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Measurement of effective pulmonary blood flow by soluble gas uptake in patients with chronic airflow obstruction

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ABSTRACT A study was designed to assess the accuracy and reproducibility of rebreathing and single breath soluble gas uptake measurements of effective pulmonary blood flow ($\dot{Q}$) in patients with airways obstruction. Both rebreathing (RB) and single breath (SB) estimates of $\dot{Q}$ were compared with direct Fick and thermodilution (TD) measurements of cardiac output at rest and during exercise in eight patients with chronic, poorly reversible airflow obstruction with mean FEV_1 65% predicted and mean FEV_1/FVC 53%. The mean (SD) resting values obtained were $\dot{Q}_{RB}$ 3·47 (0·46), $\dot{Q}_{SB}$ 4·75 (1·15), $\dot{Q}_{Fick}$ 4·77 (0·97), and $\dot{Q}_{TD}$ 5·15 (0·98). $\dot{Q}_{RB}$ was significantly lower than the other three estimates, which did not differ significantly from each other. Exercise produced significant increases in all four estimates for the group. The mean exercise values were $\dot{Q}_{RB}$ 6·23 (1·19), $\dot{Q}_{SB}$ 7·62 (1·97), $\dot{Q}_{Fick}$ 8·97 (1·96), and $\dot{Q}_{TD}$ 9·09 (1·00), both $\dot{Q}_{RB}$ and $\dot{Q}_{SB}$ being significantly less than $\dot{Q}_{Fick}$ and $\dot{Q}_{TD}$. Analysis of variance of the rest, exercise, and combined data showed highly significant relationships with the TD and Fick measurements for both $\dot{Q}_{RB}$ and $\dot{Q}_{SB}$ over the range of values studied. In addition, the reproducibility of $\dot{Q}_{RB}$ and $\dot{Q}_{SB}$ was assessed in 15 other patients with chronic airflow obstruction (mean FEV_1 42% predicted, FEV_1/FVC 43%) and in 10 normal subjects. The coefficients of intrasubject variability for a single measurement for $\dot{Q}_{RB}$ were 8·7% in normal subjects and 10·2% in patients and for $\dot{Q}_{SB}$ were 11·7% in normal subjects and 16·1% in patients. The group differences from morning to afternoon, between days, and over a month were not significant in the normal subjects. In the patients $\dot{Q}_{RB}$ was slightly higher in the afternoon than in the morning of the same day, but the differences between days and over a month were not significant for either test. Although both tests detected the increase in pulmonary blood flow during exercise, the single breath test was more accurate at rest. Some underestimation was present for rebreathing at rest and for both tests during exercise, but this can be allowed for. In patients with mild airflow obstruction the reproducibility of the soluble gas uptake methods was similar to that of invasive catheter methods of cardiac output estimation. The single breath test in particular was, however, less reproducible in patients with more severe airflow obstruction, and the rebreathing method may be more useful for detecting increases in pulmonary blood flow in these patients.

The measurement of pulmonary blood flow by soluble gas uptake has been established by the use of two different breathing techniques—namely, the single breath and the rebreathing methods. The single breath method was first introduced by Krogh and Linhard in 1912[1] and has since been evaluated further in dogs and normal human subjects.[2] One particular advantage of the single breath method is that it can be applied to individual lobes and segments of the lungs, as has been reported in normal subjects and in patients with lung disease.[3–5] Its accuracy in patients with cardiac disease has recently been reported.[6] The rebreathing method introduced by Cander and Forster in 1955[7] and developed by Petrini *et al*[8] and Peterson *et al*[9] has been evaluated in animals, normal human subjects, and patients with pulmonary oedema.[10 11] The theoretical basis of both the single

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breath and the rebreathing method has been reviewed recently by Denison *et al.*[12]

These methods attempt to measure pulmonary capillary blood flow, which is equivalent to the total cardiac output minus the anatomical shunt. There are, however, theoretical problems with their application to patients with widespread airways obstruction. The first is that the soluble gas may not reach the whole of the pulmonary vascular bed owing to lack of ventilation—perfusion homogeneity. The soluble gas methods will measure only that part of the total cardiac output that comes into contact with ventilated lung tissue—hence the term "effective" pulmonary blood flow. This might be expected to cause underestimation of the total pulmonary blood flow, more so during a single breath than during rebreathing, in which greater equilibration between the inspired and the alveolar gas occurs. Another problem, previously demonstrated in normal subjects,[13-15] is that cardiac output may be altered by the mechanical effects of the breathing manoeuvres themselves. This effect may be exaggerated by the greater intrathoracic pressure swings that occur in patients with airflow obstruction, but may be corrected for by comparing oxygen uptake measurements before and during the manoeuvres.[15]

Given these possible limitations in patients with airways obstruction, there is great potential usefulness for the soluble gas uptake methods because of their non-invasive nature. There have been no comprehensive studies of the accuracy and reproducibility of these methods in patients with airways disease, in whom non-invasive measurements of pulmonary blood flow would be of considerable value in following the natural history of disease and its response to therapeutic manipulation. The aim of this study was to establish the accuracy of both the single breath and the rebreathing method by comparing them with the "standard," invasive methods—namely, direct Fick and thermodilution—in patients with moderately severe lung disease. A further aim was to establish the reproducibility of these methods in such patients compared with normal subjects.

