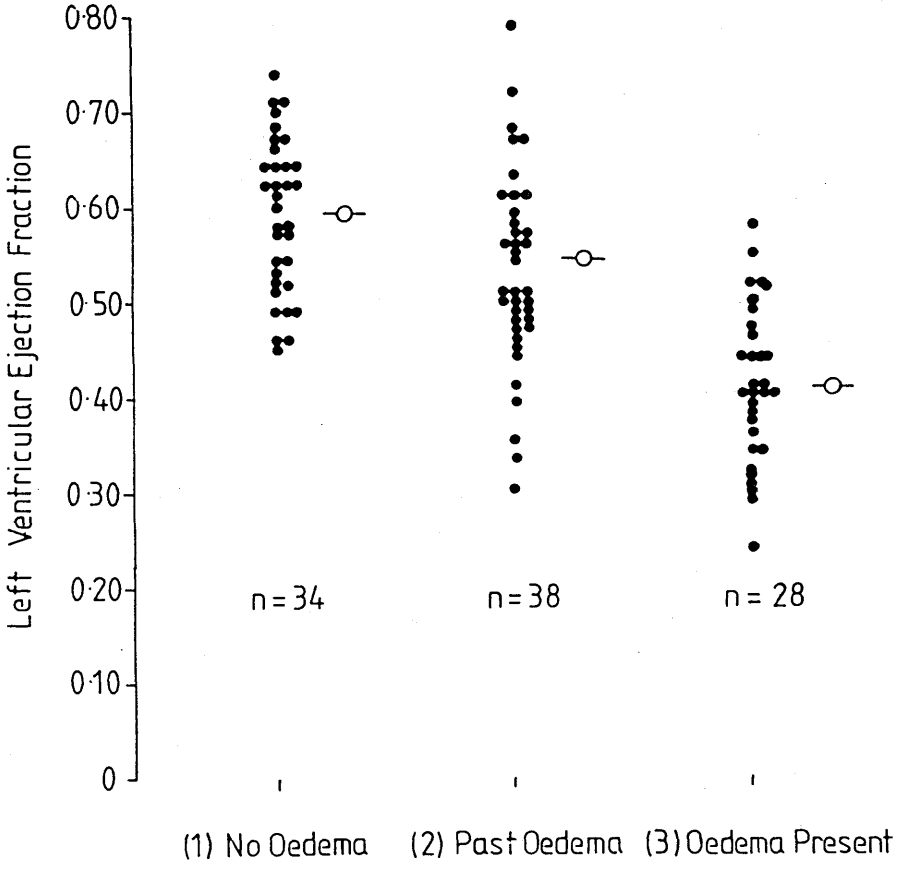


Figure 29 Left ventricular ejection fractions in patients with chronic bronchitis and emphysema with (1) no history of oedema, (2) past history of oedema, (3) oedema when studied. Individual results (●) and mean values (–o–) are shown.

Statistical analysis

(1) vs (2) NS; (1) vs (3) $p < 0.001$; (2) vs (3) $p < 0.001$.

(LVEF 0.41 $\pm$ 0.08) compared with those who had oedema in the past (LVEF 0.54 $\pm$ 0.09, $p < 0.001$) or those who had never had oedema (LVEF 0.59 $\pm$ 0.08, $p < 0.001$) (figure 29). Twenty of the 28 patients (71%) with oedema present at the time of study, had an abnormal LVEF, whereas none of the 34 patients who had never had oedema had a low LVEF, and only 3 of the 38 patients (8%) with past evidence of oedema had a low LVEF (table 4). Of the 23 patients who had a low LVEF only 5 had a normal RVEF, and in each of these patients the values of RVEF and LVEF were borderline for normality. The reverse, however, was not true, since 17 of the 35 patients who had a low RVEF had a normal LVEF.

The mean LVEF at rest in those 25 patients who exercised was 0.57 $\pm$ 0.09 which was not significantly different from the mean LVEF of the total population of 100 patients. LVEF did not change significantly in these patients when exercising ($LVEF_{exercise}$ 0.58 $\pm$ 0.09, NS). LVEF increased normally in only 6 of the 25 patients when exercising (figure 25) (table 5b). There was no correlation between the change in RVEF and LVEF in response to exercise. In contrast to the right ventricle, the degree of desaturation while exercising did not correlate significantly with the change in LVEF during exercise in these patients.

Relationship between PAP and RVEF (table 6)

There was no significant correlation between RVEF and either systolic or mean PAP (figure 30) ($r = -0.15$, NS) in the 50 patients with chronic bronchitis and emphysema where simultaneous measurements PAP and RVEF were made. However, in 20 of these patients, where pulmonary vascular resistance was calculated, there was a significant

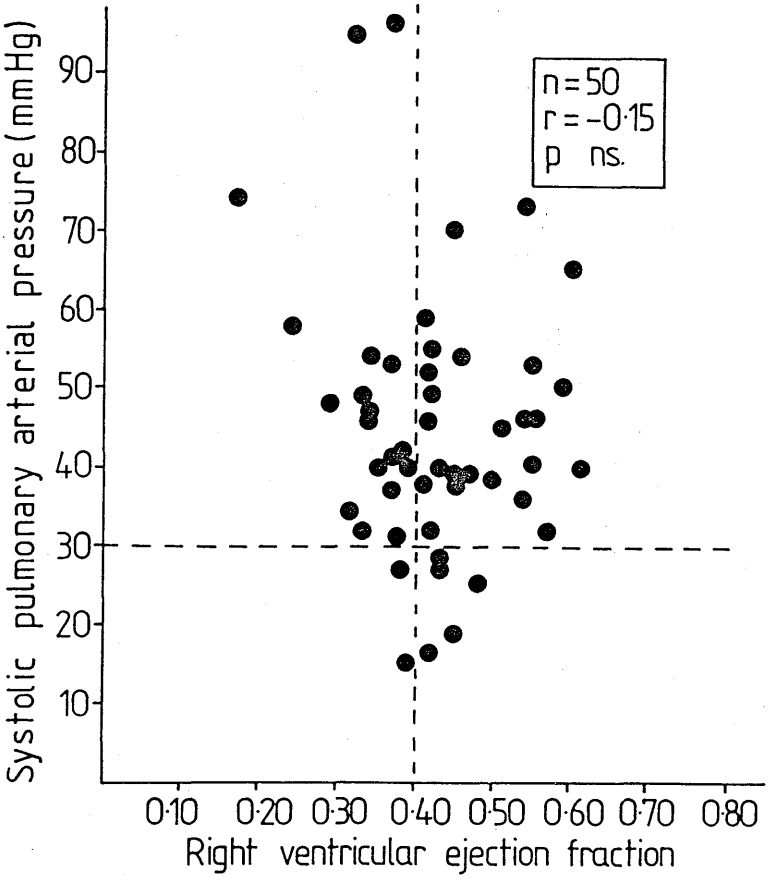


Figure 30A Relationship between systolic pulmonary arterial pressure (PAP) and simultaneous measurements of right ventricular ejection fractions in 50 patients with chronic bronchitis and emphysema (CB&E).
The dotted lines indicate the upper and lower limits of normal of PAP and RVEF respectively.

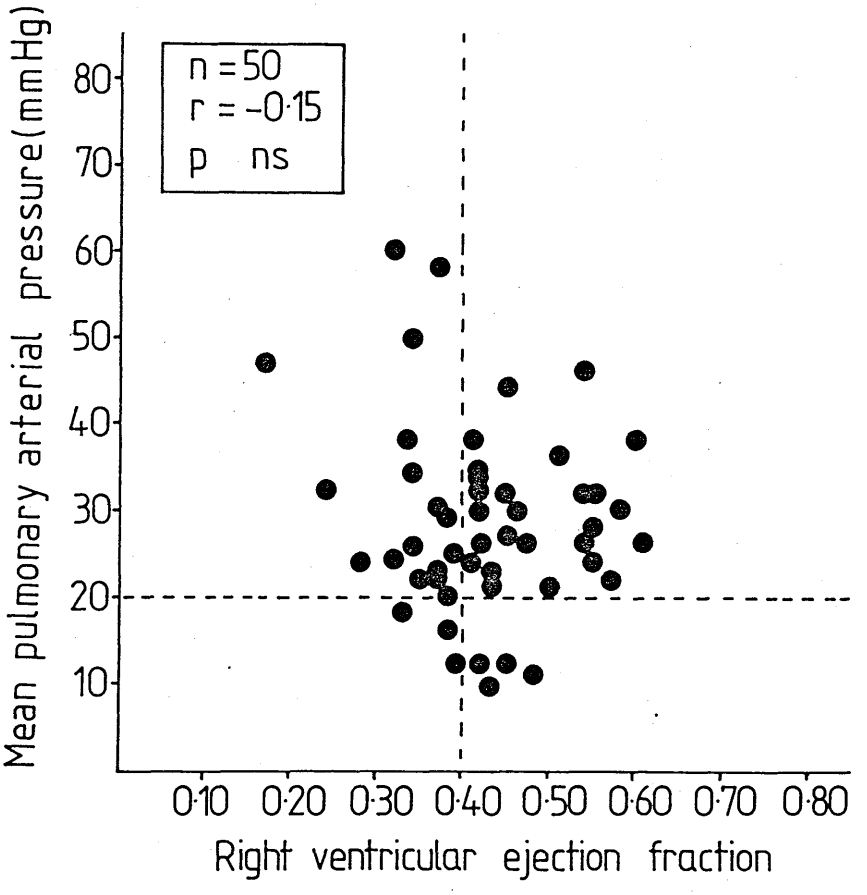


Figure 30B Relationship between mean pulmonary arterial pressure (PAP) and simultaneous measurements of right ventricular ejection fractions in 50 patients with chronic bronchitis and emphysema (CB&E).
The dotted lines indicate the upper and lower limits of normal of PAP and RVEF respectively.

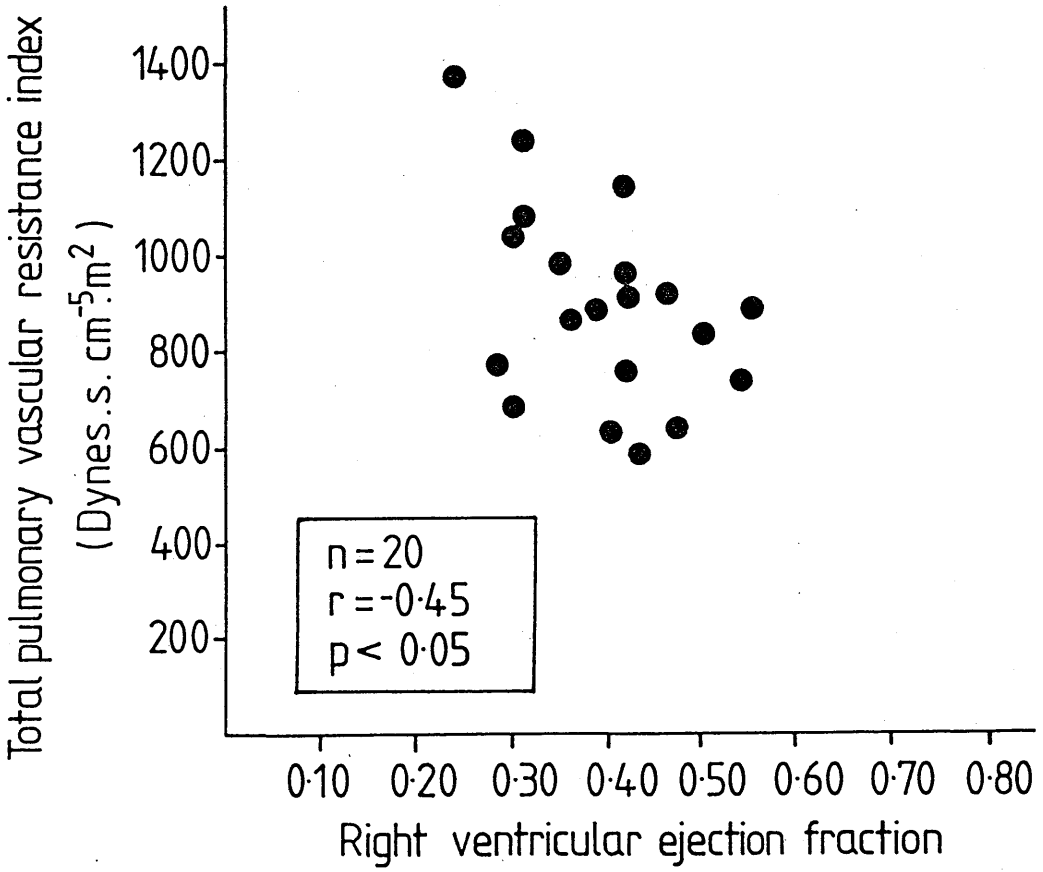


Figure 31 Relationship between right ventricular ejection fraction and total pulmonary vascular resistance in 20 patients with chronic bronchitis and emphysema.

resistance ($r = -0.45$, $p < 0.05$) (figure 31).

Relationship between RVEF and ECG

In 45 patients the relationship between RVEF and the ECG findings was studied. There was no significant difference in the mean RVEF in those patients who had a normal electrocardiograph when compared with those who had ECG findings usually associated with cor pulmonale (40, 259) ie right axis deviation, p pulmonale and right ventricular hypertrophy (figure 32).

DISCUSSION

The normal values for right ventricular ejection fraction measured by the gated equilibrium radionuclide technique vary in the literature from a mean of 0.43 ± 0.06 to a mean of 0.62 ± 0.09 (table 7). A similar degree of variability has been reported for absolute values of RVEF measured by the first pass technique (table 7). This variability in the reported normal values of RVEF, as discussed in chapter 3, results from the lack of a standardised technique for measuring RVEF. This has two consequences. Firstly, in interpreting data from any laboratory, reference values from a normal population should be available. Secondly, unless a technique, which has been adequately validated, as described in this thesis, has been used in measuring RVEF, comparisons of absolute values of RVEF cannot be made between different studies. The mean and range values of RVEF in the normal subjects in this study are, however, similar to those previously quoted in the literature. In this, as in all other published studies, RVEF increases during exercise in normal subjects by between 7 and 37%, the largest increases occurring during maximum

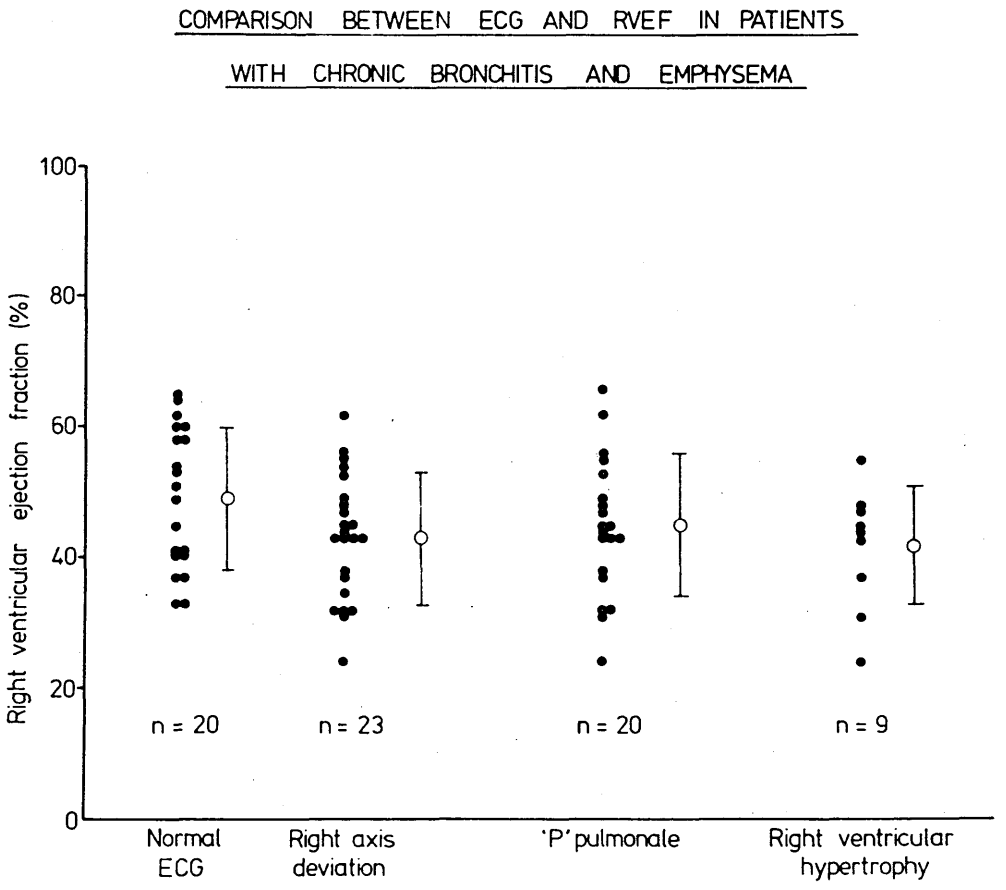


Figure 32 Comparison of the electrocardiographic findings and the right ventricular ejection fraction (RVEF) in 45 patients with chronic bronchitis and emphysema. The points are individual values (•) with the mean RVEF for each electrocardiographic group (o $\pm$ SD).

exercise. In assessing the effects of exercise on RVEF I have chosen a submaximal exercise protocol since exercise tolerance in bronchitic patients is often limited by dyspnoea consequent upon their ventilatory capacity which may prevent the completion of the 5 minute exercise protocol necessary for data acquisition in the measurement of RVEF. Thus the exercise protocol for the patients with chronic bronchitis and emphysema was fixed at 50% of the patients maximum voluntary exercise capacity which was assessed prior to each study. This protocol was chosen so as to produce comparable levels of exercise in individual patients. The fixed workload of 75 watts, used in the normal subjects, was not suitable for the majority of bronchitic patients who were unable to sustain this level of exercise for the length of time necessary for data acquisition.

The correlation which I have found between the right and left ventricular ejection fractions, in normal subjects, has not been previously reported. However, although this correlation was statistically significant, it was not sufficiently strong to allow prediction of RVEF from the value of LVEF. This correlation between RVEF and LVEF could result from an interaction between the ventricles. Indeed such myocardial interaction between the ventricles has been proposed in several studies (199, 293, 325, 344). However, the contractile mechanics of either ventricle are more likely to be influenced by the other ventricle in diseased states rather than in normal subjects. Another explanation could be that the method used in measuring RVEF is greatly influenced by the left ventricular counts, as a result of overlapping of the chambers. This is unlikely firstly because separation of both ventricles, as seen on the movie image, was considered to be a prerequisite in the

separation in the response of the right and left ventricular ejection fractions to inotropic therapy in patients with good right but poor left ventricular function. In this case the RVEF increased after the inotrope was given without any significant change in LVEF (364).

Right ventricular ejection fraction in chronic bronchitis and emphysema

To date, this study represents the largest population of patients with chronic bronchitis and emphysema in whom ejection fractions have been measured by radionuclide ventriculography. The results confirm our earlier findings in a smaller number of patients (206). Moreover, this population of patients had a wide range of disability, as measured by their ventilatory capacity and arterial blood gas values. In addition, since patients with historical, clinical or electrocardiographic evidence of co-existing cardiac disease (other than pulmonary heart disease) were excluded from this population (although occult disease has not been excluded), the data accurately represent the effects of chronic bronchitis and emphysema on ventricular performance. Also excluded from this population were those patients who had received domiciliary oxygen (> 12 hours oxygen/24 hours), since there is evidence that this treatment alters the course of the disease (225, 251), and may have influenced the measurement of RVEF.

Although the mean RVEF at rest in these 100 patients with chronic bronchitis and emphysema was significantly lower than that of normal subjects, there was a wide range of values of RVEF in these patients. This wide range of values of RVEF in bronchitic patients as has been confirmed by others (table 8). The mean value of RVEF in the

patients in this study was 0.44 ± 0.10, which was similar to the values quoted in the literature measured mainly by first pass radionuclide ventriculography (table 8). Seventy five per cent of the patients in this study had a normal RVEF (> 0.40). Few of these patients had low values of RVEF such as have previously been reported in acute right ventricular infarcts (267, 333). How can we explain the wide range of values of RVEF in patients with chronic bronchitis and emphysema?

The RVEF in chronic bronchitis and emphysema seems to be related to the severity of the disease. Although there was no significant correlation between RVEF and the indices of ventilatory capacity in these patients, there were significant correlations between RVEF and PaO_2 and $PaCO_2$. Berger et al (24), in a study of 36 patients with chronic bronchitis and emphysema found that those with severe impairment of pulmonary function, arbitrarily defined as an FEV_1 of < 1 litre, had a lower mean RVEF than those whose pulmonary function was less impaired. Correlation coefficients are not quoted in this study but a personal analysis of the data showed no significant correlations between RVEF and PaO_2, $PaCO_2$, FEV_1 or FVC. Slutksy et al (307) have also shown that RVEF is lower in those patients with more severe abnormalities of pulmonary function. However, in these studies pulmonary function data could not completely separate patients with a normal or an abnormal RVEF.

As I have discussed previously, the definition of cor pulmonale is a pathological one (361). However, the results of this study indicate that the presence of oedema (for which no cause other than 'cor pulmonale' can be found) in patients with chronic bronchitis and emphysema is associated with a reduction in RVEF in 86% of cases.

values of RVEF were only just above the lower limit of normal (0.42, 0.41, 0.43, 0.40). Interestingly, however, only 5 of the 28 patients (18%) with oedema when studied, had an RVEF of < 0.30, which is the level of LVEF which would be normally considered to be associated with severe left ventricular dysfunction (77, 78). Thus even with clinical findings of decompensated `cor pulmonale', RVEF is relatively well preserved in the majority of patients with chronic bronchitis and emphysema. Further evidence of the relationship of RVEF to clinical evidence of oedema in these patients comes from the fact that those patients with a previous history of oedema but no oedema when studied, also had a lower mean RVEF than those with no previous evidence of oedema. Only 4 of the 34 patients (12%) who had no present or past history of oedema had a low RVEF. Three of these patients developed peripheral oedema within a year of being studied. Thus a low RVEF, in a patient with chronic bronchitis and emphysema and no previous oedema, may be an early indicator of right ventricular dysfunction and may herald the development of peripheral oedema. A normal RVEF, however, can occur in a patient who has been treated for past episodes of peripheral oedema.

Berger et al (24) also found that in a group of 36 patients with chronic bronchitis and emphysema with `cor pulmonale', RVEF was low but, as in the present study, only 1 of these patients had an RVEF of < 0.30. In this study `cor pulmonale' was defined as electrocardiographic evidence of right ventricular hypertrophy (214). However, the electrocardiographic findings in the patients in this present study did not relate closely to the right ventricular function, at least as measured by the ejection fraction. Although several studies have shown a correlation between the

emphysema and the presence of right ventricular hypertrophy at post mortem (39, 171, 282), hyperinflation of the lungs in such patients may result in the heart adopting a more vertical position which may obscure both clinical, radiographic and electrocardiographic evidence of right ventricular enlargement (113, 259). I have been able to relate the functional data obtained from the measurements of RVEF to pathological evidence of right ventricular enlargement in only a few patients. Preliminary data, however, seems to indicate that a normal RVEF can occur in patients with pathologically confirmed right ventricular hypertrophy (unpublished observations).

Right ventricular ejection fraction during exercise

A submaximal exercise protocol was chosen for this study which differed from that used routinely in assessing patients with coronary or valvular heart disease. This protocol was used for two reasons. Firstly, because exercise in patients with chronic bronchitis and emphysema is usually limited by ventilatory impairment rather than myocardial ischaemia (343). In addition, I felt that a submaximal exercise protocol, at a workload of 50% of the patients maximum voluntary exercise capacity should ensure that these patients exercised below their anaerobic threshold (342).

Twenty-eight per cent of the 25 patients who took part in the exercise study had a normal increase in RVEF when exercising and none of the patients whose RVEF was low when at rest had a normal response to exercise. However, exercise uncovered occult right ventricular dysfunction in 63% of the patients whose RVEF was normal at rest. In this and other studies (220, 255, 309), although the majority of patients with chronic bronchitis and emphysema have a relatively

RVEF when exercising.

It has been assumed that failure of RVEF to rise during exercise in patients with chronic bronchitis and emphysema has been as a result of an augmented right ventricular afterload. Several factors have been implicated to account for the increase in pulmonary arterial pressure which is known to occur in response to mild supine exercise (170). These include changes in airways resistance and hence alveolar pressure (141), and concomitant changes in arterial oxygen tensions during exercise (170). There is certainly a variability in the degree of oxygen desaturation which occurs in patients with chronic bronchitis and emphysema and this has been related to the pathophysiological type of chronic bronchitis and emphysema in individual patients (172, 213). The results of this non-invasive study do not indicate the cause of the impaired right ventricular function which occurs during exercise in the majority of patients with chronic bronchitis and emphysema, but this study does suggest that the presence of a normal or abnormal right ventricular response when exercising relates to the degree of desaturation which occurred during exercise, the fall in SaO_2 being much more significant in those patients whose RVEF did not increase normally when exercising, compared with those whose RVEF did increase normally. Thus, there was a correlation between the change in RVEF and the degree of desaturation which occurred during exercise.

Although the change in RVEF during exercise in patients with chronic bronchitis and emphysema has been shown, in several studies, to be very variable (24, 220, 221, 255, 309), it has not previously been related to the degree of desaturation which occurred during exercise.

appear to have significant desaturation during exercise, unlike the patients in this study. It is interesting that most of these previous studies were performed in North America where desaturation during exercise in patients with chronic bronchitis and emphysema appears less common than in patients from the UK (54, 55, 56, 343).

These findings together with the correlation between $PaCO_2$ and RVEF might indicate that there is a relationship between right ventricular response to exercise and the clinico-pathological type of chronic bronchitis and emphysema in any individual patient. In this study all of the patients who had a normal right ventricular response when exercising appeared to be clinically of the 'pink and puffing' type with a normal $PaCO_2$ but with variable degrees of hypoxaemia (PaO_2 range 7.5 - 11.3 kPa) At least some of those whose RVEF did not increase normally when exercising were of the 'blue and bloated' type with carbon dioxide retention. However, until a reliable method of diagnosing and quantifying emphysema in life becomes available, the relationship between the RVEF and the underlying lung pathology remains speculative.

Left ventricular ejection fraction

Left ventricular performance in patients with chronic bronchitis and emphysema has been the subject of much debate (16, 89, 111, 113, 125, 173, 242). However, it is clear that a degree of left ventricular dysfunction does occur in some patients. What is unclear is whether the left ventricular dysfunction occurs as a result of primary pathology affecting the right ventricle, or as a result of coincidental disease affecting the left ventricle (202).

with chronic bronchitis and emphysema, without other overt evidence of ischaemic hypertensive or valvular heart disease, is significantly lower than the mean LVEF of normal subjects. However, when measured at rest, the mean LVEF for these 100 patients was still within the normal range. Moreover, only 23% of these patients had a low LVEF and only one patient had an LVEF of < 0.30, indicating severe left ventricular dysfunction. As with the right ventricle, a low LVEF in a patient with chronic bronchitis and emphysema was related to the presence of oedema. Similarly, there were significant (but unimpressive)correlations between the LVEF and the arterial oxygen and carbon dioxide tensions, and in addition there was a significant correlation between the RVEF and LVEF. Similar correlations have not previously been reported in studies of left ventricular function in chronic bronchitis and emphysema (23, 184, 218, 219, 221, 255, 307, 308, 311, 312) (table 9). Berger et al (23), in one of the few studies to examine such relationships, found no correlation between LVEF and RVEF or indeed between LVEF and arterial oxygen or carbon dioxide tensions. In Berger`s study (23), arterial blood gas samples were not withdrawn immediately before the radionuclide ventriculograms as in this present study but were measured within 48 hours of the ventriculogram. Since some of the patients were not in a stable condition, arterial blood gas values could have altered over this period and have resulted in the lack of correlation with RVEF or LVEF.

In all previous radionuclide studies in patients with chronic bronchitis and emphysema, the mean LVEF has been within the normal range (table 9), as is the case in the present study. However, Slutsky et al (308) reported that in patients with severe `chronic

obstructive pulmonary disease the first third LVEF, which is considered to be a more sensitive index of left ventricular function, was depressed in 40%. In addition Slutsky (308) found that this index had a significant positive correlation with the RVEF ($r = 0.73$, $p < 0.01$).

Of the patients studied during exercise, only one of the 25 patients had a low LVEF when at rest and LVEF fell during exercise in this patient. However, occult left ventricular dysfunction was encountered in a further 15 of the 25 patients, since in these patients' LVEF did not increase normally during exercise, and indeed fell in 9. These results imply that occult left ventricular dysfunction is present in the majority of patients with chronic bronchitis and emphysema.

It might be argued that since the filling of one ventricle has an important effect on the distensibility and thus the function of the other chamber (16, 293, 325), then any left ventricular dysfunction is secondary to impairment of right ventricular function. However, this is not supported by the independence of the right and left ventricle responses in this study during exercise. Previous studies have described conflicting results of the effect of exercise on left ventricular performance (table 9). Some have reported a normal increase in LVEF during exercise in the majority of patients with chronic bronchitis and emphysema (221, 255), whereas others, as in this study, have shown that most patients have an abnormal left ventricular response during exercise (51, 217). However, in the two previous studies which showed a normal left ventricular response to exercise (221, 255), the patients studied differed fundamentally from those in this present study, since they did not significantly

ventricular response to exercise was abnormal in most patients (51, 217) do not quote the changes in arterial oxygen saturation during exercise.

Further evidence in support of the presence of left ventricular dysfunction in patients with chronic bronchitis and emphysema stems from the finding of left ventricular hypertrophy at post mortem in such patients (228, 246). In addition, increased left ventricular filling pressures have been observed in patients with chronic bronchitis and emphysema and have been cited as indicative of left ventricular dysfunction (20). Jezek and Schrijen (169) studied the effects of augmenting left ventricular afterload, by increasing systemic arterial pressures with an infusion of angiotensin, in patients with chronic bronchitis and emphysema. This augmentation of the left ventricular afterload produced abnormalities of left ventricular performance in those patients who had had evidence of 'cor pulmonale' but not in those with no evidence of 'cor pulmonale'. Similar results have also been reported by Baum et al (20). This data supports the findings of this present study of a low LVEF occurring almost exclusively in those patients with a history of oedema. The results of Jezek (169) and Baum (20) have, however, been challenged in two further studies (219, 357) where the pressor agent methoxamine was given to patients with chronic bronchitis and emphysema and it did not affect LVEF, stroke volume index or pulmonary capillary wedge pressure.

Moreover, Khaja and Parker (181) found normal left ventricular pressures both at rest and during exercise in patients with chronic obstructive pulmonary disease.

From a review of the literature it would appear that left ventricular function is normal when at rest except in those patients with decompensated 'cor pulmonale'. During exercise, at least some indices of left ventricular function, including the left ventricular ejection fraction are abnormal revealing occult evidence of left ventricular dysfunction. Furthermore, it has been suggested that the left ventricular dysfunction which occurs in decompensated 'cor pulmonale' is largely related to concomitant coronary artery disease or hypertension (311). The results of this present study do not support this, although the presence of occult coronary artery disease in the patients in this present study cannot be excluded.

Several factors have been proposed to account for the left ventricular dysfunction in patients with chronic bronchitis and emphysema, including hypoxaemia, acidosis, bulging of the interventricular septum into the left ventricular cavity and alterations in intra-thoracic pressures (16, 20, 52, 169, 173). The correlation between LVEF and PaO_2 in this study suggests that arterial hypoxaemia might have some role in producing left ventricular impairment. In addition, the marked negative swings in pleural pressure which occur during inspiration in patients with chronic bronchitis and emphysema, particularly on exercise, may contribute to an increased pulmonary arterial pressure, hence an increased venous return to the right heart. The resultant right ventricular dysfunction may cause the left ventricle to be effectively stiffer, and thus produce an increase in left ventricular end-diastolic pressure, which would decrease pulmonary venous return, and hence reduce left ventricular stroke volume (279). Moreover, left ventricular afterload may also increase as a result of the fall

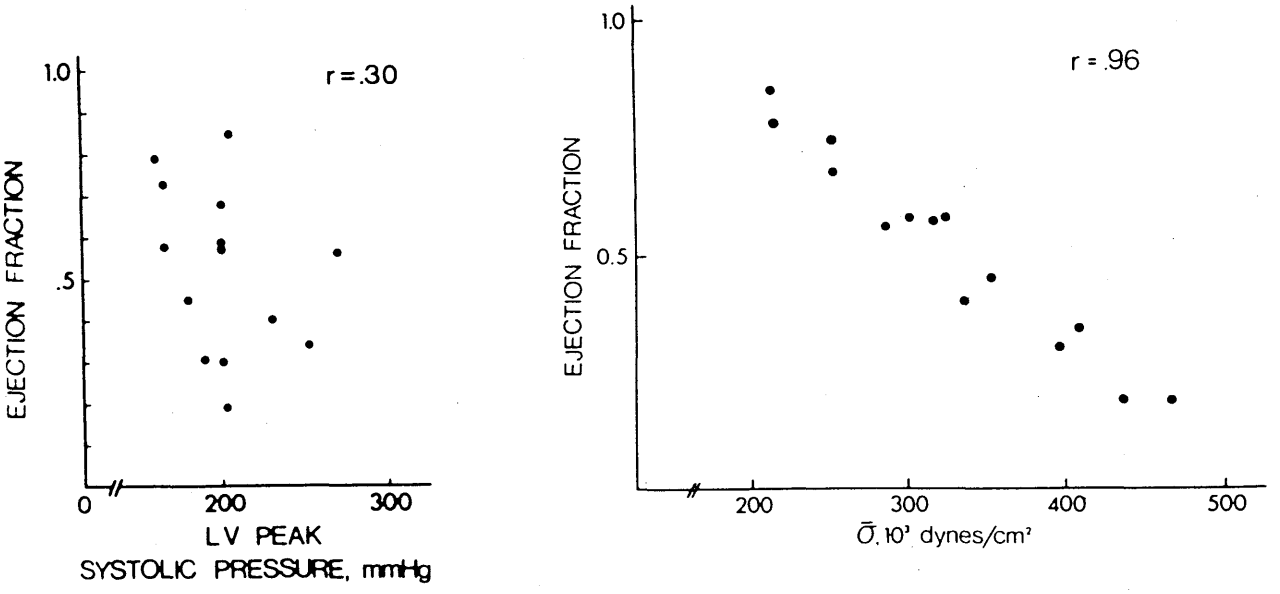
increase in left ventricular end-diastolic volume. The consequence of this fall in pleural pressure, therefore, may be to increase left ventricular end-diastolic volume and hence decrease LVEF (52, 360). The correlation between RVEF and LVEF seems to indicate an inter-dependence of the ventricles suggesting the reduction in LVEF is as a result of left ventricular dysfunction. Data from studies later in this thesis support this hypothesis.

Lack of correlation between PAP and RVEF

In this study there was no significant correlation between simultaneous measurements of RVEF and PAP in 50 patients with chronic bronchitis and emphysema, who had a wide range of values of both PAP and RVEF. Previous data in the literature has shown wide variations in the correlation between PAP and RVEF (table 10). Several factors may account for this variability. Firstly, there is a variation in the type of patient studied. Only three of these studies were exclusively in patients with chronic bronchitis and emphysema (46, 92, 210). The other studies were of normal subjects (240) or included patients with valvular or ischaemic heart disease (53, 72, 123, 189, 241, 360). In contrast to the present study, measurements of PAP and RVEF were not made simultaneously in the majority. A lapse of 2-6 days occurred in some instances between measurements (92, 123, 189, 241, 360).Conflicting results are quoted of the correlation between RVEF and PAP in each group of patients studied (table 10). Whereas Korr et al (189) and Morrison et al (241) found a significant correlation between PAP and RVEF in normal subjects and in patients with ischaemic or valvular heart disease. Winzelberg et al (360) found the opposite result in a similar group of patients. In a study by Ellis et al (92) of patients with

chronic bronchitis and emphysema no significant correlation between PAP and RVEF could be found, whereas Brent et al (46) has published the opposite finding. However, these latter authors, in a similar group of patients, have also published results showing no significant correlation between PAP and RVEF (210). However, there may be more fundamental reasons why a good correlation between PAP and RVEF should not be expected.

Ventricular systolic function is influenced by numerous factors (table 11). In broad terms these can be classified as afterload, contractility and preload. Which is the most important determinant of RVEF is still debated (63). Studies which have shown a highly significant correlation between PAP and RVEF have suggested that RVEF is very dependent on afterload (46). Right ventricular afterload is, by definition, the stress or tension acting on the fibres of the ventricular wall immediately after the onset of shortening (62), and is paramount in determining the quantity of blood ejected by the ventricle. Thus, right ventricular afterload can be measured as the force per unit cross-sectional area acting on the right ventricular wall (43, 44). Assessment of right ventricular wall stress requires measurements of both right ventricular volume and wall thickness. Because of the complex and variable geometric configuration of the right ventricle, these measurements have not been possible. Thus estimates of right ventricular afterload have been made from the pulmonary arterial pressure, which represents only a fraction of the true right ventricular afterload, and assumes that intra-cavity pressure closely approximates to transmural pressure (263). This assumption may not be valid in patients with air flow limitation. Pulmonary vascular resistance may be a slightly more accurate reflection of the true right ventricular afterload but it is



Relationship between ejection fraction and LV peak systolic pressure (left) and mean midwall circumferential wall stress (right)
(Gunther and Grossman, circulation 1979; 59 : 679)

Figure 33 In patients with aortic stenosis there was no significant correlation between left ventricular ejection fraction (LVEF) and the peak left ventricular systolic pressure (left). However, in the same patients LVEF did correlate with the mean mid wall circumferential wall stress (right), which accurately reflects the true left ventricular afterload.

It may be useful to examine similar relationships in the left ventricle, where measurements of afterload are easier to obtain. In a study by Gunther and Grossman (132) in patients with aortic stenosis, a situation of pressure overload hypertrophy somewhat analogous to patients with pulmonary hypertension, there was no significant correlation between peak left ventricular systolic pressure (analogous to right ventricular systolic pressure or pulmonary arterial pressure in the right ventricle) and the LVEF (figure 33). Gunther and Grossman argued that although the LVEF was dependent on ventricular afterload, together with preload and contractility, the peak left ventricular systolic pressure represented only a fraction of the true left ventricular afterload resulting in a lack of significant correlation with the LVEF. However, in these patients, when mean left ventricular mid wall circumferential wall stress was measured, which represents the true left ventricular afterload, there was a highly significant correlation between this and the LVEF (figure 33). It may be that if measurements of right ventricular wall stress could be made they would correlate significantly with the RVEF.

Some support for this argument comes from this present study, where although there was no significant correlation between PAP and RVEF, the ejection fraction did correlate significantly with simultaneous measurements of total pulmonary vascular resistance, which may reflect right ventricular afterload more accurately than does PAP (figure 31). In addition, the assessment of ventricular wall stress includes a measurement of the ventricular wall thickness which would become a more important determinant of afterload in patients with

have right ventricular hypertrophy.

Two other factors from table 11 may have lead to the lack of correlation between PAP and RVEF. Firstly, the presence of occult tricuspid incompetence which may have been present in some of our patients since the clinical criteria for the diagnosis of tricuspid incompetence is extremely insensitive (196). Tricuspid incompetence would result in a falsely high RVEF. Secondly, the presence of right coronary artery stenosis, which may not have been apparent clinically could have affected the RVEF (100).

Conclusions

1. Right ventricular ejection fraction, although lower than in normal subjects, is well preserved in the majority of patients with chronic bronchitis and emphysema.
2. In these patients the presence of oedema at the time of study, isassociated with a lower right ventricularejection fraction compared to those without oedema.
3. Right ventricular ejection fraction in patients with chronic bronchitis and emphysema is significantly correlated with arterial oxygen and carbondioxide tensions and with the left ventricular ejection fraction.
4. Occult right ventricular dysfunction can be demonstrated during exercise in most patients. The change in right ventricular ejection fraction during exercise is related to the change in arterial oxygen saturation.
5. Left ventricular ejection fraction is normal in the majority of patients with chronic bronchitis and emphysema but is low when these patients have oedema.

arterial oxygen and carbon dioxide tensions.

