

# Ventilatory function in the Eisenmenger syndrome

C G C MacARTHUR, D HUNTER, AND G J GIBSON<sup>1</sup>

*From the Department of Medicine (Clinical Cardiology and Respiratory Medicine), Royal Postgraduate Medical School, Hammersmith Hospital, London, UK*

**ABSTRACT** Ventilatory function and carbon monoxide transfer factor were studied in nine adult patients with post-tricuspid intracardiac defects and the Eisenmenger syndrome. A consistent mild defect of ventilatory function was found, with raised residual volume and closing capacity and reduction of other lung volumes and maximal expiratory flows. Maximal expiratory flow was particularly reduced at low lung volumes. One of the four subjects in whom pressure-volume studies were performed showed loss of normal elastic recoil at low lung volumes. A significant poorly ventilated space was excluded since the volume of distribution of helium during a 10 second breath-hold at full inspiration was close to plethysmographically measured total lung capacity. Carbon monoxide transfer factor, after correction for haemoglobin concentration, was 77% of predicted normal values. Sequential assessment of carbon monoxide transfer factor might be useful in the early diagnosis of pulmonary vascular disease in infants with large intracardiac defects, since it is likely to be raised early due to high pulmonary blood flow and will fall with the development of pulmonary vascular disease.

There have been few reports of the effects of hypertensive pulmonary vascular disease on ventilatory function. Furthermore, most reports have reflected a mixed population with both pre- and post-tricuspid shunts (McIlroy and Apthorp, 1958; Auchincloss *et al*, 1959; Woolf, 1963; McCredie *et al*, 1964; Kimball and McIlroy, 1966). In general, respiratory function has appeared to be little affected by pulmonary vascular disease, and no consistent defect has been defined.

McKenzie *et al* (1977) have shown that the ventilatory washout of an injected bolus of radioactive nitrogen-13 was delayed compared with the clearance of an inhaled bolus in children with hypertensive pulmonary vascular disease. They proposed that the delayed clearance of the injected bolus was caused by the presence of poorly ventilated but perfused alveoli, possibly in association with an increased closing capacity.

The purpose of this study was to measure ventilatory function and gas transfer in a well-defined group of adult patients with post-tricuspid shunts and the Eisenmenger syndrome, to investigate the proposed mechanism for the results of the nitrogen-13 test, and to assess whether any consistent ventilatory defects occur in hypertensive

pulmonary vascular disease, which might aid early diagnosis of this condition.

## Subjects and methods

Cardiac catheterisation had proved that all subjects had post-tricuspid intracardiac defects, equal pulmonary and systemic pressures, and severely increased pulmonary vascular resistance (table 1). There were five men and four women aged between 20 and 46 years (mean 27). Two of the men were smokers (table 2). None of the subjects had any respiratory symptoms other than dyspnoea on exertion.

Forced expiratory volume in one second (FEV<sub>1</sub>) and vital capacity (VC) were measured with a dry spirometer (McDermott *et al*, 1968) and total lung capacity (TLC) by plethysmography (Dubois *et al*, 1956). Maximum values for FEV<sub>1</sub> and VC were taken, but for TLC the mean of the two to four highest values agreeing to within 5% was taken. Residual volume (RV) was computed by subtracting VC from TLC.

Single breath carbon monoxide transfer factor (TLCO) was measured by the method of Ogilvie *et al* (1957), the average of three readings being taken. This was repeated in one subject after haemoglobin reduction by repeated venesections.

<sup>1</sup>Present address: Regional Cardiothoracic Centre, Freeman Hospital, Freeman Road, Newcastle-upon-Tyne NE7 7DN.