Methods

ROUTINE PULMONARY FUNCTION TESTS

All patients and control subjects had routine respiratory function assessment performed. Flow-volume curves were obtained using a Hewlett-Packard heated pneumotachograph system (47804 A), and single

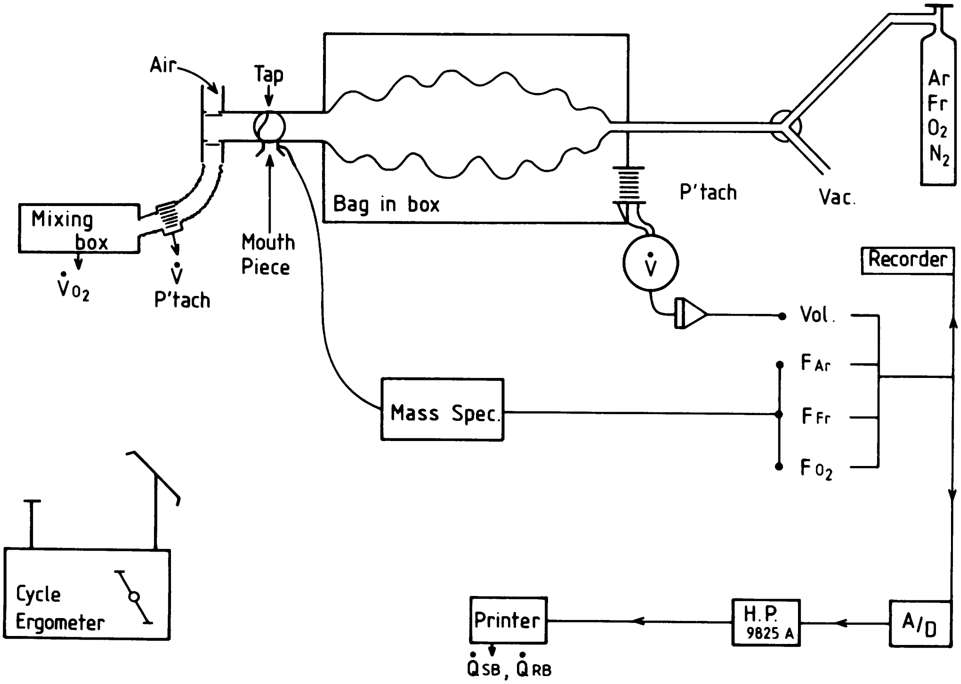

Fig 1 *Diagrammatic illustration of the breathing apparatus and equipment used in the study. F_{Ar}, F_{Fr}, F_{O_2}—fractional concentrations of argon, freon, and oxygen; P'tach—pneumotachygraph; $\dot{V}$—flow transducer; $\dot{V}_{O_2}$—oxygen consumption; A/D = analogue to digital converter; HP—calculator; $\dot{Q}_{SB}$ and $\dot{Q}_{RB}$—single breath and rebreathing measurements of pulmonary blood flow.*

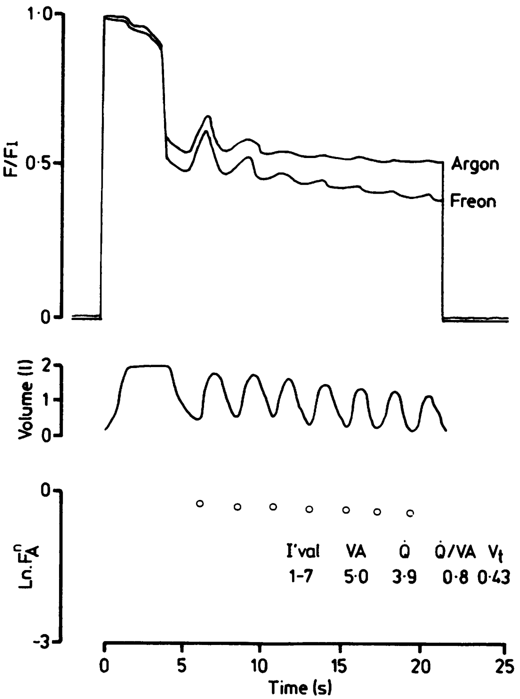

Fig 2 *Typical rebreathing estimate of effective pulmonary blood flow from a patient with chronic airflow obstruction based on the equation* $\dot{Q}_{RB} = (V_A \times 760/(P_B - 47) + \alpha V_T) \times 1/\alpha \times$ *slope (see appendix for derivation). F/Fi—ratio of expired to initial concentration;* $Ln.F_A{}^n$*—logarithm of inst. alveolar fractional concentration of freon relative to that of argon; I'val—interval;* V_A*—effective alveolar volume;* $\dot{Q}$*—pulmonary blood flow;* V_T*—lung tissue volume (l).*

breath carbon monoxide transfer factor was measured (PK Morgan). Arterial blood gas analysis was performed in the patients (Radiometer ABL2).

SOLUBLE GAS UPTAKE STUDIES

We used a gas mixture containing 3·0% difluoromonochloromethane (Freon 22) as the soluble gas, 8·0% argon as the insoluble gas, 40% oxygen, and nitrogen as the balance. The breathing circuitry used is shown in figure 1. The subject breathed on a mouthpiece attached to a valve, which could be switched between a "bag in box" system for pulmonary blood flow measurements and a two way non-rebreathing valve (Hans Rudolph) for determination of gas exchange. Flow was measured with a pneumotachograph, displayed on an oscilloscope screen and integrated to a volume signal during soluble gas uptake manoeuvres. The expiratory side of the Hans Rudolph valve was connected via a second pneumotachograph (expired volume) to a mixing box for measurement of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). Gas concentrations were sampled at the lips with a mass spectrometer (Centronics MGA 200) and from the mixing box with a Servomex OA250 oxygen analyser and a Beckman LB2 carbon dioxide analyser.

Volume (bag in box) and mouthpiece gas concentration signals were recorded on a multichannel chart recorder. These were also converted to digital form, and on line calculation of pulmonary blood flow was performed with a programmed Hewlett-Packard 47804A calculator, which printed the gas concentration recordings and results. Full details of the equations used for rebreathing and single breath manoeuvres are given in the appendix.

Rebreathing method

A typical rebreathing manoeuvre record is shown in fig 2. The rebreathing bag was filled with a volume of test gas equal to 2/3 of the patient's vital capacity (VC). After exhaling to residual volume, the patient inspired this volume and then rebreathed at a frequency of 0·5 Hz for a period of approximately 20 seconds.