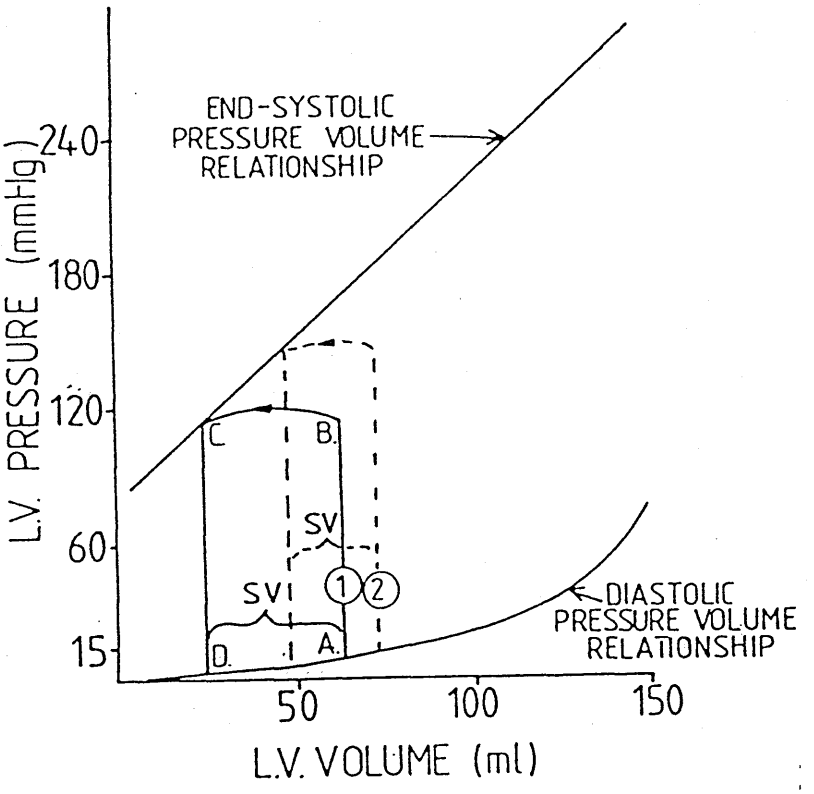
7. The change in left ventricular ejection fraction is not related to the change in right ventricular ejection fraction during exercise, but there is a correlation between these variables when measured at rest.

8. Right ventricular ejection fraction cannot be used in patients with chronic bronchitis and emphysema to predict pulmonary arterial pressure but is related to afterload as measured by the total pulmonary vascular resistance.

RIGHT VENTRICULAR SYSTOLIC FUNCTION IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND PULMONARY ARTERIAL HYPERTENSION

As described in chapter 4, right ventricular performance, as assessed by the right ventricular ejection fraction, is well preserved in the majority of patients with chronic bronchitis and emphysema. Although dependent on right ventricular afterload, the ejection fraction does not appear to be related to the pulmonary arterial pressure, at least in the patients studied in this dissertation. However, the right ventricular ejection fraction is influenced by the loading conditions of the ventricle, independent of changes in muscle function, and thus may not be an accurate assessment of muscle or 'pump' function of the ventricle in patients with an increased afterload (43). To determine the 'contractility' or inotropic state of the right ventricle, as distinct from its performance, as assessed by the RVEF, we must assess a function of the right ventricle which is independent of changes in preload or afterload.

In recent years, new indices have been developed to assess left ventricular function. These indices, reviewed in detail by Sagawa (291) depend on the relationship between the pressure and volume of the ventricle at end-systole. The concept of the end-systolic pressure/volume relation was first developed in isolated heart preparations (290), but more recently, has also been shown to be applicable in intact man (129, 226). The changes in the relationship between left ventricular pressure and volume in isolated heart preparations, can be plotted as a continuous pressure-volume loop, which is useful in understanding the ventricular response to



AFTER BRAUNWALD (ed). Text book of Cardiovascular Medicine. W.B. Saunders Philidelphia: 1980

Figure 34 Effects of varying afterload (with the level of contractility remaining constant) on the left ventricular (LV) end-systolic pressure/volume relationship. Contraction (1) results in the pressure volume loop A-B-C-D. An increase in aortic systolic pressure (contraction [2]) reduces stroke volume. However, the ratio of end-systolic pressure/volume remains constant.

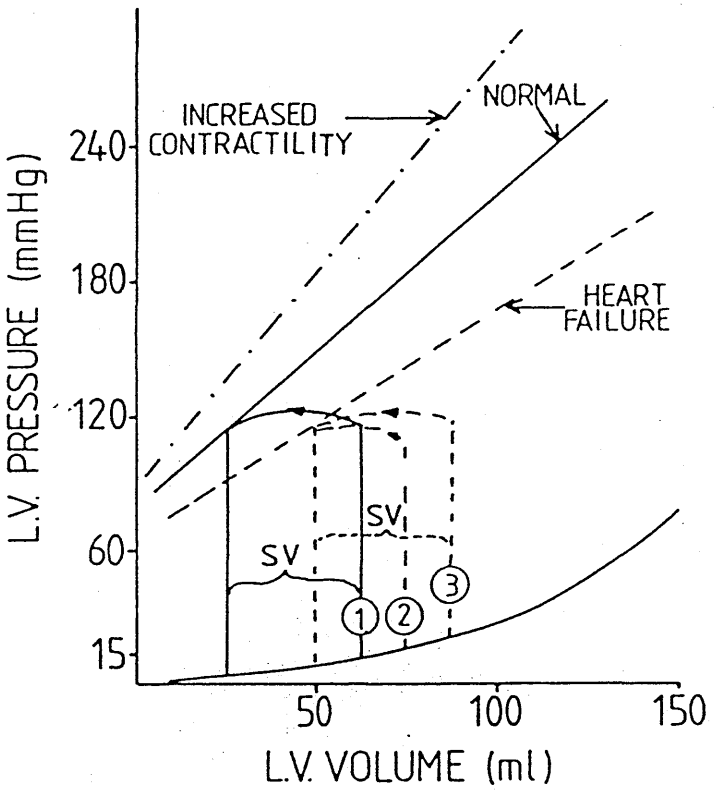


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Figure 35 In the presence of heart failure the left ventricular (LV) end-systolic pressure/volume relationship remains linear, but is displaced downwards and to the right. Thus, in heart failure, the stroke volume will be diminished (contraction 2) unless the end-diastolic volume increases further. In conditions of increased contractility, the end-systolic pressure/volume relationship is displaced upwards and to the left. The normal pressure volume loop (contraction 1) is shownfor comparison.

volume, has been shown to be independent of the initial ventricular volume, and is thus independent of the preload (321). Moreover, the relationship between end-systolic force, or afterload, and end-systolic length is also linear (figure 34) (344). Thus, for a given contractile state when afterload increases there is less complete emptying of the ventricle, and the end-systolic volume is greater. However, the end-systolic pressure/volume ratio remains constant, indicating that this relationship is also independent of changes in afterload. The linear relationship between end-systolic pressure and volume in the left ventricle, shifts downwards and to the right in states of decreased contractility such as heart failure, and upwards and to the left, increasing its slope, during infusion of a positive inotrope (figure 35) (43, 44). Thus, this relationship is particularly important since it defines the inotropic state of the ventricle, independent of the end-diastolic volume (preload) or the outflow tract pressure (as an estimate of afterload) (291). The end-systolic pressure/volume ratio is therefore sensitive to acute changes in the contractility of the ventricle.

In this chapter I will describe a study where measurements of RVEF were combined with simultaneous, but independent, measurements of the stroke volume, by thermodilution to quantify right ventricular volume, a parameter which has been difficult to estimate in the right ventricle before the introduction of radionuclide techniques. Simultaneous recording of right ventricular pressure thus enabled measurements of the end-systolic pressure/volume relationship to be calculated in patients with chronic bronchitis and emphysema, and in this way to assess right ventricular muscle function or contractility in these patients.

Patients and method

Twenty patients with severe chronic bronchitis and emphysema were studied (table 12). All of these patients had severe airflow limitation, were hypoxic with variable degrees of hypercapnia, and all had pulmonary arterial hypertension at the time of study (table 13). Eleven of these patients had a past history of peripheral oedema, when a diagnosis of `cor pulmonale' was made. At the time of study, however, all of the patients were in a stable condition since they were being assessed for long term domiciliary oxygen. Their recent clinical condition was unchanged, with no episodes of oedema or infective exacerbations of their bronchitis within three weeks of the study date. In addition their body weight, arterial blood gas values and ventilatory capacity were stable over this period. None of these patients manifested clinical evidence of hypertensive, ischaemic or valvular heart disease and, in particular, none had clinical evidence of tricuspid incompetence. Drug therapy in these patients consisted of inhaled beta-sympathomimetics in all patients, together with inhaled ipratropium bromide in nine of the twenty who were studied. None of the patients were receiving domiciliary oxygen, theophyllines or digoxin at the time of study. Of the eleven patients who had previous episodes of peripheral oedema, eight continued to receive diuretics in the form of 80-120 mg of frusemide with potassium supplements. In each case the patient`s medication was given on the evening before the study, but not on the morning of the study, so as to ensure haemodynamic stability throughout. Patients were studied in the post prandial state, in the afternoon, without premedication.

Right and left ventricular ejection fractions were measured by gated equilibrium radionuclide ventriculography, as described in detail in chapter 3.

Haemodynamic techniques

These patients were studied while resting semi-supine breathing room air. A fine arterial line (Vigon Ltd 18F) was inserted into the non-dominant brachial artery, under local anaesthetic to allow sampling of arterial blood. A Swan ganz balloon tipped thermodilution pulmonary arterial catheter (No 7F) was passed from either an antecubital vein or from the femoral vein to the pulmonary artery. Heart rate and rhythm were monitored continuously from the electrocardiogram. Intra-vascular pressures were zero referenced to a point 5 cm below the angle of Lewis. All intra-cardiac pressures were measured by averaging over at least three respiratory cycles. Mean pressures were calculated by electronic integration. Cardiac output was measured by the thermodilution technique (thermodilution computer Edwards laboratories) the average of three measurements with a variability of less than 10% was used in the analysis.

At least 15 minutes were allowed after the insertion of the arterial and pulmonary catheters before any haemodynamic parameters were recorded. All measurements, including the radionuclide ejection fractions, were made simultaneously, and where this was not possible sequentially (eg PAP and right ventricular systolic pressure measurements). From the haemodynamic and ejection fraction measurements the following variables were derived:

Body surface area

Stroke volume index (SVI) (ml. m^{-2}) = $\frac{\text{Cardiac index x 1000}}{\text{Heart rate}}$

Total pulmonary vascular resistance (PVR) (dynes.s.cm^{-5}) = $\frac{\text{80 x mean PAP}}{\text{cardiac output}}$

Systemic vascular resistance (SVR) (dynes.s.cm^{-5}) = $\frac{\text{80 x mean arterial pressure}}{\text{cardiac output}}$

Right ventricular end-diastolic volume index (RVEDVI) (ml.m^{-2}) = $\frac{\text{SVI}}{\text{RVEF}}$

Right ventricular end-systolic volume index (RVESVI) (ml.m^{-2}) = RVEDVI - SVI

Right ventricular stroke work index (RVSWI) (g.m.m^{-2}) = systolic RV pressure - diastolic RV pressure x SVI x 0.0136

In ten of these patients, who did not have significantly different arterial blood gas values, ventilatory capacity or PAP from the group as a whole, control measurements were made and thereafter haemodynamic, radionuclide and arterial blood gas measurements were repeated during intravenous infusion with sodium nitroprusside, at an

at least 5 mmHg. Thus right ventricular performance, as assessed by the relationship between end-systolic pressure and volume could be assessed at a reduced afterload, and compared with the control measurements.

Normal values of cardiac index, and right sided cardiac pressures published by Gurtner et al (133) were combined with measurements of RVEF in normal subjects (from this thesis) to estimate the normal right ventricular volumes.

RESULTS

All of the 20 study patients had severe airflow limitation; mean FEV_1 0.7 l (range 0.4 - 1.31), mean FVC 1.81 (range 0.8 - 3.31) (table 12). All were hypoxaemic (PaO_2 7.1 kPa, range 4.5 - 8.8 kPa) when breathing air, and the majority had carbon dioxide retention ($PaCO_2$ 6.6 kPa, range 4.4 - 8.6 kPa). The hydrogen ion concentrations in arterial blood were normal in the majority of patients although a few patients had a minimal elevation of the hydrogen ion concentration when breathing room air (mean H^+ ion 42 nmol/l, range 35 - 48 nmol/l).

Since the aim of this study was to assess the effects of pulmonary hypertension on the right ventricular performance, all of the patients had pulmonary hypertension of variable severity (table 13). The mean PAP for the group was 29 mmHg, on average, (range 20 - 46 mmHg) (normal mean PAP < 20 mmHg, table 15). Right ventricular systolic pressure (RVSP) was also elevated in all of the patients

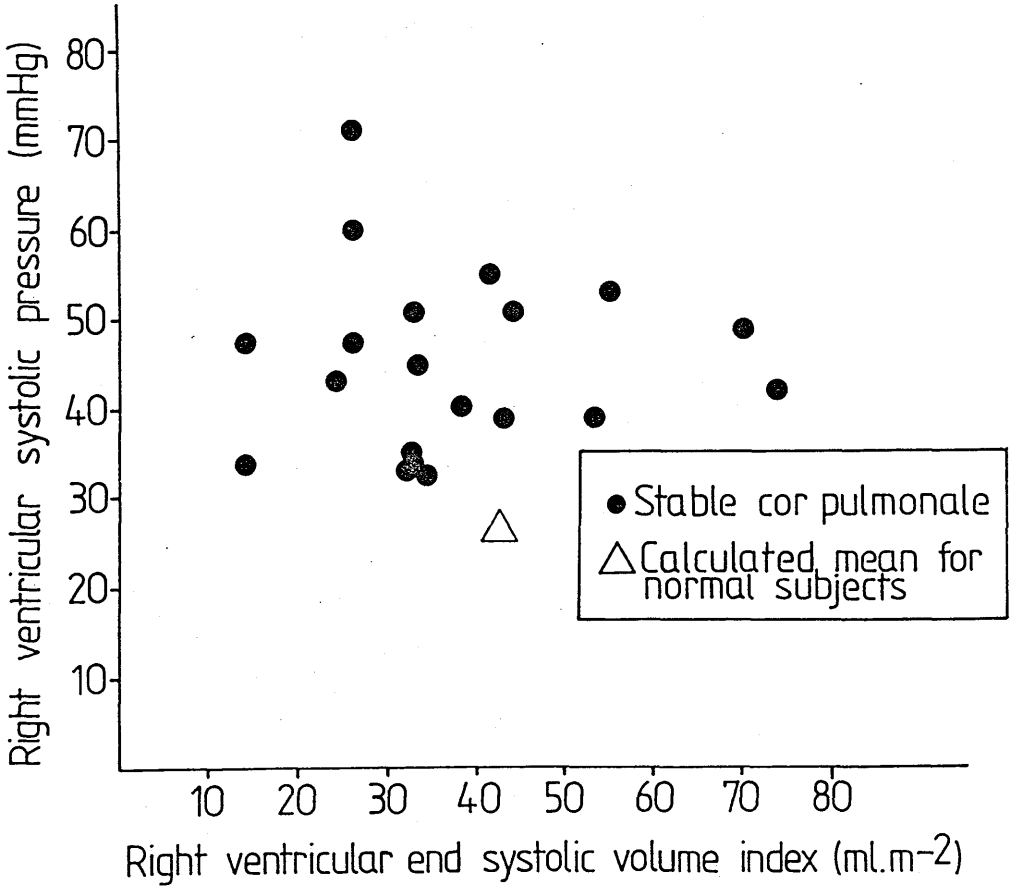


Figure 36 Individual right ventricular end-systolic pressure/volume points (P/V) (●) in 20 patients with chronic bronchitis and emphysema and pulmonary hypertension.

Most of the right ventricular pressure/volume points in the patients lie upwards and to the left of the calculated mean right ventricular P/V point for normal subjects (Δ).

ventricular end diastolic pressure was 6 $\pm$ 2 mmHg, and was abnormally high in only 3 patients. The average cardiac index was at the lower end of the normal range (mean CI 2.61 $\pm$ 0.57 ml. min^{-1}. m^{-2}). None of the 20 patients had an elevated cardiac index. However, the cardiac index was below normal in 8. The total pulmonary vascular resistance (PVR) was elevated in every patient (mean PVR 545 $\pm$ 141 dynes. s. cm^{-5}). The right ventricular end-diastolic volume averaged 68 $\pm$ 21 ml. m^{-2} which was lower than the mean estimated for normal subjects (79 ml. m^{-2}). The mean right ventricular end systolic volume index was 37 $\pm$ 16 ml. m^{-2} and was not dissimilar to the value calculated for normal subjects (table 14). The mean right ventricular ejection fraction in these patients was 0.46 $\pm$ 0.09, and was abnormal (RVEF < 0.40) in only 4 patients. Mean left ventricular ejection fraction was 0.57 $\pm$ 0.09, and was normal (LVEF > 0.45) in all of the patients.

The mean right ventricular stroke work index (RVSWI) in these 20 patients with chronic bronchitis and emphysema was 16.3 $\pm$ 6.2 g.m.m^{-2} which was significantly higher than the mean RVSWI for normal subjects (12.3 $\pm$ 3.1, $p < 0.01$, table 14).

The mean right ventricular end-systolic pressure volume relation, indexed to body surface area (P/V) was 1.41 $\pm$ 0.68, compared with the calculated mean for normal subjects of 0.78 (table 14). When individual right ventricular end-systolic P/V points for the 20 patients are plotted on a pressure volume diagram (figure 36) most of the points lie above and to the left of the estimated mean end-systolic P/V point of normal subjects.

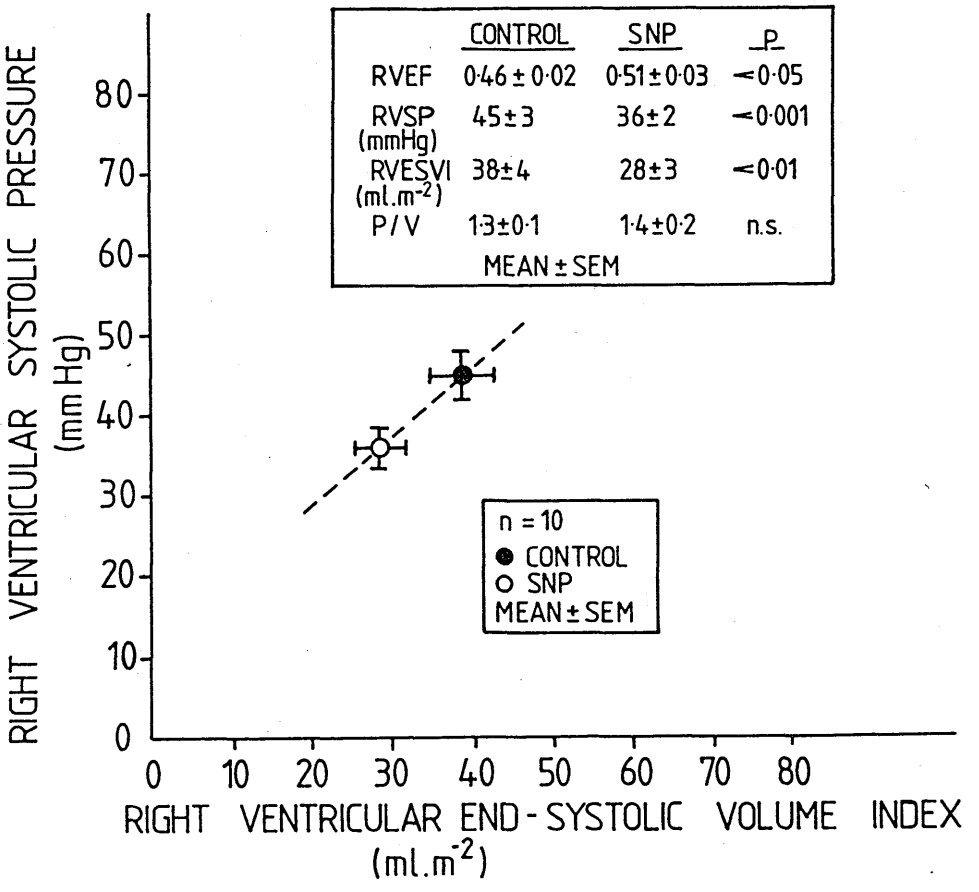


Figure 37 Sodium nitroprusside displaced the mean right ventricular end-systolic pressure/volume point in 10 patients with chronic bronchitis and emphysema downwards and to the left. However, since the right ventricular systolic pressure (RVSP) and right ventricular end-systolic volume index (RV_{ESVI}) were both reduced by similar amounts, there was no significant change in the right ventricular end-systolic pressure volume index (P/V).

correlated significantly with the right ventricular end-systolic pressure volume index ($r = 0.80$, $p < 0.001$). There was no correlation between the RVEF and the cardiac index ($r = -0.03$) but there was a significant correlation between the RVEF and the end-diastolic volume index ($r = -0.61$, $p < 0.01$).

The effect of pulmonary vasodilatation

During infusion with sodium nitroprusside (SNP) in 10 patients (table 16) heart rate increased significantly, cardiac index was unchanged, and therefore stroke volume index fell by a small but significant amount. Mean PAP fell from 30 ± 6 to 22 ± 6 mmHg ($p < 0.01$) as did RVSP from 45 ± 10 to 36 ± 8 mmHg ($p < 0.01$). Pulmonary vasodilatation occurred since cardiac index was unchanged by SNP and the total pulmonary vascular resistance fell from 540 ± 126 to 400 ± 140 dynes. s. cm^{-5} ($p < 0.001$). This pulmonary vasodilatation produced no significant change in arterial oxygen saturation. The right ventricular stroke work decreased significantly from 17.2 ± 6.2 to 12.8 ± 5.1 g. m. m^{-2} ($p < 0.01$). The RVEF increased from 0.46 ± 0.07 to 0.51 ± 0.11 during the infusion with SNP ($p < 0.05$). Both the right ventricular end-diastolic and end-systolic volume indexes fell from control values of 70 ± 16 to 57 ± 11 ml. m^{-2} ($p < 0.01$) and from 39 ± 12 to 28 ± 9 ml.m^{-2} ($p < 0.01$) respectively.

Despite the reduction in pulmonary vascular resistance which produced an increase in RVEF, the right ventricular end-systolic pressure/volume ratio did not change significantly from a control value of 1.25 ± 0.44 to 1.39 ± 0.67 during infusion with SNP (figure 37). The measurement of the pressure/volume relationship at two levels of right ventricular afterload allowed definition of the

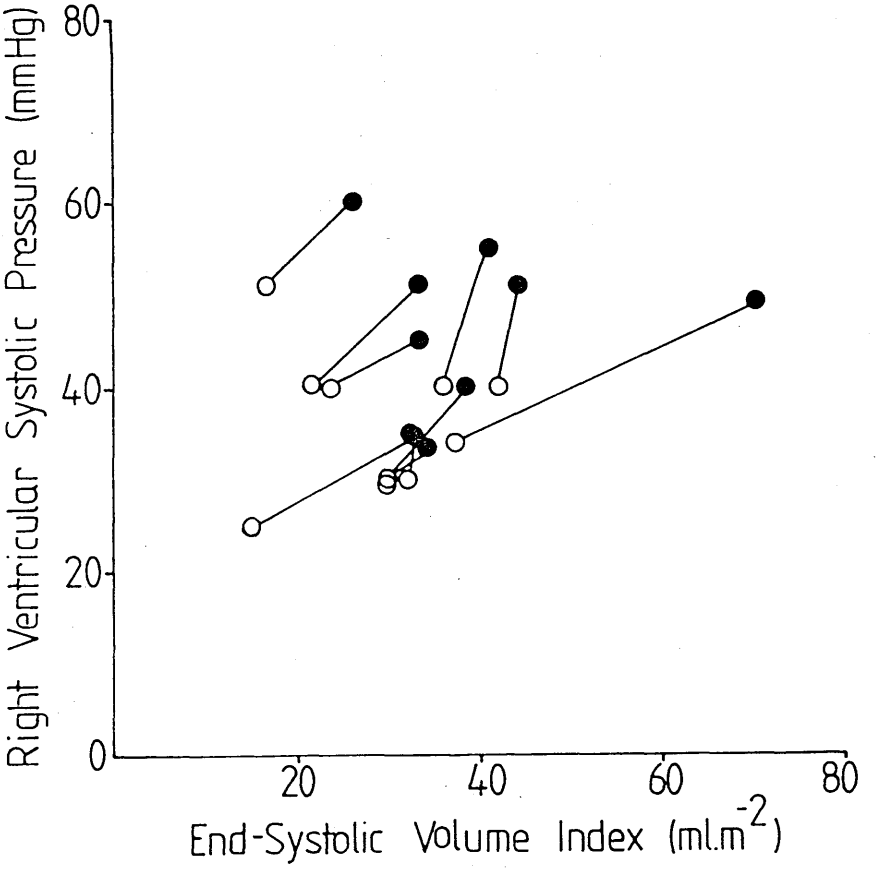


Figure 38 Individual right ventricular end-systolic pressure/volume points (P/V) in 10 patients with chronic bronchitis and emphysema before (●) and during infusion with sodium nitroprusside (o). Although the slopes of individual P/V lines joining these points are variable, most of the slopes are greater than unity, and sodium nitroprusside displaces the P/V points downwards and to the left in all cases.

slope of the line (E) joining these two pressure volume points could be calculated according to the equation: RVSP = E x RVESVI + B (RVSP = right ventricular systolic pressure, RVESVI = right ventricular systolic volume index, E is the slope describing their relation, B = pressure when the end-systolic volume is zero). The individual slopes of the pressure volume lines in these 20 patients were very variable (figure 38) mean E = 1.73 $\pm$ 1.81. There was no significant correlation between the right ventricular ejection fraction and the slope (E) of the pressure volume relation.

DISCUSSION

The traditional view of the consequences of chronic hypoxia in patients with chronic bronchitis and emphysema, is the development of pulmonary hypertension. This leads to increased right ventricular work and hence compensatory right ventricular enlargement and eventually `right ventricular failure' (figure 2) (113, 202). However, the results I have presented of measurement of RVEF in a population of patients with chronic bronchitis and emphysema have suggested that right ventricular performance is well preserved in the majority of patients, except those who have clinical evidence of oedema at the time of study. Moreover the right ventricular ejection fraction correlated poorly with the level of the pulmonary arterial pressure. These findings led to the study described in this chapter in which I have attempted to measure not only the `performance' but the `contractility' of the right ventricle in patients with severe chronic bronchitis and emphysema who were hypoxic, had pulmonary hypertension, and in the majority had previous episodes of oedema. Importantly, however, all of the patients were

In addition to measurements of pulmonary and right ventricular haemodynamics, simultaneous measurements of RVEF in this study enabled calculation of right ventricular volume, which is difficult using any other technique. Thus the right ventricular end-systolic pressure/volume relation could be calculated and used as a measure of right ventricular contractility (289). Although this index of ventricular function has been used extensively to study left ventricular mechanics (76, 167, 186) its use in the right ventricle has been very limited (46, 186). In fact, only one previous study has been undertaken to calculate this ratio in patients with chronic bronchitis and emphysema (46).

For ethical reasons I have not been able to compare the results of measurements of right ventricular mechanics in patients with those of normal subjects since such invasive studies would be unjustified in normal subjects. However, right heart catheterisation was performed in the patients as part of the routine assessment for long term domiciliary oxygen. For comparison, however, I have used the mean of measurements of pulmonary and right ventricular haemodynamics from 20 normal subjects studied by Gurtner et al (133) (table 14). I have combined these measurements with the mean RVEF which I have measured in 30 normal subjects (chapter 4). Thus I have been able to estimate the right ventricular volume, and hence the pressure/volume relation in normal subjects. Although not ideal, these measurements serve as a useful comparison since values of right ventricular volumes, derived from combined haemodynamic and radionuclide studies in normal subjects, have not been published previously.

I have used the normal values quoted by Gurtner (133) for several reasons. Firstly, the age range of these normal subjects is similar to those in whom I have measured RVEF. In addition Gurtner quotes complete haemodynamic data, in particular measurements of right ventricular systolic pressure (RVSP) and cardiac index which allows calculation of the right ventricular pressure/volume relation indexed to the body surface area. Moreover, I have not included any measurements from patients in Gurtner`s study where the quoted cardiac index or right ventricular systolic pressure is outwith the range of normal values quoted in standard texts (44). Having excluded such subjects from the analysis, I have calculated mean values of right ventricular systolic and cardiac index data from 20 normal subjects (table 14).

Although cardiac index and right ventricular ejection fractions were lower in the patients with chronic bronchitis and emphysema than in normal subjects, both variables were within normal limits in the majority of these patients. In previous studies in patients with chronic bronchitis and emphysema, the cardiac index has been found to be normal (57, 181), although those patients with high pulmonary vascular resistance have had either a high normal or low normal cardiac index. It has been suggested that the level of the cardiac index in patients with chronic bronchitis and emphysema may be related to the clinical pattern of the disease (57). Thus those with hypoxaemia and hypercapnia and the `blue and bloated' clinical picture tended to have a higher cardiac output at rest than those of the `pink and puffing' clinical type (57). The patients in this present study who all had elevated pulmonary vascular resistance were in the main of the `blue and bloated' type. However, in contrast to

normal range.

In all of the studies in this thesis I have used total pulmonary vascular resistance rather than pulmonary vascular or pulmonary arteriolar resistance. The reason for this is that the latter measurement includes a measurement of pulmonary capillary wedge pressure. There is controversy regarding the reliability of the measurement of pulmonary capillary wedge pressure in patients with severe chronic bronchitis and emphysema. In particular, there is debate as to whether this measurement truly reflects the left atrial pressure in patients with chronic lung diseases (197, 273). For this reason I have calculated the total pulmonary vascular resistance so as to avoid introducing a further error in the measurement of resistance.

The right ventricular end-diastolic and end-systolic volumes were similar in both normal subjects and patients with chronic bronchitis and emphysema. At a given level of contractility, if right ventricular afterload increases, the ventricle should empty less completely and end-systolic volume should increase. The fact that right ventricular end-systolic volume is relatively normal, despite the presence of increased pulmonary vascular resistance in these patients, suggests that right ventricular contractility may, in fact, be increased in these patients.

The right ventricular stroke work was also higher in the patients with chronic bronchitis and emphysema than in the normal subjects. The increase in right ventricular stroke work index in the patients in this present study was entirely due to the increase in pressure

5, 13, 14). Khaja et al (181) in a study of patients with chronic bronchitis and emphysema with and without `cor pulmonale', showed that although the relationship between right ventricular end-diastolic pressure and stroke index suggested that right ventricular function was depressed in those patients with cor pulmonale, when the right ventricular stroke work index was plotted against the right ventricular end-diastolic pressure, right ventricular function in response to exercise appeared normal. Khaja suggested that this paradox existed because the increased right ventricular work in these patients was as a result of work done against an increased afterload or `pressure work' and this resulted in a lower stroke volume index with a consequent reduction in the work expended in producing the stroke volume or `output work'. The findings of this present study would support these conclusions.

In this study the mean end-systolic pressure/volume ratios for the patients with chronic bronchitis and emphysema was similar to the calculated normal value (table 13, 14,) (figure 36). This would again indicate that right ventricular function is relatively well preserved in these patients despite the presence of pulmonary hypertension.

The right ventricular pressure/volume indexes in this study tended to be higher than those from the one previous study by Brent et al (45) where similar measurements have been made in patients with chronic bronchitis and emphysema. This difference can be accounted for by the higher right ventricular end-systolic volume in Brent`s study (Brent et al RV_{ESVI} 61 $\pm$ 22 ml. m^{-2}; this study RV_{ESVI} 37 $\pm$ 16 ml. m^{-2}) which resulted from a lower mean RVEF (RVEF 0.39 $\pm$ 0.07) compared

particularly in RVEF, are present despite a similar level of pulmonary arterial pressure in both studies. These contrasting results may be due to methodological differences in the measurement of RVEF as discussed previously in this thesis.

Several theoretical limitations must be taken into account when considering the use of the right ventricular end-systolic pressure/volume relation as a measure of right ventricular contractility. Firstly, the theoretical basis for the use of the end-systolic pressure/volume relationship as an indicator of contractility independent of ventricular loading conditions, comes mainly from studies in the left ventricle (38, 129, 226). It is possible that the use of this index may not be applicable to the more distensible right ventricle. However, Maugham et al, in studies of isolated canine ventricles, has suggested that the right ventricular end-systolic pressure/volume relation is analogous to that found in the left ventricle (224). Konstam et al also demonstrated a linear relation between end-systolic pressure and volume in the right ventricle in 10 patients with pulmonary hypertension as a result of cardiomyopathy or cardiac failure secondary to ischaemic heart disease or primary pulmonary hypertension (188).

One further criticism of the results presented here is the use of peak right ventricular systolic pressure and not the end-systolic pressure in the measurement of the pressure/volume relation. However, Marsh et al (215) demonstrated a close correlation between the slope of the pressure/volume relation obtained using either the peak or the end-systolic pressure from the left ventricle. These results have been confirmed by others (167). Thus at least in the

pressure. Furthermore, the use of the pressure/volume relationship may be limited by the fact that the right ventricular systolic prssure may not be an accurate measure of right ventricular afterload particularly if the dimensions of the right ventricle are altered. Afterload is the force which opposes ejection, that is, force = pressure x area. When this force is applied to a thick walled chamber, as may occur in the presence of right ventricular hypertrophy, then the La Place relation is more applicable:

$$\text{Stress} = P \cdot r/2h$$

(P = pressure; r = radius; h = thickness)

Thus the use of ventricular wall stress, which corrects for variability in wall thickness and chamber radius, is a more accurate reflection of afterload. However, such measurements have not been made for the right ventricle.

It is likely, as is the case in the left ventricle, that it is the slope of the end-systolic pressure/volume relation, rather than the ratio of pressure to volume itself which is the most sensitive measure of the inotropic status of the ventricle (290). It was Grossman who initially demonstrated the linearity of the end-systolic pressure/volume relation in the left ventricle, and its independence of the ventricular loading conditions, by measuring the end-systolic pressure volume relation at two different levels of left ventricular afterload (129). More recently, Mehmel convincingly demonstrated the linearity of the left ventricular end-systolic pressure volume relation by measuring the pressure volume relation at three different levels of right ventricular afterload (226). The assessment of this

therapeutic intervention which may not be indicated or ethical in some patients. Thus, as a simplification, in some studies, the end-systolic pressure/volume ratio has been used as a measure of contractility (167). When the line relating end-systolic pressure/volume passes through or near the origin, then any individual pressure volume ratio is a measure of the slope of the line defining the end-systolic pressure/volume relation, since in the equation:

$$RVSP = E \times RVESVI + B,\ B \text{ is zero.}$$

RVSP/RVESVI is therefore a measure of the slope E (RVESVI = right ventricular end-systolic volume index). As this is not the case in the majority of patients (figure 38) this simplification is often unjustified. However, if we assume that at higher right ventricular outflow pressure there will be a larger right ventricular volume given the same inotropic state, then a smaller ventricular volume for a given pressure indicates more complete ventricular contraction, suggesting an increase in the inotropic state of the ventricle. As RVSP was elevated in the patients in this study and the end-systolic and end-diastolic volumes were still relatively normal this suggests that right ventricular contractility was normal or even enhanced in these patients. The fact that RVEF was relatively well preserved supports this conclusion.

In order to determine the linearity of the right ventricular end-systolic pressure/volume relation and to measure the slope of the line describing this relation, 10 patients had measurements made before and after RVSP was reduced by an infusion of sodium

properties, but with no inotropic action. Sodium nitroprusside produced both systemic and pulmonary and vasodilatation as shown by the fall in systemic and pulmonary vascular resistance (table 13). These changes, however, did not produce any significant change in the cardiac index despite a small increase in heart rate since there was a small fall in stroke volume index. This probably occurred because of a reduction in right ventricular pre-load as a result of the venodilator properties of sodium nitroprusside. Thus both RVSP and RVESVI fell during the infusion with sodium nitroprusside producing no significant change in the pressure/volume relation. Although the slopes of the individual pressure volume lines varied widely (figure 38), there was no significant change in the mean pressure volume index for the group during infusion with sodium nitroprusside compared with the control value. This data supports the proposition that, as in the left ventricle, the right ventricular end-systolic pressure/volume relation is linear and relatively independent of the loading conditions of the ventricle.

Unfortunately I have no data for comparison of the slope of the pressure/volume relation in normal subjects. However, in 60% of the patients studied, the slope of the end-systolic pressure/volume relation (E) was greater than unity and E was < 0.50 in only 2 patients. This would suggest normal right ventricular contractility in the majority of these patients despite the presence of pulmonary hypertension.

The results presented in this study conflict with those of Brent et al (46) who found in a group of patients with chronic bronchitis and emphysema with a similar degree of pulmonary hypertension that the

was less than unity in all but one of the cases studied (mean E = 0.65 $\pm$ 0.21). Brent also found a poor correlation between the RVEF and either the pressure/volume index (P/V) or the slope of the pressure volume line at end-systole. This suggested that RVEF was a poor indicator of right ventricular contractility, again in contrast with the findings of the present study, and with results from studies of the left ventricle, where both the slope and the P/V index have been shown to correlate with the LVEF (226).

The data presented in this study suggests that the right ventricular performance is well maintained against a raised pulmonary arterial pressure. This finding is supported by a study by Konstam (188) who measured the pressure/volume relation in a population of patients with pulmonary hypertension secondary to left ventricular dysfunction or with primary pulmonary hypertension. These patients had much higher levels of pulmonary arterial pressure (mean PAP 47 $\pm$ 12 mmHg) than the patients with chronic bronchitis and emphysema in the present study (mean PAP 29 $\pm$ 7 mmHg). The slopes of the right ventricular pressure/volume relation (E) in Konstam`s study, were very variable. However, the mean E for these patients was similar to that measured by Brent et al (46) who studied patients with much lower levels of pulmonary arterial pressure (Brent et al E = 0.65 $\pm$ 0.25, Konstam et al E = 0.67 $\pm$ 0.70). Despite these very high levels of pulmonary arterial pressure in the patients studied by Konstam, (188) (E) was more than unity in many of the patients suggesting relatively normal right ventricular contractility.

Previous studies measuring other indices of right ventricular performance have also indicated relatively normal right ventricular

measured the right ventricular maximal isovolumic rate of development of ventricular pressure (dP/dt), and found this index of ventricular performance to be normal even in those patients with pulmonary hypertension and clinical evidence of `right ventricular failure' consequent on left ventricular dysfunction. Wroblewski et al (267) studied patients with pulmonary hypertension secondary to mitral stenosis, and assessed right ventricular performance curves by plotting stroke work against end-diastolic pressure , and stroke volume against end-diastolic pressure and Khaja et al (181) made a similar analysis in bronchitic patients. Both studies concluded that right ventricular function remained normal in these patients.

In conclusion:

1. In patients with stable chronic hypoxic bronchitis and emphysema, with pulmonary hypertension, the majority had normal RVEF and LVEF.
2. RVEF may not be a good indicator of right ventricular performance in the face of an increased right ventricular afterload.
3. The linearity of the right ventricular end-systolic pressure/volume relation has been demonstrated in patients with chronic bronchitis and emphysema, at different levels of right ventricular afterload.
4. Analysis of both the end-systolic pressure/volume ratio and the slope of the line describing this relation, indicates that right ventricular contractility is normal, or may even be enhanced in such patients despite the presence of chronic pulmonary hypertension.