Table 1 Results of cardiac catheterisation

Case No	Age (yr)	Diagnosis	PAP (mmHg)	SAP (mmHg)	Qp (L/Min/M <sup>2</sup> )	Qs (L/Min/M <sup>2</sup> )	PAR (Units × M <sup>2</sup> )
1	9	VSD, ASD	125/85	130/90	5.6	5.8	17
2	32	VSD	120/65	120/75	1.4	3.1	48
3	21	PDA	120/60	120/80	2.8	4.0	29
4	24	VSD, PDA	100/60	100/60	1.9	4.7	42
5	11	DORV	100/60	105/65	2.5	3.7	31
6	17	SV	115/50	115/75	4.2	1.9	18
7	22	SV	110/70	110/75	2.5	3.2	34
8	27	PDA	120/70	125/80	2.0	1.7	38
9	17	VSD	145/80	140/95	1.9	3.0	50

VSD=Ventricular septal defect; ASD=Atrial septal defect; PDA=Patent ductus arteriosus; DORV=Double outlet right ventricle; SV=Single ventricle; PAP=Pulmonary artery pressure; SAP=Systemic arterial pressure; Qp=Pulmonary blood flow; Qs=Systemic blood flow; and PAR=Pulmonary arteriolar resistance.

Table 2 Clinical data and results of spirometry and plethysmography

Case No	Sex	Age (yr)	Smoker	PEFR Per cent of predicted normal values	FEV <sub>1</sub>	VC	FEV <sub>1</sub> /VC	RV	TLC	RV/TLC
1	M	20	NO	68	63	64	96	88	68	128
2	M	46	NO	115	79	88	91	86	86	99
3	M	29	YES	71	87	95	90	107	97	110
4	M	24	YES	69	76	92	81	134	100	133
5	M	22	NO	79	93	100	94	121	103	117
6	F	24	NO	88	91	98	85	100	99	101
7	F	26	NO	89	78	74	103	116	86	136
8	F	33	NO	82	79	77	94	137	97	142
9	F	20	NO	84	72	83	85	126	92	134
Mean				82 <sup>2</sup>	80 <sup>1</sup>	86 <sup>1</sup>	91 <sup>1</sup>	113	92 <sup>2</sup>	122 <sup>1</sup>

<sup>1</sup>P < 0.01; <sup>2</sup>P < 0.05; difference from predicted normal values.

The CO uptake was also assessed in terms of the transfer coefficient (Kco), which was obtained by dividing TLC by the alveolar volume (VA) estimated by helium dilution during the breath-holding manoeuvre.

Maximum expiratory flow-volume (MEFV) curves were obtained using a pressure-corrected variable volume plethysmograph (Mead, 1960), in which the seated subject performed a forced expiration from TLC through a Fleisch pneumotachograph, the flow at the mouth being displayed against change in thoracic gas volume (TGV) on a storage oscilloscope, from which MEFV curves were copied. The maximum value of peak expiratory flow rate (PEFR) was taken from these curves. The nitrogen concentration during slow expiration, after a vital capacity inhalation of oxygen, was recorded in the same plethysmograph and displayed against volume. Closing volume (CV) and the slope of the phase 3 plateau of N<sub>2</sub> concentration (N<sub>2</sub> slope) were measured as the mean of between two and four records in which the expired volume was at least 95% VC. Closing capacity (CC) was derived by adding RV to CV.

Transpulmonary pressure was measured by the oesophageal balloon method (Milic-Emili *et al*, 1964) in four subjects seated in a variable volume plethysmograph. Several static expiratory pressure-volume curves were obtained in each subject, and the line of best fit was drawn by eye through at least three sets of data, where the pressure at a given volume agreed to  $\pm 1$  cm H<sub>2</sub>O (0.1 kPa).