Single breath method

A typical record of the manoeuvre is shown in fig 3. The initial bag volume used was equal to 80% of the patient's vital capacity. After inhaling this volume of test gas rapidly from residual volume, the patient then slowly expired at a constant rate. Expiratory flow rates of 0·125 l/sec for patients and 0·25 l/sec for normal subjects were maintained by having the subject match the flow signal on the oscilloscope screen to a calibrated reference line. These expiratory flow rates were chosen so that a full expiration could be achieved in 15–20 seconds before recirculation

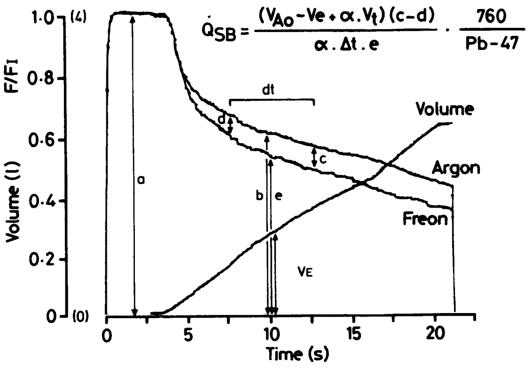

Fig 3 *Typical single breath estimate of effective pulmonary blood flow from a patient with airflow obstruction showing the equation used (see appendix for derivation). The linear measurements a–e are used in the calculation. F/Fi—ratio of expired to inspired concentration; Ve—volume expired.*

occurred. Lines of best fit were drawn on the argon and freon tracings to eliminate the effect of cardiogenic oscillations and the difference in their slopes determined. Values for $\dot{Q}_{SB}$ and $\dot{Q}_{SB}/VA$ were then calculated.

ACCURACY STUDY

To determine the accuracy of the soluble gas uptake methods, the results were compared with those obtained by Fick and thermodilution methods in eight patients with chronic, poorly reversible airflow obstruction. These eight patients were all in hospital undergoing preparation for surgery for peripheral lung cancer at the time of study. A Swan-Ganz flow directed right heart catheter (Edwards Laboratories 93A 131H 7F) was inserted during the study and was left in place for monitoring during surgery, which was performed the following day. In no case did the tumour affect a major bronchus or cause a substantial defect in either ventilation or perfusion as determined by lung scans. All patients were receiving regular medication with β sympathomimetic drugs, theophylline, and inhaled and/or oral corticosteroids. They had all been in a stable clinical state for at least one month before entry into the study. All had an FEV_1/FVC of less than 65% and less than a 15% increase in FEV_1 after administration of salbutamol 200 μg by metered aerosol.

On the first of two study days routine respiratory function tests, as outlined above, and an incremental exercise test were performed on each patient. The exercise test was performed on a cycle ergometer (Elema-Schoenander Model 238) with 16 watt work increments at one minute intervals and measurement of ventilation, $\dot{V}O_2$, $\dot{V}CO_2$, heart rate, and electrocardiographic (ECG) responses. The gas exchange variables were determined by using the mass spectrometer on line to the Hewlett-Packard 9825A calculator in a manner similar to that described by Sue *et al*[16]; the anaerobic threshold was determined as described by Wasserman *et al*.[17]

On the second study day, with the patient supine, the Swan-Ganz catheter was passed into the main pulmonary artery via an antecubital approach and a radial artery catheter was inserted. The patient was then seated on the cycle ergometer at rest and allowed to come into steady state. Two series of the four measurements of blood flow were then performed. Each series consisted, in random order, of rebreathing and single breath manoeuvres as described above, thermodilution (twice), and direct Fick estimates of cardiac output. The patient was then instructed to start cycling and a further set of the four measurements was made once a steady state had been achieved. The ergometer work rate used was that which had produced an approximate doubling of resting $\dot{V}O_2$ during the incremental test, provided that this work rate was below the patient's anaerobic threshold (which it was in all cases), so that steady state conditions could be achieved readily.

The thermodilution estimates of cardiac output ($\dot{Q}_{TD}$) were made with an Edwards Laboratories cardiac output computer (9520A) with 10 ml boluses of ice cold saline injected at end expiration during tidal breathing. The direct Fick estimates ($\dot{Q}_{Fick}$) were obtained from paired pulmonary and radial artery blood samples withdrawn over 30 seconds and the corresponding $\dot{V}O_2$ measurement[18] after conversion of oxygen partial pressures to contents.[19] Each series of four estimates required about 15 minutes because of a five minute washout period after each of the soluble gas manoeuvres. The order of measurements within the series was the same for all three series in any patient but was randomised between patients. Any residual foreign gas concentrations still present at the start of the next soluble gas uptake manoeuvre were minimal and were subtracted from the baseline of that manoeuvre.

To determine the effect of the breathing manoeuvres themselves on resting cardiac output, comparison was made between the $\dot{V}O_2$ immediately before the rebreathing manoeuvre and that measured from the uptake of oxygen during rebreathing, as previously described in normal subjects.[15]

To assess possible causes of any underestimation of pulmonary blood flow by the soluble gas uptake methods in the presence of airways obstruction, a calculation of shunt fraction was also made for each patient.[18 19] The slope of phase III as an index of ventilatory inhomogeneity was also measured from the single breath argon trace.

Analysis of variance was used to assess the relationships between methods. Student's *t* test was used to compare the four measurements of pulmonary blood flow at rest, on exercise, and for the increment between rest and exercise for each of the four. The effect of adjusting the rebreathing estimate with the $\dot{V}O_2$ derived corrections for cardiac output change was also determined. Linear correlation was used to assess the relationship between the degree of baseline lung function abnormality and the discrepancy observed between the soluble gas uptake and invasive methods.

REPRODUCIBILITY STUDY

To determine the reproducibility of the soluble gas uptake methods, serial measurements were made on a group of 15 outpatients with stable, poorly reversible airflow obstruction of moderate to severe degree and on a group of 10 normal, non-smoking volunteer subjects. Routine respiratory function tests were per-

Table 1 *Baseline respiratory function test results (means with 1 SD in parentheses)*

Subjects	*Accuracy study*	*Reproducibility study*	
	CAO	*CAO*	*Normal*
n	8	15	10
Age (y)	63 (5)	61 (17)	37 (16)
FEV_1 (% pred)	64 (11)	42 (20)	112 (12)
FVC (% pred)	93 (9)	86 (28)	115 (10)
FEV_1/FVC (%)	53 (10)	43 (11)	77 (5)
T_{LCO} (% pred)	97 (16)	69 (28)	111 (14)

CAO—chronic airflow obstruction; FVC—forced vital capacity; T_{LCO}—single breath transfer factor for carbon monoxide; % pred = percentage of mean predicted normal values.

formed in all subjects.