The effects of oxygen on right ventricular performance in patients with chronic bronchitis and emphysema

The association between the chronic hypoxaemia, which develops in some patients with chronic bronchitis and emphysema, and pulmonary hypertension is well known (140). The presence of pulmonary hypertension, as discussed previously, is associated with a poor prognosis (80, 351). Oxygen, when given acutely to such patients, in relatively high inspired concentrations, reduces PAP (3, 105, 159, 359). Two controlled trials have now shown that long term domiciliary oxygen given in inspired concentrations of 24 - 35% can prolong survival in patients with hypoxic chronic bronchitis and emphysema (225, 251). Neither of these trials, however, showed that oxygen therapy given for 15 - 24 hours/day produced a significant fall in PAP. However, the slow progression of pulmonary hypertension which is seen in such patients (350) was prevented by domiciliary oxygen therapy. Oxygen might be expected to improve right ventricular function at rest, or during exercise, both when given acutely, and over the longer term, and should presumably delay the development of 'cor pulmonale'. Detailed studies of the effects of oxygen, given in inspired concentrations currently used during acute exacerbations of chronic bronchitis and emphysema, or as domiciliary oxygen, have not been published.

The aims of the studies in this chapter were to assess the effect of 'controlled' oxygen on right ventricular performance in patients with hypoxic chronic bronchitis and emphysema, when given acutely at rest, on exercise, and over a period of 6 months.

Thirty four patients with chronic bronchitis and emphysema were studied (table 17).

The acute effects of oxygen at rest

Eight patients with severe chronic bronchitis and emphysema (table 17, group I) had simultaneous measurements of left and right ventricular ejection fractions, and pulmonary and right ventricular haemodynamics made when at rest, breathing air or oxygen, both given at a flow rate of 3 litres/minute by nasal prongs in a single blind, random order. All of these patients were being assessed for domiciliary oxygen therapy. They were current non-smokers, had a longstanding history of chronic bronchitis and emphysema, were in a stable condition at the time of study, as shown by stable arterial blood gas values FEV_1 and body weight and had no evidence of infective exacerbations over the 3 week period prior to study. All had pulmonary arterial hypertension and had previous episodes of oedema when a diagnosis of cor pulmonale was made. Patients were considered suitable for domiciliary oxygen if their arterial oxygen tension when breathing air was less than 8 kPa when their condition was stable, with or without carbon dioxide retention and if carboxyhaemoglobin measurements indicated that the patient was not smoking. One patient had a PaO_2 which was greater than 8 kPa (group I, patient number 3) and was being assessed for long term oxygen therapy since he had had episodes of oedema in the past indicative of cor pulmonale.

The preparation for cardiac catheterisation, the methods of measurement of the haemodynamic variables and the radionuclide techniques are described in Chapter 4. None of the patients had

previously received domiciliary oxygen therapy. Their routine medications, which consisted of inhaled bronchodilators and in some cases diuretic therapy were given on the night prior to the study so as to ensure haemodynamic stability. All of the 8 patients had previous episodes of peripheral oedema at which time a diagnosis of cor pulmonale was made. None of the patients had oedema at the time of study.

The acute effects of oxygen during exercise

The effects of exercise and oxygen on right ventricular performance were studied in a further 16 patients with chronic bronchitis and emphysema, with less severe disability (Table 17, group II). In this study ventricular ejection fractions were measured by radionuclide ventriculography together with ear oxygen saturation non-invasively, using a Hewlett Packard ear oximeter. All of the measurements were made when the patients were upright except as described later in 6 patients who performed supine exercise. Measurements were made at rest and during upright exercise when breathing air or oxygen (both given at a flow rate of 3 litres/minute by nasal prongs). The order of the periods of rest or exercise and whether oxygen or air was breathed were randomised.

Six of these patients also had, in addition, simultaneous measurements of pulmonary arterial pressures after the insertion under local anaesthetic of a Swann Ganz catheter as described earlier. In these patients arterial blood gas samples were taken from an indwelling fine arterial catheter placed in the brachial artery. The pulmonary and arterial catheters were inserted under local anaesthetic 30 minutes before the measurements were made. In these 6 patients measurements of pulmonary arterial pressure were

cardiac catheterisation were also being assessed for long term domiciliary oxygen but were different patients from those in Group I. Measurements of pulmonary arterial pressure were not made in all 16 patients who exercised since right heart catheterisation was not ethically justified in these mildly disabled patients.

Before the exercise study was undertaken each patient performed a trial period of exercise to determine if they could complete the protocol. In addition, this `trial run' allowed calculation of the patient`s maximum voluntary exercise tolerance (MVET). During the study the exercise workload was fixed at 50% of MVET, each patient exercising at this fixed workload for 5 minutes while measurements were made.

Following the injection of technetium^{99m} HSA as described previously, data was acquired for 4-5 minutes for the measurement of ejection fractions when at rest and during exercise. Measurements of ear oxygen saturation or arterial blood gas tensions, and in 6 pulmonary arterial pressure, were made during the 4th - 5th minute of exercise. A fall in oxygen saturation and rise in pulmonary arterial pressure occurred during the first 3 minutes of exercise, the levels becoming constant between the 3 - 5 minute. A submaximal exercise protocol was chosen to ensure relative steady state, and to avoid the potential adverse effects on myocardial contractility of lactic acidosis due to anaerobic metabolism. I chose not to measure oxygen consumption during exercise because this would require the patients to breathe from a mouthpiece which could not be tolerated in all of the patients.

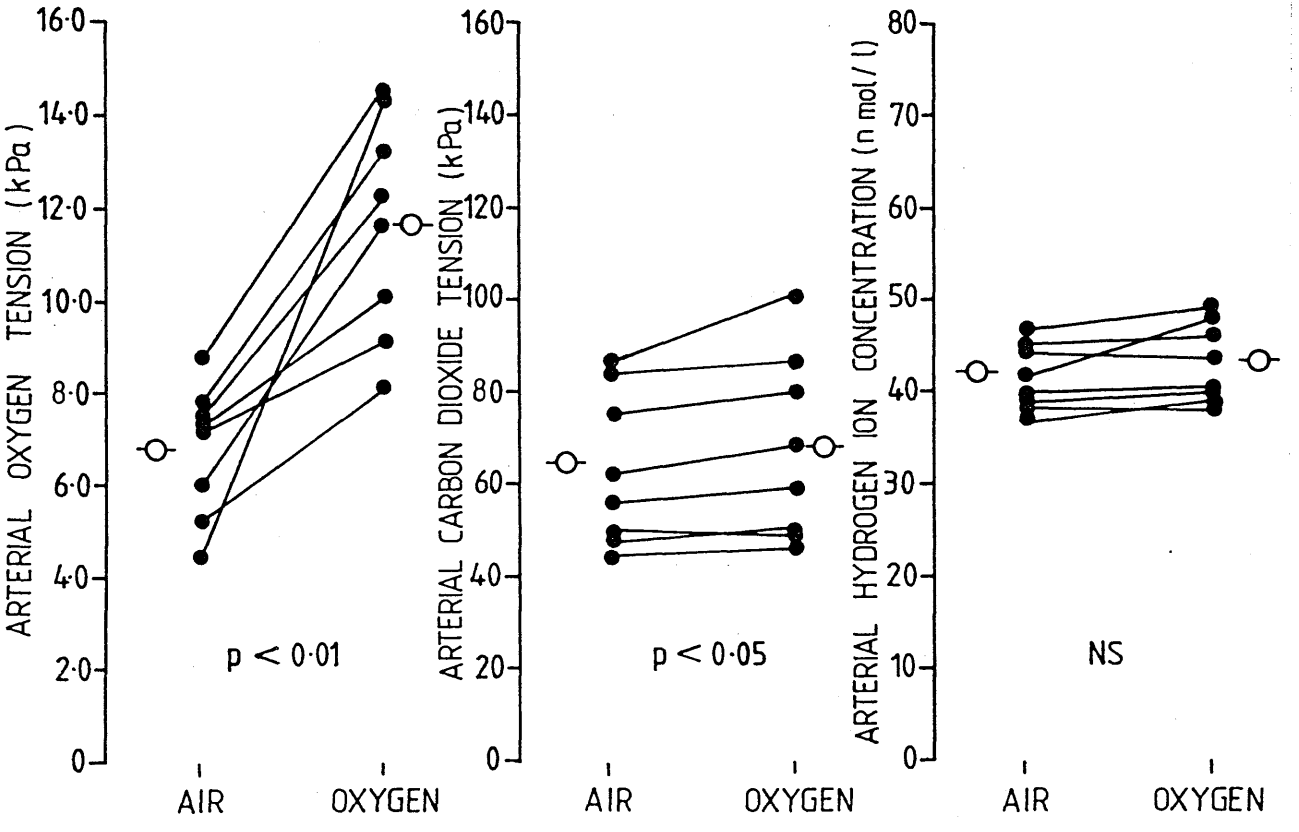


Figure 39 The effects of oxygen (3 litres/minute, nasal prongs) on arterial blood gas tensions in 8 patients with chronic bronchitis and emphysema at rest.

of oxygen or air given in a single blind random fashion by nasal prongs at a flow rate of 3 litres/minute for at least 20 minutes or until the ear oxygen saturation or the arterial PaO_2 was stable for at least 5 minutes.

The effect of long term oxygen

Ten patients (Table 17, group III) had measurements of PAP and ventricular ejection fractions when at rest, breathing room air, before and after 6 months long term domiciliary oxygen was given at a flow rate of 1 -3 litres/minute by nasal prongs for 15 - 24 hours/day. The exact flow rate of oxygen was chosen so as to produce an arterial oxygen tension of at least 8 kPa without producing a rise in $PaCO_2$ sufficient to change the arterial hydrogen ion concentration. Each study was undertaken when the patients clinical condition was stable with no change in FEV_1, body weight, arterial blood gas tensions and no clinical evidence of peripheral oedema or infective exacerbations of bronchitis for 3 weeks prior to study.

Formulas for derived haemodynamic variables are shown on page (99). In addition, the following variables were calculated:

arterial and mixed venous oxygen contents

$(CaO_2$ and $CVO_2)$ (ml/100 ml) = $(1.34 \times Hb \times SO_2) + (0.0031 \times PO_2)$

systemic oxygen delivery

$(ml/min/m^2) = CI \times CaO_2$

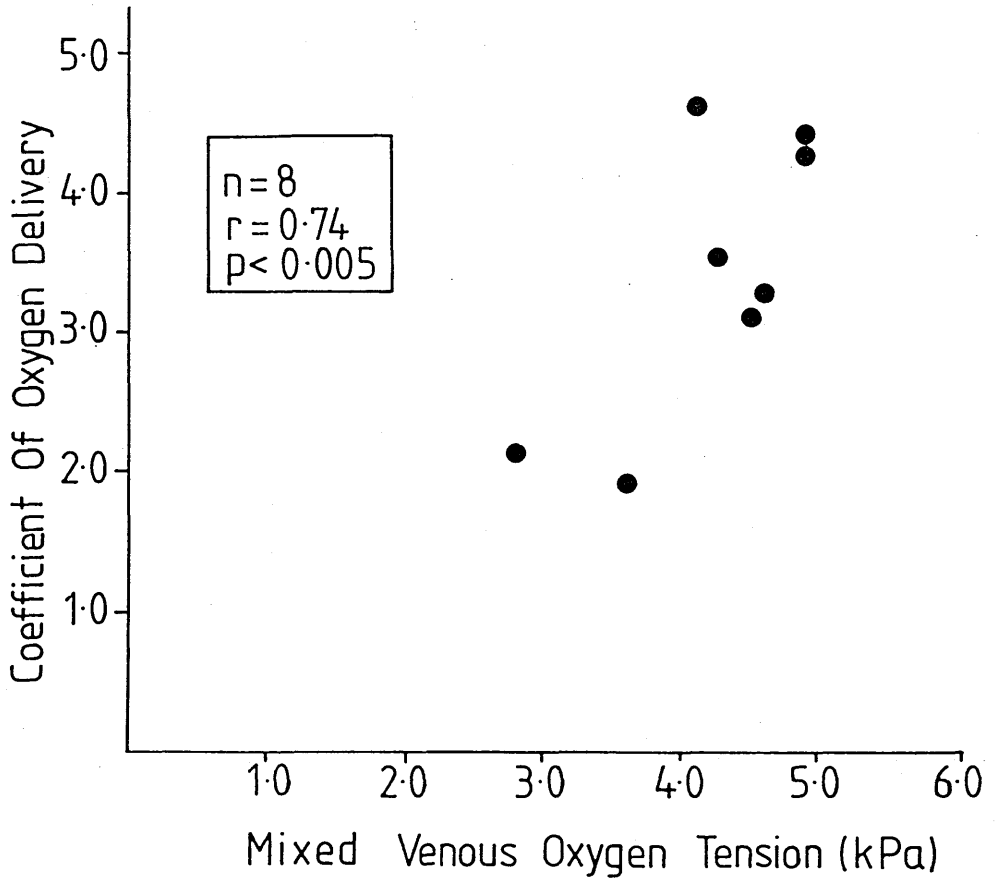


Figure 40 Relationship between the mixed venous oxygen tension and the coefficient of oxygen delivery in 8 patients with chronic bronchitis and emphysema.

$$CaO_2 - CvO_2$$

Results

Acute effects of oxygen at rest

Arterial blood gas data

Oxygen, when given at rest to 8 patients increased PaO_2 from 6.8 $\pm$ SEM 0.4 kPa to 11.6 $\pm$ 0.8 kPa ($p < 0.01$) (table). A rise in PaO_2 above 8 kPa occurred in all patients and in SaO_2 to a level above 90%. As is often the case in patients with type II respiratory failure breathing oxygen, even at inspired concentrations of between 24 - 35% can, by the partial removal of the hypoxic ventilatory drive, lead to an increase in $PaCO_2$ (208, 234). In these patients breathing oxygen resulted in a small rise in $PaCO_2$ from 6.5 $\pm$ 0.5 kPa to 6.9 $\pm$ 0.6 kPa ($p < 0.05$), but this did not produce any significant change in the arterial hydrogen ion concentration (table 18, figure 39). Mixed venous oxygen tension (PVO_2) also increased in every patient while breathing oxygen, from a mean of 4.3 $\pm$ 0.2 kPa to 5.1 $\pm$ 0.2 kPa ($p < 0.05$). This resulted in an increase in systemic oxygen delivery from 41 $\pm$ 4 to 48 $\pm$ 4 ml/min/m^2 ($p < 0.01$). The increases in arterial and venous oxygen contents were similar when breathing oxygen, and therefore the arteriovenous oxygen difference was unchanged. The increase in arterial oxygen content also resulted in an increase in the coefficient of oxygen delivery which occurred in every patient while breathing oxygen. There was a signficiant correlation between the mixed venous oxygen tension and the coefficient of oxygen delivery in these 8 patients when measured at rest, breathing air (figure 40) ($r = 0.69$, $p < 0.05$).

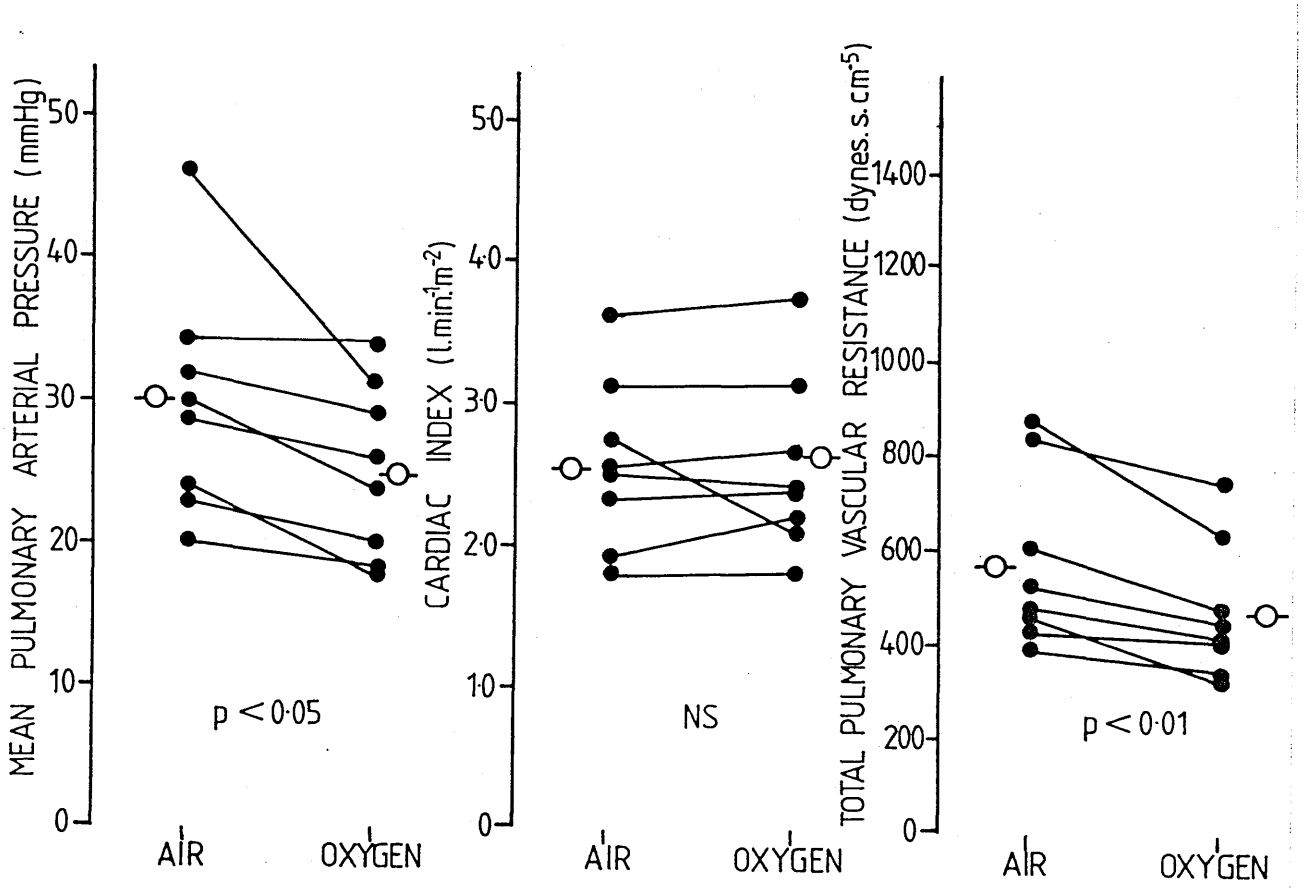


Figure 41 The effects of oxygen (3 litres/minute, nasal prongs) on pulmonary artery pressure, cardiac index and pulmonary vascular resistance when given to 8 patients with chronic bronchitis and emphysema at rest.

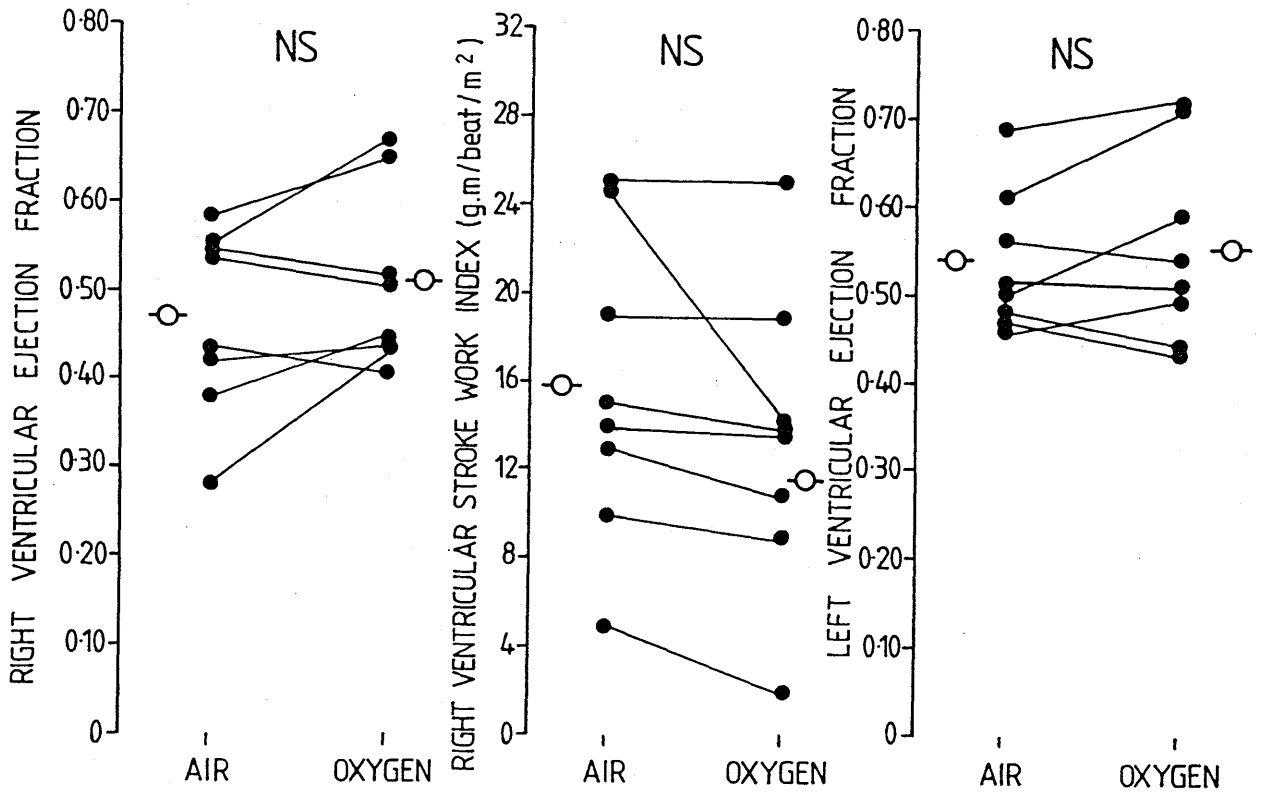


Figure 42 Effects of oxygen (3 litres/minute, nasal prongs) on right and left ventricular ejection fraction and right ventricular stroke work index, when given to 8 patients with chronic bronchitis and emphysema at rest.

Heart rate, mean systemic blood pressure, cardiac index and stroke volume index were similar whether the patients breathed air or oxygen. Thus, in these patients, oxygen did not produce any change in the systemic vascular resistance. However, oxygen did produce pulmonary vasodilatation since the cardiac index was unchanged and mean PAP fell from 30 $\pm$ 3 to 25 $\pm$ 2 mmHg ($p < 0.05$). Thus the total pulmonary vascular resistance fell in all 8 patients when breathing oxygen from a mean of 570 $\pm$ 67 to 477 $\pm$ 51 dynes.s. cm^{-5} (figure 41). Those patients with the highest values of PAP or total pulmonary vascular resistance when breathing air, tended to have the greatest fall in these variables when breathing oxygen. However, the correlation between the baseline PAP and change in PAP ($r = -0.65$, NS) or between baseline total pulmonary vascular resistance and change in total pulmonary vascular resistance while breathing oxygen ($r = -0.68$ NS) did not quite achieve statistical significance.

Despite these changes in pulmonary vascular resistance the mean right ventricular ejection fraction in these 8 patients did not change significantly when breathing oxygen compared with the value when breathing air (although RVEF did increase in 5 of the 8 patients studied) (figure 42). There was also no change in the right ventricular stroke work index or the left ventricular ejection fraction. There were no significant correlations between the change in RVEF when breathing oxygen and the baseline RVEF, or between the change in RVEF and the baseline or change in PAP or total pulmonary vascular resistance ($r = -0.65$ to 0.68). There was a trend for oxygen to produce a fall in both right ventricular end-diastolic and end-systolic volume indexes, although the change in the mean values of these variables did not achieve statistical significance. Thus

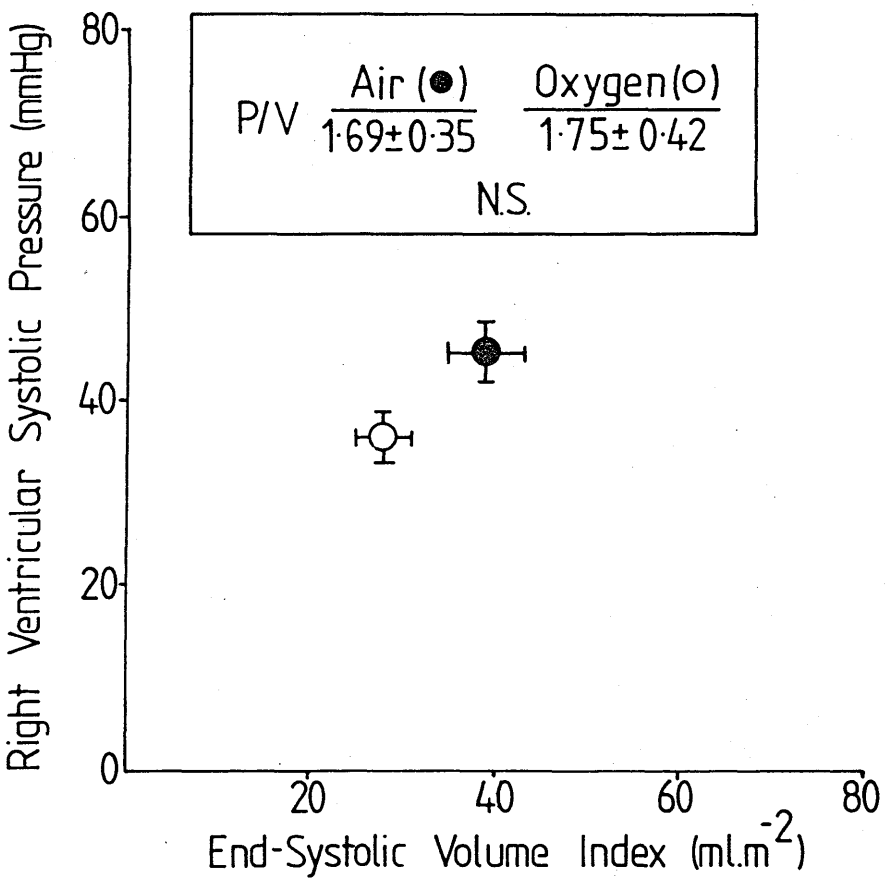


Figure 43 Mean right ventricular end-systolic pressure/volume point (error bars = 1 SEM) in 8 patients with chronic bronchitis and emphysema while breathing air (●) or oxygen (o) at rest. Breathing oxygen displaces the right ventricular pressure volume point downwards and to the left without any significant change in the P/V ratio.

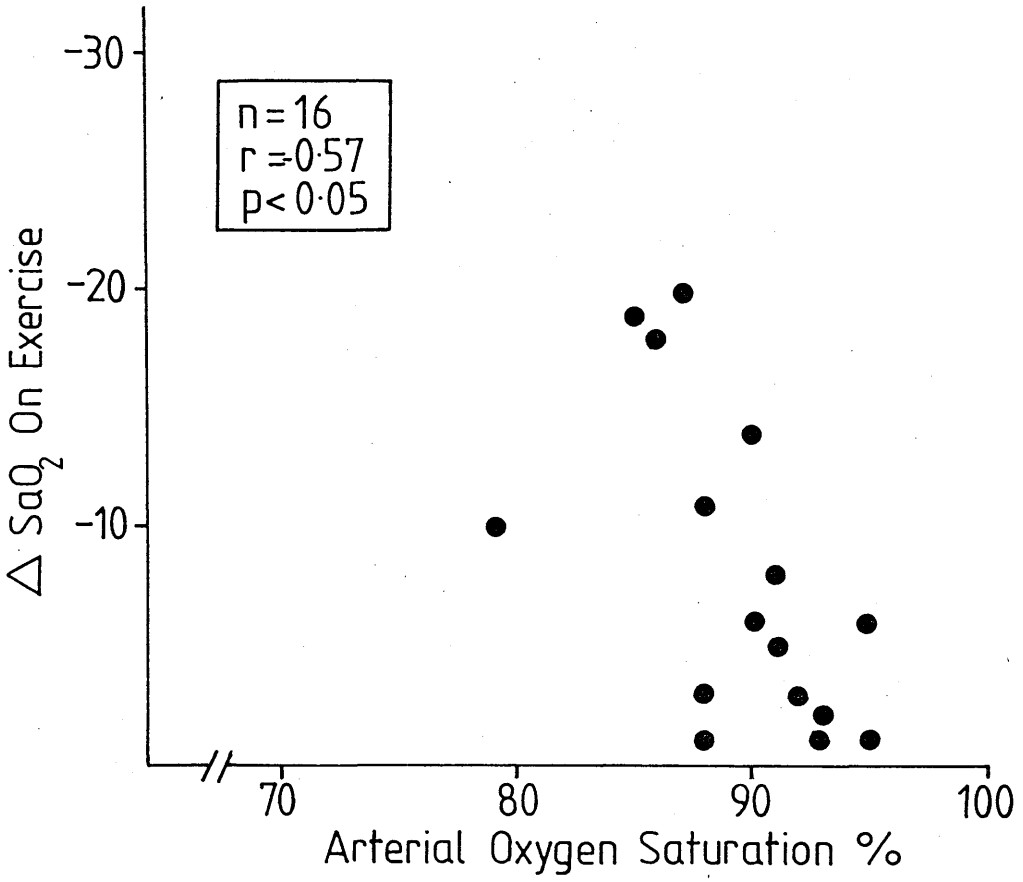


Figure 44 Relationship between the resting arterial oxygen saturation (SaO_2) when breathing air and the fall in SaO_2 (ΔSaO_2) during exercise in 16 patients with chronic bronchitis and emphysema.

calculated, before and after oxygen, the mean value for the 8 patients did not change significantly when breathing oxygen (table 18, 19).

The mean right ventricular end-systolic pressure/volume relation in these 8 patients when breathing air at rest was displaced downwards and to the left when breathing oxygen (figure 43) in a similar fashion to the displacement of the end-systolic pressure/volume relation produced by sodium nitroprusside, as described in Chapter 5 in a similar group of patients. Individual changes in right ventricular pressure and volume were too small in some of the patients to make any meaningful calculation of the slope of the P/V relation, at end-systole, in individual patients.

The acute effects of oxygen during exercise (Table 20)

The heart rate both at rest and during exercise was not significantly different when these patients breathed air or oxygen. The ear oxygen saturation (SaO_2) fell in all 16 patients while exercising breathing air, from a mean of 89 $\pm$ SEM 1% at rest to 81 $\pm$ 2% during exercise ($p < 0.01$) (table 20). However, the change in SaO_2 during exercise was very variable from -1 to -20%. The fall in oxygen saturation during exercise correlated with the resting SaO_2 ($r = 0.57$, $p < 0.05$) (figure 44). Breathing oxygen produced an increase in the SaO_2 when at rest to 95 $\pm$ 1% ($p < 0.01$). and although there was still a significant fall in SaO_2 when exercising breathing oxygen, the fall in SaO_2 during exercise was less when breathing oxygen (SaO_2, - 4 $\pm$ 1%) compared with the fall in SaO_2 when breathing air (SaO_2, - 8 $\pm$ 2%, $p < 0.001$).

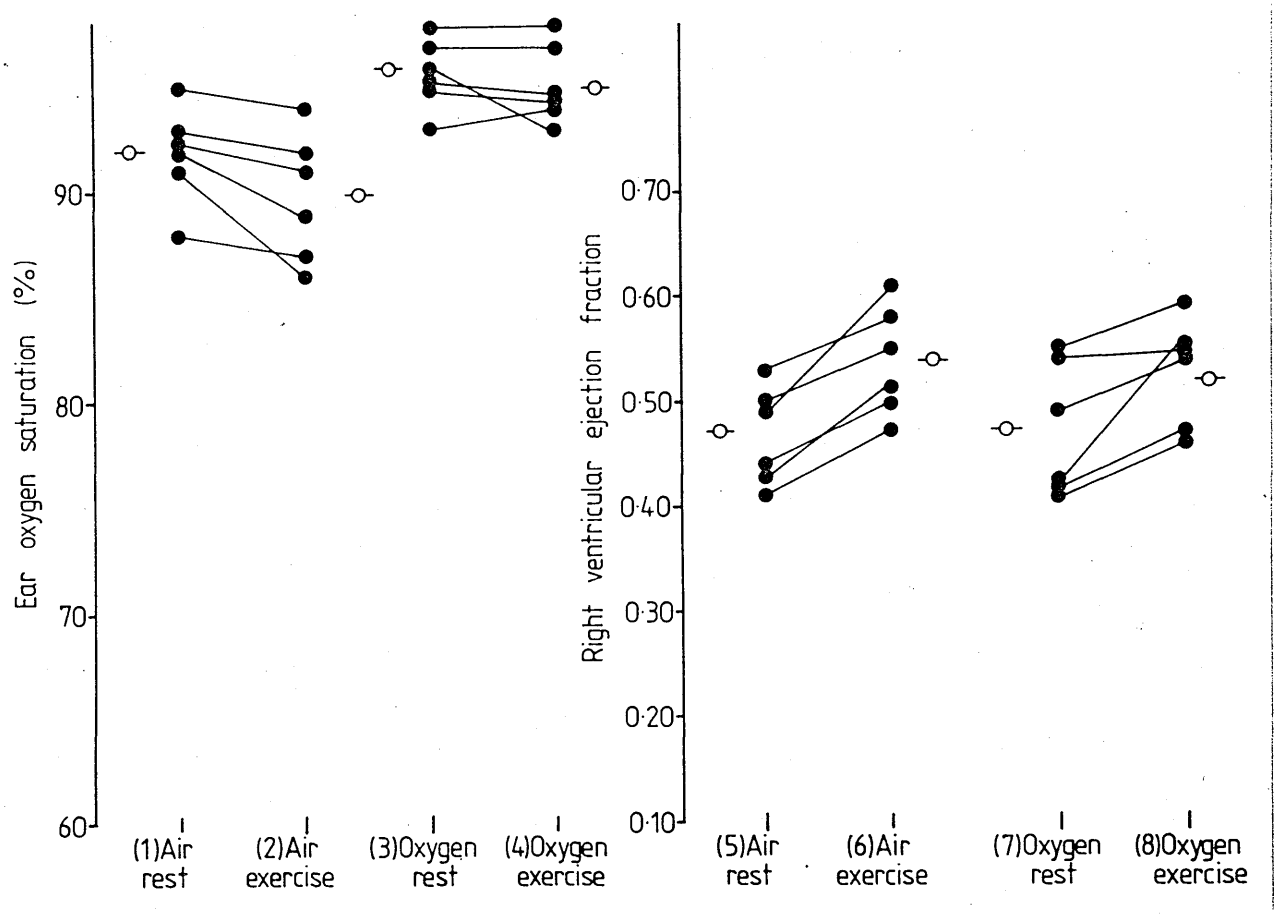


Figure 45A Ear oxygen saturation and right ventricular ejection fraction (RVEF) in patients with chronic bronchitis and emphysema whose RVEF increased normally (Δ RVEF $\geq$ 0.04, n = 6) on exercise breathing air. Individual values (●) and the means (-o-) are shown at rest and on exercise when breathing air or oxygen (3 litres/minute, nasal prongs)

Statistical analysis

(1) vs (2) $p < 0.05$; (3) vs (4) NS.
(1) vs (3) $p < 0.05$; (2) vs (4) $p < 0.05$.
(5) vs (6) $p < 0.05$; (7) vs (8) $p < 0.05$.
(5) vs (7) NS; (6) vs (8) NS.

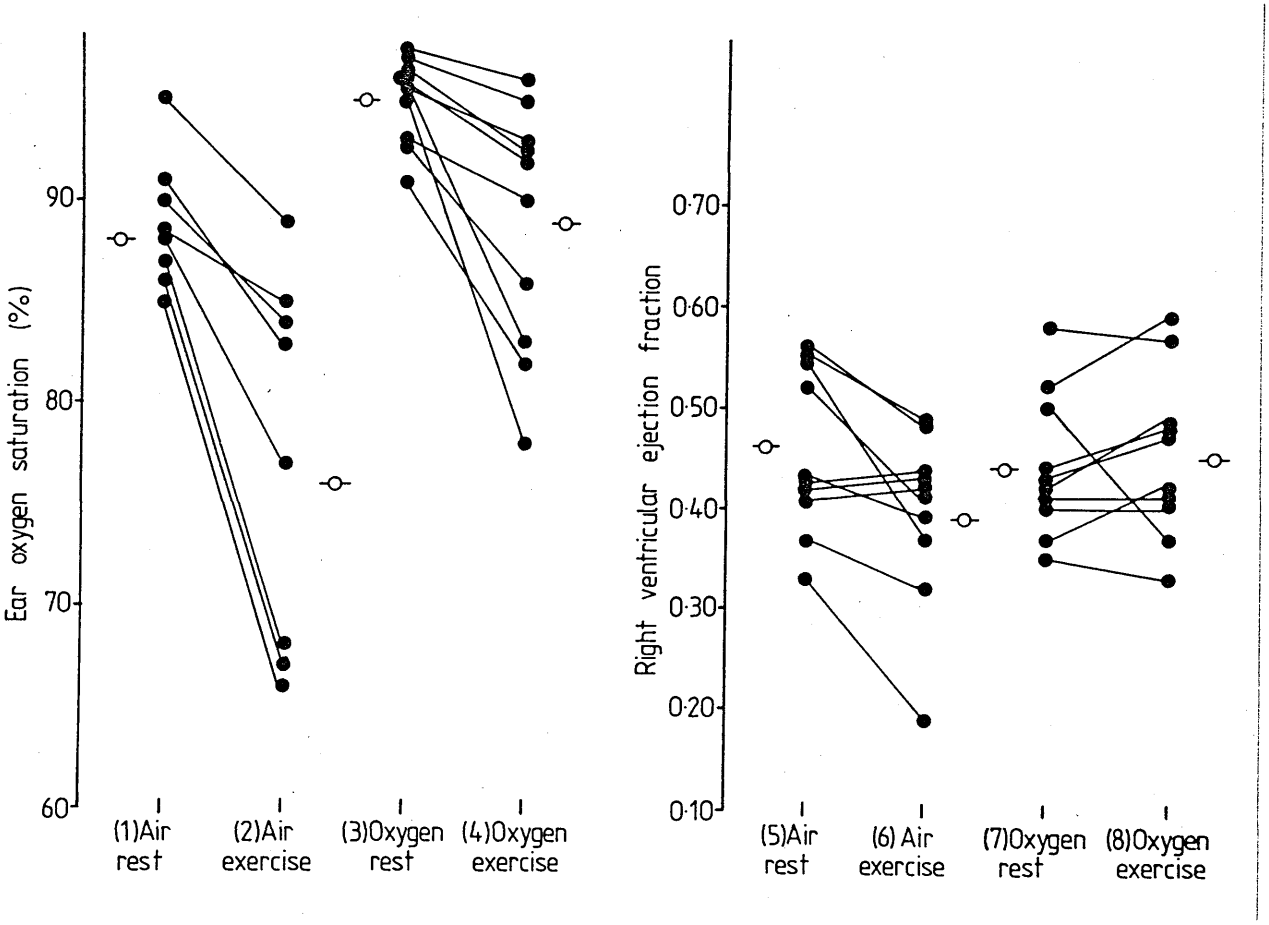


Figure 45B Ear oxygen saturation and right ventricular ejection fraction (RVEF) in patients with chronic bronchitis and emphysema whose RVEF did not increase normally (RVEF < 0.04, n = 10) on exercise breathing air. Individual values (●) and the means (-o-) are shown at rest and on exercise when breathing air or oxygen (3 litres/minute, nasal prongs).

Statistical analysis

(1) vs (2) $p < 0.001$; (3) vs (4) $p < 0.01$.
(1) vs (3) $p < 0.01$; (2) vs (4) $p < 0.01$.
(5) vs (6) $p < 0.02$; (7) vs (8) NS.
(5) vs (7) NS; (6) vs (8) $p < 0.01$.

when at rest (table 20). The mean RVEF did not change significantly during exercise when breathing air. These results are similar to those in a larger group of 25 patients reported in Chapter 4, which included the 16 patients in this study. For the present group of 16 patients breathing oxygen did not change the RVEF in these patients when at rest and again RVEF did not change significantly when exercising breathing oxygen (table 20). There was also no significant change in mean LVEF during exercise when breathing air (table 20). When oxygen was breathed there was also no change in LVEF when at rest. However, LVEF increased significantly from 0.54 $\pm$ 0.03 at rest to 0.57 $\pm$ 0.03 ($p < 0.01$), during exercise when breathing oxygen.

