

Comparison of estimates of cardiac output by indicator dilution and freon 22 uptake during gas mixing in dogs

Hazel A Jones, S Lakshminarayan, J M Becket, J M B Hughes

Abstract

Study objective — The aim was to measure cardiac output while rebreathing tidal volumes, by correction of soluble gas uptake for gaseous mixing.

Design — Simultaneous measurements of cardiac output by indocyanin green and freon 22 uptake during rebreathing were made. Mixing for a hypothetical gas of identical gaseous diffusivity to freon 22 was calculated by interpolation between concentrations of two insoluble gases, helium and sulphur hexafluoride. Mixing efficiency was estimated by the number of breaths for helium to become 99% equilibrated with lung gas (n99-He).

Experimental material — Five anaesthetised dogs rebreathed at intervals with 300 ml of test gas.

Measurements and main results — 63 comparisons of cardiac output using indocyanin green and freon 22 uptake (over breaths 7-13 using the mean mixed volume of distribution), gave a mean (95% confidence interval) underestimation of 0.345 (0.093-0.597) litre·min⁻¹ (14%). Exclusion of 12 points in which n99-He was greater than 15 resulted in a mean underestimation of 0.052 (-0.163-0.267) litre·min⁻¹ (2%). Without correction for gaseous mixing, freon 22 uptake for these data overestimated blood flow by a mean of 1.31 litre·min⁻¹ (overestimation = 2.7 over breaths 5-11). Use of the equilibrium volume of distribution resulted in an overestimation of blood flow relative to green dye of 1.2 litre·min⁻¹ (breaths 5-11) and 0.76 litre·min⁻¹ (breaths 7-13).

Conclusions — Estimates of cardiac output by soluble gas uptake are optimal when correction is made for mixing of gas of identical diffusivity. The mean mixed gas volume gives the best correlation with the reference method, implying a selective distribution of blood flow to the better ventilated areas.

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Key words: cardiac output; indicator dilution; gas mixing efficiency; rebreathing

Submitted 31 July 1990

Accepted 27 November 1990

The measurement of cardiac output by rebreathing soluble gases is non-invasive and has a long history.¹ Validation has been carried out by comparison with the indirect Fick² and dye dilution curves.³ However, most of the soluble gas uptake methods have involved rebreathing large volumes. This accelerates the mixing of the test gas with the gas resident in the lungs, especially in normal subjects. Complications arise when patients with lung disease are studied, as they are unable to rebreathe large volumes quickly enough to obtain adequate data for analysis before recirculation occurs. They also have inhomogeneities of ventilation distribution. A mathematical model developed by Petrini⁴ demonstrates that the accuracy of measurement is degraded in the presence of maldistribution of gas. This has prevented widespread application of the technique for non-invasive determination of cardiac output.

During tidal volume rebreathing even in normal subjects, the rate of mixing is dependent on gaseous diffusivity⁵ and is slow relative to mixing with larger volume breaths. The disadvantage of breathing with large tidal volumes is that the manoeuvre itself increases the cardiac output (Q).^{6,7} Sackner *et al*⁸ have normalised acetylene concentrations during rebreathing to simultaneously measured helium (He) concentrations, to correct for mixing effects. The differences in molecular weight of the gases (He = 4, C₂H₂ = 26) will cause them to mix at different rates during rebreathing.⁵ Thus ideally the soluble gas should be normalised to an insoluble gas of identical molecular weight. This becomes more important if the soluble gas is one of a high molecular weight, such as freon 22 (MW 86), which is used by several groups, because it can safely be breathed in higher concentrations than can acetylene.⁹ We have developed a technique based on Graham's law using interpolation between mixing of He and sulphur hexafluoride (SF₆), both insoluble gases but with very different gaseous diffusivity, to calculate the appropriate mixing and volume of distribution for an insoluble gas with a diffusivity identical to that of freon 22. We have normalised the measured freon 22 concentrations to those of this hypothetical gas, breath by breath during the rebreath. The uptake of freon 22 measured thus was used to calculate pulmonary capillary blood flow and these values compared with simultaneous dye dilution estimates of cardiac output.