Triplicate estimates of pulmonary blood flow by both the rebreathing and the single breath method were made after the subject had been resting quietly in a chair for a minimum of 30 minutes. Each patient was first studied in the morning. The set of measurements was then repeated on the same afternoon, the next day and one month later. The order of the manoeuvres within each set of measurements was randomised between patients but held constant for each patient. The apparatus and methodology used in the accuracy study was also used to estimate $\dot{Q}_{RB}$ and $\dot{Q}_{SB}$. About an hour was required to complete the set of six manoeuvres.

The coefficient of variation was calculated from the triplicate estimates of each test in each patient on each occasion. Analysis of variance was used to compare the results of measurements made at the different times. Student's *t* test was used to compare results obtained in patients with those from normal subjects.

Results

The mean ages and results of baseline respiratory function tests for the three groups are shown in table 1.

ACCURACY STUDY

The group data for each of the four estimates of pulmonary blood flow are shown in table 2. At rest $\dot{Q}_{Fick}$, $\dot{Q}_{TD}$ and $\dot{Q}_{SB}$ did not differ significantly, but $\dot{Q}_{RB}$ gave significantly lower values than all of these. During exercise, $\dot{Q}_{RB}$ and $\dot{Q}_{SB}$ both gave significant underestimates by comparison with $\dot{Q}_{Fick}$ and $\dot{Q}_{TD}$, which gave similar results. $\dot{Q}_{RB}$ remained significantly lower than $\dot{Q}_{SB}$ during exercise. Individual rebreathing data are plotted in fig 4, which shows the comparisons with the TD and Fick methods. The corresponding single breath measurements are shown in fig 5. All four estimates of pulmonary blood flow increased significantly on exercise from their resting values.

The reproducibility errors of the duplicate resting estimates of the four blood flow measurements yielded coefficients of variation of 10·5% for $\dot{Q}_{RB}$, 8·8% for $\dot{Q}_{SB}$, 13·6% for $\dot{Q}_{Fick}$, and 7·3% for $\dot{Q}_{TD}$. These were not significantly different from each other (F = 2·09). The most appropriate statistical approach was thus analysis of variance on the basis of the model given in the appendix (equations 11 and 12). Analysis of the resting data showed significant differences in cardiac output between patients (F = 13·6, $p < 0·001$) and also a significant difference between methods (F = 44·8, $p < 0·001$). Corresponding analysis of the exercise data also gave significant results (patient differences: F = 7·0, $p < 0·01$; test differences: F = 21·5, $p < 0·001$).

There was also evidence of physiological disturbance by the rebreathing and single breath methods themselves, leading to random fluctuations in the resting data (order of tests randomised in this study) that were larger than the fluctuation due to the reproducibility errors alone. This was less evident in the exercise data. Analysis of variance taking the methods of measurement in pairs was also performed (appendix equation 13). Because the factors of proportionality (β) between each pair of methods did not differ significantly between rest and exercise, the two sets of data could be pooled and the standard error weighted mean values were calculated. These values

Table 2 *Pulmonary blood flow ($\dot{Q}$) estimated by the rebreathing (RB), single breath (SB), direct Fick, and thermodilution (TD) methods* (means with 1 standard deviation in parentheses)*

Method	$\dot{Q}_{RB}$	$\dot{Q}_{SB}$	$\dot{Q}_{Fick}$	$\dot{Q}_{TD}$
Rest	3·47 (0·46)	4·75 (1·15)	4·77 (0·97)	5·15 (0·98)
Exercise	6·23 (1·19)	7·62 (1·97)	8·97 (1·96)	9·09 (1·00)

Rest: $\dot{Q}_{RB}$ vs $\dot{Q}_{SB}$ $p < 0·01$; $\dot{Q}_{RB}$ vs $\dot{Q}_{Fick}$ $p < 0·001$; $\dot{Q}_{RB}$ vs $\dot{Q}_{TD}$ $p < 0·001$.

Exercise: $\dot{Q}_{RB}$ vs $\dot{Q}_{SB}$ $p < 0·005$; $\dot{Q}_{SB}$ vs $\dot{Q}_{Fick}$ $p < 0·05$; $\dot{Q}_{RB}$ vs $\dot{Q}_{Fick}$ $p < 0·001$; $\dot{Q}_{RB}$ vs $\dot{Q}_{TD}$ $p < 0·001$; $\dot{Q}_{SB}$ vs $\dot{Q}_{TD}$ $p < 0·05$.

*All horizontal differences not assigned a p value were not significant; all indices increased significantly between rest and exercise.

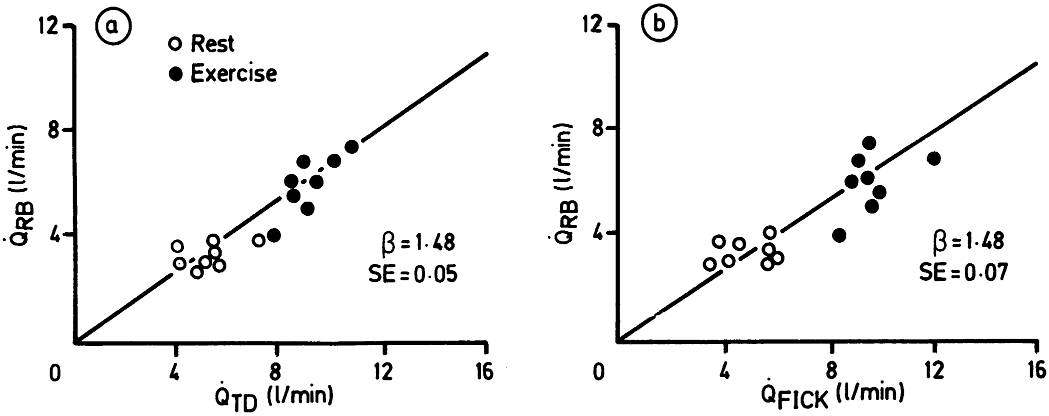

Fig 4 *Comparison of rebreathing ($\dot{Q}_{RB}$) with thermodilution ($\dot{Q}_{TD}$) and direct Fick ($\dot{Q}_{Fick}$) measurements of pulmonary blood flow at rest and during exercise in eight subjects with chronic airflow obstruction. The constants of proportionality (β) given with their standard errors were derived by analysis of variance. The line is that of best fit and has slope β.*

for β determine the slopes of the lines drawn in figs 4 and 5. Comparison of the TD and Fick estimates yielded a value for β of 1·003 (SEM = 0·03).