The change in RVEF which occurred during exercise when breathing air was very variable from -0.18 to +0.12. As previously described in Chapter 4, in order to determine whether the presence or absence of a normal right ventricular response to exercise was related to the change in SaO_2, the 16 patients were divided into 10 patients whose RVEF did not rise by 0.05 (figure 45b) and 6 who had a normal increase in RVEF of at least 0.05 when exercising breathing air (figure 45a). The resting mean RVEF in these 2 groups were similar (0.46 $\pm$ 0.03 vs 0.47 $\pm$ 0.02 respectively, NS). However, whereas the mean RVEF increased from 0.46 $\pm$ 0.03 to 0.54 $\pm$ 0.02) in those with a normal response to exercise in those with an abnormal response, mean RVEF fell from 0.47 $\pm$ 0.02 to 0.39 $\pm$ 0.03 ($p < 0.02$) during exercise breathing air. Moreover, this fall in RVEF was prevented when these patients exercised when breathing oxygen (figure 45b), so that the change in RVEF from rest to exercise (Δ RVEF) was significantly different when breathing air ($\Delta RVEF_{air}$ -0.01 $\pm$ 0.01) when compared

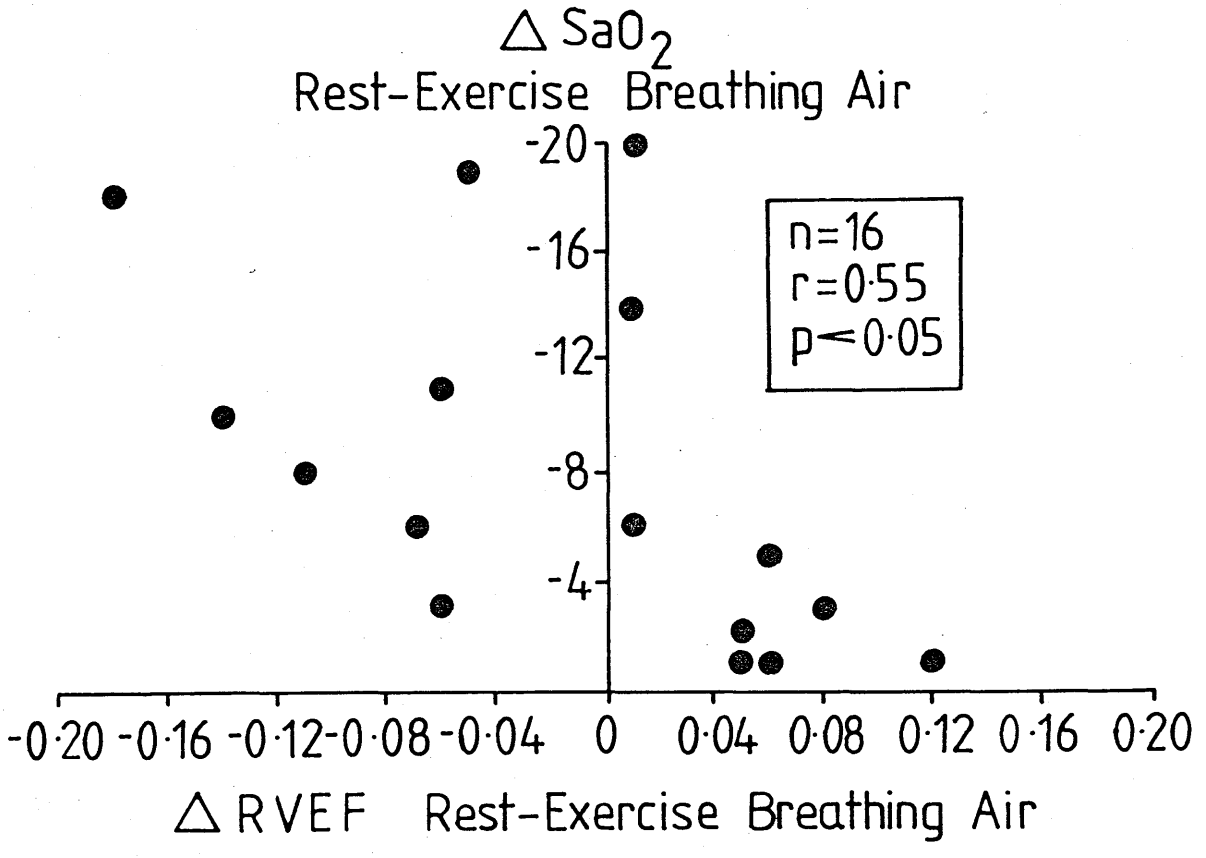


Figure 46A Relationship between the change in RVEF (Δ RVEF) and the change in ear oxygen saturation (ΔSaO_2) from rest to exercise in 16 patients with chronic bronchitis and emphysema when breathing air.

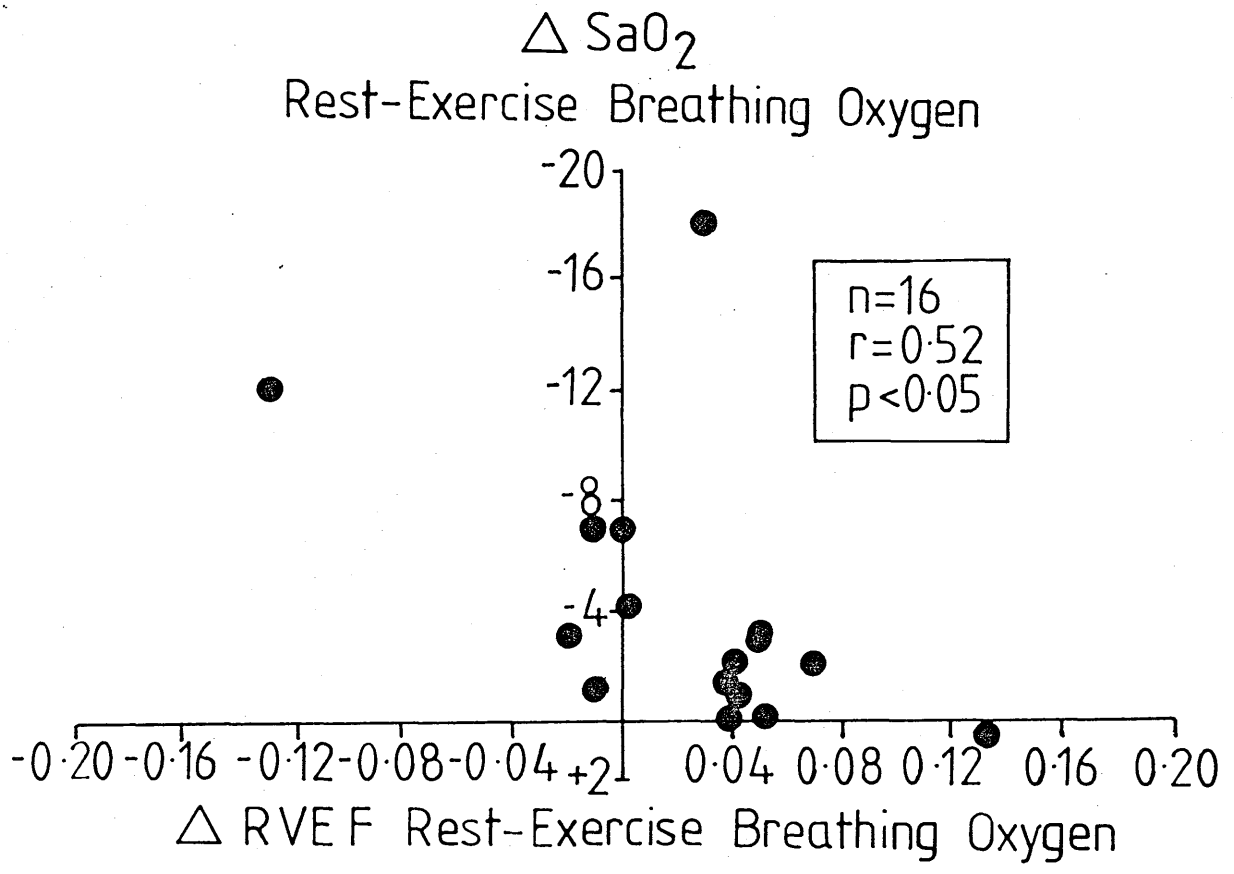


Figure 46B Relationship between the change in RVEF (ΔRVEF) and the change in ear oxygen saturation (ΔSaO_2) from rest to exercise in 16 patients with chronic bronchitis and emphysema when breathing oxygen.

0.01, $p < 0.05$).

The 6 patients whose RVEF increased normally during exercise, had a small but significant fall in mean SaO_2 from 92 $\pm$ 1 to 90 $\pm$ 1% ($p < 0.05$) when exercising breathing air. However, this fall in SaO_2 was abolished when exercising breathing oxygen (SaO_2 at rest 96 $\pm$ 1%, SaO_2 during exercise 95 $\pm$ 1%, NS) (figure 45a). In contrast those patients in whom the RVEF did not increase normally during exercise had a fall in SaO_2 from 88 $\pm$ 4% when at rest to 76 $\pm$ 3% ($p < 0.001$) (figure 45b) during exercise breathing air. Again the fall in SaO_2 was less and the SaO_2 was higher when breathing oxygen both at rest (SaO_2 95 $\pm$ 1%) and during exercise (SaO_2 88 $\pm$ 2%, $p < 0.01$). Thus, although oxygen breathing did not prevent desaturation during exercise in those patients whose RVEF did not increase normally during exercise, the fall in oxygen saturation during exercise was less and was associated with a higher RVEF. More simply, in the 16 patients when exercise was performed breathing air there was a significant correlation between the change in RVEF and the change in SaO_2 from rest to exercise ($r = 0.55$, $p < 0.05$) (figure 46a). Furthermore, a similar significant correlation was obtained between the change in RVEF and change in SaO_2 when exercise was performed breathing oxygen ($r = 0.52$, $p < 0.05$) (figure 46b).

In contrast the changes in LVEF from rest to exercise whether breathing air or oxygen were independent of changes in the RVEF. Secondly, the degree of desaturation was not significantly different in those patients whose LVEF did or did not increase normally during exercise.

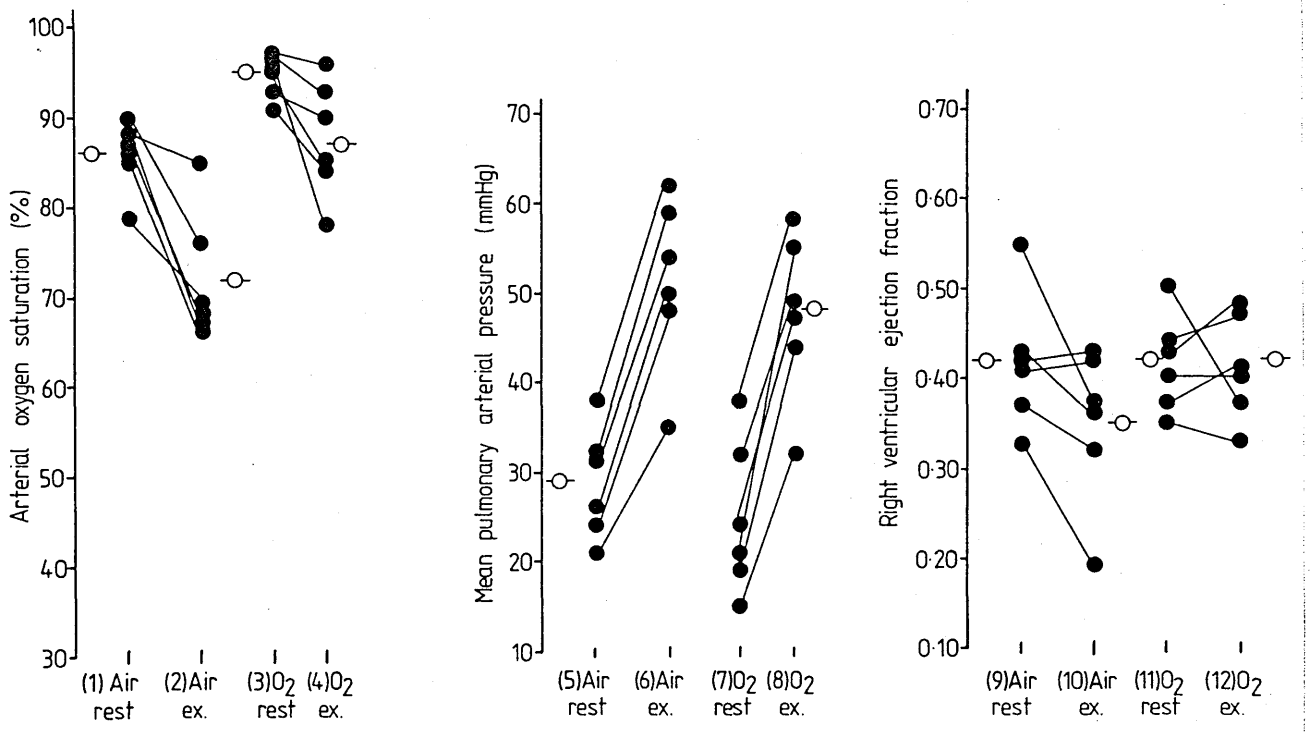


Figure 47 Arterial oxygen saturation, mean pulmonary arterial pressure and right ventricular ejection fraction in 6 patients with chronic bronchitis and emphysema, at rest or during exercise (EX) when breathing air or oxygen (3 litres/minute, nasal prongs). Individual values (●) and the mean values (-o-) are shown.

Statistical analysis

(1) vs (2) $p < 0.001$; (3) vs (4) $p < 0.01$.
(1) vs (6) $p < 0.01$; (2) vs (6) $p < 0.01$.
(5) vs (6) $p < 0.01$; (7) vs (8) $p < 0.01$.
(5) vs (7) $p < 0.05$; (6) vs (9) $p < 0.01$.
(9) vs (10) $p < 0.05$; (11) vs (12) NS.
(9) vs (11) NS; (10) vs (12) $p < 0.05$.

exercise in addition to measurements of RVEF had significant desaturation during exercise when breathing air or oxygen. Again the SaO_2 both at rest and during exercise was higher when breathing oxygen (figure 47). The mean PAP during exercise was slightly lower when breathing oxygen (PAP 47 $\pm$ 4 mmHg) compared with the level of PAP during exercise when breathing air (PAP 51 $\pm$ 4 mmHg, $p < 0.05$). However, the increase in PAP from rest to exercise was very similar both when breathing air (ΔPAP 22.5 $\pm$ 5.4 mmHg or when breathing oxygen (Δ PAP 22.5 $\pm$ 6.4 mmHg). As in the 16 patients as a group the fall in RVEF on exercise when breathing air in this subgroup of 6 patients was prevented when exercise was performed when breathing oxygen (figure 47).

The effect of long term oxygen (Table 21)

There was no significant change in $FEV_{1.0}$, FVC, heart rate, systemic arterial blood pressure, PaO_2, $PaCO_2$, hydrogen ion concentration or 12 minute walking distance in the 10 patients studied before and after 6 months domiciliary oxygen. Mean PAP fell significantly from 32 $\pm$ 2 to 26 $\pm$ 2 mmHg ($p < 0.01$) (table 21) after 6 months oxygen. This change in PAP was associated with a small but significant fall in right ventricular end-diastolic pressure from 6 $\pm$ 1 to 4 $\pm$ 1 mmHg ($p < 0.02$). The fall in pulmonary arterial pressure did not produce any significant change in right or left ventricular ejection fraction.

DISCUSSION

The purpose of this section of the thesis was to study the effects of oxygen on right ventricular performance in patients with hypoxic

oxygen were similar to those used in the treatment of patients with respiratory failure with long term domiciliary oxygen (225). The reason for initiating these studies was that to date, long term oxygen therapy is the only treatment which is known to improve survival in such patients. However, as discussed earlier, neither of the two controlled trials of long term oxygen showed that this treatment could reverse the pulmonary arterial hypertension in patients with respiratory failure, and in addition, continuous oxygen appeared to benefit only those patients with the lowest values of pulmonary vascular resistance (251). These findings suggest that we should look for reasons other than the reduction of pulmonary hypertension and the prevention of cor pulmonale to account for the improved survival in patients treated with long term oxygen. Indeed the survival data from the MRC trial seems to suggest that, at least in some patients, oxygen does not influence the prognosis, since the survival for the treated and untreated groups was not significantly different until after 500 days of treatment (225). Before dismissing the relevance of the cardiovascular effects of oxygen in the treatment of patients with hypoxic chronic bronchitis and emphysema, I felt it would be worthwhile re-examining the effects of 'controlled oxygen' on right ventricular mechanics using a combination of measurements of RVEF and pulmonary haemodynamics.

The acute effects of oxygen at rest

Recently much attention has been focussed on the factors which determine oxygen delivery to the tissues, principally the cardiac index and the pulmonary vascular resistance, as distinct from the pulmonary arterial pressure, which may not differ markedly from one patient with hypoxic chronic bronchitis and emphysema to another (29,

different processes. Firstly, convectional transport to the tissues in the vascular system, which is dependent on both the oxygen delivery and the oxygen consumption. The ratio of these two variables, the coefficient of oxygen delivery (COD) was introduced by Mithoefer (235). Secondly, the mixed venous oxygen tension can be considered to be an approximation of the 'mean tissue oxygen tension' which cannot be measured, and is a determinant of the diffusional transport of oxygen to the tissues, which in turn is dependent on the driving pressure head of oxygen.

A recent study in patients with hypoxic chronic bronchitis and emphysema has suggested that the variables which were most important in distinguishing survivors from non-survivors, were a higher arterial oxygen tension and a higher mixed venous oxygen tension, rather than the PAP or pulmonary vascular resistance (178). The coefficient of oxygen delivery was, however, similar in both survivors and non-survivors. By inference, these authors suggested that the oxygen supply to the tissues was a critical factor in determining survival in such patients, and that the diffusional (mixed venous) component of tissue oxygen supply was more important than the convectional transport of oxygen in the vascular system as measured by the COD. Mixed venous oxygen tension is, of course, dependent on the cardiac output and it has been proposed that in patients with chronic bronchitis and emphysema who have a decreased oxygen carriage, the maintenance of a normal, or indeed high normal cardiac output, may be an adaptive mechanism in order to maintain a normal tissue oxygen supply. Thus failure to maintain cardiac output may worsen survival (177).

at a flow rate of 3 litres/minute by nasal prongs increased PaO_2 by an average of 4.8 kPa, but $PaCO_2$ only rose by an average of 0.4 kPa, which did not result in any change in arterial hydrogen ion concentration. The mean PVO_2 in these patients was low (< 4.7 kPa) but was increased to a normal level in all but one of the 8 patients when breathing oxygen. The lowest coefficient of oxygen delivery occurred in the patient with the lowest PVO_2 when breathing air, and oxygen breathing produced the largest increases in COD in patients with low PVO_2 (< 4.7 kPa) and arterial carbon dioxide retention. These effects of oxygen on tissue oxygen delivery have been confirmed by others (75, 235). The coefficient of oxygen delivery was low (< 4) in most of these patients and increased in all patients when breathing oxygen, but remained abnormally low in 2 of the 8 patients. In these 2 patients cardiac index fell when breathing oxygen in contrast to the majority of patients where cardiac index increased slightly. Degaute has also shown, in 35 patients who presented with acutely decompensated chronic obstructive lung disease, that oxygen therapy does not necessarily increase the COD to normal if cardiac output decreases (75). Thus at least in some patients the beneficial effects of oxygen therapy may be counterbalanced by a fall in cardiac output resulting in no significant change in the oxygen delivery to the tissues (29, 75, 326). This may be one reason why oxygen fails to improve the prognosis in some patients treated with long term oxygen therapy.

Of the 8 patients given oxygen in this study, both the PVO_2 and the COD increased to normal in the majority. This improvement in tissue oxygenation might have been expected to improve right ventricular performance. The results of this study show that the

but significant fall in pulmonary arterial and systolic right ventricular pressure. Heart rate and cardiac index were unchanged and hence oxygen produced a small fall in total pulmonary vascular resistance without changing the systemic vascular resistance. These haemodynamic changes are similar to those previously reported in other studies of the effects of oxygen on pulmonary haemodynamics in patients with chronic bronchitis and emphysema (3, 66, 157, 159, 243, 355, 358). However, in most of these studies oxygen was given in higher inspired concentrations. I have elected not to study the effects of higher inspired concentrations of oxygen since it is likely that such concentrations would produce further carbon dioxide retention, in these patients with respiratory failure, leading to a worsening of the respiratory acidosis which may have adverse effects on cardiac performance. In addition, I was interested in assessing the effects of oxygen in inspired concentrations which are used therapeutically in such patients.

Despite a significant fall in total pulmonary vascular resistance, which occurred in every patient, there was no significant increase in RVEF or change in right ventricular stroke work index although the right ventricular stroke work index fell in 5 of the 8 patients and remained unchanged in 3. Moreover, since the end-systolic pressure/volume ratio did not change in these patients, despite a reduction in right ventricular systolic pressure, this would suggest that in reducing pulmonary vascular resistance and displacing the end-systolic P/V point, oxygen acted as a pulmonary vasodilator without producing any change in right ventricular contractility.

As I have discussed in the results section some of the changes in

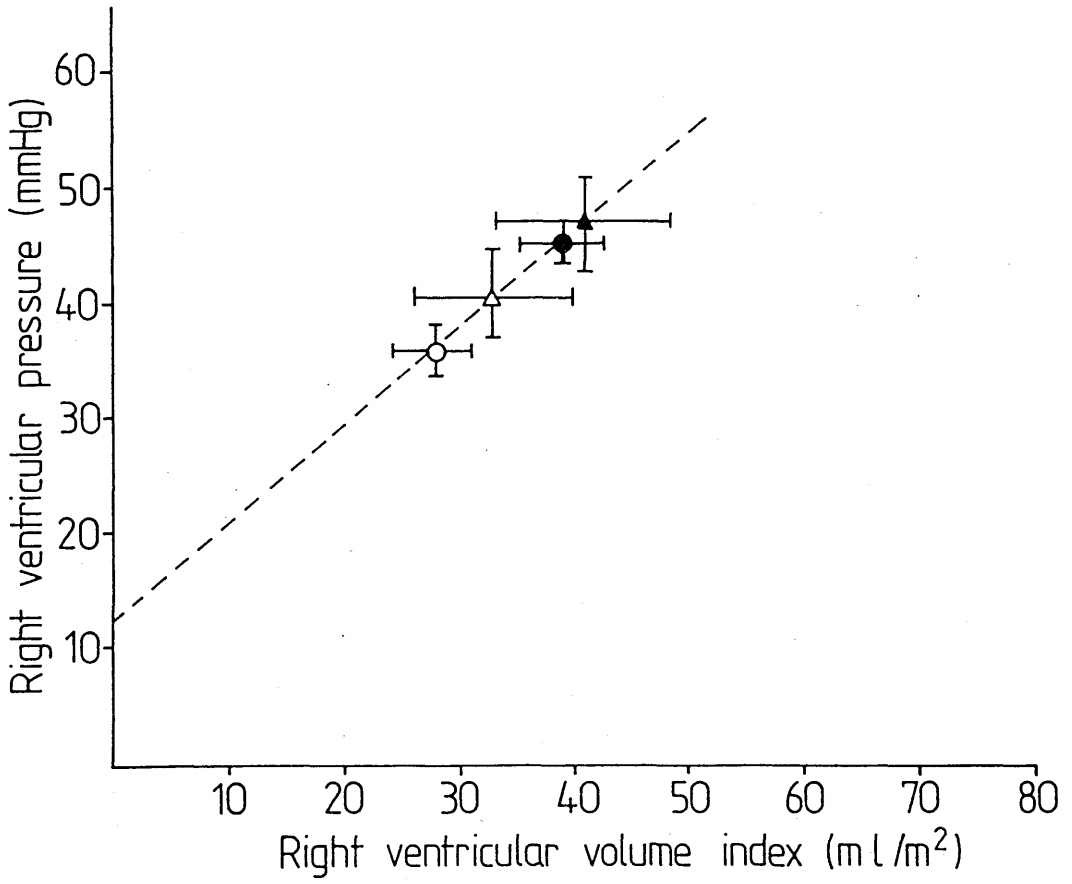


Figure 48 Mean right ventricular end-systolic pressure/volume points before (●) and during infusion with sodium nitroprusside (○) (n = 10) and while breathing air (▲) or oxygen (△) (n = 8) in patients with chronic bronchitis and emphysema. The displacement of the pressure volume point is similar in both circumstances.

the pressure volume relation. However, it is interesting to compare the changes in the mean pressure volume relations produced by oxygen (indexed to body surface area) with those in 10 patients in whom pulmonary vasodilatation was produced by intravenous infusion of sodium nitroprusside (see Chapter 5). Both groups of patients had very similar ventilatory capacity and arterial blood gas values when breathing air. The displacement of the mean right ventricular end-systolic pressure volume point was also very similar (figure 48). Moreover, neither oxygen nor sodium nitroprusside produced any significant change in the P/V ratio. Thus although I have previously shown a correlation between RVEF and PaO_2 in patients with chronic bronchitis and emphysema which might have suggested that hypoxaemia had a direct cardio-depressive action. The relief of hypoxia with oxygen, at least when given acutely in the inspired concentrations used in this study, produced pulmonary vasodilatation but had no direct effect on right ventricular contractility in these patients.

The effects of long term oxygen

Oxygen was given in this study for at least 15 hours/day over a period of 6 months in a similar way to the MRC trial (225). Compliance with the treatment was established since in all cases oxygen was supplied by an oxygen concentrator and the hours of usage could be calculcated from the meter on the machine. The small fall in PAP and right ventricular systolic pressure which oxygen produced when given acutely to 8 similar patients, as described above, also occurred after 6 months therapy with oxygen. In addition there was a small fall in the right ventricular end-diastolic pressure which was probably of no clinical significance. Several uncontrolled

produce a small fall in PAP, which represents a significant reversal of the tendency for PAP to rise, albeit slowly, in patients with hypoxic pulmonary hypertension (350). However, in the Nott trial (251) pulmonary vascular resistance was only slightly reduced after 6 months therapy with oxygen. In the MRC trial (225) the PAP continued to rise at a mean rate of 3 mmHg/year in the control group who did not receive oxygen, whereas those given oxygen for 15 hours/day had no change in PAP or pulmonary vascular resistance.

In the patients in this study the mean RVEF was normal at rest before oxygen and did not change significantly after 6 months treatment despite a reduction in PAP. Thus, oxygen both when given acutely and over the longer term did not produce any significant change in RVEF. Ellis in contrast found, in a preliminary study, that long term oxygen did produce a small increase in RVEF (92). In the present study the fall in PAP produced by oxygen was small. Indeed the level of PAP remained abnormal after 6 months treatment. These changes in PAP may have been too small to produce any change in RVEF. However, I have previously found no correlation between PAP and RVEF in patients with chronic bronchitis and emphysema (Chapter 4). Thus I would not expect that a small change in PAP would influence the RVEF. The lack of change of RVEF also suggests that the relief of hypoxaemia even over the long term has no direct influence on right ventricular performance.

It is interesting that 7 of the 8 patients given oxygen acutely and 8 of the 10 patients given oxygen over 6 months had a fall in PAP after oxygen. Recent evidence has suggested that the haemodynamic response to oxygen therapy both in the short (12) and in the long

where PAP falls in response to oxygen may have a better prognosis. However, the results of this present study indicate that this fall in PAP does not produce any significant improvement in right ventricular performance, and hence it is unlikely that the effect of oxgyen therapy in improving survival in patients with chronic respiratory failure, is mediated through a direct effect on the right ventricle.

The effects of oxygen during exercise

As shown in Chapter 4, patients with chronic bronchitis and emphysema may have a normal right ventricular ejection fraction at rest, which becomes abnormal during exercise. In addition, in these patients, it is known that exercise increases PAP, pulmonary wedge and right ventricular end-diastolic pressures (55, 159, 170, 297, 356). The change in PAP during exercise appears to be related to the severity of the disease as shown by recent clinico-pathological studies (362). The level of pulmonary arterial pressure during exercise in these patients when breathing oxygen is reduced (FIO_2 80 - 100%) when compared with the value during exercise when breathing air (55, 157, 159). In this study I have confirmed that when patients with chronic bronchitis and emphysema breathe oxygen at inspired concentrations of between 30 - 35%, a small fall in the absolute level of PAP occurs both at rest and on exercise. However, the change in PAP from rest to exercise when breathing air or oxygen is not significantly different. It is not certain from previous studies (220, 221, 255, 309) if the right ventricular response to exercise is related to the degree of resting hypoxaemia or the degree of desaturation which occurs in such patients during exercise. Indeed the previously reported variability in the response of the right ventricle during exercise was unexplained and, in previous studies,

have also confirmed (chapter 4) a wide individual variation in the change in the RVEF during exercise when breathing air. This variability seems to be related to the degree of arterial desaturation during exercise, those with a greater degree of desaturation having an abnormal right ventricular response to exercise.

Oxygen desaturation in patients with chronic bronchitis and emphysema when measured at rest probably results from impaired ventilation perfusion matching and the further desaturation which occurs during exercise might imply either worsening of this matching or a reduction in oxygen saturation in venous blood returning to the lungs, or a combination of both factors. I have found that the fall in SaO_2 during exercise (when breathing air) correlates with the SaO_2 at rest. The fall in SaO_2 during exercise may itself have directly impaired ventricular peformance leading to the failure of the RVEF to rise on exercise. The lack of change in RVEF in response to acute or chronic administation of oxygen, described earlier in this chapter, does not support any direct effect of oxygen on the right ventricular myocardium. However, the fall in RVEF, during exercise when breathing air, was partially reversed when exercise was repeated when breathing oxygen. It might be argued that the fall in RVEF during exercise was only partially reversed because the inspired concentration of oxygen did not completely abolish the desaturation which occurred during exercise. Thus, if higher inspired concentrations of oxygen had been given the RVEF may have responded normally to exercise. I think it is unlikely that the small reduction in the level of the exercise PAP which occurred when oxygen was breathed had any influence on the improvement in the RVEF. I

would favour an explanation other than a direct effect of oxygen on PAP or the right ventricle to account for the results of this study.

There are several possible explanations for the increase in the pulmonary arterial pressure which occurs during exercise in patients with chronic bronchitis and emphysema (see chapter 1). A recent clinicopathological study has shown that the pulmonary haemodynamic effects of exercise, performed pre-operatively in patients undergoing lung resection, seems to correlate with the extent of the emphysema, the airways disease and hypertensive changes in the pulmonary arteries found in the resected lung (362). This study showed that the greater the extent of the disease in the resected specimen the greater was the increase in PAP which occurred during exercise when the patient was studied pre-operatively. The authors suggest that gas trapping, resulting in increased alveolar and pleural pressures, is the major factor which increases PAP during exercise in patients with chronic bronchitis and emphysema. They also suggested that the small reduction in the level of the exercise PAP which occurred when oxygen was breathed, was due to an effect of oxygen in shortening time constants in peripheral lung units leading to a fall in the intrathoracic pressure. This theory must be confirmed by studies of the effects of oxygen on simultaneous measurements of PAP and intrathoracic pressure. However, it may be that the changes in lung mechanics which occur during exercise, rather than the consequences of these changes such as oxygen desaturation or changes in pulmonary haemodynamics, have a direct effect on the right ventricular peformance during exercise. Thus, changes in intrathoracic pressure may be very important in determining the right ventricular response to exercise.

bronchitis and emphysema and found that the mean RVEF did not change on exercise when breathing air but, as in this study, individual changes in RVEF during exercise were very variable. In contrast to this present study, however, Olvey found a significant rise in mean RVEF in the same patients when exercise was performed breathing oxygen. Individual values of SaO_2 or PaO_2 are not quoted but the mean PaO_2 during exercise did not fall when breathing air, suggesting that the patients studied by Olvey were similar to the subgroup of patients in the present study who had only a trivial fall in SaO_2 during exercise and an increase in RVEF.

Conclusions

1. Despite producing a fall in both pulmonary arterial pressure, and pulmonary vascular resistance, and an increase in the supply of oxygen to the tissues, oxygen, when given at rest to patients with hypoxic chronic bronchitis and emphysema, did not produce any significant change in RVEF.
2. In addition, long term oxygen had no significant effect on RVEF even in the face of a reduction in pulmonary arterial pressure.
3. Calculation of the end-systolic pressure/volume relation of the right ventricle, in patients with hypoxic chronic bronchitis and emphysema, showed that the acute administration of oxygen resulted in pulmonary vasodilatation, without any direct effect on right ventricular contractility.
4. From these results it can be inferred that the effect of long term oxygen in improving the prognosis of such patients is not through a direct effect on the right ventricle.

bronchitis and emphysema, both when breathing air or oxygen is related to the degree of desaturation which occurs during exercise.

6. The fall in RVEF which occurs in some patients when exercising breathing air, can be prevented when the exercise is repeated when breathing oxygen.

7. The mechanism of the improvement in the right ventricular response to exercise when breathing oxygen is unexplained, but probably does not result from any direct effect of oxygen on either the pulmonary arterial pressure or the right ventricular myocardium. It may, be that oxygen produces changes in lung mechanics during exercise which may have an indirect effect on the right ventricular performance during exercise.

THE EFFECTS OF A BETA AGONIST ON RIGHT VENTRICULAR PERFORMANCE

The treatment of patients with chronic bronchitis and emphysema and 'cor pulmonale' is unsatisfactory, and has not advanced over the past 20 years (102, 103, 104, 115, 161, 202). There are several general therapeutic approaches in this condition. The first relates to treatment of the underlying respiratory failure (208) with oxygen, bronchodilators, and the treatment of respiratory infections. The second aims to reverse pulmonary arteriolar vasoconstriction and the third, and most controversial, is to improve the cardio-circulatory response to the right ventricular pressure overload.

During periods of acute decompensation when oedema develops with or without co-existing acute on chronic respiratory failure, treatment of the 'right ventricular failure' is non-specific and therapies are directed towards the treatment of the underlying respiratory failure. Traditional measures aimed at improving cardio-circulatory function have not undergone close scrutiny because of the difficulties in assessing right ventricular function. Thus relatively few studies of patients with decompensated pulmonary heart disease have been undertaken. Some aspects of decompensated pulmonary heart disease will be discussed in Chapter 8.

Until recently the treatment of chronic cor pulmonale in patients with chronic bronchitis and emphysema has also been neglected. Much more attention has been devoted to new therapeutic measures for the much rarer condition of primary pulmonary hypertension (116, 117, 253, 274), where vasodilators have been used with very variable

specific forms of therapy have been employed; long term oxygen (225, 251), pulmonary vasodilators, and inotropic agents (164, 207, 261, 296, 316, 323). The use of vasodilators and or inotropes remains controversial (161) principally because of the deleterious effects which they may have on ventilation/perfusion matching (323, 336), and also because the long term efficacy of these drugs in cor pulmonale and hence their effect on patient survival has not been documented.

This study in patients with hypoxic chronic bronchitis and emphysema and pulmonary hypertension, was conceived to measure the cardiovascular effects of pirbuterol, a beta sympathomimetic drug structurally similar to salbutamol, with both vasodilator and inotropic actions (13, 14, 73). Both the acute effects and those of chronic administration of the drug over six weeks were studied. A comparison was made of the effects of this drug on right ventricular performance with those of sodium nitroprusside in the same patients.

Patients and methods

Twelve patients with chronic bronchitis and emphysema (6 men, 6 women) were studied (table 22) when in a stable condition. All of the patients were hypoxic (mean PaO_2 7.3 $\pm$ 0.8 kPa), most were hypercapnic ($PaCO_2$ 6.4 $\pm$ 0.7 kPa), and all had pulmonary arterial hypertension when breathing room air at rest (mean PAP 30 $\pm$ 5 mmHg).

Acute studies

As in previous haemodynamic studies each patient's medication (which included inhaled bronchodilators and diuretics in most) was given on the evening prior to study. No medication was given on the morning of the study day. Each patient was studied while semi-supine,

breathing room air, in the afternoon after a light lunch. No pre-medication was given. Ten of the 12 patients had taken part in the study of the effects of sodium nitroprusside (see Chapter 4). The haemodynamic measurements were made with a Swan Ganz flow directed, triple lumen catheter, inserted into the pulmonary artery. Radionuclide ventriculograms were performed and analysed as described in detail in Chapter 4.

Derived haemodynamic and oxygen delivery values were calculated according to the equations in Chapters 4 and 5.

In 10 of the patients (Nos 1-10) haemodynamic and radionuclide measurements were made after haemodynamic stability had been achieved, with the patients at rest and during infusion of sodium nitroprusside as described in Chapter 4. When all of the haemodynamic parameters had returned to baseline, oral pirbuterol was given in a dose of 22.5 mg (patients 1-6) or 15 mg (patients 7-12) by mouth. Measurements were repeated at 30 minute intervals for 2 hours. Two patients (Nos 11, 12) underwent the same study protocol but were not given sodium nitroprusside.

Chronic study

Nine of the 12 patients who were studied acutely also received oral pirbuterol 15 mg three times/day for 6 weeks in addition to their usual therapy. At this time pulmonary arterial pressure, RVEF, LVEF, arterial blood gas values, and ventilatory capacity were remeasured. Three patients did not complete the chronic study; two developed an arrhythmia possibly associated with pirbuterol (atrial fibrillation in one, multi-focal ventricular and supraventricular ectopic beats in another) and one further patient developed an acute infective

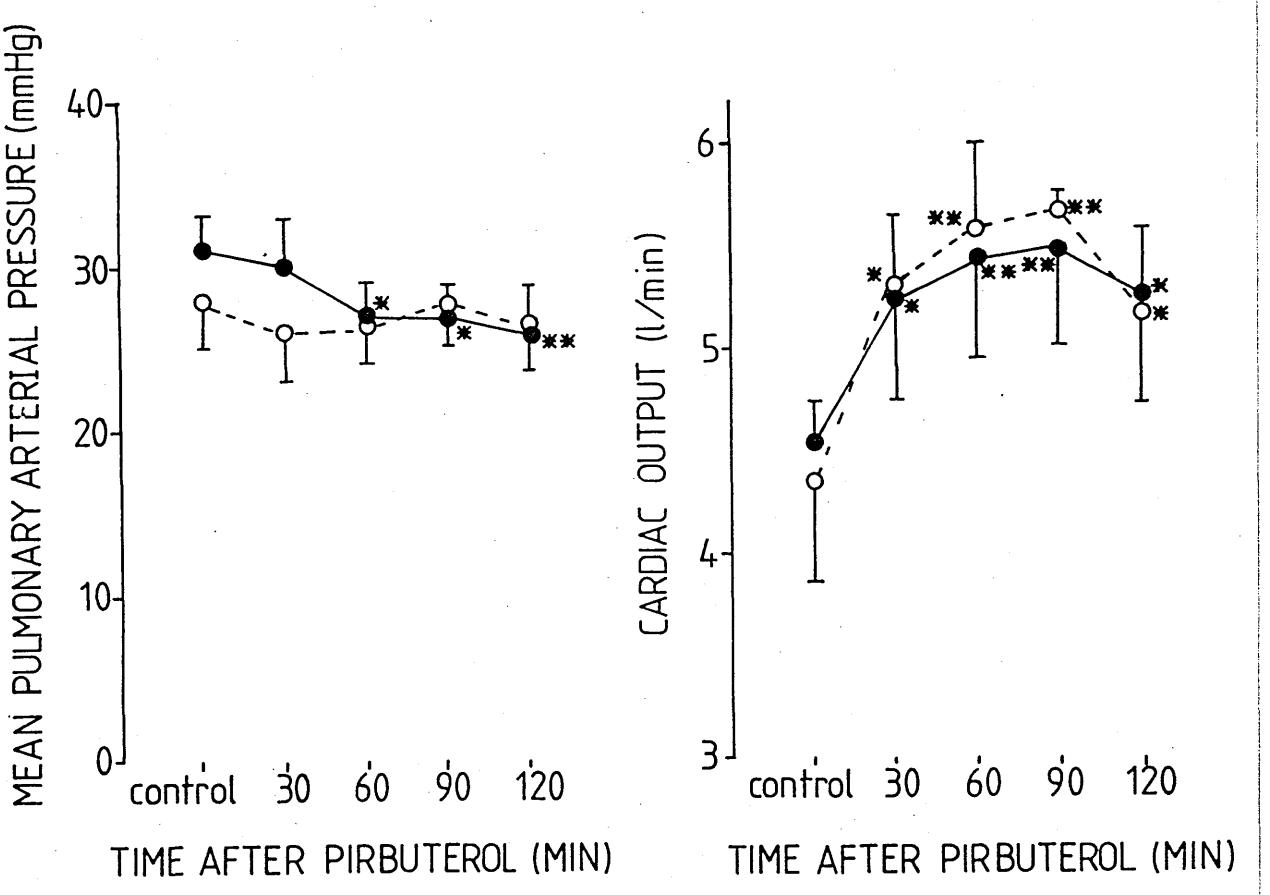


Figure 49A The acute effects of pirbuterol in a single oral dose (22.5 mg, n = 6, o--o; 15 mg, n = 6, ● - - ●) in patients with chronic bronchitis and emphysema.
Mean values are shown and the error bars represent 1 SEM.
Significant differences from the control values:
* $p < 0.05$; ** $p < 0.01$.