The results were compared with predicted normal values obtained from the regression equations of Leiner *et al* (1963) for PEFR; Kory *et al* (1961) for FEV<sub>1</sub> and FEV<sub>1</sub>/VC in men; Ferris *et al* (1965) for FEV<sub>1</sub> and Berglund *et al* (1963) for FEV<sub>1</sub>/VC in women; Goldman and Becklake (1959) for TLC, RV, and VC; Bradley *et al* (personal communication) for the results of the carbon monoxide uptake test, which were corrected for haemoglobin concentration by the equation of Cotes *et al* (1972) and Buist and Ross (1973a and b) for CV/VC, CC/TLC, and N<sub>2</sub> slope. Statistical analysis of these comparisons was performed using the Wilcoxon matched-pairs signed-ranks test (Siegel, 1956). The MEFV curves were compared with the normal range from Gibson

*et al* (1976), and the pressure-volume curves with a normal range derived from 20 non-smoking subjects aged 20–35 years.

**Results**

FEV<sub>1</sub>, both in absolute terms and when expressed as a proportion of VC, was reduced compared with predicted normal values (table 2). Both TLC and VC were also reduced. RV tended to be raised, but this was only significant when expressed as a proportion of TLC.

V<sub>A</sub> measured by helium dilution during the 10 second breath-hold of the carbon monoxide uptake test was close to TLC measured plethysmographically, having a mean value of 98% TLC (table 3). Carbon monoxide transfer factor (TLCO) was reduced in nearly all subjects, to a mean for the whole group of 77% of predicted normal values. Kco was similarly reduced to 80% of predicted normal values.

Analysis of the MEFV curves showed that PEFR was reduced in all except one subject (table 2), and that maximum flow was low throughout expiration, being particularly reduced at low lung volumes (fig 1). CV/VC was not significantly raised; and, indeed, when CV was related to predicted VC, to eliminate the effects of the generally small VC in the group, the mean value was close to predicted (table 4). CC was, however, considerably raised, both as a proportion of actual TLC and when related to predicted

Table 3 Results of single breath carbon monoxide uptake test

Case No	Haemoglobin g/dl	V <sub>A</sub> litre	V <sub>A</sub> /TLC per cent	TLCO Per cent of predicted normal values	Kco Per cent of predicted normal values
1	20.4	4.3	102	90	122
2	20.7	5.3	91	60	74
3	25.6	7.0	96	85	82
3*	16.6	7.0	96	72	70
4	19.4	6.4	102	86	79
5	23.6	5.8	102	87	80
6	20.5	5.3	100	102	93
7	19.7	4.0	103	57	65
8	15.3	5.0	98	53	51
9	17.2	3.8	90	79	86
Mean			98	77 <sup>1</sup>	80 <sup>2</sup>

Results for TLCO and Kco after correction for haemoglobin concentration are shown.

<sup>1</sup>P < 0.01; <sup>2</sup>P < 0.05; difference from predicted normal values.

\*This patient was studied before and after chronic venesection.

TLC. N<sub>2</sub> slope was not significantly different from predicted normal values.

**Discussion**

Ventilatory function and gas transfer in this well-defined group of patients with the Eisenmenger syndrome shows a consistent, albeit mild, defect. The reduction in TLC, VC, and TLCO are similar to but more severe than those found by Hallidie-Smith *et al* (1977) in patients with persistent pulmonary hypertension after repair of large ventricular septal defects. In that series, however, a part of