Values for blood flow per unit of effective alveolar volume ($\dot{Q}/V_A$) were calculated for the soluble gas methods. $\dot{Q}/V_A$ values from both the rebreathing and the single breath method gave statistical associations on comparison with the results of the Fick and thermodilution methods very similar to those of the absolute $\dot{Q}$ measurements. The results for $\dot{Q}/V_A$ and V_A for the two soluble gas methods are given in table 3. The values for V_A were higher for the single breath method than for rebreathing. This is related at least partly to the larger inspired bag volume used for the single breath test. The values for $\dot{Q}/V_A$ showed no significant difference between the rebreathing and single breath tests either at rest or on exercise, and both methods showed a significant increase in $\dot{Q}/V_A$ between rest and exercise ($p < 0·001$).

Comparison of the $\dot{V}O_2$ before and during rebreathing suggested that this manoeuvre had increased resting cardiac output by a mean of 8%.

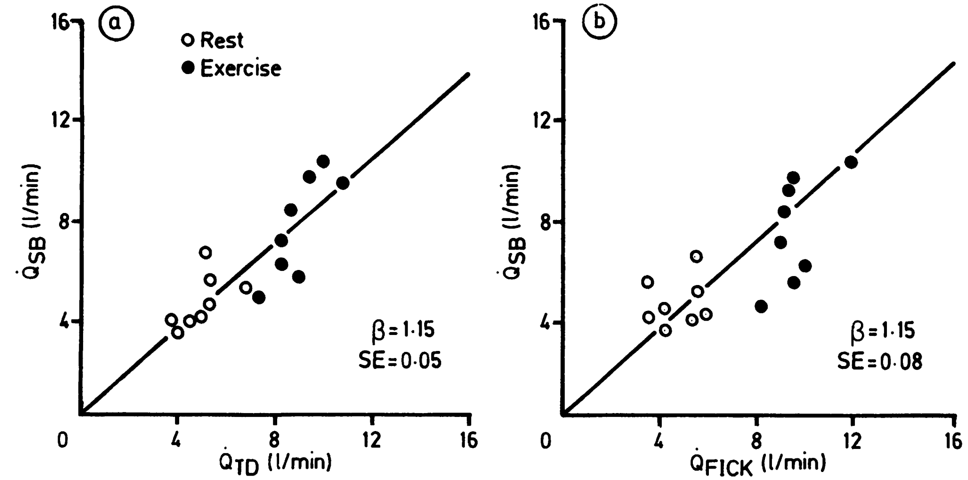

Fig 5 *Comparison of single breath ($\dot{Q}_{SB}$) with thermodilution ($\dot{Q}_{TD}$) and direct Fick ($\dot{Q}_{Fick}$) measurements of pulmonary blood flow at rest and during exercise in eight patients with chronic airflow obstruction. The constants of proportionality (β) and their standard errors were derived by analysis of variance. The line is that of best fit and has slope β.*

Table 3 *Effective alveolar volume (V_A) and pulmonary blood flow per unit of effective alveolar volume ($\dot{Q}/V_A$) for rebreathing (RB) and single breath (SB) methods* (means with 1 standard deviation in parentheses)*

	VA_{RB}		VA_{SB}	$\dot{Q}_{RB}/VA$	$\dot{Q}_{SB}/VA$
Rest	3·03 (0·37)	$p < 0.001$	4·82 (0·58)	1·16 (0·23)	1·00 (0·23)
Exercise	3·24 (0·35)	$p < 0.001$	5·11 (0·67)	1·93 (0·41)	1·56 (0·51)

*All horizontal differences not assigned a p value were not significant; all indices increased significantly between rest and exercise.

Correcting $\dot{Q}_{RB}$ appropriately did not improve its relationship with $\dot{Q}_{Fick}$ or $\dot{Q}_{TD}$ significantly.

The underestimate produced by the rebreathing method during exercise, as represented by the ratio $\dot{Q}_{RB}/\dot{Q}_{TD}$, showed a significant inverse correlation with the slope of phase III as an index of inhomogeneity of ventilation ($r = -0.69$, $p < 0.05$). Correlations of this index of underestimation for both soluble gas uptake methods with FEV_1 and other baseline lung function indices of severity of disease, and with the calculated shunt fraction all failed to reach significance.

REPRODUCIBILITY STUDY

The mean age and routine lung function data for the two subject groups are shown in table 1. The mean results for the two soluble gas uptake methods at each of the four measurement times are shown in table 4. The coefficient of intrasubject variability for a single rebreathing test was 10·2% in the patients and 8·7% in the controls, and for the single breath test the corresponding results were 16·1% for the patients and 11·7% for the normal subjects. These coefficients were not significantly different between the two tests, or between the patients and the normal subjects. In this group of patients with chronic airflow obstruction the results for $\dot{Q}_{SB}$ were significantly higher than those for $\dot{Q}_{RB}$ only for the morning measurements on the first day ($p < 0.05$). At the other time intervals in the patients and universally in the normal subjects $\dot{Q}_{SB}$ and $\dot{Q}_{RB}$ were not significantly different. Values for $\dot{Q}/V_A$ were not significantly different between rebreathing (mean 1·04 (SD 0·27)) and single breath (0·94 (0·37)) methods in the 15 patients with airflow obstruction; but in the normal subjects $\dot{Q}/V_A$ was slightly higher ($p < 0.05$) for the rebreathing test (1·22 (0·33)) than for the single breath test (1·00 (0·33)).

Analysis of variance showed no significant differences between morning and afternoon, between successive days, or over the month for either test in the normal subjects. In the patients with chronic airflow obstruction $\dot{Q}_{RB}$ was slightly higher in the afternoon than on the same morning ($p < 0.05$), but the differences between consecutive days and between measurements one month apart were not significant. The single breath results were not significantly different between morning and afternoon and, although the values were slightly lower one day and one month later, these differences did not reach significance.