Methods

Five dogs (mean weight 28 kg) were anaesthetised with thiopentone sodium (induction 5 mg·kg⁻¹, maintenance 2.5 mg·kg⁻¹·h⁻¹). Ventilation was via an endotracheal tube at a tidal volume of 20 ml·kg⁻¹ and a rate of 15 strokes·min⁻¹. Catheters were introduced into the inferior vena cava via the femoral vein, for injection of green dye, and the aorta via the femoral artery for sampling dye concentration with respect to time for calculation of cardiac output (Waters Instruments Inc). Arterial and mixed venous blood were monitored throughout the experiments together with packed cell volume, blood pressure, heart rate, and rectal temperature.

EXPERIMENTAL PROTOCOL

Prior to each rebreathing manoeuvre a constant volume history was followed; the lungs were inflated to a pressure of 30 cm H₂O by obstructing the expiratory port of the ventilator. After 5 min the ventilator was disconnected from the endotracheal tube at end expiration, when the pressure was zero, and replaced by a syringe containing 300 ml of test gas, comprising 10% each of He, SF₆, freon 22, and 30% oxygen in argon. The dog was rebreathed for 15 breaths with positive pressure from the syringe and then reconnected to the ventilator. Green dye was injected during the first breath of the rebreath. Twenty four paired comparisons of freon 22 uptake and green dye curves were made with an interval of less than 2 min between each pair; in these cases the volume history was not repeated for the second measurement. The other 39 measurements and the first of the paired measurements were all at least 10 min apart.

The rate of rebreathing was 1 Hz for all measurements; the stroke volume of the syringe was 300 ml. This tidal volume in these dogs was 10.7 ml·kg⁻¹ body weight, which is equivalent to a 700 ml tidal volume in adult human subjects. Back pressure of freon 22 was measured on five occasions by performing a rebreath with the syringe initially filled with air within 2 min of a rebreathing manoeuvre with test gas.

MEASUREMENT OF GAS CONCENTRATIONS

Concentrations of all gases present (excluding water vapour) were monitored at 50 Hz by a mass spectrometer (Centronic 200MGA) linked to a microcomputer. Volume was measured by a potentiometer on the syringe and transferred at 50 Hz to the computer after being delayed to correct for the measured delay of the mass spectrometer for argon. For each 20 ms sample this "delayed" change in volume was multiplied by the mass spectrometer signals for all gases and divided by the total volume of the breath. These volume weighted concentrations were summed to unity to give the fractional dry gas concentrations of each breath. These data together with the time and volume of each breath were transferred to diskette at the end of each rebreath for off line analysis.

CALCULATIONS

Pulmonary capillary blood flow was calculated from the equation:

$$\dot{Q}_c = \frac{\lambda \text{ freon 22 } (V_s + \alpha V_{\text{tiss}}) * 760}{\alpha * (760 - 50)}$$

where \dot{Q}_c = blood flow; λ = rate constant of freon 22 removal·s⁻¹; V_s = volume of distribution of gas in the system (lung + bag) at STPD; V_{tiss} = tissue volume of the lungs including capillary blood and was calculated as 10 g·kg⁻¹ body weight (see results below); α = solubility of freon 22 in dog blood = 0.84 ml·ml⁻¹·atm⁻¹ (see¹⁰); and 50 is the saturated water vapour pressure at 38°C (dog body temperature).