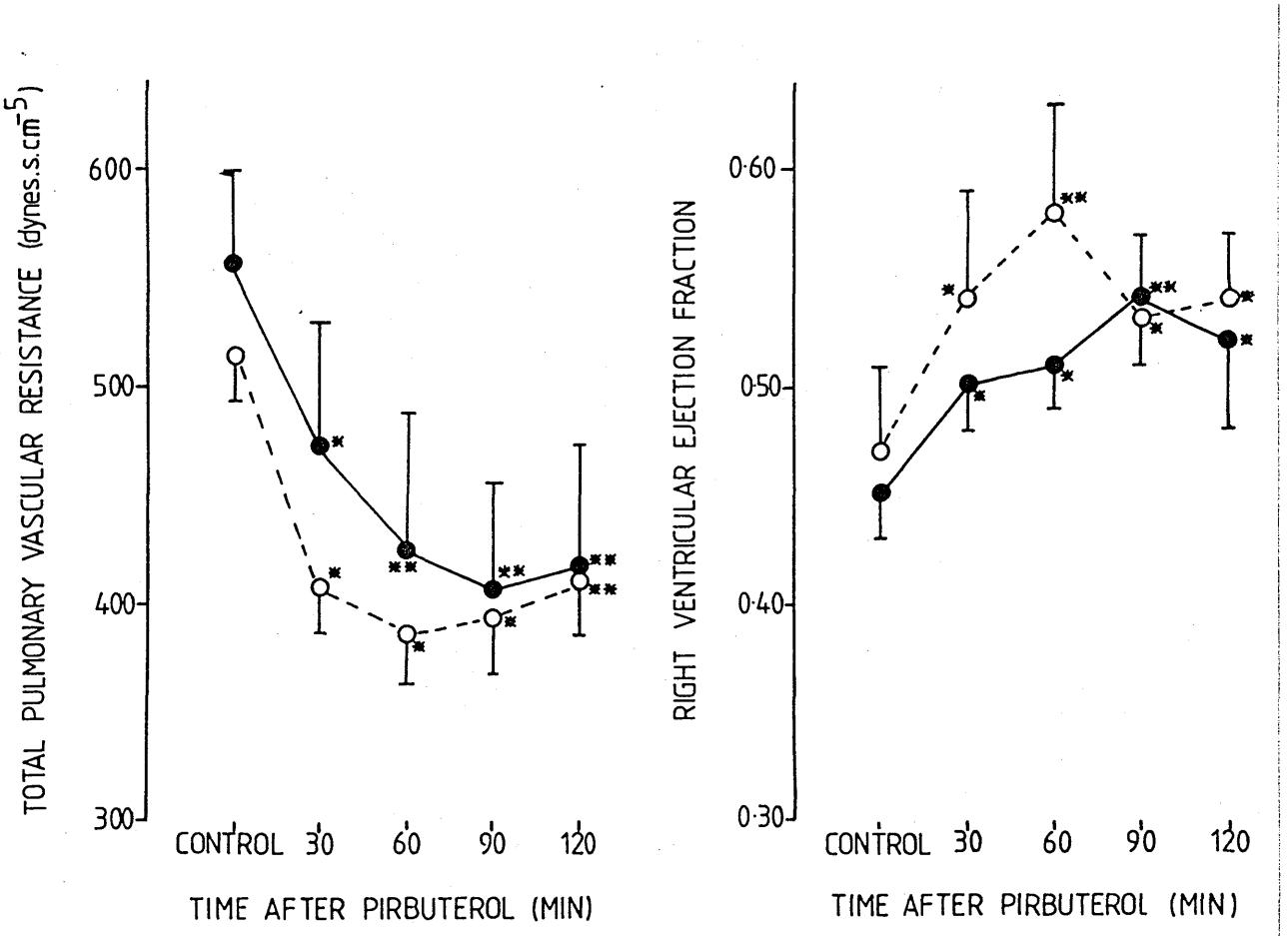


Figure 49B The acute effects of pirbuterol in a single oral dose (22.5 mg, n = 6, o--o; 15 mg, n = 6, ● - - ●) in patients with chronic bronchitis and emphysema.
Mean values are shown and the error bars represent 1 SEM.
Significant differences from the control values:
* $p < 0.05$; ** $p < 0.01$.

planned. Pirbuterol concentrations were assayed in venous plasma (99) in 10 patients one and two hours after the drug was given.

Results

The maximum effects of pirbuterol on pulmonary vascular resistance occurred 90 minutes after the drug was given therefore only these results are reported (figure 49a and b). The effects of each of the dose regimes on pulmonary vascular resistance were similar. Although there was no significant change in mean PAP at the lower dose, the effects of both dose regimes which occurred 90 minutes after each dose have been combined in the analysis.

Acute effects of pirbuterol (table 22, 23)

In these 12 patients, there was a small but significant increase in heart rate from 87 $\pm$ 13 to 97 $\pm$15 b/min ($p < 0.01$) 90 minutes after pirbuterol was given. Cardiac index also increased from 2.62 $\pm$ 0.58 to 3.15 $\pm$ 0.62 $l/m/m^2$ ($p < 0.01$). Although cardiac index increased in every patient, the change in stroke volume index was not significant. Mean PAP fell from 30 $\pm$ 5 to 27 $\pm$ 5 ($p < 0.05$) resulting in a fall in total pulmonary vascular resistance from 566 $\pm$ 149 before to 428 $\pm$ 114 dynes.s.cm^{-5} after pirbuterol ($p < 0.001$), a fall occurring in every patient (figure 50). Pirbuterol also reduced systemic vascular resistance significantly from 1819 $\pm$ 588 to 1469 $\pm$ 525 dynes.s.cm^5 ($p < 0.001$). Although right ventricular systolic pressure fell in 7 of the 12 patients studied, pirbuterol did not produce any signficant change in right ventricular systolic or diastolic pressures. Mean RVEF increased significantly from a control value of 0.46 $\pm$ 0.08 to 0.55 $\pm$ 0.10 ($p < 0.001$) after pirbuterol, an increase in RVEF occurring in 11 of the 12 patients

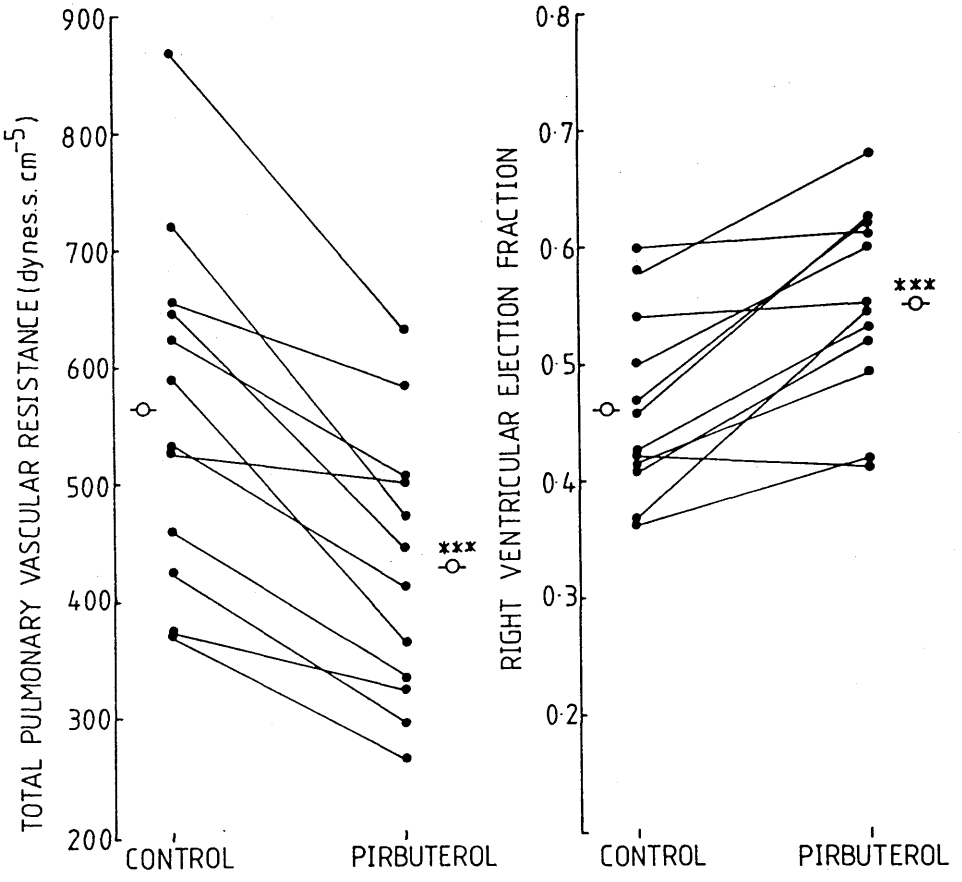


Figure 50 Acute effects of pirbuterol in 12 patients with chronic bronchitis and emphysema. Individual values (•) and the mean values (-o-) are shown.
Significant differences from control values:
*** $p < 0.001$.

pirbuterol despite a fall in systemic vascular resistance. Although pirbuterol did not change right ventricular end-diastolic volume index (table 23), the RV end-systolic volume index fell significantly from 38 $\pm$ 14 to 29 $\pm$ 1 $ml.m^{-2}$ ($p < 0.05$).

Thus the right ventricular end-systolic pressure/volume relation increased from an average of 1.40 $\pm$ 0.74 to 1.77 $\pm$ 1.02 ($p < 0.05$). The right ventricular stroke work index averaged 16.9 $\pm$ 6.2 $g.m/m^2$ and was unchanged by pirbuterol (RVSWI after pirbuterol 17.4 $\pm$ 6.6 $g.m/m^2$).

There were no significant correlations between the changes in RVEF produced by pirbuterol and the changes in PAP, right ventricular systolic pressure, or total pulmonary vascular resistance.

These changes in pulmonary haemodynamics produced by pirbuterol resulted in a significant fall in arterial oxygen tension from 7.3 $\pm$ 0.8 to 6.6 $\pm$ 0.9 kPa ($p < 0.05$) (table 22) without any significant change in $PaCO_2$. PVO_2 was low in these patients (mean PVO_2 4.4 $\pm$ 0.2 kPa) and did not change significantly after pirbuterol. Despite a reduction in PaO_2 after pirbuterol the systemic oxygen delivery (SDO_2) increased from 44.5 $\pm$ 6.9 to 51.1 $\pm$ 7.4 $ml/min/m^2$ ($p < 0.01$) and the coefficient of oxygen delivery (COD) also increased from 3.4 $\pm$ 0.5 to 4.1 $\pm$ 0.9 ($p < 0.02$). Since there was a small fall in the arterial oxygen content after pirbuterol, the increase in systemic oxygen delivery was as a result of an increase in cardiac output.

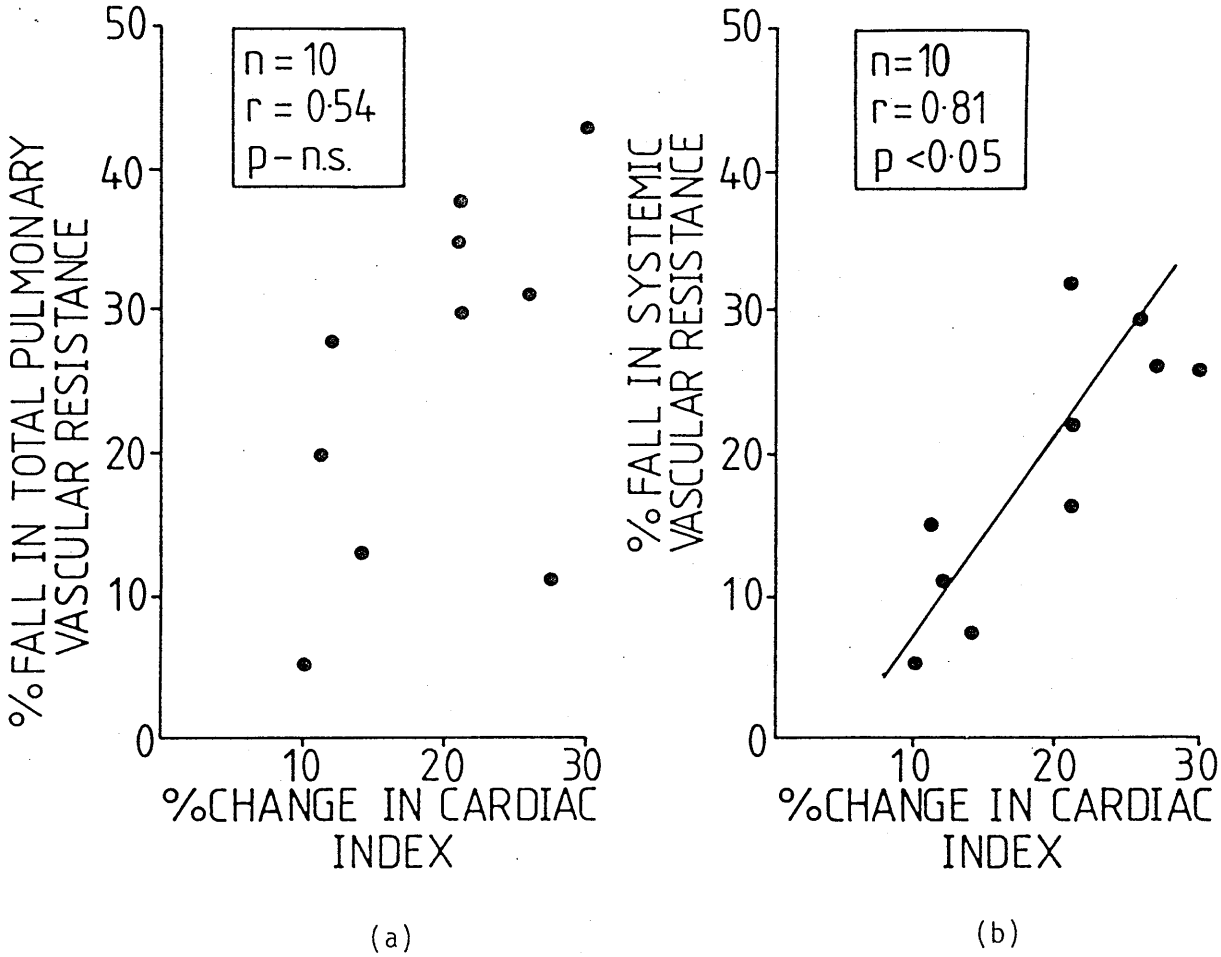
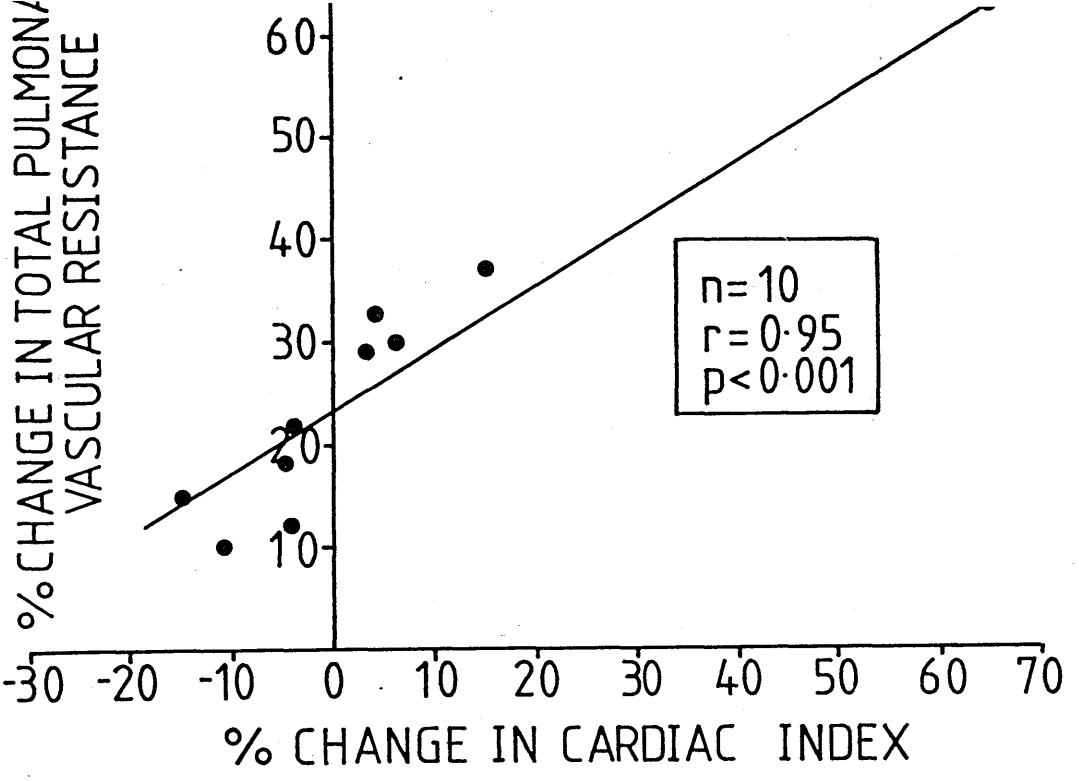


Figure 51 a & b Relationship between changes in cardiac index, and the corresponding changes in either (a) total pulmonary vascular resistance or (b) systemic vascular resistance produced by pirbuterol in 10 patients with chronic bronchitis and emphysema.

(a)



(b)

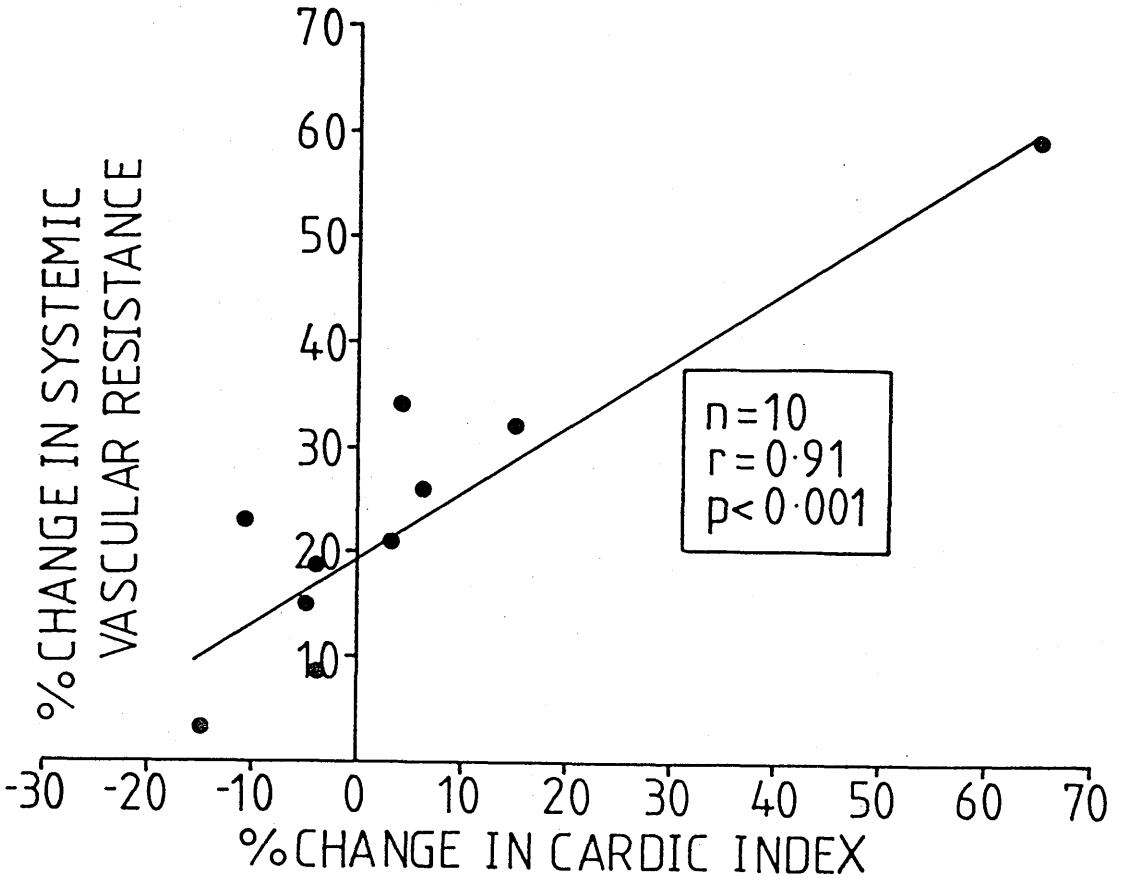


Figure 52 A & B Relationship between changes in cardiac index, and the corresponding changes in either (a) total pulmonary vascular resistance or (b) systemic vascular resistance produced by sodium nitroprusside in 10 patients with chronic bronchitis and emphysema.

A comparison of the acute effects of pirbuterol and sodium nitroprusside

In a comparison of the haemodynamic effects of sodium nitroprusside and pirbuterol (table 24) in 10 patients with chronic bronchitis and emphysema, both drugs produced a significant fall in mean PAP, which was more significant after sodium nitroprusside. Both drugs also produced a reduction in total pulmonary vascular and systemic vascular resistances (table 24). However, whereas cardiac index increased in every patient after pirbuterol was given, the change in cardiac index was very variable during infusion with sodium nitroprusside, so that the mean cardiac index did not change significantly in these patients, during infusion with this drug.

The changes in PAP or total pulmonary vascular resistance produced by either drug did not show any significant correlation with the baseline values of these variables ($r = 0.43 - 0.27$). There was also no significant correlation between the baseline PAP and the change in pulmonary vascular resistance produced by either drug. Since both drugs produced an acute reduction in pulmonary vascular resistance in every patient this variable did not distinguish any difference in the action of either drug.

To determine if the changes in systemic and pulmonary vascular resistances occurred entirely as a result of changes in cardiac output, I have correlated the percentage change in cardiac index with the changes in either total pulmonary vascular resistance or systemic vascular resistance produced by either drug (figure 51a and b, 52a and b). For both drugs there was a good correlation between the percentage change in cardiac index and the percentage change in systemic vascular resistance. In contrast, although there was a good

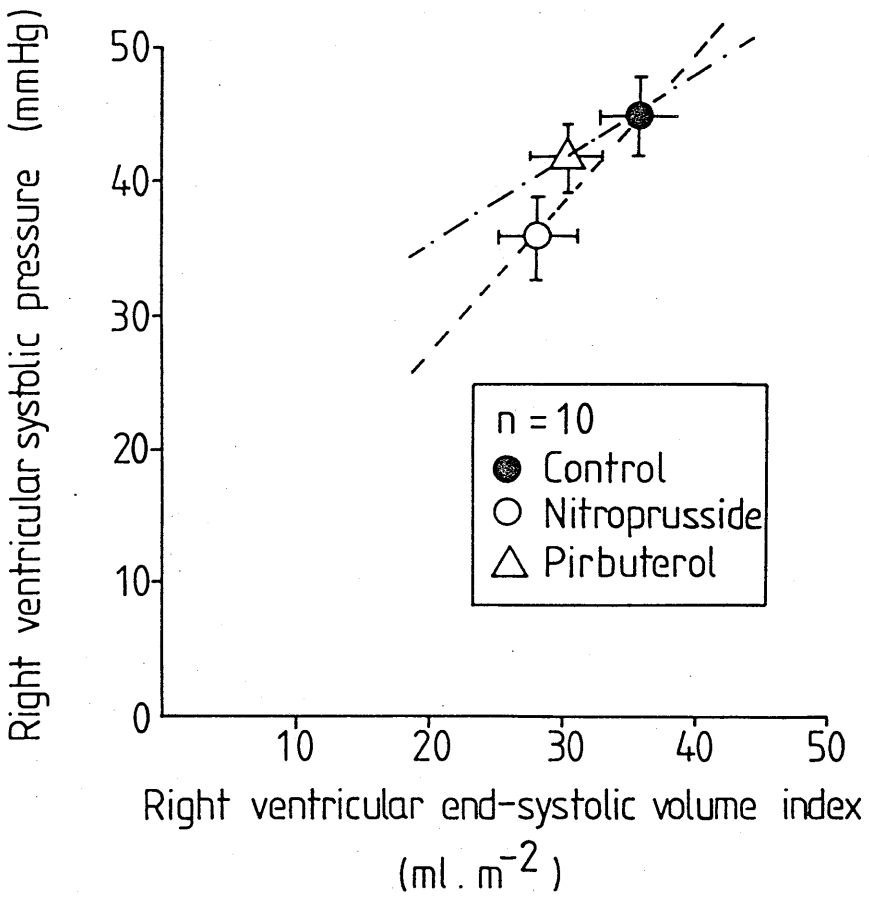


Figure 53 Mean right ventricular end-systolic pressure/volume relationship in 10 patients with chronic bronchitis and emphysema (●). Sodium nitroprusside displaces the end-systolic P/V point as shown (o), whereas pirbuterol displaces the P/V point further to the left. The error bars represent 1 SEM.

correlation between the percentage change in cardiac index and the percentage change in pulmonary vascular resistance produced by sodium nitroprusside, there was no significant correlation between percentage change in cardiac index and the percentage change in pulmonary vascular resistance produced by pirbuterol (figure 51a). Moreover, during infusion with sodium nitroprusside, the mean percent change in the systemic and pulmonary vascular resistances were not significantly different. In contrast, however, in all but one patient the percentage change in total pulmonary vascular resistance after pirbuterol was more than the corresponding change in systemic vascular resistance. The only patient in whom this was not the case was, in fact, the only one in whom PAP rose after pirbuterol (table 24, patient no 5). Thus, the mean percentage change in the total pulmonary vascular resistance after pirbuterol was $-25.4 \pm 12.6\%$, which was significantly greater than the mean percentage change in systemic vascular resistance which was $-18.9 \pm 9.5\%$ ($p < 0.05$), whereas the corresponding changes in pulmonary and systemic vascular resistances produced by sodium nitroprusside were similar (-26.6 ± 15.8 vs 24.0 ± 15.3, NS).

The effects of these drugs on the right ventricular end-systolic pressure/volume relation were also different (table 24). Sodium nitroprusside infusion produced no significant change in the right ventricular end-systolic P/V index, whereas this ratio was significantly increased by pirbuterol. In the case of pirbuterol this had the effect of displacing the right ventricular end-systolic P/V point further to the left on the pressure volume diagram (figure 53).

Plasma pirbuterol concentrations varied (table 25). There were no

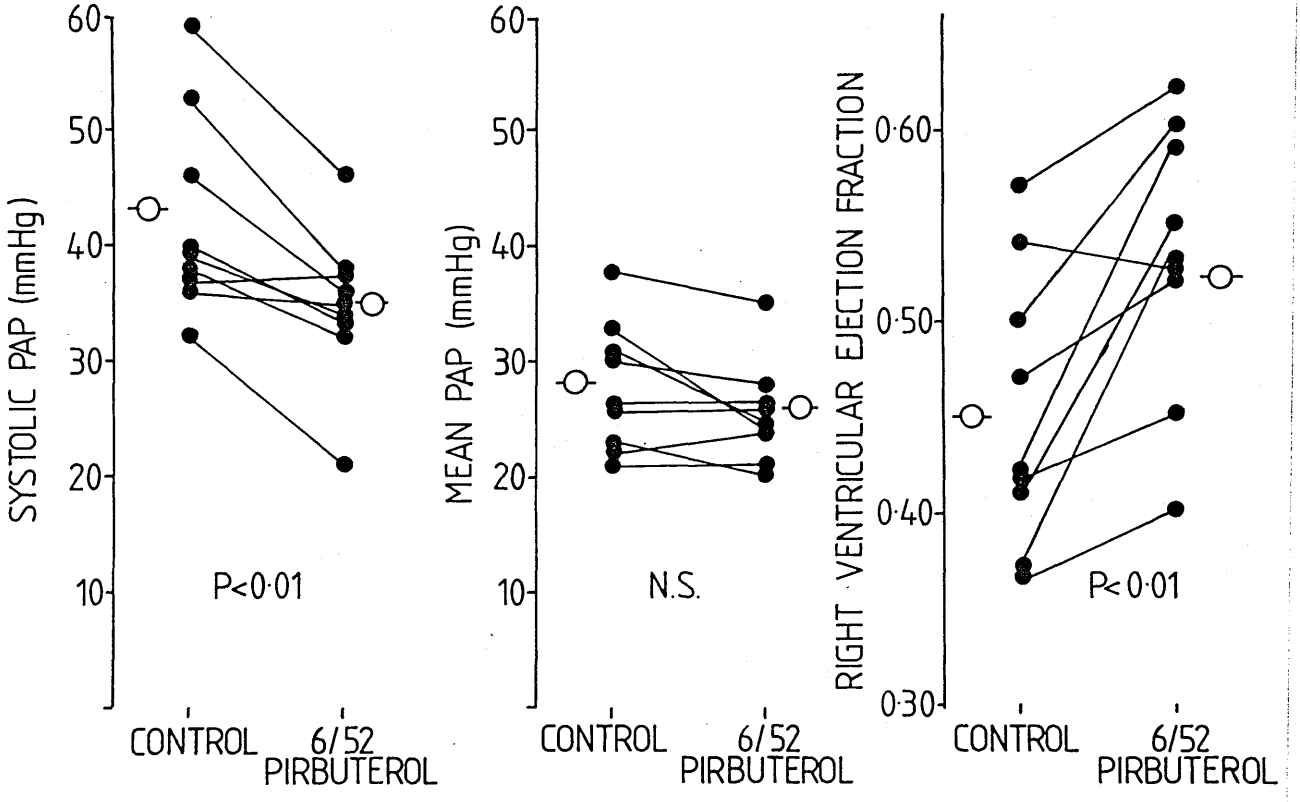


Figure 54 Effects of pirbuterol (15 mg tid) given for 6 weeks to 9 patients with chronic bronchitis and emphysema. Individual (●) and mean (–o–) values are shown.

pirbuterol and any of the haemodynamic variables.

Chronic effects of pirbuterol (table 26)

In the nine patients who completed 6 weeks' treatment with pirbuterol in a dose regime of 15 mg thrice daily, heart rate, arterial blood pressure, gas tensions and hydrogen ion concentrations were unchanged by the drug. Systolic (but not mean) PAP fell from 43 $\pm$ 3 before to 35 $\pm$ 2 mmHg ($p < 0.01$) after 6 weeks' treatment (figure 54) and mean RVEF rose from 0.45 $\pm$ 0.04 to 0.52 $\pm$ 0.03 ($p < 0.01$), without any significant change in LVEF. Oral pirbuterol did not produce any changes in ventilatory capacity or in exercise tolerance, as assessed by the 12 minute walking distance.

DISCUSSION

The role of vasodilators and inotropic agents in the treatment of patients with hypoxic pulmonary hypertension and cor pulmonale remains unclear (164). There are several problems in assessing the potential benefits of vasodilators on the pulmonary circulation. Not least among these is the difficulty which stems from the complex relationship of pressure to flow in the pulmonary circulation which reflects the resistance. This relationship in the normal lung is curvilinear. Thus, as flow increases, vascular resistance decreases sharply (140), then more gradually. Thus any assessment of a drug on the pressure flow relationship, particularly in a diseased lung, based on an assessment of two points on the pressure flow curve, when both parameters are changing, is very difficult. In addition, since we cannot measure resistance directly, its calculation from measurements of flow and pressure may make the interpretation of

implicit changes in resistance misleading. Moreover, increases in pulmonary blood flow can occur in the pulmonary circulation as a result of recruitment of unused vessels, rather than by true vasodilatation (274).

The primary aim in this chapter was to measure the cardiovascular effects of pirbuterol, a beta-agonist, which has been shown to have beneficial cardiovascular effects in congestive cardiac failure, secondary to ischaemic heart disease (286, 300). Debate exists over whether the mechanism of these haemodynamic effects are due to the drug acting as an inotrope, or simply secondary to its vasodilator action (14, 73, 247, 286, 300). It was hoped that a comparison of the effects of pirbuterol and those of sodium nitroprusside, a vasodilator with no inotropic action, would be useful in elucidating the mode of action of this drug in patients with chronic bronchitis and pulmonary hypertension. Arguably, sodium nitroprusside is not the best vasodilator to be contrasted with pirbuterol because of its combined arterial and venous effects. However, the comparison may be valid, since pirbuterol is also thought to have venodilator properties (13).

Pirbuterol produced a small but significant increase in heart rate, which may have been due to an effect on cardiac beta-1 receptors. A small but significant decrease in PAP occurred 90 minutes after oral pirbuterol, which was associated with a consistent rise in cardiac index in all patients. Thus, pulmonary vascular resistance fell in every patient after pirbuterol. In contrast, sodium nitroprusside produced a greater fall in PAP than pirbuterol, without producing a significant change in cardiac index, resulting in a similar fall in pulmonary vascular resistance. Both drugs produced a similar

pirbuterol this was as a result of an increase in cardiac output, whereas the systemic vascular resistance fell during sodium nitroprusside infusion, largely as a result of a fall in systemic BP.

One potential hazard of vasodilators used specifically to promote pulmonary vasodilatation in patients with chronic bronchitis and emphysema, is that they often produce marked systemic vasodilatation without an equal or greater degree of pulmonary vasodilatation, thus producing systemic hypotension (135), such as can occur with hydrallazine (336). This effect, however, did not appear to occur with pirbuterol which produced no significant fall in systemic blood pressure. Further evidence of the more specific pulmonary vasodilator effect of pirbuterol comes from the correlation between the changes in cardiac index and the changes in systemic and pulmonary vascular resistance. Although one would expect a correlation between these variables for both drugs, since the calculation of resistance includes a measure of cardiac index, the change in cardiac index correlated more with the change in systemic vascular resistance than the change in pulmonary vascular resistance after pirbuterol, whereas similar correlations between these variables occurred during sodium nitroprusside infusion. This would suggest that the change in pulmonary vascular resistance produced by pirbuterol was less dependent on an increase in flow which might result from recruitment of vessels, and was more likely to be as a result of a true change in pulmonary vasomotor tone. Further support for a more pronounced specific pulmonary vasodilator action for pirbuterol comes from the greater percentage fall in the pulmonary vascular compared to systemic vascular resistance produced by this drug. These results contrast with sodium nitroprusside

resistance. The effects of pirbuterol in producing a greater fall in pulmonary, compared with systemic resistance, the fall in PAP without significant effect on systemic pressure, together with a rise in cardiac output are the factors which Rich et al have identified as being those which indicate true pulmonary vasodilatation in patients with primary pulmonary hypertension (274). Rich looked retrospectively at various previous published reports of the effects of vasodilators in primary pulmonary hypertension and found that if a pulmonary vasodilator in an individual patient did not reduce PAP, then that patient did not have a significantly greater fall in pulmonary as compared to systemic vascular resistance in the face of a rise in cardiac output. Of the 12 patients I have studied, only two had these haemodynamic effects after pirbuterol (table 23, patients 5 and 12), and both had a rise in PAP after this drug.

Great caution should be exercised when comparing concepts developed for vasodilator therapy in primary pulmonary hypertension with those in hypoxic pulmonary hypertension (200). However, lessons can be learned from a study of this condition. It appears, as in primary pulmonary hypertension, that the acute haemodynamic effects of vasodilators may be variable in different individuals and are very dependent on the homogeneity of the group under study. Moreover, the acute effects of vasodilators do not necessarily predict their long term effects (164, 274).

How did the effects of sodium nitroprusside and pirbuterol on the pulmonary and systemic vascular resistance affect ventricular performance in these patients? Sodium nitroprusside produced a significant increase in LVEF which was not seen after pirbuterol.

than with sodium nitroprusside. This may seem contradictory, particularly as sodium nitroprusside produced a greater fall in PAP. However, these findings can be explained by the fact that PAP and RVEF are not well correlated in patients with chronic bronchitis and emphysema, since PAP is not a true reflection of the right ventricular afterload (Chapter 4). I have shown that RVEF correlated better with total pulmonary vascular resistance which was reduced by a similar degree by both drugs in this study. However, as discussed above, the fall in total pulmonary vascular resistance produced by pirbuterol was probably due to a true reduction of pulmonary vasomotor tone. In addition, the increase in RVEF produced by pirbuterol could have been as a result of an increase in right ventricular contractility. This concept is supported by the significant increase in the right ventricular end-systolic pressure/volume relation and the displacement of the pressure volume point further to the left after pirbuterol compared to the effects of sodium nitroprusside. In order to confirm that pirbuterol had an additional inotropic, as well as a vasodilator, action, it would be necessary to compare the slope of the pressure volume relation obtained at different levels of right ventricular afterload after these patients had taken pirbuterol, which was not done in this study. However, as discussed previously, the fact that the P/V index increased after pirbuterol despite no significant change in right ventricular systolic pressure, suggests that this drug produced an enhancement of right ventricular contractility.

The effects of pirbuterol on RVEF were sustained after 6 weeks' therapy, and although systolic PAP was still reduced when compared with control value before the drug was given, the mean PAP was

This study of the haemodynamic effects of pirbuterol confirms and extends studies of the effects of other Beta-agonists in patients with chronic bronchitis and emphysema. Terbutaline, has been shown to have similar effects on pulmonary vascular resistance and cardiac output to those of pirbuterol, at least when given intravenously (316) or subcutaneously (47). Terbutaline has also been shown to increase RVEF when given subcutaneously (47, 323) and recently oral salbutamol has also been shown to increase RVEF (359). However, isolated measurements of RVEF (323, 359) are not useful in predicting a good clinical response of a drug which may have both inotropic and vasodilator properties. Thus, RVEF must be combined with more invasive haemodynamic measurements such as in the study by Brent et al of the effects of terbutaline on pulmonary haemodynamics (47). I would, however, disagree with Brent's conclusions regarding the mechanism of the increased RV performance produced by terbutaline, which he attributed to a fall in pulmonary vascular resistance due to Beta-2 adrenoceptor stimulation. Since Brent and others (47, 323) have found that this drug produced a small or insignificant change in PAP, I feel it is more likely that the effect of terbutaline in increasing right ventricular ejection fraction is as a result of a positive inotropic action as with pirbuterol.