Discussion

All four methods of measurement of pulmonary blood flow showed a significant increase between rest and exercise in this group of patients with stable airflow obstruction of moderate severity. The relationships between the results of the non-invasive soluble gas uptake methods and of the cardiac catheter based methods—direct Fick and thermo-

Table 4 *Results of reproducibility study (means with standard deviations in parentheses)*

	AM	PM	Day 1	Day 2	Month 1	Month 2
Normal (n = 10)						
$\dot{Q}_{RB}$	6·09 (1·43)	5·87 (2·03)	6·26 (1·57)	5·87 (1·98)	5·87 (2·00)	5·69 (1·72)
$\dot{Q}_{SB}$	5·61 (1·42)	5·72 (1·29)	5·78 (1·49)	5·90 (1·52)	5·85 (1·52)	5·74 (1·25)
CAO (n = 15)						
$\dot{Q}_{RB}$	3·37 (0·85)	3·67 (0·81)	3·53 (0·89)	3·38 (1·05)	3·44 (0·87)	3·40 (1·21)
	$p < 0.05$ (AM vs PM)					
$\dot{Q}_{SB}$	3·92 (0·79)	3·76 (0·91)	3·76 (1·03)	3·32 (0·97)	3·53 (0·90)	3·13 (1·27)

*Horizontal differences not significant except where p value given.
CAO—chronic airflow obstruction.

dilution—were highly significant when all rest and exercise data points were combined and also when the rest and exercise data were analysed separately. These relationships were of the same order as the relationship between the Fick and thermodilution estimates themselves, and in the light of the difference in individual patients between Fick and thermodilution estimates it is not clear which of these two should be taken as the gold standard against which to make comparisons regarding accuracy. The use of a commercial thermodilution method, with its slightly poorer reproducibility,[20] may partly explain the error variance of the thermodilution results. The discrepancy between the invasive methods is also partly related to the randomisation of test order used in this study. There are few previously reported data comparing Fick and thermodilution measurements of cardiac output in patients with lung disease.

The rebreathing soluble gas uptake method underestimated pulmonary blood flow both at rest and on exercise in this group of patients. Measurements of oxygen consumption before and during rebreathing suggest that the manoeuvre itself increased resting cardiac output, so that mechanical factors cannot be invoked for the underestimation of the resting measurements. On the other hand, the significant correlation between the degree of underestimation ($\dot{Q}_{RB}/\dot{Q}_{TD}$) and the slope of the argon phase III suggests that the degree of ventilatory inhomogeneity is an important determinant of this underestimation. We found no similar significant relationship between the degree of underestimation and any other index of baseline lung function. Nor did the degree of shunt correlate with the degree of underestimation, although the assumptions implicit in the shunt estimation limit its accuracy in patients with airflow obstruction.

In the eight patients who underwent catheter studies, both resting and exercise values for $\dot{Q}_{SB}$ were significantly higher than the $\dot{Q}_{RB}$ results, but the values for $\dot{Q}/V_A$ did not differ significantly between the two methods. The values for effective alveolar volume were higher for the single breath than for the rebreathing method, and this relates partly to the fact that a smaller bag volume was used for rebreathing so that the patients would not have to perform the manoeuvre at a lung volume up near total lung capacity. Differences in gas mixing between the two methods would also contribute to the difference between their V_A results. Since $\dot{Q}/V_A$ did not differ significantly between the two methods, much of the observed difference in $\dot{Q}$ may be due simply to a difference in equilibration of the inspired gas with the ventilated compartment between the two methods. It remains possible, however, that an interaction of other factors, such as a difference in the effect of the manoeuvres themselves on cardiac output or any dependance of $\dot{Q}$ on the lung volume at which it is measured, is contributing to the difference between the $\dot{Q}_{SB}$ and $\dot{Q}_{RB}$ estimates. Rebreathing estimates of pulmonary capillary blood flow (Q_c) have been shown by Kallay *et al*[21] to be relatively independent of the V_A, inspiratory and rebreathing volumes, and respiratory frequency in normal subjects. The effect of varying these factors in rebreathing in patients with airflow obstruction, in whom gas mixing is less complete, warrants further study, as does their effect on single breath estimates.

The patients studied all had relatively little bronchodilator responsiveness and would not be expected to have much change in airway calibre with exercise. This group was chosen because we wished to study a predominantly circulatory change without a coincident bronchial response. The changes in the soluble gas uptake measurements in relation to a primarily bronchial response have been reported previously.[22] In that study terbutaline given either intravenously or by inhalation to asthmatic patients produced an increase in both estimates of pulmonary blood flow, due largely to the increase in accessible alveolar volume. Pulmonary blood flow per unit lung volume also increased in that study, although only for the single breath method. This may have been due to a real increase in cardiac output induced by terbutaline or to recruitment of peripheral units of low $V/\dot{Q}$ into the volume accessible in a single breath, as shown by Wagner *et al*,[23] to produce a fall in mean $V/\dot{Q}$ ratio. In the present study, changes in measured accessible alveolar volume between rest and exercise were small in relation to the changes in $\dot{Q}/V_A$, and thus the increase in the $\dot{Q}$ measurements is a reflection of the real increase of cardiac output.

Although the rebreathing method caused greater underestimation, when its results were compared with those of $\dot{Q}_{Fick}$ and $\dot{Q}_{TD}$, than did the single breath method in these patients with airflow obstruction, it is possible to correct for the underestimation by using the appropriate proportionality factor—β (see figs 4 and 5)—obtained from comparison with the other methods. The underestimation of $\dot{Q}$ by the rebreathing method in these patients with airflow obstruction contrasts with the good agreement found by Triebwasser *et al*[24] between acetylene rebreathing $\dot{Q}_c$ and dye dilution estimates of cardiac output in normal subjects.