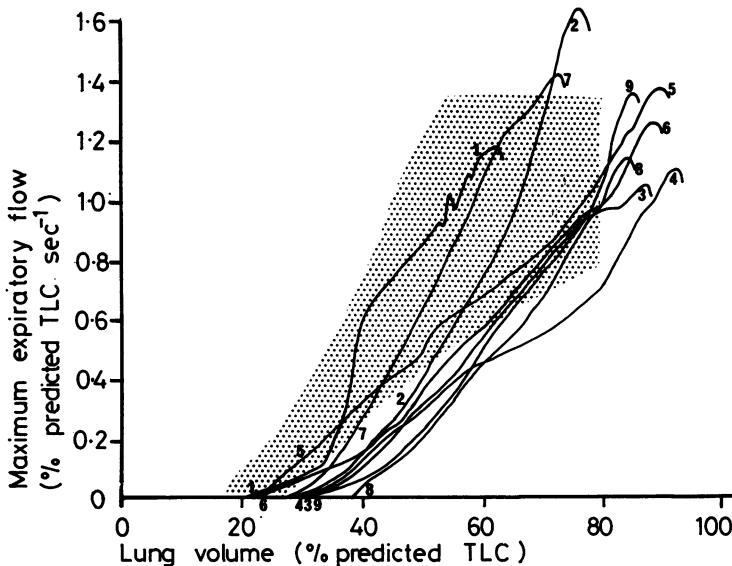


Fig 1 MEFV curves for the nine patients with a range (stippled area) for 16 normal non-smoking subjects.

Table 4 Results of single breath nitrogen test

Case No	CV litre	N <sub>s</sub> slope Per cent/litre	CV/VC Per cent of predicted normal values	CV/Predicted/VC	CC/TLC	CC/Predicted TLC	N <sub>s</sub> slope
1	0.46	1.81	192	127	163	112	199
2	0.60	1.40	91	78	110	95	120
3	0.75	0.70	129	125	135	131	70
4	0.28	0.53	73	66	136	137	56
5	0.40	0.74	110	113	129	133	80
6	0.37	1.05	102	99	138	137	84
7	0.34	1.98	129	98	163	139	156
8	0.50	2.33	129	111	171	165	175
9	0.27	0.53	107	95	171	160	43
Mean			118	101	146 <sup>1</sup>	134 <sup>1</sup>	109

<sup>1</sup>P < 0.01; difference from predicted normal values.

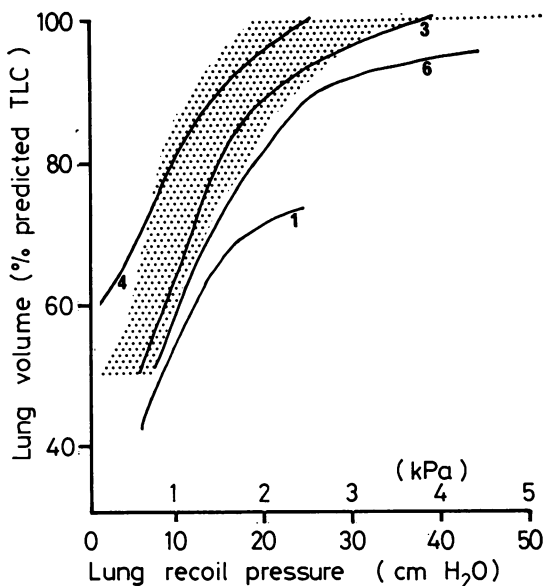


Fig 2 Pressure-volume curves for four of the patients with a range (stippled area) for 20 normal non-smoking subjects.

the ventilatory defect could have been secondary to cardiac surgery, which had not been performed on any of the patients in this series. One explanation for the decreased TLC and VC might be cardiac enlargement. Comparison of the reduction in TLC from the predicted normal value with cardiac volume assessed from biplane chest radiographs by the ellipsoid method (Barnhard *et al*, 1960) showed no correlation. Probably, therefore, the reduced TLC is not solely caused by cardiac enlargement, but may result from defective pulmonary growth, possibly secondary to reduced growth of the thoracic cavity. The low values of

FEV and PEFR are probably partly due to the reduced lung volumes.

The low FEV<sub>1</sub>/VC, disproportionately reduced maximum expiratory flow at low lung volumes, and raised RV and CC all indicate mild airflow obstruction. The two subjects who smoked had the greatest reduction in PEFR and were also both below average for the group in FEV<sub>1</sub>/VC. The reduction in maximum flow at low lung volumes in these two subjects, however, was average for the group; and seems, therefore, to be caused by pulmonary vascular disease rather than by smoking. Airflow obstruction in pulmonary vascular disease may be due either to loss of elastic recoil at low lung volumes or to intrinsic narrowing or obliteration of small airways. The pressure-volume curve of patient 4 suggested that the former mechanism might be important. A similar appearance of the pressure-volume curve has been described in patients with mitral stenosis (Wood *et al*, 1971).