One further factor has to be taken into account in assessing the effects of a drug on the pulmonary vasculature and that is its effect on intrathoracic pressure, which may alter the pulmonary vascular resistance. Although it is possible that pirbuterol affected the pulmonary mechanics, circumstantial evidence indicates that this was not the case. Firstly, over the long term, there was no change in

irreversible airflow obstruction. However, in addition, re-analysis of the pulmonary arterial pressure trace, from the acute study, did not show any significant changes in the amplitude of the intrathoracic pressure swings in these patients after pirbuterol, which indicates indirectly that there was no change in intrathoracic pressure.

Data confirming the haemodynamic effects of pirbuterol in this study have now been published in a study by Peacock (261).

One concern regarding the use of vasodilators in patients with lung disease is the possible aggravation of hypoxaemia as a consequence of a loss of the hypoxic regulation in the pulmonary circulation. Thus, vasodilatation can occur in underventilated areas of the lungs which would worsen the ventilation/perfusion matching. This effect has been variably demonstrated with vasodilators such as hydrallazine (201, 284, 285) and nifedipine (180, 227, 304, 320). The effect appears to depend on the patients studied. In this present study, as in the study by Peacock (261) pirbuterol reduced the PaO_2. A similar fall in PaO_2 has not been demonstrated in patients with chronic bronchitis and emphysema who were given another Beta-agonist - terbutaline (47, 323). This potentially deliterious effect of pirbuterol may be offset by the fact that pirbuterol did not alter the mixed venous oxygen tension significantly and may, in fact, have increased the oxygen delivery to the tissues, since the systemic oxygen delivery and the coefficient of oxygen delivery increased as a result of an increase in cardiac output. However, this fall in PaO_2 may have a greater impact during exercise when further desaturation may occur. It may be that a combination of long term oxygen and

over a period of six weeks, pirbuterol produced no significant change in arterial blood gas tensions.

Whether any of the haemodynamic effects of a drug which has both pulmonary vasodilator and inotropic actions will influence the long term prognosis in patients with cor pulmonale remains speculative and awaits the outcome of a long term study. Two points, however, are worthy of consideration in the design of any long term study of the effects of vasodilators. Firstly, the changes in PAP produced by all pulmonary vasodilators in previous studies in patients with chronic bronchitis and emphysema, including this study, are trivial or insignificant (164). If the criteria for an ideal vasodilator with which to study the effects on survival was the reduction of pulmonary arterial pressure to normal, then none of the vasodilator drugs would be suitable. Thus, the search for better drugs which have a predominantly pulmonary vasodilator activity, or are metabolised in a single pass through the pulmonary circulation, and are effective when given by mouth, is urgently needed.

Secondly, if the effects of a drug which has both a vasodilator and an inotropic action is to be studied over the long term, it is important that its effects are studied in a homogenous group of patients with chronic bronchitis and emphysema, particularly in a group with the same level of cardiac output. It may be, as suggested by Bergofsky (29) that those patients with chronic bronchitis and emphysema and cor pulmonale who fail to maintain a high normal cardiac output, and hence fail to maintain adequate oxygen delivery to the tissues, have a worse prognosis. Such patients may benefit from the effects of a drug with vasodilator and inotropic

inotropic therapy in the majority of patients studied in this thesis with chronic stable cor pulmonale, in whom I have found a normal or enhanced inotropic state. Consideration of the right ventricular end-systolic pressure/volume relation is therefore useful as an indicator of the baseline ventricular contractility in such patients, and may shed some light on the longstanding controversy over the conflicting effects of digoxin in patients with cor pulmonale (26, 51, 102, 128, 223).

CONCLUSIONS

1. The Beta-agonist pirbuterol, when given acutely by mouth, produced significant pulmonary vasodilatation in patients with hypoxic chronic bronchitis and emphysema and pulmonary hypertension.

2. Pirbuterol also produced a fall in systemic vascular resistance, largely as a result of an increase in cardiac output, since systemic blood pressure remained unchanged.

3. An analysis of the pressure flow changes produced by pirbuterol in the pulmonary circulation, together with the relatively greater fall in pulmonary vascular resistance produced by the drug, compared with its effects on systemic vascular resistance, suggested that pirbuterol had an effect in decreasing pulmonary vascular tone.

4. Both sodium nitroprusside and pirbuterol produced increases in right ventricular ejection fraction in these patients.

5. The increase in right ventricular ejection fraction may have been partially due to pulmonary vasodilatation. However, an analysis of the right ventricular end-systolic pressure/volume relation suggested that pirbuterol had, in addition, a positive inotropic action, in contrast to sodium nitroprusside which was shown to be a vasodilator with no inotropic action.

6. These haemodynamic effects of pirbuterol were associated with a fall in PaO_2 but this did not have a detrimental effect on tissue oxygen delivery.

7. The acute effects of pirbuterol on systolic PAP and RVEF were sustained over a period of 6 weeks' therapy with the drug, without producing any change in arterial blood gas tensions, ventilatory capacity or exercise tolerance.

Although the dire consequences of a sudden increase in right ventricular afterload, such as occurs in massive pulmonary embolism, are well known (134, 202, 212, 313), the effects on right ventricular function of progressive increases in pulmonary arterial pressure, with or without intravascular volume loading, have received less attention. In primary pulmonary hypertension (116, 117) it is easy to imagine that the high levels of pulmonary arterial pressure found in this condition would lead to afterload dependent right ventricular hypertrophy, and eventually right ventricular `pump' failure, analogous to the situation in the left ventricle, when faced with systemic arterial hypertension. However, the effects of severe chronic bronchitis and emphysema on right ventriclar performance are much more complicated. Firstly, the levels of the pulmonary arterial hypertension in this condition are seldom as high as those found in primary pulmonary hypertension, which often approach systemic values (116). In my experience the mean pulmonary arterial pressure in most patients with chronic respiratory failure as a result of chronic bronchitis and emphysema, is between 20-35 mmHg. However, most studies suggest that during acute exacerbations of respiratory failure the pulmonary arterial pressure rises further (152, 366) probably as a result of several mechanisms which include worsening hypoxaemia, acidosis, and changes in pulmonary mechanics (197, 198). Acute changes in pulmonary arterial pressure also occur, to a variable degree, during exercise (197) on a background of mild pulmonary hypertension which is present even when the patient`s condition is stable. This varying pulmonary hypertension leads to a

addition, chronic hypoxia may itself have a direct effect on the right ventricular myocardium.

Not every patient who develops pulmonary hypertension as a result of hypoxic chronic bronchitis and emphysema, who presents with acute on chronic respiratory failure, develops clinical signs of heart failure. The sequence events which result in the development of oedema in this syndrome are unknown and depend on these adaptive mechanisms. There is, as discussed previously, controversy as to whether the clinical syndrome of acute decompensated cor pulmonale or pulmonary heart disease, with its associated oedema and a raised jugular venous pressure is indeed really due to `heart failure' (60, 276). It is still true to say that the cause of the oedema in decompensated pulmonary heart disease is unknown.

The data presented earlier in this thesis indicates that the right ventricular ejection fraction remains relatively normal in most patients with chronic bronchitis and emphysema, except in those who are oedematous at the time of study. Moreover analysis of the right ventricular end-systolic pressure/volume relation suggests that right ventricular contractility is normal, in patients with chronic bronchitis and emphysema, who have pulmonary hypertension and previous episodes of right ventricular failure, but whose condition is stable. I felt it would be important to extend the measurements of right ventricular mechanics to patients who presented acutely, with oedema and the clinical syndrome of right `heart failure'.

The aim of the study in this chapter was to assess the right ventricular pressure/volume relation in such patients using a

radionuclide ventriculography. Moreover, the acute effects of oxygen were also studied, and compared with data obtained in patients with pulmonary hypertension who were studied when their clinical condition was stable.

Patients and methods

Six patients with chronic bronchitis and emphysema were studied (table 27). All of these patients had presented acutely, and were admitted to hospital in respiratory failure, with gross peripheral oedema, when a diagnosis of pulmonary heart disease was made. The patients were selected if there was no other obvious acute precipitating cause for their 'heart failure' such as acute pulmonary embolus (although it was impossible to completely exclude this diagnosis). Four of the 6 patients were presenting with oedema for the first time having had chronic bronchitis and emphysema for at least 10 years. The patients were studied within 48 hours of their admission after the purpose of the study and its research nature had been explained to them, and their written informed consent had been obtained. Initial emergency treatment was undertaken as appropriate before each study, which included nebulised bronchodilators and oxygen in every case, and intravenous diuretics and antibiotics if these were considered necessary. None of the patients were receiving theophyllines or digoxin. Patients were excluded from the study if they required treatment for acute on chronic respiratory failure in the form of respiratory stimulants. If a patient had a respiratory acidosis on admission, the study was delayed until this was controlled so as to avoid any potential depressant effect which acidosis might have on the myocardium. The timing of the study was also delayed until the patient's clinical condition permitted the

particularly no diuretic therapy, for at least 12 hours prior to study. None of the patients were known to have previous evidence of hypertensive, valvular or ischaemic heart disease.

If any patient's condition was such that these entry criteria could not be met within 48 hours of admission, he was excluded from the study. The aim was therefore to study patients who were considered to have 'acute right heart failure' secondary to chronic bronchitis and emphysema and respiratory failure and not those who were in the convalescent phase or who did not present acutely but who had worsening oedema perhaps as a result of a recent change in diuretic therapy. The study was approved by the hospital's Ethical Committee.

The patients were studied semi-supine. A Swan Ganz catheter was inserted under local anaesthetic using a Seldinger technique into the femoral vein and hence to the pulmonary artery. Pressures were recorded from the fluid filled catheter in the right atrium, right ventricle pulmonary artery and pulmonary capillary wedge positions. As described previously, pressures were averaged over at least three respiratory cycles. Mean pressures were derived by electrical integration. Cardiac output was recorded in triplicate and an average of three values with a variability of $< 5\%$ was used in the analysis.

A fine arterial line (Vigon gauge 18) was inserted into the non-dominant brachial artery under local anaesthetic to facilitate withdrawal of arterial blood gas samples. Systemic arterial pressures were recorded using a sphygmomanometer.

750 mBq of technetium^{99}m labelled human serum albumin was injected into a peripheral vein and allowed to equilibrate in the blood pool. The patient was then placed under the gamma camera for the measurement of ejection fractions by gated equilibrium radionuclide ventriculograhy as previously described (chapter 3).

Measurements were made with the patients breathing room air or oxygen given at 1-3 litres/minute by nasal prongs. The exact flow rate of oxygen was determined so as to obtain an adequate arterial oxygen tension but not to increase arterial carbon dioxide tension such that the hydrogen ion concentration rose to > 50 nmol/l. Air or oxygen was breathed by the patient in a random single blind fashion. If air was the first gas to be breathed then the patient would not have breathed oxygen for at least one hour before measurements were made. Oxygen was breathed for at least 30 minutes before any measurements were made.

At least 20 minutes were allowed for haemodynamic stability, after all of the intravascular lines were in place, before any measurements were made. Derived haemodynamic and oxygen delivery values were calculated from the equations described in Chapters 5 and 6.

Results (table 28, 29, 30)

All of the patients were hypoxic when breathing air (mean PaO_2 5.2 $\pm$ (SD) 1.2 kPa) and hypercapnic (mean $PaCO_2$ 8.0 $\pm$ 1.2 kPa) but with a normal arterial hydrogen ion concentration (mean $[H^+]$ 43 $\pm$ 3 nmol/l), except one patient whose hydrogen ion concentration was minimally elevated at 46 nmol/l (table 28).

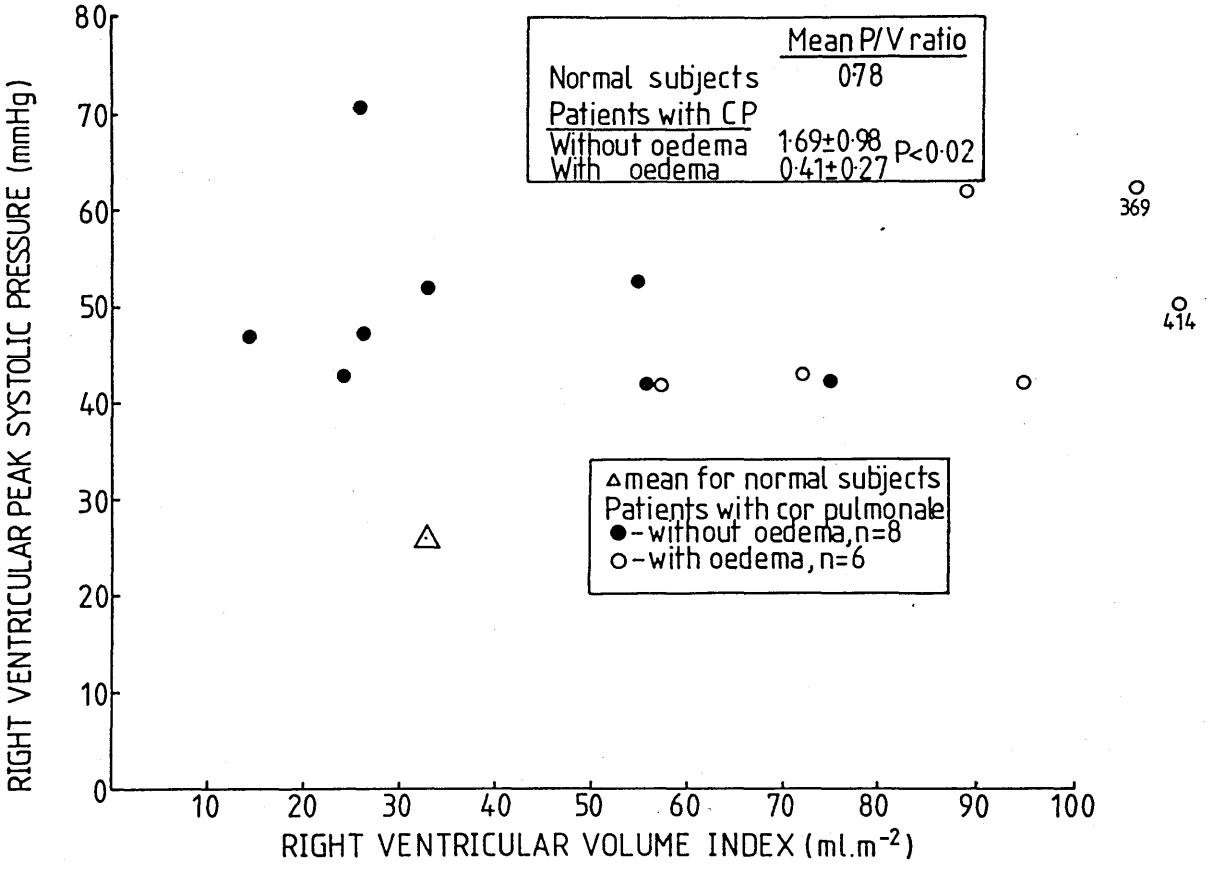


Figure 55 Individual right ventricular end-systolic pressure/volume points in 8 patients with cor pulmonale studied when their clinical condition was stable (●), and in 6 patients with cor pulmonale presenting acutely with oedema (o). The calculated mean right ventricular end-systolic pressure/volume point for normal subjects (Δ) is also shown.

3.9 ± 0.4 kPa) while breathing room air. The coefficient of oxygen delivery was quite variable in these patients, and was low in 3 of the 6 patients studied.

All of the patients had an elevated mean PAP (range 25 - 40 mmHg) and an elevated right ventricular systolic pressure (range 42 - 62 mmHg). The right ventricular end-diastolic pressure was elevated in the majority (mean 12 ± 8 mmHg). Pulmonary capillary wedge pressure was normal (mean 8 ± 4 mmHg) in all but one patient (table 29).

Mean cardiac index was also normal for the group (mean 3.65 ± 1.00) and was above normal in one patient and below normal in one other patient. Total pulmonary vascular resistance was high in every patient (mean 453 ± 106 dynes. s. cm^5). RVEF was also low in every patient (mean RVEF 0.23 ± 0.11) and was very low, ie < 0.30 in 3 of the 6 patients. LVEF was more variable (mean 0.42 ± 0.12) and was abnormal in 3 of the 6 patients studied. The right ventricular stroke work index was well maintained (mean 18.8 ± 6.6 $g.m.m.^{-2}$).

Calculated right ventricular end-diastolic volume index was high in the majority of patients (table 30). The mean right ventricular end-systolic pressure/volume index was also low (mean P/V index 0.41 ± 0.27). When plotted on a pressure volume diagram, the individual P/V points lay above and to the right of the calculated mean right ventricular pressure/volume point for normal subjects (figure 55).

Oxygen (1-3 l/min), when breathed by these patients for a period of 30 minutes, increased PaO_2 to a mean of 9.0 ± 2.6 ($p < 0.01$). One patient (no 5) did not achieve a very satisfactory level of PaO_2 when

in this patient led to rapid CO_2 retention and acidosis. Therefore the relatively low level of PaO_2 when breathing oxygen was accepted. $PaCO_2$ also rose significantly to 8.6 $\pm$ 1.3 kPa ($p < 0.01$) when breathing oxygen, which produced a significant increase in the hydrogen ion concentration (table 28), 3 of the 6 patients becoming significantly acidotic. The PVO_2 also increased significantly when breathing oxygen, to a mean of 5.3 $\pm$ 0.7 kPa ($p < 0.01$) and was within the normal range in all but one patient when breathing oxygen.

The arterial oxygen content increased significantly while breathing oxygen when compared with the value when breathing air, as did the systemic oxygen delivery. However, there was no significant change in the coefficient of oxygen delivery which increased in 4 patients and fell in 2 while breathing oxygen (table 28).

Oxygen breathing did not change the mean heart rate or the mean systemic blood pressure significantly. However, there was a small but significant increase in systemic vascular resistance from 1197 $\pm$ 624 to 1292 $\pm$ 653 dynes. s. cm^{-5} ($p < 0.02$) (table 30). An increase in systemic vascular resistance occurred in every patient when breathing oxygen, as a result of a fall in the cardiac index from an average of 3.65 $\pm$ 1.00 to 3.42 $\pm$ 1.04 $l/min/m^2$ ($p < 0.01$).

Mean PAP and right ventricular systolic pressure both fell significantly when breathing oxygen by an average of 15% and 8% respectively, a fall in both variables occurring in every patient (table 30). However, there was no significant change in right ventricular end-diastolic, right atrial, or pulmonary capillary wedge pressure while breathing oxygen. Despite this fall in pulmonary

the total pulmonary vascular resistance although a fall in pulmonary vascular resistance occurred in 5 of the 6 patients studied, an increase occurring in one patient as a result of a marked fall in cardiac index (patient no 2). Moreover, oxygen in these 6 patients did not produce any significant change in the right ventricular stroke work index, which was 18.0 $\pm$ 7 $gm.m.^{-2}$ while breathing air, and 16.7 $\pm$ 7 $gm.m.^{-2}$ while breathing oxygen.

Calculated right ventricular end-diastolic and end-systolic volume indices did not change significantly on average while oxygen was breathed. However, individual falls in these volume indices were very variable from 0 to 74% (table 26). Moreover oxygen breathing did not produce any significant change in the mean right ventricular end-systolic pressure/volume index.

The effects of acute administration of oxygen in these 6 patients with acute decompensation of their pulmonary heart disease were compared with those in 8 patients, also with pulmonary hypertension and previous episodes of oedema but who were studied when their clinical condition was stable. The results of breathing oxygen in these patients has been discussed previously in chapter 6 (table 17, group I, table 18, table 19). The age and ventilatory capacity in both groups of patients was not significantly different (table 27). As expected the PaO_2 was lower and the $PaCO_2$ was higher in those patients studied in the decompensated state (table 27). Interestingly, the right ventricular systolic, mean pulmonary arterial pressure, and right ventricular end-diastolic pressure together with total pulmonary vascular resistance were not significantly different in either group of patients but the cardiac

was stable (mean cardiac index 2.58 $\pm$ 0.6 l/min/m^2) compared with those who were studied when acutely decompensated (mean cardiac index 3.65 $\pm$ 1.0 l/min/m^2, $p < 0.05$).

The stroke volume index was also similar in both groups of patients as was the LVEF. However, the mean RVEF was only 0.24 $\pm$ 0.11 in those with oedema compared with an average of 0.47 $\pm$ 0.10 ($p < 0.01$) in those who were studied when stable. The right ventricular end-diastolic volume index was also significantly higher (mean RVEDVI 218 $\pm$ 116 vs 69 $\pm$ 26 $ml.m^{-2}$, $p < 0.05$) and the right ventricular end-systolic P/V index was lower in those with oedema (P/V 0.41 $\pm$ 0.27) compared with those patients who were studied when stable (P/V 1.61 $\pm$ 0.41, $p < 0.02$). The right ventricular stroke work index was similar in both groups (table 27).

When breathing oxygen both groups tended to have similar changes in arterial blood gas tensions. However, the effect on $PaCO_2$ was more pronounced in those who had presented acutely (table 20). Although PVO_2 and systemic oxygen delivery increased when breathing oxygen in both groups of patients, the coefficient of oxygen delivery was not changed significantly by oxygen in either group.

Similar reductions in PAP and right ventricular systolic pressure occurred while either group breathed oxygen. However, in contrast to those who were studied when stable, where oxygen produced no change in cardiac index, those who were studied when acutely decompensated had a significant fall in cardiac index and thus no significant fall in total pulmonary vascular resistance. In neither group was the right ventricular stroke work index or the right

significantly by breathing oxygen.

DISCUSSION

The prime aim of this section of the dissertation was to determine whether patients with chronic respiratory failure who present acutely with oedema could truly be considered to have `heart failure'. Previous reviews of the literature on this topic have been based on relatively few studies and have been somewhat contradictory (60, 104, 113, 202, 276). Most take the classical view that whatever changes may take place in renal blood flow, or in renal hormone levels to account for the oedema of cor pulmonale, during periods of acute decompensation, the right ventricle `fails' in the clinical sense as a pump due principally to an augmented right ventricular afterload.

Let us put this theory to the test by considering the data presented in this chapter. In interpreting the results,it must borne in mind that these patients were a highly selected group who presented acutely with decompensation of their pulmonary heart disease and in whom gross oedema was the main reason for their presentation.

Firstly, the ability of these 6 patients to maintain their cardiac output was preserved, and was normal in all but 2 patients. Of these 2 patients one had a cardiac index which was only minimally reduced and the other had a slightly increased cardiac index. Indeed, for the group as a whole, the cardiac index was significantly higher, (although still within the normal range) than that of a comparable group of patients who had pulmonary hypertension and cor pulmonale but did not have oedema when studied (chapter 6). Cardiac

with decompensated pulmonary heart disease (4, 6, 152, 170, 197). This confirms the findings of a review of the earlier literature by Wade and Bishop (338) which concluded that there was no evidence to support the earlier contention that acutely decompensated pulmonary heart disease is a form of `high output' cardiac failure (102). Neither is this a condition of `low output' failure, such as occurs with the left ventricle as a result of hypertensive, ischaemic or rheumatic heart disease. Indeed, the right ventricular stroke work in this study was similar in those patients with and without oedema and was well maintained or even increased as compared with the values found in normal subjects (133, 181).

As discussed in Chapter 5, the data from a study by Khaja (181) in patients with cor pulmonale (admittedly defined as `cardiac enlargement or failure' associated with lung disease, ie not necessarily patients presenting acutely with oedema) has shown that during the stress of exercise, although the stroke index may be compromised and the right ventricular end-diastolic pressure rises during exercise suggesting depressed right ventricular function, when the right ventricular end-diastolic pressure is plotted against the right ventricular stroke work index, these patients appear to have a normal right ventricular response to exercise. Similar findings have been presented in a study by Jezek (170) and in a single patient study by Berglund (26)

The traditional view is that as cor pulmonale progresses abnormally high filling pressures occur in the right ventricle to maintain cardiac output, particularly during exercise, and that eventually this results in an abnormal right ventricular end-diastolic pressure

The right ventricular end-diastolic pressure was higher than normal in 4 of the 6 patients in this study (and would be expected to be even higher during exercise). However, this does not necessarily indicate that the right ventricle is failing. Indeed despite gross oedema, 2 patients had normal right ventricular end-diastolic pressure , which has to be explained. Several other factors can influence the right ventricular end-diastolic pressure such as intrathoracic pressure and increased blood volume. Indeed fluid retention alone can increase ventricular end-diastolic pressure in the absence of cardiac failure (90). Moreover, right ventricular hypertrophy can decrease right ventricular compliance and lead to an increased right ventricular end-diastolic pressure in non-failing hearts (170).

The range of right ventricular end-diastolic pressure in the patients in this study was very wide, from 3 to 27 mmHg in a population of patients with acutely decompensated pulmonary heart disease. I have also found elevations in right ventricular end-diastolic pressure in a population of patients with chronic bronchitis and emphysema without oedema (see chapter 5, table 13). Unexplained elevations in end-diastolic pressures in the right ventricle have also been found in normal subjects (133). I have no data on the effects of exercise on the right ventricular end-diastolic pressure in these patients but it has been suggested that although right ventricular end-diastolic pressure rises in patients with pulmonary heart disease during exercise, it is those patients who in addition have no corresponding increase in stroke volume who have truly depressed right ventricular function (170). The right ventricular end-diastolic pressure may therefore be a relatively poor indicator of right ventricular

In this study I have been able to measure the increase in right ventricular end-diastolic volume which takes place in order to maintain a normal cardiac output in these patients. In some cases the increase in right ventricular end-diastolic volume was up to five times the calculated normal value (see chapter 5). This increase in right ventricular end-diastolic volume was reflected in the large increase in cardiac size seen clinically in such patients (260). The increase in right ventricular end-diastolic volume at least in some patients (eg numbers 5 and 6) in this study occurred at the expense of an increase in end-diastolic pressure as predicted by Starling's Law.

In addition to the haemodynamic measurements discussed above, I have extended this study to an analysis of right ventricular mechanics which has not been considered in previous studies because of the difficulty in assessing right ventricular volumes. Moreover, although there have been previous studies of patients with chronic bronchitis and oedema (4, 6, 152, 170, 197), in only one study are details given so as to determine whether patients were studied when they presented acutely with decompensated pulmonary heart disease (6). In this important study by Abraham and colleagues, which is the most comparable with this present study, 8 patients with chronic bronchitis and emphysema were studied who presented with acute respiratory failure (although the mean pH was normal in these patients). Only 6 of these patients, in fact, had oedema. Haemodynamic parameters were studied on the day of admission and thereafter, daily for 5 days, and again on recovery. As in this present study, these patients were treated as necessary prior to

Abraham (6) that the most convincing evidence comes to suggest a rise in pulmonary arterial pressure and pulmonary vascular resistance during an acute exacerbation of chronic bronchitis which subsequently falls during recovery. I have not, as yet, studied the patients in this present study when they have recovered. However, it is interesting that the mean PAP and pulmonary vascular resistance in these patients who presented acutely with oedema was not significantly different from a similar group of patients studied when stable (table 29). It is surprising that those patients with oedema had both an increase in the right ventricular end-diastolic volume index and a reduction in the right ventricular end-systolic pressure/volume relation when compared to those patients without oedema, since this suggests depressed right ventricular contractility despite the presence of similar levels of right ventricular systolic pressure. This is illustrated by the displacement of the right ventricular end-systolic pressure/volume points further to the right in the pressure volume diagram, in those patients presenting acutely with oedema, when compared with those who were studied when stable (figure 55).

Although oxygen reduced pulmonary arterial and right ventricular systolic pressures in the 6 patients in this study, it did not change total pulmonary vascular resistance significantly and the cardiac index fell on average while breathing oxygen. Similar results were also described by Abraham in patients with acute respiratory failure (6). Thus although on average the right ventricular end-systolic P/V relation did not change when breathing oxygen which might indicate that oxygen acted primarily as a vasodilator and had no direct effect on right ventricular contractility, individual changes

slope of the end-systolic P/V relation in the right ventricle, using the two end-systolic pressure/volume points while breathing air or breathing oxygen, was not justified. In fact, in some of the patients the P/V index increased considerably due to a decrease in right ventricular end-diastolic volume, suggesting that in at least some of these patients, oxygen may have had an effect on right ventricular contractility. Further studies are in progress to calculate the slope of the right ventricular end-systolic pressure/volume relation in patients with acutely decompensated pulmonary heart disease during infusion with sodium nitroprusside. One of the problems, however, in interpreting data obtained from this study is that no data is available of the slope of the right ventricular end-systolic pressure/volume relation in normal subjects.

In these patients with oedema, the reduction in the mean right ventricular end-systolic P/V ratio was as a result of an increase in the right ventricular end-diastolic volume. These increases were very variable in this small group of patients. This variability probably reflects the degree of adaptation required by the right ventricle in patients who present acutely with oedema in order to maintain cardiac output. Thus, the results of this study suggest diminished right ventricular contractility in patients with chronic bronchitis and emphysema and respiratory failure who present acutely with oedema, since both the end-systolic P/V ratio and the RVEF are low in such patients. The fact that at least in t of adaptation required by the right ventricle in patients who present acutely with oedema in order to maintain cardiac output. Thus, the results of this study suggest diminished right ventricular contractility in patients with chronic bronchitis and emphysema and respiratory

P/V ratio and the RVEF are low in such patients. The fact that at least infusion of oxygen to these patients did not appear to normalise the right ventricular end-systolic pressure/volume relation, (although the effect was variable), suggesting that oxygen did not have any consistent effect on right ventricular contractility.

I would, however, tend to agree with Harris and Heath (140) who, in describing patients with acute decompensated pulmonary heart disease, state that "although these patients are oedematous and have a raised systemic venous pressure and increased cardiac size, the term 'cardiac failure' seems hardly appropriate to describe a condition in which the cardiac output is normal. The term seems even less apt in the light of the normal response of the cardiac output to exercise.

The fall in cardiac index seen in this study when these patients breathe oxygen has been reported in other studies (3, 358). Thus, although the arterial oxygen tension, the PVO_2 and the systemic oxygen delivery increased when oxygen was breathed, the coefficient of oxygen delivery did not increase. Since the arterial oxygen content rose when these patients breathed oxygen, the coefficient of oxygen delivery fell because of an increase in the arterial venous oxygen content difference, which resulted from a fall in cardiac output. Thus, as suggested by Bergofsky (29), and in two other previous studies (178, 326), any beneficial effects of oxygen on pulmonary arterial pressure and arterial oxygen tension may be offset in some cases by an alteration of the adaptive mechanisms which have developed to maintain cardiac output. Thus, in this present study, oxygen produced a dramatic fall in right ventricular end-diastolic

maintain a normal cardiac output. The result was an acute fall in cardiac output and on average no significant rise in the coefficient of oxygen delivery.

Whether or not these variables, which measure tissue oxygen delivery, change when oxygen is breathed depends on the balance between the rise in arterial oxygen tension (more particularly the oxygen saturation) and the fall in the cardiac index produced by oxygen. It is possible that the addition of an inotropic agent to oxygen in the treatment of these patients could counterbalance this effect, although whether this would be important clinically is not clear.

The fall in cardiac output when breathing oxygen, which I have shown in these patients, may also have implications for the unrestricted use of loop diuretics (150, 249) which may further lower the cardiac index.

Finally, although I have previously shown a reduction in the LVEF in patients with chronic bronchitis and emphysema who have oedema, the range of values of LVEF in the patients in this present study was very wide from 0.29 to 0.52. The mean pulmonary capillary wedge pressure in these patients was 8 ± 4 mmHg and there was no evidence, at least in the patients I have studied, of grossly elevated pulmonary capillary wedge pressures as reported in some studies (150, 197). Thus, the relatively normal pulmonary capillary wedge pressures in these patients does not suggest that the reduction in LVEF which occurred in some patients was as a result of left ventricular failure. However, I have expressed doubts as to the accuracy of pulmonary capillary wedge pressures as a true reflection

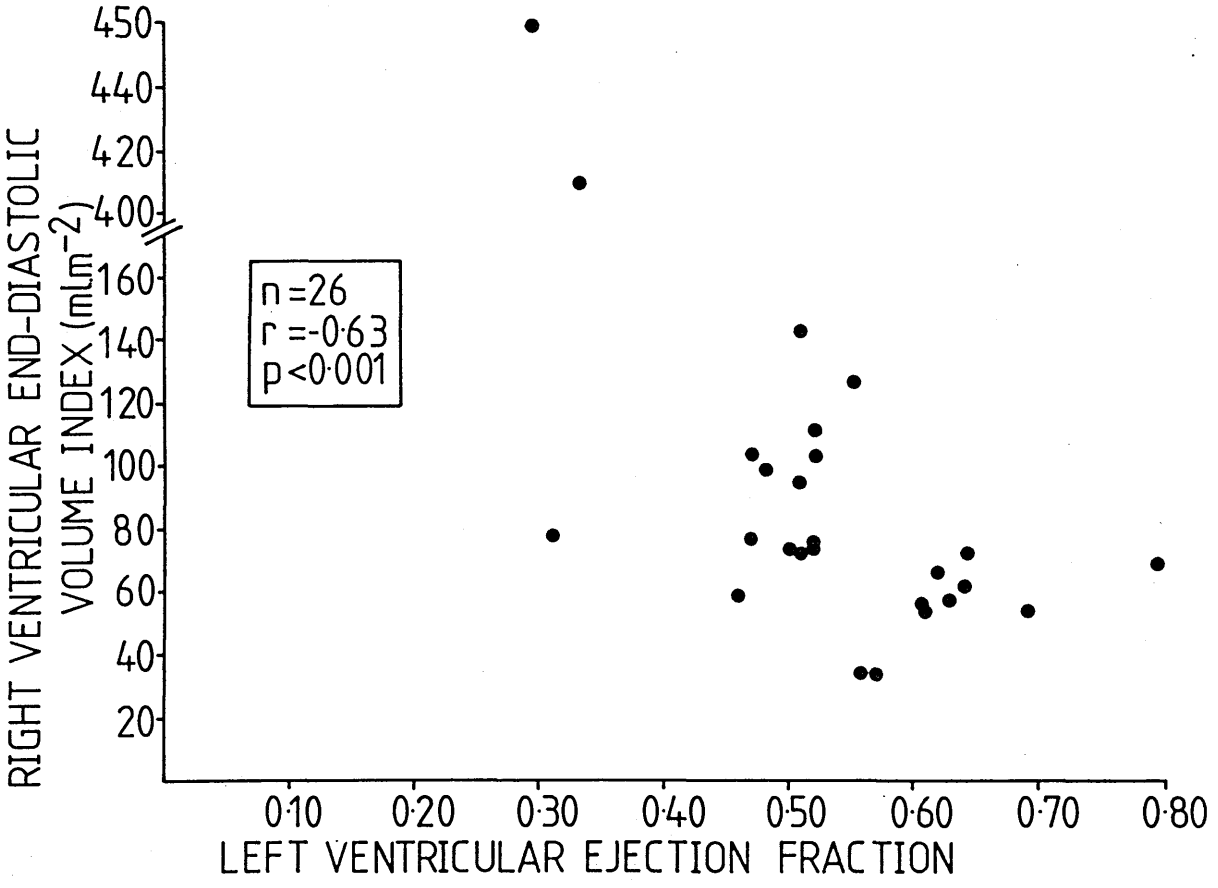


Figure 56 Relationship between left ventricular ejection fraction and right ventricular end-diastolic volume index in 26 patients with chronic bronchitis and emphysema.

emphysema and these views are supported by others (31, 256, 273). I would suggest that the large increases in right ventricular end-diastolic volume which occur in these patients produces a degree of impairment of left ventricular function. Although in the 6 patients in this study there was no significant correlation between the LVEF and the right ventricular end-diastolic volume index, there was a significant correlation between these two variables when a similar analysis was made in 26 patients pooled from the various studies in this thesis (figure 56).

CONCLUSIONS

1. In 6 patients presenting acutely with oedema as a result of decompensated respiratory failure, the right ventricular ejection fraction and the right ventricular end-systolic pressure/volume relation suggested that right ventricular contractility was depressed in these patients.

2. However, cardiac output and right ventricular stroke work index were well maintained by an adaptive mechanism involving large increases in the right ventricular end-diastolic volume index, much as Starling's Law would predict.

3. Isolated measurements of right ventricular ejection fractions in such patients are not helpful in understanding the complex haemodynamic changes which occur, but when combined with measurements of cardiac output and right ventricular pressure, can improve our understanding of cardiac performance in pulmonary heart disease.

4. In a comparison of two groups of patients with chronic bronchitis and emphysema and cor pulmonale with and without oedema, those who presented acutely with oedema had a reduction in right ventricular performance when compared with those studied when stable, which did not appear to be as a result of an acute increase in the pulmonary arterial pressure.

5. The relief of hypoxaemia in both groups of patients did not have any significant effect on the right ventricular end-systolic pressure/volume relation, nor on the right ventricular ejection fraction despite producing a fall in pulmonary arterial pressure. These results suggest that oxygen in both groups of patients had no consistent effect on right ventricular contractility.

6. In those patients who presented acutely with oedema, oxygen produced a reduction in cardiac output which could theoretically have deleterious effects on tissue oxygenation.

7. The range of values of left ventricular ejection fraction in these patients was very wide but even in those with diminished left ventricular ejection fraction, there was little evidence to support the presence of left ventricular failure.

8. The reduction in left ventricular ejection fraction in patients with chronic bronchitis and emphysema may result from an increase in the right ventricular end-diastolic volume.

General discussion and future directions

In this thesis I have endeavoured to measure the haemodynamic changes which occur in patients with chronic bronchitis and emphysema. In particular, I have used the relatively new technique of radionuclide ventriculography to measure the right ventricular ejection fraction, in an assessment of right ventricular function in such patients.

Simultaneous measurements of right ventricular ejection fraction and conventional pressure and flow measurements obtained at right heart catheterisation, allowed a more detailed analysis of right ventricular mechanics, particularly in those patients with pulmonary hypertension and `cor pulmonale'. The data obtained from the studies in this thesis has raised many questions. A detailed discussion and summary of the conclusions drawn from the various studies in this thesis is given at the end of each chapter. However, it may be useful to attempt to answer the questions which I posed previously (page 14-15) and also to discuss possible future studies which might follow from the present work.

1. Is right or left ventricular function impaired in patients with chronic bronchitis and emphysema?

The results in Chapter 4 indicate that in patients with chronic bronchitis and emphysema, right ventricular ejection fraction is, on average, lower than in normal subjects. Although this difference is significant, the vast majority of patients with chronic bronchitis and emphysema have a relatively normal right ventricular ejection fraction. Moreover, the left ventricular ejection fraction is normal in the majority of such patients.

It is of interest to determine the significance of a single measurement of right ventricular ejection fraction in a patient with chronic bronchitis and emphysema. Left ventricular ejection fraction is of considerable prognostic significance in patients after myocardial infarction where there is permanent myocardial damage (77). However, in a small number of patients in whom I have repeated measurements of right ventricular ejection fraction over the course of three years, I have found little change in the right ventricular ejection fraction when the patients are studied in a stable condition (unpublished observations). In addition preliminary data on the variability of RVEF in individual patients, comparing measurements which are made when the patients are stable and in the decompensated state indicates, as might be expected, that right ventricular ejection fraction does appear to vary in an individual patient depending on the influence of changes in pulmonary arterial pressure, right ventricular pre-load and contractility. Moreover, right ventricular ejection fraction may be abnormal during (and probably for a period after) an acute exacerbation of chronic bronchitis and emphysema and return to relative normality during the recovery period (unpublished observations). Thus, a single measurement of right ventricular ejection fraction in a patient with chronic bronchitis and emphysema is unlikely to be a good predictor of survival particularly as I have shown that right ventricular ejection fraction does not correlate with pulmonary arterial pressure, which itself predicts survival. Preliminary data in 45 patients with chronic bronchitis and emphysema who were followed up for a period of 2 years after an initial measurement of right ventricular ejection fraction, seems to indicate that right ventricular ejection fraction is not a good predictor of survival

in this thesis after the initial measurement of right ventricular ejection fraction is in progress.