Variability of the single breath method in patients with airflow obstruction was also observed in the few patients studied by Alkayam *et al*.[6] This variability relates partly to difficulty in determining the slope of changing gas concentrations in the presence of cardiogenic oscillations, which may be of different amplitude at different points during a single expiration, and also to variations in expiratory flow rate, which in this study were greater in the patients with chronic airflow obstruction than in the normal subjects. Measurement of V_A from single breath manoeuvres in patients with severe airflow obstruction, who have a steep phase III is also very dependent on the value taken as the average expired concentration of inert marker gas. We chose the average between the value at end expiration and the value extrapolated back along phase III to the point at which the deadspace had been exhaled (Fowler's method[18]) as the best compromise in these circumstances. Other factors in the variability of both methods are minute to minute changes in cardiac output and variations in the subjects' performance of the breathing manoeuvres.

The study of Alkayam *et al*[6] showed good agreement between single breath and thermodilution methods at rest in normal subjects and in patients with mild airways obstruction. They suggested that when FEV_1/FVC is less than 60% the single breath method gives less satisfactory results. Our eight patients, who had catheter studies, had more severe airflow obstruction (mean FEV_1/FVC 53%), yet the difference between single breath and thermodilution estimates was not significant (mean difference 0·32 (SD 1·02) l compared with 0·03 (0·76) l for their normal subjects). Alkayam's coefficients of variation (three or more estimates) in normal subjects were 8·7% for $\dot{Q}_{SB}$ and 7·0% for $\dot{Q}_{TD}$. Again, these figures are very similar to those in our eight patients with airways obstruction who underwent catheter studies, in whom the corresponding figures (based on two estimates) were 8·8% for $\dot{Q}_{SB}$ and 7·0% for $\dot{Q}_{TD}$. In the 15 patients in our reproducibility study, however, airflow obstruction was even more severe (mean FEV_1 42% of predicted normal, mean FEV_1/FVC 43%) and the coefficient of variation (based on three estimates) of $\dot{Q}_{SB}$ in this group was much higher at 16·1%. We would agree therefore that the results of the single breath test in particular become less reproducible in patients with more severe airflow obstruction, but would suggest that in patients with FEV_1/FVC not less than 50% its variability is not much greater than that found in normal subjects.

The number of estimates on which a single measurement is based is an important determinant of the reproducibility of that measurement ($SEM = SD/n^{0\cdot5}$), but the time required for washout of foreign gases between soluble gas uptake estimates imposes limitations on the number of estimates that can practically be performed for routine clinical purposes. A review of the published studies of the reliability of thermodilution in clinical use[20] suggests that the standard error of this method is 5%, and a figure similar to this was obtained for the duplicate rest measurements in our eight patients who had catheter studies. Corresponding figures, based on triplicate estimates for normal subjects from our reproducibility study, are 5·0% for the rebreathing and 6·8% for the single breath method. For our patients with airways obstruction the corresponding figures are 5·9% for $\dot{Q}_{RB}$ and 9·3% for $\dot{Q}_{SB}$. Since the 95% confidence intervals are $\bar{x} \pm 2$ SEMs and a difference of 3 SEMs is required for this order of confidence (actually about 96%) that a difference between two measurements is not due to chance, the ability to detect small changes in pulmonary blood flow is limited for all these methods. All methods were easily able to detect the relatively large acute increase in pulmonary blood flow associated with the moderate level of exercise in this study but their sensitivity in detecting change in other clinical settings requires separate evaluation. The slightly greater reproducibility of the rebreathing method in patients with more severe airflow obstruction suggests that it may be the more useful of the two soluble gas uptake methods at following changes in blood flow in these patients.

In conclusion, both soluble gas uptake methods were found able to detect exercise induced changes in pulmonary blood flow. The rebreathing method yielded lower values at rest than did the Fick and thermodilution methods, as did both methods during exercise. This shortfall may relate to the fact that these methods measure "effective" pulmonary blood flow—that is to say, that which comes into contact with ventilated space—and may be regarded as a measure of the effective damage to pulmonary gas exchange. Nevertheless, the relationships between the estimates from the soluble gas uptake methods and conventional invasive measurements of cardiac output were of the same order as the relationship between the results of the two "standard" invasive methods used. The rebreathing method was slightly more reproducible than the single breath test in patients with more severe airflow obstruction.

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Appendix

EQUATIONS

Rebreathing method

We used a mathematical approach similar to that of Overland *et al*,[11] and previously described by Cander and Forster.[7] Firstly, the volume of distribution of the inhaled gas is calculated by means of the following equation:

$$Vs = Vi \cdot \frac{Fi_{Ar}}{Fe_{Ar}} \cdot \frac{273}{273 + T} \cdot \frac{(P_b - P_{H_2O})}{760}, \quad (1)$$

where Vs (STPD) is the dilution volume of the insoluble gas argon, Vi (ATPD) is the volume of gas initially in the bag, Fi_{Ar} (ATPD) is the initial argon concentration and Fe_{Ar} (ATPS) is the average end tidal argon concentration during the measurement interval.

The alveolar volume, VA (STPD), in which the soluble gas freon comes into contact with pulmonary blood flow, is given by

$$V_A = V_s - V_d, \quad (2)$$

where Vd is the total apparatus and anatomic (estimated by 0·0022 × body weight (kg)) deadspace. The alveolar fractional concentration ($F_A{}^n$) of freon in relation to the corresponding concentrations of the insoluble gas argon were calculated for each breath during the rebreathing manoeuvre by means of the equation:

$$F_A{}^n = \frac{Fe_{Fr}{}^n}{Fi_{Fr}} \cdot \frac{Fi_{Ar}}{Fe_{Ar}{}^n}, \quad (3)$$

where $Fe_{Fr}{}^n$ and $Fe_{Ar}{}^n$ are the end tidal concentrations of freon and argon for the n^{th} breath and Fi_{Fr} and Fi_{Ar} are the respective initial concentrations of these gases. A semilogarithmic plot of $F_A{}^n$ versus time can be prepared that represents the disappearance of freon from the system. The data are examined to determine which series of four or more consecutive points with a correlation coefficient $p < 0{\cdot}05$ has the greatest slope. This technique attempts to overcome any errors due to incomplete mixing, which cause the first points to be low, and errors from recirculation, which cause the last points to be high. Both these effects tend to lower the slope and intercept of the disappearance curve. The slope and the intercept at time zero were calculated by linear regression analysis (least squares method) for the series of points that met the above criteria. Time zero was defined as the point at which one half of the initial inspired volume of gas from the bag had passed the subject's anatomic deadspace. This attempts to compensate for soluble gas uptake during the initial inspiration. Lung tissue volume, V_T (STPD), is calculated with the following equation:

$$V_T = \frac{V_s \cdot \frac{760}{(Pb - 47)}}{\alpha}\left[\frac{1}{\text{intercept}} - 1\right], \quad (4)$$

where α is the Bunsen solubility coefficient at 37°C (α_{Fr} = 0·74 ml gas (STPD)/ml liquid/atm) and the intercept is that calculated from the $\ln(F_A{}^n)$ versus time plot. $\dot{Q}_{RB}$ is then calculated according to the equation:

$$\dot{Q}_{RB} = \frac{V_A \cdot \frac{760}{(Pb - 47)} + \alpha V_T}{\alpha} \times \text{slope}, \quad (5)$$

where the slope term is also obtained from the $\ln(F_A{}^n)$ versus time plot.