Although the development of the Eisenmenger syndrome due to simple intracardiac defects is now rare, it still occurs early in the history of some infants with more complicated cardiac anatomy, such as transposition of the great arteries. Byrne *et al* (1978) have emphasised the need to diagnose pulmonary vascular disease early in these infants, who are otherwise only suitable for palliative surgery. The nitrogen-13 test was encouraging in this respect (McKenzie *et al*, 1977), but its mechanism remains uncertain. Although this study has shown a ventilatory defect including considerably raised closing capacity in the Eisenmenger syndrome, reduced ventilation of perfused alveoli is unlikely to be the mechanism of delayed clearance of injected nitrogen-13. There are two lines of evidence for this. Firstly, the close correlation of OVA and TLC indicates that the proportion of TLC in the patients in this series that has not equilibrated with

helium during a 10 second breath-hold is small. Secondly, the near-normality of the  $N_2$  slope shows that there is no significantly abnormal non-uniformity of alveolar ventilation in the Eisenmenger subjects.

The considerable inter-individual variation in CV and  $N_2$  slope in this study was probably partly due to the intrinsic variability and poor repeatability of the single breath nitrogen test (McCarthy *et al*, 1975). For this reason, as well as difficulty in performing the test in infants, the abnormally raised closing capacity is unlikely to be useful for detecting pulmonary vascular disease.

The other major abnormality shown in this study was the reduction in TLCO which after correction for haemoglobin concentration was more than 10% below predicted normal values in seven of the nine patients and averaged 77% predicted. Previous studies have shown that TLCO tends to be lower in patients with intracardiac defects who have developed pulmonary vascular disease (Auchincloss *et al*, 1959; McCredie *et al*, 1964). The reduction was greater in this study than in previous studies, perhaps reflecting the severity of pulmonary vascular disease in the patients studied. TLCO is also reduced in primary pulmonary hypertension (Burgess, 1974).

The correction for haemoglobin concentration (Cotes *et al*, 1972) in this study reduced the measured TLCO by a mean of 10%. The validity of this correction must be questioned since it assumes that the ratio of the alveolar membrane diffusing capacity (Dm) to the capillary blood volume (Vc) is 0.7. It is likely that hypertensive pulmonary vascular disease predominantly reduces Vc (Burgess, 1974), and that the ratio Dm/Vc is, therefore, greater than 0.7. This is supported by our finding that the corrected transfer factor tended to be lower in those patients with the lowest haemoglobin; and that the corrected TLCO in patient 3 fell after venesection. Furthermore, although the correction has been shown to be accurate in anaemia (Cotes *et al*, 1972; Clark *et al*, 1978), two studies (Burgess and Bishop, 1963; Herbert *et al*, 1965) have shown that it is too small in polycythaemia. Thus the quoted results in this study for TLCO and Kco may be slight overestimates; and the true abnormality of gas transfer may have been greater than our results indicate.

In infants without polycythaemia, or in whom the degree of polycythaemia is fairly constant, repeated measurements of carbon monoxide transfer factor, as first suggested by Auchincloss *et al* (1959), might allow early diagnosis of pulmonary vascular disease. Naturally, the single-breath

technique would not be suitable for this, but a steady state technique would be feasible. When pulmonary blood flow is high in the absence of pulmonary vascular disease the TLCO will probably be raised (Auchincloss *et al*, 1959; McCredie *et al*, 1964); although Bedell (1961) found this only to be the case with atrial septal defects. With the development of pulmonary vascular disease, the TLCO should progressively diminish. It would also be expected to decrease should the intracardiac defects spontaneously close, but this is unlikely to produce clinical confusion.

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Requests for reprints to: Dr C G C MacArthur, Department of Medicine (Clinical Cardiology), Hammersmith Hospital, Ducane Road, London W12 0HS.