Although it may not be an indicator of survival, an isolated measurement of right ventricular ejection fraction does give a general indication of right ventricular performance in patients with chronic bronchitis and emphysema. It is also possible that a low value of right ventricular ejection fraction in a patient with chronic bronchitis and emphysema, who does not have oedema at the time of study, may foretell the development of cor pulmonale. Thus right ventricular ejection fraction may be useful as a general, non-invasive assessment of cardiac function in patients with chronic bronchitis and emphysema who have developed respiratory failure and who are in danger of developing pulmonary heart disease. Studies are in progress to answer this question.

2. How does right ventricular function, as assessed by the right ventricular ejection fraction, relate to the clinical parameters of disease in patients with chronic bronchitis and emphysema?

The results described in Chapter 4 indicate that the right ventricular ejection fraction correlates with indices of the severity of the disease, such as the arterial blood gas tensions. Although these correlations were significant, they were not strong. An important finding in this study was that right ventricular ejection fraction is reduced in the vast majority of patients who have oedema.

The lack of correlation which I have found between right ventricular ejection fraction and pulmonary arterial pressure is disappointing, but not surprising, as discussed in Chapter 4. This finding

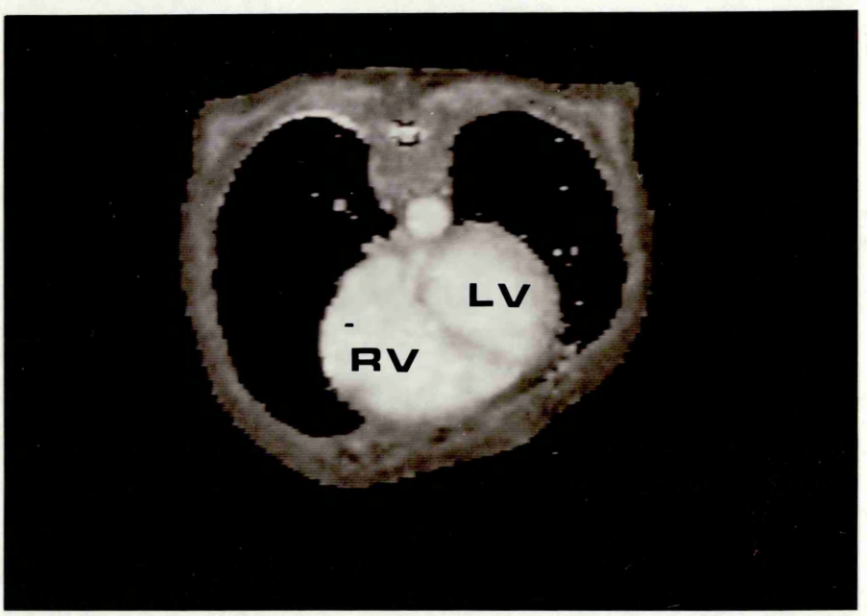


Figure 57 The static image from an NMR scan of a patient with decompensated pulmonary heart disease shows a dilated right ventricle (RV) and a relatively normal left ventricle (LV).

is fundamental to an understanding of the limits of the ejection fraction as a measure of ventricular performance, to realise that it is dependent on three variables, pre-load, contractility and afterload. A further fundamental premis is that the pulmonary arterial pressure is not a true reflection of the right ventricular afterload which is best measured by the right ventricular wall stress. Thus, a good correlation between pulmonary arterial pressure and right ventricular ejection fraction should not be expected. Right ventricular ejection fraction is not a non-invasive measure of pulmonary arterial pressure and the search for a technique which accurately, and non-invasively, measures pulmonary arterial pressure must continue (352).

In order to relate right ventricular ejection fraction to right ventricular afterload, right ventricular wall stress must be measured. This requires an estimation of right ventricular wall thickness and volume. As discussed previously, this is difficult to measure in the right ventricle because of its complex geometry. However, cardiac scanning using nuclear magnetic resonance may allow such measurements to be made in the future in the right ventricle (figure 57). Gating techniques can now produce NMR movie images and may enable the measurements necessary for the calculation of the right ventricular wall stress to be made and correlated with the right ventricular ejection fraction.

3. <u>How does the presence of pulmonary hypertension affect right ventricular function in patients with chronic bronchitis and emphysema?</u>

The combination of simultaneous measurements of right ventricular

ventricular volume. The right ventricular end-systolic pressure/volume relation can therefore be calculated producing new, and more detailed, information on right ventricular function. The data in this study indicates that even in the face of an increased pulmonary arterial pressure, right ventricular contractility is normal in patients with chronic bronchitis and emphysema, or may even be enhanced.

The results of this study could be extended in several ways. Firstly, in order to prove the linearity of the right ventricular end-systolic pressure/volume relation, three measurements of this variable should be made at different levels of right ventricular afterload, using increasing doses of sodium nitroprusside. To determine the change in the slope of the end-systolic pressure/volume relation under conditions of increased contractility, measurements of the end-systolic pressure/volume ratio are necessary, during infusion of an inotrope such as dobutamine with simultaneous reduction of right ventricular afterload by sodium nitroprusside. Such studies would determine whether the right ventricular end-systolic pressure volume relation (as in the left ventricle) is independent of loading conditions but sensitive to changes in contractility, which the results of this study seem to suggest.

In this thesis I have not been able to make measurements of the right ventricular end-systolic pressure/volume relation in normal subjects but have derived this value from normal data in the literature. In order to conclusively confirm normal right ventricular contractility in patients with pulmonary hypertension, it would be necessary to compare measurements of the end-systolic pressure/volume in patients

Studies are also in progress to derive continuous right ventricular pressure/volume loops in the right ventricle, in a more detailed analysis of right ventricular mechanics. These studies involve continuous recording of right ventricular pressure recorded by right heart catheter, together with continuous estimation of ventricular volumes, derived from the time activity curves of the right ventricular radio nuclide ventriculogram. Analysis of this data by digital computer should allow derivation of a continuous pressure/volume loop. These measurements would allow analysis of the adaption of the right ventricle to increasing pulmonary arterial pressure.

4. What are the effects on right ventricular function of reducing pulmonary arterial pressure?

As expected, reduction of right ventricular pressure by sodium nitroprusside did not change the right ventricular end-systolic pressure/volume relation and hence the right ventricular contractility. Similarly, oxygen produced only trivial pulmonary vasodilatation without change in the right ventricular ejection fraction or the pressure/volume relation in patients with chronic bronchitis and emphysema and pulmonary hypertension. Thus, there was no evidence from the results presented in Chapter 5 to indicate that either acute or long term oxygen had any direct effect on right ventricular function. Thus, the effect of oxygen in improving survival in patients with hypoxic chronic bronchitis and emphysema is not the result of a direct effect on right ventricular function. Further research is needed to predict which patients benefit from long term oxygen and also to determine the mode of action of oxygen

systolic pressure/volume relation may be an important advance in assessing the mode of action of drugs used in the treatment of pulmonary heart disease.

5. How does the right ventricle function in patients with pulmonary hypertension and clinical signs of right ventricular failure?

Measurement of right ventricular volumes in patients with chronic bronchitis and emphysema and oedema has shown that right ventricular ejection fraction is reduced as a result of an increase in right ventricular end-diastolic volume. This increase in right ventricular end-diastolic volume appears to be an adaptive mechanism allowing the right ventricle to maintain stroke volume, just as Starling`s law would predict (250). Studies in patients with pulmonary heart disease and oedema are being extended at present by re-studying these patients when oedema free during recovery, to determine if the reduction in right ventricular ejection fraction and the change in the end-systolic pressure/volume relation is reversible.

From the data presented in this thesis, the alteration in right ventricular end-diastolic volume which occurs in patients with pulmonary heart disease and oedema does not appear to be as a direct result of an increase in pulmonary arterial pressure. The mechanism of the oedema in `cor pulmonale' remains unexplained (276). However, several studies seem to indicate that changes in renal hormones and renal blood flow in chronic hypoxic bronchitis and emphysema may play a central role in the development of the oedema of pulmonary heart disease. The most consistent observation, in the relatively few studies of renal function in patients with `cor

oedema (2, 264, 318). In addition there is a variable fall in glomerular filtration rate. Although the changes in renal blood flow are not closely related to the changes in arterial blood gas tensions which occur during recovery, it seems likely that hypoxia, and possibly hypercapnia, may have a role in producing local renal vasoconstriction (2).

Reduced renal blood flow stimulates release of renin which occurs in the majority of patients with chronic bronchitis and emphysema and oedema (337). Renin stimulates angiotensin production and hence aldosterone and retention of salt and water. The conversion of angiotensin I to angiotensin II requires angiotensin converting enzyme which is abundant in the pulmonary vascular endothelium. Recently, it has been shown that hypoxia tends to reduce the activity of this enzyme in peripheral blood (230). It has also been shown in normal subjects that in response to hypoxia there is a variability in the fall in angiotensin converting enzyme (231). It is likely that a similar variability exists in patients with chronic bronchitis and emphysema, some of whom may fail to reduce angiotensin converting enzyme when hypoxic leading to the conversion of more angiotensin I to angiotensin II and hence to aldosterone, resulting in salt and water retention. These interesting hypotheses require further study.

Thus, it can be seen that several mechanisms may produce the oedema of `cor pulmonale'. Further research during the acute and recovery phase of patients with acute decompensated pulmonary heart disease are needed to determine the sequence of events producing this syndrome and to relate the changes in renal haemodynamics to the

APPENDIX I

The work for this thesis was carried out entirely in the Departments of Medicine, Royal Infirmary, Edinburgh and Respiratory Medicine, Rayne Laboratory, City Hospital, Edinburgh, under the supervision of Dr A L Muir, Reader, Department of Medicine, and Professor D C Flenley, Department of Respiratory Medicine, University of Edinburgh. The practical work was carried out entirely by myself. In the assessment of the reproducibility of the measurement of ejection fractions, I was assisted by Dr Q F Xue. During some of the catheter studies I was helped by Dr A D Morgan, Dr C G Wathen, Dr K Prince and Dr K W Whyte. My appointments during the preparation of this thesis have been MRC Research Fellow/Lecturer, Department of Respiratory Medicine, University of Edinburgh and, more recently, Senior Registrar in Respiratory Medicine, Lothian Health Board.

All of the studies in this thesis were approved by the hospital's Ethical Committee.

Part of the work in this thesis has appeared in published form or has been presented at scientific societies:

1. MacNee W, Xue Q F, Hannan W J, Flenley D C, Adie C J, Muir A L. Assessment by radionuclide angiography of right and left ventricular function in chronic bronchitis and emphysema.

2. Xue Q F, MacNee W, Flenley D C, Hannan W J, Adie C J, Muir A L. Can right ventricular performance be assessed by equilibrium radionuclide ventriculography? Thorax 1983; 38: 486-93.

3. MacNee W, Wathen C G, Hannan W J, Flenley D C, Muir A L. Effects of pirbuterol and sodium nitroprusside on pulmonary haemodynamics in hypoxic cor pulmonale. Br Med J 1983; 287: 1169-72.

4. MacNee W, Prince K, Flenley D C, Muir A L. The effects of pulmonary hypertension on right ventricular performance. Progress in Respiratory Research 1985 (in press).

5. MacNee W, Morgan A D, Wathen C G, Muir A L, Flenley D C. Right ventricular performance during exercise in COPD - the effects of oxygen. Respiration 1985 (in press).

FACTORS CONTRIBUTING TO THE DEVELOPMENT OF PULMONARY HYPERTENSION

Increased pulmonary vascular resistance resulting from:

Loss of capillaries due to disease processes, eg emphysema, pulmonary embolism.

Changes in respiratory gases.

Alterations in pulmonary mechanics.

Increased cardiac output.

Increased pulmonary blood volume.

Increased viscosity of blood.

Raised pulmonary venous pressure.

TABLE 2

RIGHT AND LEFT VENTRICULAR FUNCTION IN

30 NORMAL SUBJECTS

SUBJECT No	AGE (yrs)	SEX	RVEF		LVEF	
			REST	EXERCISE	REST	EXERCISE
1	32	M	0.59	0.71	0.67	0.80
2	34	M	0.59	0.65	0.60	0.73
3	27	M	0.49	0.54	0.50	0.56
4	27	M	0.48	0.56	0.55	0.71
5	24	M	0.47	0.66	0.54	0.63
6	28	M	0.57	0.66	0.54	0.59
7	33	M	0.48	0.53	0.52	0.64
8	26	M	0.59	0.63	0.56	0.66
9	41	M	0.50	0.58	0.74	0.79
10	50	M	0.60	0.65	0.55	0.75
11	28	M	0.48	--	0.60	--
12	32	M	0.50	--	0.51	--
13	21	M	0.83	--	0.62	--
14	49	F	0.62	--	0.54	--
15	50	F	0.64	--	0.70	--

TABLE 2 (cont'd)

RIGHT AND LEFT VENTRICULAR FUNCTION IN

30 NORMAL SUBJECTS

SUBJECT No	AGE (yrs)	SEX	RVEF		LVEF	
			REST	EXERCISE	REST	EXERCISE
16	61	M	0.66	--	0.69	--
17	31	F	0.66	--	0.75	--
18	58	M	0.69	--	0.70	--
19	34	M	0.75	--	0.64	--
20	63	M	0.55	--	0.70	--
21	46	F	0.58	--	0.51	--
22	60	M	0.51	--	0.65	--
23	45	M	0.52	--	0.57	--
24	36	M	0.60	--	0.59	--
25	30	M	0.55	--	0.65	--
26	37	M	0.53	--	0.52	--
27	42	M	0.50	--	0.61	--
28	52	M	0.61	--	0.58	--
29	28	M	0.68	--	0.84	--
30	58	M	0.67	--	0.63	--
Mean	39.4		0.58	0.62	0.61	0.69
SD	12.5		0.09	0.06	0.08	0.08

OF 100 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	SEX	AGE (yrs)	PaO_2 (kPa)	$PaCO_2$ (kPa)	$FEV_{1.0}$ (l)	FVC (l)	RVEF	LVEF	RV Failure
1	F	60	5.5	7.6	0.4	1.7	0.31	0.37	Present
2	M	53	5.9	7.5	0.8	2.4	0.32	0.49	No
3	M	63	7.6	5.9	1.1	3.7	0.45	0.49	Past
4	F	64	7.2	6.3	1.2	1.5	0.58	0.67	Past
5	M	52	7.2	5.4	1.2	2.8	0.49	0.54	No
6	M	57	7.2	7.7	0.5	1.2	0.43	0.46	Present
7	M	48	7.3	6.5	0.7	2.1	0.40	0.40	Present
8	F	67	7.1	7.7	0.6	1.6	0.43	0.54	Past
9	M	50	8.7	5.7	0.7	1.8	0.44	0.62	No
10	M	57	5.1	8.2	0.6	2.9	0.37	0.30	Present
11	F	59	5.7	6.5	0.8	2.2	0.54	0.56	Past
12	M	68	8.7	6.8	0.5	1.8	0.51	0.62	No
13	M	49	8.3	6.0	0.9	2.3	0.40	0.49	No
14	M	80	7.6	5.8	0.4	0.7	0.64	0.62	No
15	M	78	7.4	7.9	0.7	2.2	0.43	0.39	Past
16	M	68	4.8	8.3	0.5	1.7	0.35	0.34	Present
17	F	67	6.9	7.1	0.6	1.2	0.41	0.49	Past
18	M	63	6.1	7.1	0.6	3.7	0.53	0.51	Past
19	M	55	6.8	6.7	0.6	2.0	0.41	0.44	Present
20	M	50	5.3	7.3	0.6	1.1	0.30	0.61	Past
21	F	70	6.9	6.7	0.7	1.7	0.38	0.36	Present
22	F	60	9.5	4.9	0.6	1.5	0.55	0.57	Past
23	F	67	5.0	10.8	0.4	0.9	0.35	0.30	Past
24	F	64	7.1	7.1	0.4	1.0	0.38	0.40	Present
25	M	66	8.4	6.7	0.6	2.3	0.62	0.66	No

OF 100 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	SEX	AGE (yrs)	PaO_2 (kPa)	$PaCO_2$ (kPa)	$FEV_{1.0}$ (l)	FVC (l)	RVEF	LVEF	RV Failure
26	M	58	6.3	5.2	1.4	2.5	0.33	0.29	Present
27	M	60	4.7	9.2	0.5	2.4	0.32	0.32	Present
28	M	71	7.0	6.7	0.6	1.6	0.38	0.44	Present
29	M	59	9.2	6.5	0.8	1.5	0.33	0.60	No
30	F	57	6.5	9.3	0.3	1.2	0.62	0.72	Past
31	M	58	8.0	4.5	0.8	1.8	0.43	0.46	Past
32	M	45	5.6	8.5	0.2	0.5	0.24	0.50	Present
33	M	67	9.5	4.9	1.4	3.6	0.65	0.67	No
34	M	71	7.3	6.8	1.2	2.9	0.42	0.64	No
35	M	52	9.2	5.5	1.7	2.7	0.54	0.74	No
36	M	61	9.5	5.3	1.2	2.2	0.58	0.57	No
37	M	67	5.5	8.1	0.6	3.3	0.41	0.50	Past
38	F	70	8.6	5.4	0.6	1.2	0.56	0.49	No
39	F	65	6.0	7.1	0.5	1.6	0.41	0.79	Past
40	M	71	6.9	7.1	0.7	1.8	0.32	0.40	Present
41	F	70	7.1	7.3	0.6	1.6	0.44	0.47	Past
42	M	58	6.3	6.7	0.5	1.5	0.44	0.63	Past
43	M	70	6.5	6.4	0.5	1.4	0.47	0.51	Past
44	M	58	8.3	6.3	1.3	3.3	0.46	0.64	No
45	M	55	8.3	5.7	0.7	1.6	0.54	0.64	No
46	F	71	7.2	6.1	1.0	2.3	0.50	0.62	No
47	M	44	7.6	7.5	0.5	1.4	0.37	0.52	Present
48	F	41	6.7	5.2	0.7	1.2	0.60	0.52	No
49	M	55	8.0	7.1	0.7	2.2	0.37	0.61	Past
50	F	58	8.3	6.4	0.7	1.4	0.42	0.52	No

OF 100 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	SEX	AGE (yrs)	PaO_2 (kPa)	$PaCO_2$ (kPa)	$FEV_{1.0}$ (l)	FVC (l)	RVEF	LVEF	RV Failure
51	F	66	7.1	8.0	0.5	1.7	0.57	0.52	No
52	M	67	5.2	8.4	0.5	1.0	0.42	0.51	Past
53	F	69	6.0	7.6	0.5	2.0	0.54	0.50	Past
54	M	67	8.8	6.2	0.7	1.5	0.38	0.61	No
55	M	42	7.5	5.6	1.0	2.8	0.43	0.48	Past
56	F	70	7.8	5.5	0.4	0.8	0.58	0.56	Past
57	F	70	7.4	5.4	0.9	1.8	0.28	0.47	Present
58	M	65	7.2	4.4	1.1	3.7	0.55	0.46	No
59	F	60	8.1	5.2	0.9	3.0	0.49	0.53	No
60	F	58	8.0	6.0	0.7	1.4	0.41	0.52	No
61	M	65	8.1	6.1	1.3	3.6	0.44	0.48	Past
62	M	62	7.6	5.2	0.9	2.5	0.52	0.68	No
63	M	57	9.4	5.8	0.7	2.1	0.43	0.71	No
64	M	65	7.2	4.4	1.4	2.1	0.55	0.67	No
65	M	62	6.8	5.9	0.5	1.6	0.41	0.51	Past
66	M	65	6.8	6.0	0.5	1.1	0.37	0.55	Present
67	M	58	8.6	6.1	0.8	2.0	0.42	0.71	No
68	F	56	9.5	5.8	0.8	2.3	0.56	0.58	No
69	F	65	9.8	6.1	1.0	2.2	0.50	0.64	No
70	M	52	11.3	4.2	2.9	4.7	0.55	0.51	No
71	F	62	7.6	6.7	0.3	0.9	0.55	0.59	Past
72	F	55	7.4	5.6	1.7	2.4	0.43	0.46	No
73	F	65	8.0	6.3	1.0	2.3	0.42	0.34	Present
74	F	50	4.6	7.8	0.4	0.7	0.35	0.38	Present
75	F	70	6.0	6.7	0.3	1.5	0.33	0.49	Present

OF 100 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	SEX	AGE (yrs)	PaO_2 (kPa)	$PaCO_2$ (kPa)	$FEV_{1.0}$ (l)	FVC (l)	RVEF	LVEF	RV Failure
76	F	64	6.4	5.6	0.3	1.2	0.38	0.44	Present
77	M	66	7.0	6.2	0.5	2.6	0.34	0.61	Past
78	M	64	7.5	5.3	0.5	1.1	0.57	0.55	Past
79	F	62	6.0	6.3	0.5	1.9	0.46	0.67	Past
80	F	58	6.7	5.7	0.3	1.4	0.38	0.41	Present
81	M	65	7.1	4.8	0.9	2.2	0.24	0.40	Present
82	F	66	8.2	5.9	0.4	0.7	0.55	0.70	No
83	F	70	6.6	8.1	0.5	1.7	0.36	0.41	Present
84	M	70	8.9	5.7	0.9	1.3	0.43	0.57	Past
85	M	65	7.6	6.2	0.5	1.6	0.51	0.68	Past
86	F	62	7.3	5.8	0.5	1.0	0.42	0.50	Past
87	M	68	5.3	7.5	1.0	2.3	0.34	0.39	Present
88	M	50	8.7	5.5	0.7	2.6	0.39	0.45	No
89	M	65	7.5	5.4	1.1	2.6	0.42	0.41	Past
90	M	56	8.2	5.9	0.5	3.1	0.48	0.57	No
91	M	70	6.2	7.4	0.4	2.0	0.34	0.58	Present
92	M	65	8.5	5.3	0.9	4.3	0.45	0.47	Past
93	M	56	7.0	7.0	0.7	2.6	0.47	0.52	Past
94	M	62	8.4	5.8	0.6	1.7	0.33	0.46	Past
95	M	42	8.0	6.0	0.8	1.9	0.39	0.61	Past
96	F	62	7.0	6.4	0.8	2.3	0.17	0.24	Present
97	F	64	7.1	6.1	1.0	1.4	0.35	0.56	Past
98	F	70	5.3	6.9	0.7	1.6	0.30	0.52	Present
99	M	65	7.2	7.4	1.2	2.3	0.26	0.31	Present
100	M	79	6.3	4.9	1.0	2.2	0.58	0.58	Past
Mean		62	7.3	6.4	0.75	1.98	0.44	0.52	
SD		8	1.3	1.2	0.38	0.80	0.10	0.11	

PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND

NO HISTORY OF OEDEMA

PATIENT No	AGE (yrs)	FEV_1 l	FVC l	PaO_2 kPa	$PaCO_2$ kPa	RVEF	LVEF
1	53	0.8	2.4	5.9	7.5	0.32	0.49
2	52	1.2	2.8	7.2	5.4	0.49	0.54
3	50	0.7	1.8	8.7	5.7	0.44	0.62
4	68	0.5	1.8	8.7	6.8	0.51	0.62
5	49	0.9	2.3	8.3	6.0	0.40	0.49
6	80	0.4	0.7	7.6	5.8	0.64	0.62
7	66	0.6	2.3	8.4	6.7	0.62	0.66
8	59	0.8	1.5	9.2	6.5	0.33	0.60
9	67	1.4	3.6	9.5	4.9	0.65	0.67
10	71	1.2	2.9	7.3	6.8	0.42	0.64
11	52	1.7	2.7	9.2	5.5	0.54	0.74
12	61	1.2	2.2	9.5	5.3	0.58	0.57
13	70	0.6	1.2	8.6	5.4	0.56	0.49
14	58	1.3	3.3	8.3	6.3	0.46	0.64
15	55	0.7	1.6	8.3	5.7	0.54	0.64
16	71	1.0	2.3	7.2	6.1	0.50	0.62
17	41	0.7	1.2	6.7	5.2	0.60	0.52
18	58	0.7	1.4	8.3	6.4	0.42	0.52
19	66	0.5	1.7	7.1	8.0	0.57	0.57
20	67	0.7	1.5	8.8	6.2	0.38	0.61
21	65	1.1	3.7	7.2	4.4	0.55	0.46
22	60	0.9	3.0	8.1	5.2	0.49	0.53
23	58	0.2	1.4	8.0	6.0	0.41	0.52
24	62	0.9	2.5	7.6	5.2	0.52	0.68
25	57	0.7	2.1	9.4	5.8	0.43	0.71
26	65	1.4	2.1	7.2	4.4	0.55	0.67
27	58	0.8	2.0	8.6	6.1	0.42	0.71
28	56	0.8	2.3	9.5	5.8	0.56	0.58
29	65	1.0	2.2	9.8	6.1	0.50	0.64
30	52	2.9	4.7	11.3	4.2	0.55	0.51
31	55	1.7	2.4	7.4	5.6	0.43	0.46
32	66	0.4	0.7	8.2	5.9	0.55	0.70
33	50	0.7	2.6	8.7	5.5	0.39	0.45
34	56	0.5	3.1	8.2	5.9	0.48	0.57
Mean	60	0.93	2.24	8.3	5.8	0.49	0.59
SD	8	0.50	0.86	1.1	0.8	0.09	0.08

PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND

A PAST HISTORY OF OEDEMA

PATIENT No	AGE (yrs)	FEV_1 l	FVC l	PaO_2 kPa	$PaCo_2$ kPa	RVEF	LVEF
1	63	1.1	3.7	7.6	5.9	0.45	0.49
2	64	1.2	1.5	7.2	6.3	0.58	0.67
3	67	0.6	1.6	7.1	7.7	0.43	0.54
4	59	0.8	2.2	5.7	6.5	0.54	0.56
5	78	0.7	2.2	7.4	7.9	0.43	0.39
6	67	0.6	1.2	6.9	7.1	0.41	0.49
7	63	0.6	3.7	6.1	7.1	0.53	0.51
8	50	0.6	1.1	5.3	7.3	0.30	0.61
9	60	0.6	1.5	9.5	4.9	0.55	0.57
10	67	0.4	0.9	5.0	10.8	0.35	0.30
11	57	0.3	1.2	6.5	9.3	0.62	0.72
12	58	0.8	1.8	8.0	4.5	0.43	0.46
13	67	0.6	3.3	5.5	8.1	0.41	0.50
14	65	0.5	1.6	6.0	7.1	0.41	0.79
15	70	0.6	1.6	7.1	7.3	0.44	0.47
16	58	0.5	1.5	6.3	6.7	0.44	0.63
17	70	0.5	1.4	6.5	6.4	0.47	0.51
18	55	0.7	2.2	8.0	7.1	0.37	0.61
19	67	0.5	1.0	5.2	8.4	0.42	0.51
20	69	0.5	2.0	6.0	7.6	0.54	0.50

PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND

A PAST HISTORY OF OEDEMA

PATIENT No	AGE (yrs)	FEV_1 l	FVC l	PaO_2 kPa	$PaCO_2$ kPa	RVEF	LVEF
21	42	1.0	2.8	7.5	5.6	0.43	0.48
22	70	0.4	0.8	7.8	5.5	0.58	0.56
23	65	1.3	3.6	8.1	6.1	0.44	0.48
24	62	0.5	1.6	6.8	5.9	0.41	0.51
25	62	0.3	0.9	7.6	6.7	0.55	0.59
26	66	0.5	2.6	7.0	6.2	0.34	0.61
27	64	0.5	1.1	7.5	5.3	0.57	0.55
28	62	0.5	1.9	6.0	6.3	0.46	0.67
29	70	0.9	1.3	8.9	5.7	0.43	0.57
30	65	0.5	1.6	7.6	6.2	0.51	0.68
31	62	0.5	1.0	7.3	5.8	0.42	0.50
32	65	1.1	2.6	7.5	5.4	0.42	0.41
33	65	0.9	4.3	8.5	5.3	0.45	0.47
34	56	0.7	2.6	7.0	7.0	0.47	0.52
35	62	0.6	1.7	8.4	5.8	0.33	0.46
36	42	0.8	1.9	8.0	6.0	0.39	0.61
37	64	1.0	1.4	7.1	6.1	0.35	0.56
38	79	1.0	2.2	6.3	4.9	0.58	0.58
Mean	63	0.68	1.92	7.1	6.6	0.45	0.54
SD	8	0.25	0.88	1.0	1.3	0.08	0.09

PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

WITH OEDEMA WHEN STUDIED

PATIENT No	AGE (yrs)	FEV_1 l	FVC l	PaO_2 kPa	$PaCO_2$ kPa	RVEF	LVEF
1	60	0.4	1.65	5.5	7.6	0.31	0.37
2	57	0.45	1.2	7.2	7.7	0.43	0.46
3	68	0.7	2.1	7.3	6.5	0.40	0.40
4	57	0.6	2.9	5.1	8.2	0.37	0.30
5	68	0.5	1.7	4.8	8.3	0.35	0.34
6	55	0.6	2.0	6.8	6.7	0.41	0.44
7	70	0.7	1.7	6.9	6.7	0.38	0.36
8	64	0.4	1.0	7.1	7.1	0.38	0.40
9	58	1.4	2.5	6.3	5.2	0.33	0.29
10	60	0.5	2.4	4.7	9.2	0.32	0.32
11	71	0.6	1.6	7.0	6.7	0.38	0.44
12	45	0.2	0.5	5.6	8.5	0.24	0.50
13	71	0.7	1.8	6.9	7.1	0.32	0.40
14	44	0.5	1.4	7.6	7.5	0.37	0.52
15	70	0.9	1.8	7.4	5.4	0.28	0.47
16	65	0.5	1.1	6.8	6.0	0.37	0.55
17	65	1.0	2.3	8.0	6.3	0.42	0.34
18	50	0.4	0.7	4.6	7.8	0.35	0.38
19	70	0.3	1.5	6.0	6.7	0.33	0.49
20	64	0.3	1.2	6.4	5.6	0.38	0.44
21	58	0.3	1.4	6.7	5.7	0.38	0.41
22	65	0.9	2.2	7.1	4.8	0.24	0.40
23	70	0.5	1.7	6.6	8.1	0.36	0.41
24	68	1.0	2.3	5.3	7.5	0.34	0.39
25	70	0.4	2.0	6.2	7.4	0.34	0.58
26	62	0.8	2.3	7.0	6.4	0.17	0.24
27	70	0.7	1.6	5.3	6.9	0.30	0.52
28	65	1.2	2.3	7.2	7.4	0.26	0.31
Mean	63	0.62	1.74	6.4	7.0	0.34	0.41
SD	8	0.29	0.56	1.0	1.1	0.06	0.08

RIGHT AND LEFT VENTRICULAR FUNCTION AT REST AND ON EXERCISE

IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	FEV_1 (l)	FVC (l)	PaO_2 (kPa)	$PaCO_2$ (kPa)	H+ ion (nmol/l)
1	0.9	3.0	8.1	5.2	41
2	0.7	1.4	8.0	6.0	45
3	1.3	3.6	8.1	6.1	40
4	0.9	2.5	7.6	5.2	36
5	0.7	2.1	9.4	5.8	42
6	1.4	2.1	7.2	4.4	39
7	0.5	1.6	6.8	5.9	41
8	0.5	1.1	6.8	6.0	39
9	0.8	2.0	8.6	6.1	44
10	0.8	2.3	9.4	5.8	44
11	1.0	2.2	9.8	6.1	44
12	2.9	4.7	11.3	4.2	39
13	0.3	0.9	7.6	6.7	43
14	1.3	2.4	7.4	5.6	43
15	1.0	2.3	8.0	6.3	41
16	0.3	1.5	6.0	6.7	39
17	0.5	1.1	7.5	5.3	38
18	0.5	1.9	6.0	6.3	45
19	0.4	0.9	8.2	5.9	40
20	0.5	1.6	7.6	6.2	45
21	0.7	2.6	8.7	5.5	42
22	0.7	2.6	7.0	7.0	44
23	1.0	1.4	7.1	6.1	45
24	0.6	2.0	8.4	5.8	40
25	0.4	2.0	6.2	7.4	45
Mean	0.82	2.07	7.9	5.9	42
SD	0.53	0.85	1.2	0.7	3

RIGHT AND LEFT VENTRICULAR FUNCTION AT REST AND ON EXERCISE

IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	AGE (yrs)	SEX	SaO_2(%)		RVEF		LVEF	
			REST	EXERCISE	REST	EXERCISE	REST	EXERCISE
1	60	F	90	87	0.49	0.65	0.53	0.49
2	58	F	91	86	0.41	0.47	0.52	0.53
3	65	M	93	92	0.44	0.50	0.48	0.60
4	54	M	91	83	0.52	0.41	0.68	0.68
5	57	M	92	89	0.43	0.51	0.71	0.69
6	60	M	88	77	0.55	0.49	0.67	0.67
7	62	M	87	67	0.41	0.42	0.51	0.63
8	65	M	85	66	0.37	0.32	0.55	0.56
9	58	F	90	84	0.42	0.43	0.71	0.70
10	68	M	95	89	0.56	0.49	0.58	0.66
11	65	F	95	94	0.50	0.54	0.64	0.64
12	52	M	93	91	0.51	0.57	0.55	0.58
13	66	F	86	68	0.55	0.37	0.59	0.58
14	55	F	88	85	0.43	0.37	0.46	0.54
15	65	F	90	76	0.42	0.43	0.34	0.31
16	68	F	79	69	0.33	0.19	0.49	0.42
17	64	M	88	86	0.55	0.61	0.57	0.55
18	62	F	83	77	0.46	0.37	0.67	0.68
19	66	F	89	80	0.55	0.44	0.70	0.69
20	62	M	88	84	0.46	0.46	0.63	0.63
21	50	M	93	87	0.39	0.38	0.45	0.50
22	56	M	82	74	0.47	0.39	0.52	0.54
23	55	F	86	79	0.35	0.34	0.56	0.55
24	62	M	91	82	0.33	0.33	0.46	0.52
25	70	M	78	75	0.34	0.31	0.58	0.56
Mean	61		88	81	0.45	0.43	0.57	0.58
SD	5		5	8	0.07	0.10	0.09	0.09
p			< 0.05		> 0.05		> 0.05	

SIMULTANEOUS MEASUREMENTS OF PAP AND RVEF IN PATIENTS

WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	PaO_2 (kPa)	$PaCO_2$ (kPa)	Systolic PAP mmHg	Mean PAP mmHg	RVEF
1	6.0	7.1	59	38	0.41
2	7.1	7.3	52	32	0.42
3	6.3	6.7	46	33	0.42
4	6.5	6.4	39	26	0.47
5	8.3	6.3	54	30	0.46
6	8.3	5.7	36	26	0.54
7	7.2	6.1	38	21	0.50
8	7.6	7.5	53	30	0.37
9	6.7	5.2	65	38	0.60
10	8.0	7.1	37	22	0.37
11	8.3	6.4	49	30	0.42
12	7.0	8.0	32	22	0.57
13	5.2	8.4	55	34	0.42
14	6.0	7.6	46	32	0.54
15	8.8	6.2	31	20	0.38
16	7.5	5.6	40	23	0.43
17	4.5	8.6	73	46	0.54
18	7.8	5.5	50	30	0.58
19	7.4	5.4	48	24	0.28
20	7.2	4.4	53	28	0.55
21	6.9	7.1	34	24	0.32
22	6.8	5.9	38	24	0.41
23	6.8	6.0	41	32	0.37
24	7.6	6.7	46	32	0.55
25	7.4	5.6	27	21	0.43

SIMULTANEOUS MEASUREMENTS OF PAP AND RVEF IN PATIENTS

WITH CHRONIC BRONCHITIS AND EMPHYSEMA

PATIENT No	PaO_2 (kPa)	$PaCO_2$ (kPa)	Systolic PAP mmHg	Mean PAP mmHg	RVEF
26	8.0	6.3	32	26	0.42
27	6.0	6.7	49	38	0.33
28	8.7	5.5	15	12	0.39
29	7.5	5.4	16	12	0.42
30	8.2	5.9	25	11	0.48
31	6.2	7.4	47	26	0.34
32	8.5	5.3	19	12	0.45
33	8.4	5.8	32	18	0.33
34	8.0	6.0	40	25	0.39
35	7.0	6.4	74	47	0.17
36	6.3	7.7	40	22	0.35
37	5.5	7.6	46	34	0.34
38	7.6	5.9	39	27	0.45
39	5.4	8.1	96	58	0.37
40	6.1	7.1	45	36	0.51
41	5.3	7.3	40	26	0.61
42	6.3	7.7	40	24	0.55
43	6.5	7.3	27	16	0.38
44	5.1	8.2	95	60	0.32
45	5.6	8.5	58	32	0.24
46	6.5	7.2	70	44	0.45
47	6.1	6.8	28	10	0.43
48	7.0	6.2	54	50	0.34
49	6.4	5.6	42	29	0.38
50	6.3	6.8	38	32	0.45

RIGHT VENTRICULAR EJECTION FRACTION IN NORMAL SUBJECTS - A REVIEW OF THE LITERATURE

AUTHORS		No of SUBJECTS	RVEF AT REST	RVEF ON EXERCISE
FIRST PASS METHOD				
STEELE	(1976, 312)	14	0.57 ± 0.03	
BERGER	(1978, 23)	50	0.55 ± 0.05	
TOBINICK	(1978, 333)	22	0.52 ± 0.04	
JOHNSON	(1979, 171)	11	0.47 ± 0.04	0.57 ± 0.06
BERGER	(1979, 24)	14	0.54 ± 0.03	0.68 ± 0.02
WALTON	(1979, 341)	17	0.65 ± 0.08	
SLUTSKY	(1980, 307)	10	0.53 ± 0.03	
OLVEY	(1980, 255)	10	0.53 ± 0.02	0.63 ± 0.02
MATTHAY	(1980, 221)	25	0.54 ± 0.03	0.67 ± 0.03
WINZELBERG	(1981, 360)	13	0.60 ± 0.07	
PETER	(1983, 262)	10	0.44 ± 0.06	0.55 ± 0.07
KAUL	(1984, 176)	18	0.46 ± 0.08	
EQUILIBRIUM METHOD				
MADDAHI	(1979, 209)	15	0.48 ± 0.05	0.60 ± 0.07*
MADDAHI	(1979, 209)	10	0.49 ± 0.04	0.67 ± 0.08**
SLUTSKY	(1980, 306)	20	0.49 ± 0.10	0.64 ± 0.08
SORENSEN	(1980, 310)	10	0.51 ± 0.07	
SLUTSKY	(1981, 308)	10	0.50 ± 0.06	
HOLMAN	(1981, 156)	11	0.59 ± 0.08	
MORRISON	(1982, 240)	9	0.53 ± 0.05	0.69 ± 0.06
KORR	(1982, 189)	20	0.53 ± 0.06	
SLUTSKY	(1982, 309)	15	0.50 ± 0.06	0.61 ± 0.04
HENZE	(1982, 151)	9	0.52 ± 0.06	
XUE	(1983, 364)	18	0.62 ± 0.09	
KONSTAM	(1983, 187)	16	0.47 ± 0.11	
ERICKSON	(1983, 95)	20	0.48 ± 0.04	
LEGRAND	(1983, 193)	10	0.58 ± 0.08	
KAUL	(1984, 176)	18	0.43 ± 0.06	

* Submaximal exercise

** Maximal exercise

RIGHT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA - A REVIEW OF THE LITERATURE

AUTHORS	No OF PATIENTS	RVEF AT REST	RVEF ON EXERCISE
Ellis et al 1977 (92)	39	0.47 ± 0.02	-
Olvey et al 1978 (255)	18	0.43 ± 0.02	0.44 ± 0.03
Berger et al 1978 (23)	36	0.47 ± 0.12	-
Matthay et al 1980 (222)	30	0.49 ± 0.01	0.47 ± 0.02
Slutsky et al 1980 (307)	20	0.46 ± 0.09	-
Mathur et al 1981 (223)	15	0.34 ± 0.08	-
Hooper et al 1982 (158)	14	0.37 ± 0.14	-
Dahlstrom et al 1983 (72)	10	0.43 ± 0.14	0.39 ± 0.14
Erickson et al 1983 (95)	10	0.38 ± 0.11	-
Brown et al 1984 (51)	12	0.41 ± 0.04	0.44 ± 0.03
Tuxen et al 1984 (336)	9	0.33 ± 0.08	-
Brent et al 1984 (48)	30	0.41 ± 0.07	-

LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA - A REVIEW OF THE LITERATURE

AUTHORS	No OF PATIENTS	LVEF AT REST	LVEF ON EXERCISE
Steele et al 1975 (311)	28	0.52 ± 0.02	-
Kline et al 1977 (184)	18	0.64 ± 0.13	-
Olvey et al 1978 (255)	18	0.65 —	0.71 —
Berger et al 1978 (23)	35	0.58 ± 0.15	-
Matthay et al 1980 (221)	30	0.62 ± 0.02	0.71 ± 0.02
Slutsky et al 1980 (307)	20	0.58 ± 0.09	-
Slutsky et al 1981 (308)	12	0.60 ± 0.12	0.62 ± 0.11
Brent et al 1982 (46)	20	0.61 ± 0.11	-
Erickson et al 1983 (95)	10	0.59 ± 0.11	-
Brown et al 1984 (51)	12	0.59 ± 0.03	0.63 ± 0.04

CORRELATION BETWEEN PAP AND RVEF

- A REVIEW OF THE LITERATURE

AUTHOR	No OF PATIENTS/SUBJECTS	PATIENTS STUDIED	CORRELATION COEFFICIENT
Ellis et al 1977 (92)	35	COPD	-0.32 (NS)
Winzelberg et al 1979 (360)	56	Aortic and mitral valve disease	0.23 (NS)
Korr et al 1982 (189)	37	Normal subjects valvular and ischaemic heart disease	-0.82 ($p < 0.001$)
Friedman et al 1982 (123)	49	Cardiomyopathy ischaemic and valvular heart disease	-0.56 ($p < 0.05$)
Morrison et al 1983 (241)	39	Cardiomyopathy valvular and ischaemic heart disease	-0.57 ($p < 0.05$)
Morrison et al 1982 (240)	9	Normal subjects	(r not quoted) (NS)
Dahlstrom et al 1983 (72)	10	Chronic lung diseases	-0.75 ($p < 0.05$)
Brent et al 1984 (46)	30	COPD	-0.74 ($p < 0.01$)
Mahler et al 1984 (210)	12	COPD	-0.48 (NS)
Burghuber et al 1984 (53)	14	COPD	-0.75 ($p < 0.01$)

TABLE 11

DETERMINANTS OF RIGHT VENTRICULAR SYSTOLIC FUNCTION

Afterload - wall stress (62)

- Approximations
  - Pulmonary arterial pressure (353)
  - Total pulmonary vascular resistance (354)
- Additional considerations
  - Ventricular volume - volume overload (61)
  - Wall thickness (62)
  - Tricuspid regurgitation (196)
  - Intra-thoracic pressure variations (302)

Contractile function

- Free wall (possible concomitant right ventricular infarct)
- Approximations
  - Proximal high grade right coronary artery lesions (100)
  - Inferior left ventricular wall motion abnormality (267)
- Septum
- Approximations
  - Global RVEF (101)
- Additional considerations
  - Ventricular interaction (344)
  - Pattern of right ventricular contraction (11)
  - End-systolic pressure volume relation (291)

TABLE 11 (cont'd)

Pre-load - end-diastolic volume (62)

- Approximations
  - Transmural filling pressures (302)
  - Intra-cavity filling pressures
- Additional considerations
  - Ventricular interaction (344)
  - Intra-thoracic pressure variations (302)
  - Pericardial function (283)

TABLE 12

PULMONARY FUNCTION DATA IN 20 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND PULMONARY HYPERTENSION

PATIENT No	AGE (yr)	FEV_1 (l)	FVC (l)	FEV_1/FVC (%)	PaO_2 (kPa)	$PaCO_2$ (kPa)	H^+ion (nmol/l)
1	65	0.5	1.6	31	6.0	7.1	35
2	70	0.6	1.6	38	7.1	7.3	42
3	58	0.5	1.5	33	6.3	6.7	41
4	70	0.5	1.4	36	6.5	6.4	48
5	58	1.3	3.3	39	8.3	6.3	37
6	55	0.7	1.6	44	8.3	5.7	40
7	71	1.0	2.3	44	7.2	6.1	41
8	44	0.5	1.4	36	7.6	7.5	44
9	41	0.7	1.2	58	6.7	5.2	39
10	55	0.7	2.2	32	8.0	7.1	45
11	58	0.7	1.4	50	8.3	6.4	44
12	66	0.5	1.7	29	7.1	8.0	46
13	67	0.5	1.0	50	5.2	8.4	47
14	69	0.5	2.0	25	6.0	7.6	45
15	67	0.7	1.5	47	8.8	6.2	39
16	42	1.0	2.8	36	7.5	5.6	38
17	68	0.4	0.6	67	4.5	8.6	42
18	70	0.4	0.8	50	7.8	5.5	45
19	70	0.9	1.8	50	7.4	5.4	38
20	65	1.1	3.7	30	7.2	4.4	39
Mean	62	0.7	1.8	41	7.1	6.6	42
SD	10	0.1	0.8	11	1.1	1.1	4

TABLE 13

Haemodynamic data in the 20 patients with chronic bronchitis and emphysema and pulmonary hypertension

PATIENT No	MEAN PAP mmHg	RVSP mmHg	RV_{EDP} mmHg	RVEF	LVEF	SVI $ml.m^{-2}$	CI $ml_{m^{-2}}min^{-1}$	PVR dynes. s. cm^{-5}	SVR dynes. s. cm^{-5}	RVEDVI $ml.m^{-2}$	RVESVI $ml.m^{-2}$	P/V
1	38	55	4	0.41	0.79	28	2.4	720	1458	69	41	1.34
2	32	51	4	0.42	0.47	32	2.8	590	1788	76	44	1.16
3	33	45	7	0.42	0.63	24	2.3	580	1546	57	33	1.36
4	26	40	2	0.47	0.51	34	3.3	371	1383	72	38	1.05
5	30	51	7	0.46	0.64	28	2.6	655	2030	61	33	1.55
6	26	34	10	0.54	0.64	39	2.8	427	1642	72	33	1.03
7	21	34	4	0.50	0.62	33	2.0	462	2506	66	33	1.03
8	30	49	10	0.37	0.52	41	3.5	372	957	111	70	0.70
9	38	60	4	0.60	0.52	39	3.5	625	1529	65	26	2.31
10	22	33	5	0.37	0.61	19	2.0	503	2057	53	34	1.00
11	30	39	6	0.42	0.52	31	2.5	525	1347	74	43	0.91
12	22	34	2	0.57	0.57	19	1.9	545	2204	33	14	2.43
13	34	53	7	0.42	0.51	40	3.6	432	1270	95	55	0.96
14	32	43	6	0.54	0.50	29	2.3	547	1797	53	24	1.79
15	20	32	6	0.38	0.61	20	1.8	523	2536	53	33	0.97
16	23	39	4	0.43	0.48	42	3.1	396	1657	98	53	0.74
17	46	71	7	0.54	0.69	28	2.8	837	2682	54	26	2.73
18	30	47	10	0.58	0.56	19	1.9	871	3194	33	14	2.76
19	24	42	8	0.28	0.47	29	2.5	447	1991	104	74	0.57
20	28	47	4	0.55	0.46	32	2.5	463	1336	58	26	1.81
MEAN	29	45	6	0.46	0.57	30	2.6	545	1846	68	37	1.41
SD	7	10	2	0.09	0.09	8	0.6	141	558	21	16	0.68

RIGHT VENTRICULAR HAEMODYNAMICS IN 20 NORMAL SUBJECTS

- Gurtner et al 1975 (133)

Subject No	Sex	RVSP mmHg	RV_{EDP} mmHg	CI $l.min^{-1}.m^{-2}$	SVI $ml.m^{-2}$	RVSWI $g.m.m^{-2}$
1	M	15	3	3.01	40	6.5
2	M	22	4	4.20	71	17.4
3	M	27	5	3.07	43	12.9
4	M	24	4	3.13	43	11.7
5	M	23	6	4.05	55	12.7
6	M	27	4	4.13	50	15.6
7	M	30	7	4.20	51	16.0
8	M	30	8	2.86	39	11.7
9	M	28	7	2.99	51	14.6
10	M	28	6	2.76	48	14.4
11	M	28	9	3.63	52	14.9
12	M	24	4	3.04	38	10.3
13	M	24	5	3.21	46	11.9
14	F	26	7	3.72	45	11.6
15	F	27	6	3.47	37	10.6
16	M	30	8	3.86	57	17.1
17	F	25	9	3.61	39	8.5
18	M	28	7	3.45	39	11.1
19	M	22	4	3.64	36	8.8
20	F	26	9	3.27	40	8.2
MEAN		26	6.1	3.47	46	12.3
SD		4	1.9	0.46	9	3.1

ESTIMATION OF MEAN RV VOLUMES FOR NORMAL SUBJECTS

	RV SP	SVI	RVEF	RVEDVI	RVESVI	P/V
MEAN	26	46	0.58	79	33	0.78

RANGE OF NORMAL RESTING HAEMODYNAMIC VALUES

Pressures (mmHg)	Systolic	End-diastolic	Mean
Right atrium			0-8
Right ventricle	15-30	0-8	
Pulmonary artery	15-30	3-12	9-20
Pulmonary artery wedge			1-12
Cardiac index ($ml.min^{-1}.m^{-2}$)			2.5-4.2
Resistances (dynes $s.cm^{-5}$)			
Pulmonary vascular			20-120
Systemic vascular			770-1500

TABLE 16

HAEMODYNAMIC DATA IN TEN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA RECEIVING NITROPRUSSIDE

PATIENT No	HR		MEAN PAP		RVSP		RV_{EDP}		CI		SVI		MBP		SaO_2	
	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N
1	84	96	38	32	55	40	4	2	2.4	2.3	28	24	77	67	86	85
2	88	88	32	26	51	40	4	6	2.8	2.5	32	29	98	67	86	83
3	96	92	33	25	45	40	7	4	2.3	2.2	24	24	93	72	86	83
4	96	100	26	19	40	30	2	0	3.3	2.8	34	28	97	80	86	86
5	95	115	30	22	51	40	7	3	2.6	3.0	28	26	93	73	92	92
6	72	80	26	18	34	30	10	8	2.8	2.9	39	37	103	70	92	91
7	60	64	21	13	34	25	4	0	2.0	3.3	33	29	114	78	89	87
8	85	104	30	22	49	34	10	2	3.5	3.6	41	34	77	63	83	81
9	90	100	38	28	60	51	4	1	3.5	3.7	39	37	93	73	82	79
10	105	118	22	18	33	30	5	6	2.0	1.9	19	16	90	73	90	92
Mean	87	96	30	22	45	36	6	3	2.72	2.82	32	28	94	72	87	86
SD	13	16	6	6	10	8	3	3	0.6	0.6	7	7	11	5	4	5
p	<0.01		<0.001		<0.001		<0.02		NS		<0.001		<0.001		NS	

NB Units of the variables as in previous tables except: HR (heart rate), beats/min; MBP (mean systemic blood pressure), mmHg; SaO_2 (arterial oxygen saturation), %.
C = CONTROL; N = SODIUM NITROPRUSSIDE.

Patient No	Age yrs	Sex	FEV_1 l	FVC l	FEV_1/FVC %	PaO_2 kPa	$PaCO_2$ kPa	H+ nmol/l
Group I								
1	67	M	0.5	1.1	50	5.2	8.4	47
2	69	F	0.5	2.0	25	6.0	7.6	45
3	67	M	0.7	1.5	47	8.8	6.2	39
4	40	M	1.0	2.8	36	7.5	5.6	38
5	68	F	0.6	1.1	61	4.5	8.6	42
6	70	F	0.4	1.0	40	7.8	5.5	45
7	70	M	0.9	1.8	50	7.4	5.4	38
8	65	M	1.1	3.7	30	7.2	4.4	39
Mean	64.5		0.7	1.9	42	6.9	6.5	42
SD	10		0.3	1.0	12	1.5	1.6	4
Group II								
1	60	F	0.9	3.0	30	8.1	5.2	41
2	58	F	0.7	1.4	50	8.0	6.0	46
3	65	M	1.3	3.6	36	8.1	6.1	40
4	58	M	0.9	2.5	36	7.6	5.2	36
5	57	M	0.7	2.1	33	9.4	5.8	42
6	65	M	1.4	2.1	67	7.2	4.4	39
7	58	M	0.8	2.0	40	8.6	6.1	44
8	68	M	0.8	2.3	35	9.4	5.8	44
9	65	F	1.0	2.2	46	9.8	6.1	44
10	52	M	2.7	4.7	45	11.3	4.2	39
11	62	M	0.5	1.6	32	6.8	5.9	41
12	65	M	0.5	1.1	46	6.8	6.0	39
13	62	F	0.3	0.9	33	7.6	6.7	43
14	55	F	1.7	2.6	65	7.4	5.6	43
15	65	F	1.0	2.3	44	8.0	6.3	41
16	68	F	0.3	1.5	20	6.0	6.7	39
Mean	61.5		1.0	2.2	41	8.1	5.8	41
SD	5		0.6	1.0	12	1.3	0.7	3

TABLE 17 (cont'd)

The effects of controlled oxygen on right ventricular function

Patient No	Age yrs	Sex	FEV_1 l	FVC l	FEV_1/FVC %	PaO_2 kPa	$PaCO_2$ kPa	H+ nmol/l
Group III								
1	66	M	0.5	1.5	33	6.3	6.7	41
2	65	M	0.7	2.2	32	8.0	7.1	45
3	70	F	0.6	1.6	38	7.1	7.3	42
4	64	F	0.5	1.7	29	7.1	8.0	46
5	69	F	0.5	1.6	31	6.0	7.1	35
6	69	F	0.8	3.0	27	6.5	7.2	40
7	64	F	0.4	1.7	24	5.5	7.6	39
8	42	F	0.7	1.2	58	6.7	5.2	39
9	62	M	0.5	1.0	31	6.8	5.9	41
10	70	F	0.4	1.0	40	7.8	5.5	45
Mean	64		0.6	1.7	34	6.8	6.8	41
SD	8		0.1	0.6	IO	0.8	0.9	3

GROUP I - ACUTE EFFECTS OF OXYGEN AT REST

GROUP II - ACUTE EFFECTS OF OXYGEN DURING EXERCISE

GROUP III - EFFECTS OF LONG TERM OXYGEN

Arterial and mixed venous blood gas and haemodynamic data in 8 patients with chronic bronchitis and emphysema at rest while breathing air or oxygen 3 litres/min by nasal prongs (Mean ± SEM)

	AIR	OXYGEN	p
PaO_2 kPa	6.8 ± 0.4	11.6 ± 0.8	< 0.01
$PaCO_2$ kPa	6.5 ± 0.5	6.9 ± 0.6	< 0.05
SaO_2 %	84 ± 4	95 ± 2	< 0.02
$[H^+]$ nmol/l	42 ± 1	43 ± 2	NS
PVO_2 kPa	4.3 ± 0.2	5.1 ± 0.2	< 0.05
CaO_2 ml/100 ml	16.2 ± 1.0	18.2 ± 0.7	< 0.01
CvO_2 ml/100 ml	11.4 ± 1.0	13.8 ± 0.7	< 0.01
$C(a-v)O_2$ ml/100 ml	4.7 ± 0.03	4.4 ± 0.2	NS
COD	3.5 ± 0.3	4.2 ± 0.3	< 0.01
HR b/min	88 ± 3	88 ± 5	NS
Mean systemic BP mmHg	97 ± 3	95 ± 5	NS
CI l/min/m^2	2.58 ± 0.21	2.61 ± 0.22	NS
Mean PAP mmHg	30 ± 3	25 ± 2	< 0.05
SVI ml/m^2	30 ± 3	31 ± 4	NS
TPVR dynes.s.cm^{-5}	570 ± 67	477 ± 51	< 0.01
RVSP mmHg	47 ± 4	41 ± 4	< 0.01
RVEDP mmHg	7 ± 1	6 ± 1	NS
RVEF	0.47 ± 0.04	0.51 ± 0.04	NS
RVESVI ml. m^{-2}	39 ± 7	33 ± 7	NS
RVEDVI ml. m^{-2}	69 ± 9	64 ± 10	NS
RVSWI g.m/beat/m^2	15.8 ± 2.4	13.5 ± 2.4	NS
End systolic P/V ratio	1.69 ± 0.35	1.74 ± 0.42	NS
LVEF	0.54 ± 0.03	0.55 ± 0.04	NS
SVR dynes. s. cm^{-5}	1915 ± 233	1864 ± 220	NS
Systemic oxygen delivery ml/min/m^2	41 ± 4	48 ± 4	< 0.01

Table 19

Haemodynamic data in 8 patients with chronic bronchitis and emphysema while breathing air or oxygen at rest

PATIENT	HR		MPAP		RV_{SP}		RV_{EDP}		CI		SVI		MBP		PaO_2	
No	C	O	C	O	C	O	C	O	C	O	C	O	C	O	C	O
1	90	90	34	34	53	50	7	7	3.62	3.79	40	42	100	98	5.2	8.1
2	81	90	32	29	43	42	6	7	2.34	2.66	29	30	93	85	6.0	11.6
3	90	88	20	18	52	24	6	0	1.81	1.86	20	20	97	93	8.8	14.5
4	75	65	23	20	39	37	4	3	3.13	3.15	42	49	87	85	7.5	12.3
5	100	100	46	31	71	53	7	5	2.78	2.11	28	21	98	107	4.5	14.5
6	100	110	30	26	47	43	10	10	1.90	2.26	19	21	110	110	7.8	13.3
7	86	88	24	18	42	34	8	6	2.50	2.49	29	28	107	105	7.4	10.1
8	80	76	28	26	47	44	4	6	2.57	2.65	32	36	81	74	7.2	9.1
MEAN	88	88	30	25	47	41	7	6	2.58	2.61	30	31	97	95	6.8	11.6
SD	9	14	8	6	12	12	2	3	0.60	0.62	8	11	10	13	1.4	2.5
p	NS		< 0.05		< 0.01		NS		NS		NS		NS		< 0.01	

Units

HR - beats/min; MPAP - mmHg; RV_{SP} & RV_{EDP} - mmHg.

CI - litres/min/m^2; SVI - ml/m^2; MBP mmHg.

PaO_2 & PVO_2 - kPa; PVR & SVR - dynes.s.cm^{-5}.

RV_{EDVI} & RV_{ESVI} - ml.m^{-2}.

TABLE 19 (cont'd)

Haemodynamic data in 8 patients with chronic bronchitis and emphysema while breathing air or oxygen at rest

PATIENT	PVO_2		PVR		SVR		RV_{EDVI}		RV_{ESVI}		P/V		LVEF		RVEF	
No	C	O	C	O	C	O	C	O	C	O	C	O	C	O	C	O
1	4.1	5.3	429	410	1262	1183	95	95	55	53	0.96	0.94	0.51	0.51	0.42	0.44
2	4.3	5.5	608	484	1767	1420	53	58	24	28	1.79	1.5	0.50	0.59	0.54	0.51
3	3.6	4.3	520	456	2520	2354	53	48	33	28	1.58	0.86	0.61	0.71	0.38	0.44
4	4.9	5.5	392	338	1484	1560	98	119	56	70	0.70	0.53	0.48	0.44	0.43	0.41
5	2.8	5.1	844	749	1798	2586	54	41	26	20	2.73	2.65	0.69	0.71	0.54	0.52
6	4.6	5.3	873	636	3200	2691	33	32	14	11	3.36	3.91	0.56	0.54	0.58	0.65
7	4.5	5.0	447	337	1991	1962	104	65	75	37	0.56	0.92	0.47	0.43	0.28	0.44
8	4.9	5.3	450	405	1301	1152	58	53	26	17	1.81	2.59	0.46	0.49	0.55	0.67
MEAN	4.3	5.1	570	477	1915	1864	69	64	39	33	1.69	1.74	0.54	0.55	0.47	0.51
SD	0.7	0.6	212	161	736	695	26	29	21	20	0.98	1.19	0.08	0.11	0.10	0.10
p	< 0.05		< 0.01		NS		NS		NS		NS		NS		NS	

Units

HR - beats/min; MPAP - mmHg; RV_{SP} & RV_{EDP} - mmHg.

CI - litres/min/m^2; SVI - ml/m^2; MBP mmHg.

PaO_2 & PVO_2 - kPa; PVR & SVR - dynes.s.cm^{-5}.

RV_{EDVI} & RV_{ESVI} - ml.m^{-2}.

Table 2

The effect of oxygen on right and left ventricular ejection fractions in 16 patients with chronic bronchitis and emphysema, at rest and during exercise (Means ± SEM)

	(1) $Rest_{air}$	(2) $Exercise_{air}$	(3) $Rest_{oxygen}$	(4) $exercise_{oxygen}$
HR (b/min)	90 ± 4	111 ± 4	90 ± 5	111 ± 4
SaO_2 (%)	89 ± 1	81 ± 2	95 ± 1	91 ± 1
RVEF	0.46 ± 0.02	0.45 ± 0.03	0.45 ± 0.02	0.45 ± 0.02
LVEF	0.56 ± 0.03	0.58 ± 0.03	0.54 ± 0.03	0.57 ± 0.03

STATISTICAL ANALYSIS

HR: (1) VS (2) $p < 0.001$; (3) VS (4) $p < 0.001$;
(1) VS (3) NS; (2) VS (4) NS

SaO_2: (1) VS (2) $p < 0.001$; (3) VS (4) $p < 0.01$;
(1) VS (3) $p < 0.001$; (2) VS (4) $p < 0.001$

RVEF: (1) VS (2); (3) VS (4); (1) VS (3); (2) VS (4) all NS

LVEF: (1) VS (2) NS; (3) VS (4) $p < 0.01$
(1) VS (3) NS; (2) VS (4) NS

Table 21

Arterial blood gas and haemodynamic data before and after 6 months oxygen (1-3 l/min by nasal prongs) given to 10 patients (Means ± SEM) with chronic bronchitis and emphysema for at least 15 hrs/24 hrs. All measurements were made while the patients breathed room air.

	Before oxygen	After 6 months oxygen	p
PaO_2 kPa	6.8 ± 0.3	7.0 ± 0.3	NS
$PaCO_2$ kPa	6.8 ± 0.3	6.5 ± 0.3	NS
[H+] nmol/l	41 ± 1	41 ± 1	NS
SaO_2 %	85 ± 1	84 ± 1	NS
HR b/min	90 ± 4	93 ± 3	NS
Mean systolic BP mmHg	91 ± 3	90 ± 3	NS
Mean PAP mmHg	32 ± 2	26 ± 2	< 0.01
RVSP mmHg	47 ± 4	35 ± 2	< 0.01
RVEDP mmHg	6 ± 1	4 ± 1	< 0.02
RVEF	0.44 ± 0.03	0.48 ± 0.02	NS
LVEF	0.54 ± 0.04	0.59 ± 0.04	NS
12MD m	404 ± 85	423 ± 61	NS
$FEV_{1.0}$ l	0.6 ± 0.04	0.5 ± 0.04	NS
FVC l	1.7 ± 0.19	1.6I ± 0.2	NS
Weight Kg	64.5 ± 4.3	64.0 ± 4.5	NS

Table 22

Arterial blood gas and oxygen delivery data in 12 patients with chronic bronchitis and emphysema before (C) and 90 minutes after (P) oral pirbuterol

Patient No	PaO_2		$PaCO_2$		SaO_2		PVO_2		CaO_2		CVO_2		SDO_2		COD	
	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1	6.0	5.9	7.1	7.2	78	80	4.4	4.3	16.4	16.9	12.6	13.1	39.4	49.0	4.3	4.5
2	7.1	6.4	7.3	7.3	84	81	4.3	4.4	15.7	15.1	10.8	11.0	44.0	51.3	3.2	3.7
3	6.3	5.7	6.7	6.4	82	80	4.4	4.0	19.1	18.7	14.2	13.1	44.0	54.0	3.9	3.3
4	6.5	6.4	6.4	5.9	86	84	4.4	4.8	16.9	16.4	12.9	13.7	55.8	60.7	4.2	6.1
5	8.3	7.3	6.3	6.3	93	89	4.3	4.4	18.5	17.7	12.5	12.9	48.1	58.4	3.1	3.7
6	8.3	7.6	5.7	5.5	94	90	4.7	4.8	18.0	17.2	12.6	13.1	50.4	58.5	3.3	4.2
7	7.2	6.9	6.1	6.0	87	84	4.4	4.7	17.1	16.5	11.6	12.6	32.5	42.9	3.1	4.0
8	7.6	5.3	7.5	7.3	82	69	4.8	4.0	15.9	13.3	11.4	10.3	55.7	53.0	3.5	4.4
9	6.7	5.2	5.2	5.2	83	71	4.0	3.7	12.0	10.2	7.6	7.1	42.0	39.8	2.7	3.3
10	8.0	7.9	7.1	6.3	90	91	4.3	4.1	19.5	19.7	13.8	13.8	39.0	43.3	3.4	3.3
11	8.3	6.9	5.5	5.4	89	84	4.6	4.4	21.8	20.6	14.9	16.8	41.4	43.3	3.2	3.0
12	7.8	7.7	6.4	6.3	90	90	4.7	5.2	17.5	17.5	12.0	11.6	42.0	59.5	3.4	4.1
Mean	7.3	6.6	6.4	6.6	87	83	4.4	4.4	17.4	16.7	12.2	12.4	44.5	51.1	3.4	4.1
SD	0.8	0.9	0.7	0.9	5	7	0.2	0.4	2.4	2.8	1.9	2.3	6.9	7.4	0.5	0.9
p	< 0.05		NS		< 0.02		NS		< 0.01		NS		< 0.01		< 0.02	

Units

PaO_2, $PaCO_2$, PVO_2 - kPa; SaO_2 - %; CaO_2, CVO_2 - ml/100 ml; SDO_2 - $ml/min/m^2$.

Table 23

Haemodynamic data in 12 patients with chronic bronchitis and emphysema, before and 90 minutes after oral pirbuterol

Patient No	HR		MPAP		RVSP		RVEDP		CI		SVR		MBP		PVR		SVI	
	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1	84	88	38	30	55	36	4	0	2.4	2.9	1458	1144	77	73	720	471	29	33
2	88	88	32	24	51	40	4	5	2.8	3.4	1806	1230	97	81	590	365	32	39
3	96	92	33	32	45	48	7	6	2.3	2.9	1817	1296	92	93	645	446	24	32
4	96	105	26	21	40	37	2	3	3.3	3.7	1383	1234	97	95	371	267	34	39
5	95	110	30	34	51	56	7	6	2.6	3.3	2030	1496	93	87	655	584	28	30
6	72	92	26	22	34	32	10	8	2.8	3.4	1691	1420	107	105	427	298	39	37
7	60	62	21	20	34	28	4	4	1.9	2.6	2506	1860	114	110	461	338	32	42
8	85	98	30	30	49	47	10	3	3.5	4.0	957	891	77	82	373	326	42	41
9	90	103	38	34	60	60	4	2	3.5	3.9	1529	1299	93	88	625	501	39	38
10	105	114	22	22	33	34	5	6	2.0	2.2	2057	1953	87	94	529	503	19	19
11	100	115	30	24	47	38	10	7	1.9	2.1	3194	2811	110	107	871	630	19	18
12	78	100	30	32	49	53	6	7	2.4	3.4	1403	990	77	77	525	412	36	34
MEAN	87	97	30	27	47	42	6	5	2.62	3.15	1819	1469	93	91	566	428	31	34
SD	13	15	5	5	9	10	3	5	0.58	0.62	588	525	13	12	149	114	8	8
p	< 0.01		< 0.05		NS		NS		< 0.001		< 0.001		NS		< 0.001		NS	

Units

HR - beats/min; MPAP, RVSP, RV_{EDP}, MBP - mmHg.
SVR, PVR - dynes.s.cm^{-5}; SVI - $ml.m^{-2}$.

Table 23 (cont'd)

Haemodynamic data in 12 patients with chronic bronchitis and emphysema, before and 90 minutes after oral pirbuterol

Patient No	RV_{EDVI} C	RV_{EDVI} P	RV_{ESVI} C	RV_{ESVI} P	P/V INDEX C	P/V INDEX P	LVEF C	LVEF P	RVEF C	RVEF P	RVSWI C	RVSWI P
1	71	64	42	31	1.34	1.16	0.79	0.84	0.41	0.52	20	16
2	76	95	44	56	1.16	0.71	0.47	0.50	0.42	0.41	21	19
3	57	65	33	33	1.36	1.46	0.63	0.66	0.42	0.49	12	18
4	72	63	38	24	1.05	1.54	0.51	0.43	0.47	0.62	18	18
5	61	48	33	18	1.55	3.11	0.64	0.70	0.46	0.62	17	20
6	72	67	33	30	1.03	1.07	0.64	0.66	0.54	0.55	13	12
7	64	70	32	28	1.03	1.00	0.62	0.73	0.50	0.60	13	14
8	114	75	72	34	0.70	1.38	0.52	0.54	0.37	0.54	22	25
9	65	62	26	24	2.31	2.50	0.52	0.57	0.60	0.61	29	30
10	53	46	34	27	1.00	1.26	0.61	0.56	0.37	0.41	7	7
11	33	27	14	9	3.36	4.22	0.56	0.60	0.58	0.68	10	8
12	86	64	50	30	0.98	1.77	0.52	0.55	0.42	0.53	21	22
MEAN	69	62	38	29	1.40	1.77	0.58	0.63	0.46	0.55	16.9	17.4
SD	20	17	14	11	0.74	1.02	0.09	0.10	0.08	0.08	6.2	6.6
p	NS		< 0.05		< 0.05		NS		< 0.001		NS	

Units

RV_{EDVI}, RV_{ESVI} - $ml.m^{2}$; RVSWI - $g.m.m^{-2}$.

Table 24

Comparison of the effects of sodium nitroprusside and pirbuterol in 10 patients with chronic bronchitis and emphysema

PATIENT No	MPAP			RVSP			CI			PVR			RVEF			LVEF			P/V			SVR		
	C	N	P	C	N	P	C	N	P	C	N	P	C	N	P	C	N	P	C	N	P'	C	N	P
1	38	32	30	55	40	36	2.4	2.3	2.9	720	632	471	0.41	0.40	0.52	0.79	0.80	0.84	1.34	1.11	1.16	1458	1324	1144
2	32	26	24	51	40	40	2.8	2.5	3.4	590	537	365	0.42	0.41	0.41	0.47	0.49	0.50	1.16	0.98	0.71	1806	1383	1230
3	33	25	32	45	40	48	2.3	2.2	2.9	645	511	446	0.42	0.51	0.49	0.63	0.75	0.66	1.36	1.67	1.46	1817	1471	1296
4	26	19	21	40	30	37	3.3	2.8	3.7	371	314	267	0.47	0.48	0.62	0.51	0.76	0.63	1.05	0.97	1.54	1383	1345	1234
5	30	22	34	51	40	56	2.6	3.0	3.3	655	416	584	0.46	0.54	0.62	0.64	0.78	0.70	1.55	1.74	3.11	2030	138I	1496
6	26	18	22	34	30	32	2.8	2.9	3.4	427	286	298	0.54	0.54	0.55	0.64	0.65	0.66	1.03	0.83	1.07	1691	1110	1420
7	21	13	20	34	25	28	2.0	3.3	2.6	461	173	338	0.50	0.66	0.60	0.62	0.69	0.73	1.03	1.67	1.00	2506	1040	1860
8	30	22	30	49	34	47	3.5	3.6	4.0	373	266	326	0.37	0.48	0.54	0.52	0.60	0.54	0.70	0.92	1.38	957	761	891
9	38	28	34	60	51	60	3.5	3.7	3.9	625	435	501	0.60	0.69	0.61	0.52	0.56	0.57	2.31	3.00	2.50	1529	1136	1299
10	22	18	22	33	30	34	2.0	1.9	2.2	529	433	503	0.37	0.35	0.41	0.61	0.58	0.56	1.00	0.97	1.26	2057	1756	1953
Mean	30	22	27	45	36	42	2.7	2.8	3.2	540	400	410	0.46	0.51	0.54	0.60	0.67	0.64	1.25	1.39	1.82	1723	1271	1382
SD	6	6	6	10	8	11	0.6	0.6	0.6	126	140	105	0.07	0.11	0.08	0.09	0.10	0.10	0.44	0.67	1.20	428	272	321
p		*	***		***				***		***	***		*	**		***	*			*		*	*

Units

MPAP, RVSP - mmHg; CI_{-5} litres/min; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$
PVR, SVR - dynes.s.cm^{-5}.
C = control; N = sodium nitroprusside; P = pirbuterol

Table 25

Plasma pirbuterol concentrations in 10 patients 60 and 120 minutes after administration of the drug

Patient No	Dose of pirbuterol (mg)	Plasma pirbuterol (g/l) 60 min	120 min
3	22.5	45.1	34.6
4	22.5	9.6	35.2
5	22.5	4.2	45.0
6	22.5	43.7	24.8
7	15	8.1	10.0
8	15	5.3	9.7
9	15	26.1	36.2
10	15	19.4	36.8
11	15	6.9	3.7
12	15	34.9	33.9

Table 26

Haemodynamic variables (Mean ± SEM) and arterial blood gas tensions before and after 6 weeks' treatment with oral pirbuterol 15 mg thrice daily in 9 patients with chronic bronchitis and emphysema

	Control	After 6 weeks pirbuterol	p
Heart rate (beats/min)	86 ± 5	92 ± 5	NS
Arterial blood pressure (mmHg):			
Systolic	124 ± 5	121 ± 5	NS
Diastolic	73 ± 4	74 ± 3	NS
Arterial blood gas tensions (kPa):			
Oxygen	7.2 ± 0.3	6.9 ± 0.2	NS
Carbon dioxide	6.8 ± 0.2	7.2 ± 0.3	NS
Oxygen saturation (%)	86 ± 2	84 ± 2	NS
Hydrogen ion concentration (nmol/l)	43 ± 1	44 ± 1	NS
Pulmonary arterial pressure (mmHg):			
Systolic	43 ± 3	35 ± 2	< 0.01
Mean	28 ± 2	26 ± 2	NS
Right ventricular ejection fraction	0.45 ± 0.04	0.52 ± 0.03	< 0.01
Left ventricular ejection fraction	0.60 ± 0.03	0.61 ± 0.03	NS
$FEV_{1.0}$(l)	0.58 ± 0.06	0.60 ± 0.05	NS
FVC (l)	1.66 ± 0.10	1.66 ± 0.10	NS
12 minute walking distance (m)	424 ± 100	439 ± 104	NS

TABLE 27

VENTILATORY CAPACITY AND ARTERIAL BLOOD GAS DATA WHEN BREATHING AIR IN 6 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA WHO PRESENTED ACUTELY WITH OEDEMA

PATIENT No	AGE (yrs)	SEX	FEV_1 l	FVC l	PaO_2 kPa	$PaCO_2$ kPa	[H+] nmol/l	SaO_2 %
1	65	F	0.4	1.5	5.3	6.9	40	72
2	64	M	0.9	3.1	7.2	7.4	43	85
3	53	F	1.0	2.0	4.8	9.3	44	67
4	61	M	0.6	2.4	4.3	8.0	44	48
5	67	M	0.9	3.7	4.0	6.8	38	50
6	52	M	0.7	2.5	5.6	9.6	46	71
MEAN	60		0.75	2.53	5.2	8.0	43	66
SD	6		0.23	0.78	1.2	1.2	3	14

TABLE 28

Arterial blood gas and oxygen delivery data when breathing air (A) or oxygen (O_2) in 6 patients with chronic bronchitis and emphysema who presented acutely with oedema

PATIENT	PaO_2		$PaCO_2$		PVO_2		[H+]		CaO_2		CVO_2		$C(a-v)O_2$		SDO_2		COD	
NO	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2
1	5.3	13.2	6.9	7.3	3.7	5.2	40	42	12.5	16.3	8.3	9.0	4.2	7.3	36.3	45.3	3.0	2.2
2	7.2	10.2	7.4	7.4	4.3	4.9	43	45	17.2	18.6	11.5	12.9	5.7	5.7	34.9	30.1	3.0	3.3
3	4.8	8.0	9.3	9.8	4.0	5.6	44	47	12.9	17.1	10.4	14.5	2.5	2.6	61.0	75.0	5.2	6.6
4	4.3	7.8	8.0	8.9	3.5	5.2	44	47	8.3	14.8	6.2	12.2	2.1	2.6	35.7	60.7	4.0	5.7
5	4.0	5.7	6.8	7.3	3.5	4.3	38	42	11.0	15.4	8.7	11.3	2.3	4.1	41.9	57.3	4.7	3.8
6	5.6	9.3	9.6	10.4	4.4	6.4	46	49	11.4	14.7	8.4	11.9	3.0	2.8	46.7	56.9	3.8	5.3
MEAN	5.2	9.0	8.0	8.6	3.9	5.3	43	45	12.2	16.2	8.9	12.0	3.3	4.2	42.8	54.2	4.0	4.5
SD	1.2	2.6	1.2	1.3	0.4	0.7	3	3	2.9	1.5	1.8	1.8	1.4	1.9	10.0	15.2	0.9	1.6
p	< 0.01		< 0.01		< 0.01		< 0.01		< 0.01		< 0.02		NS		< 0.05		NS	

TABLE 29

Haemodynamic data when breathing air (A) or oxygen (O_2)

in 6 patients with chronic bronchitis and emphysema

who presented acutely with oedema

PATIENT No	HR		MPAP		RVSP		RV_{EDP}		RAP		PCW		MBP		CI		SVI		RVSWI	
	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2
1	97	98	25	19	43	36	3	1	4	5	4	10	110	108	2.90	2.78	31	34	16.9	16.2
2	100	98	27	25	42	39	11	11	10	3	5	3	98	97	2.03	1.62	20	17	8.4	6.5
3	100	104	29	26	42	37	12	16	12	8	11	9	81	83	4.73	4.40	47	42	19.2	12.0
4	112	110	38	35	62	59	6	5	4	5	6	5	89	87	4.30	4.10	38	37	28.9	27.2
5	107	105	36	30	50	45	10	5	8	7	6	6	70	72	3.81	3.72	36	36	19.6	19.6
6	100	102	40	34	62	57	27	23	18	14	15	12	95	100	4.10	3.87	41	38	19.5	17.6
MEAN	103	103	33	28	50	46	12	10	9	7	8	8	91	91	3.65	3.42	36	34	18.8	16.5
SD	6	5	6	6	10	10	8	8	5	4	4	3	14	13	1.00	1.04	9	8	6.6	7.0
p	NS		< 0.01		< 0.01		NS		NS		NS		NS		< 0.01		NS		NS	

TABLE 30

Haemodynamic data when breathing air (A) or oxygen (O_2)
in 6 patients with chronic bronchitis and emphysema
who presented acutely with oedema

PATIENT	TPVR		SVR		EDVI		ESVI		P/V Index		LVEF		RVEF	
No	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2	A	O_2
1	557	455	2451	2587	103	103	72	69	0.65	0.59	0.52	0.66	0.30	0.33
2	592	687	1064	1237	77	74	57	57	0.74	0.68	0.31	0.31	0.26	0.23
3	311	298	868	953	142	98	95	56	0.44	0.66	0.51	0.51	0.33	0.43
4	385	368	901	916	127	116	89	79	0.43	0.44	0.55	0.49	0.30	0.32
5	416	355	808	851	450	144	414	108	0.09	0.28	0.29	0.23	0.08	0.25
6	459	412	1092	1210	410	158	369	120	0.11	0.22	0.33	0.24	0.10	0.11
MEAN	453	429	1197	1292	218	116	183	82	0.41	0.48	0.42	0.41	0.23	0.28
SD	106	137	624	653	166	31	162	27	0.27	0.20	0.12	0.17	0.11	0.11
p	NS		< 0.02		NS		NS		NS		NS		NS	

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