Single breath method

The mathematical basis we used for the single breath technique is that of Denison *et al.*[3] The end inspiratory alveolar volume, V_{A_0} (STPD), is calculated from the dilution of argon with the equation:

$$V_{A_0} = (Vi - V_D) \cdot \frac{Fi_{Ar}}{Fe_{Ar}} \cdot \frac{273}{273 + T} \cdot \frac{Pb - P_{H2O}}{760}, \quad (6)$$

where Vi (ATPD) is the volume of gas inspired, V_D is the total anatomic and apparatus deadspace, FI_{Ar} (ATPD) is the intitial concentration of argon, and FE_{Ar} (ATPS) is the average expired argon concentration over the measurement interval. Effective pulmonary blood flow, $\dot{Q}_{SB}$, is obtained from the following equation:

$$\dot{Q}_{SB} = \frac{(V_{A_0} - Ve + \alpha . V_T)}{\alpha . P_A} \cdot \frac{dP_A}{dt} \cdot \frac{760}{Pb - 47}, \quad (7)$$

where Ve (STPD) is the volume expired from end inspiration to the centre of the measurement interval, dt is the measurement interval in minutes, V_T is the lung tissue volume, which we assume to equal 0·05 × V_{A_0}, and dP_A is the divergence of freon with respect to argon over the measurement interval. By equating dPa to c–d, Pa to e, and dt to Δt (see fig 3), equation 7 becomes

$$\dot{Q}_{SB} = \frac{(V_{A_0} - Ve + \alpha . V_t)(c - d)}{\alpha . \Delta t . e} \cdot \frac{760}{Pb - 47}. \quad (8)$$

The interval over which the measurement of $\dot{Q}$ was made was chosen according to the following criteria: (1) expiratory flow must be maintained constant; (2) the interval to start after the deadspace has been clearly washed out—that is, a steady phase III is achieved—and to end before phase IV of the argon concentration occurs; (3) the interval to be as long as possible within the constraints of (2) above but not extending beyond 20 seconds after inspiration to avoid recirculation effects; (4) intervals to be consistent in terms of expired volume, chosen between multiple measurements in the same patient.

We calculated $\dot{Q}_{SB}/V_{A_0}$ as the ratio of $\dot{Q}$ ($l\,min^{-1}$) and V_{A_0} (l, BTPS). In this case V_{A_0} is slightly different from the value obtained from equation 6, as the value of Fe_{Ar} is taken to be the average expired argon concentration over the entire expiratory interval, in an attempt to allow for the sloping phase III resulting from maldistribution of ventilation and its effect on obtaining an accurate value for the average alveolar argon concentration at end expiration.

The influence of deadspace gas on the expired argon recording was avoided by extrapolating back along phase III to the point at which the subject's deadspace (Fowler's method[18]) has been exhaled. The average argon concentration from this point to the end of expiration is then used as Fe_{Ar} in equation 6.

Shunt

Shunt fractions ($\dot{Q}_s/\dot{Q}_t$) were calculated according to the following equation:

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \frac{C\dot{c}O_2 - CaO_2}{C\dot{c}O_2 - C\bar{v}O_2}, \quad (9)$$

where $C\dot{c}O_2$, CaO_2, and $C\bar{v}O_2$ are oxygen contents of pulmonary end capillary, systemic arterial, and mixed venous blood. All oxygen contents were derived from partial pressures, as described by Stetz *et al.*[20] PaO_2 and $P\bar{v}O_2$ were measured directly from blood samples, while $Pc'O_2$ was assumed equal to ideal alveolar PO_2 and calculated from the ideal alveolar air equation.

Direct Fick

Direct Fick estimations of cardiac output were obtained by using the standard equation as follows:

$$\dot{Q}_{FICK} = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2}, \quad (10)$$

where $\dot{V}O_2$ (STP) is the average oxygen uptake over the measurement interval obtained by analysis of mixed expired oxygen and carbon dioxide and expired volume.

STATISTICAL ANALYSIS

The statistical approach we used was a model in which each observed estimate of pulmonary blood flow is proportional to the actual cardiac output (CO) apart from disturbance by random error—for example,

$$\dot{Q}_{RB} = \gamma_{RB} \cdot CO + \text{random error}$$
$$\dot{Q}_{SB} = \gamma_{SB} \cdot CO + \text{random error} \quad (11)$$

etc,

where γ = a constant of proportionality.

This model is multiplicative and can be rewritten as

$$\text{Ln}\ \dot{Q}_{RB} = \text{Ln}\ \gamma_{RB} + \text{Ln}\ CO + \text{random error}$$
$$\text{Ln}\ \dot{Q}_{SB} = \text{Ln}\ \gamma_{SB} + \text{Ln}\ CO + \text{random error} \quad (12)$$

etc.

This is in the form of a standard linear model to which analysis of variance is applicable. Similar analysis of variance taking the measurements in pairs was also performed, the proportionality between methods (β) being given by:

$$\text{Ln}\ \beta_{RB,TD} = \text{Ln}\ \gamma_{RB} - \text{Ln}\ \gamma_{TD}$$
$$\text{Ln}\ \beta_{SB,\,Fick} = \text{Ln}\ \gamma_{SB} - \text{Ln}\ \gamma_{Fick} \quad (13)$$

etc.

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