The rate constant of freon 22 uptake was calculated by two methods:

- (1) As the exponential rate of fall in concentration of inspired freon 22 with respect to time from breaths 5-11 and 7-13.
- (2) As the exponential fall in concentration of inspired freon 22, normalised to an insoluble gas, again with respect to time. Insoluble gases were (a) He, (b) SF₆, and (c) an insoluble gas of identical gaseous diffusivity to freon 22. The concentration of an insoluble gas of identical gaseous diffusivity to freon 22 was calculated by interpolation between the concentrations of He and SF₆, using Graham's law ("diffusivity is inversely proportional to the square root of the molecular weight"). Thus the predicted concentrations for an insoluble gas with the same molecular weight as freon 22 (ie, 86) may be calculated, and will lie:

$$(\sqrt{86} - \sqrt{4}) / (\sqrt{146} - 4) * 100 = 72.4\%$$

of the way between He and SF₆ data points, and each freon 22 concentration is normalised to this hypothetical gas by:

$$[\text{freon 22}] / \{([\text{SF}_6] - [\text{He}]) * 0.724\} + [\text{He}]$$

The gaseous volume of distribution was calculated as the arithmetic mean volume of distribution calculated from dilution of the hypothetical gas over the same breaths used for calculation of rate constant of freon 22 uptake (instantaneous volume). The equilibrium (maximum) volume of distribution of gas was calculated from the He equilibrium concentration (by extrapolation if necessary¹¹).

Mixing efficiency was estimated as the number of breaths required to become 99% equilibrated (n₉₉) for both He and SF₆.

Tissue volume in two dogs was obtained by measurement of drained lung weight after the studies, and measurement of wet/dry weights measured to assess the condition of the lungs. The lung weight/body weight was calculated and used as the estimate of tissue volume for the other three dogs.

All studies conformed to United Kingdom Home Office regulations on the care and use of laboratory animals.

Results

Figure 1A shows an example of data acquired during a rebreathing manoeuvre. At this rebreathing volume (300 ml) gaseous mixing is taking place throughout the measurement, influencing the slope of uptake of the soluble gas. Correction for mixing (fig 1B) shows that normalisation to He and SF₆ results in different slopes and hence different estimates of cardiac output. The high gaseous diffusivity of He results in a greater disappearance of this gas than of the soluble gas freon 22 from the bag over the initial breaths, ie, an apparent negative uptake of soluble gas. Normalisation to the interpolated insoluble gas results in an uptake of soluble gas which drops smoothly away from the line of unity after the first few breaths.

Concordance between indicator dilution and soluble gas uptake values corrected to the interpolated insoluble gas over breaths 7-13 and using the *instantaneous* gas volume is demonstrated in fig 2 which shows the difference between the estimates calculated from the two methods plotted against the mean value.¹² Open circles represent data points from measurements in which n₉₉-He exceeded 15 breaths, ie, very poor mixing. Concordance was tested by

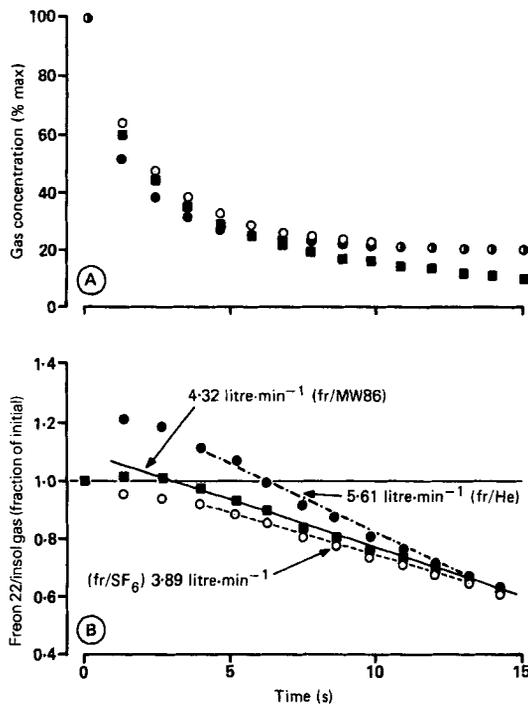


Figure 1 (A) Breath by breath concentrations of insoluble gases He (●) and SF₆ (○), and the soluble gas freon 22 (■) during rebreathing. (B) Breath by breath freon 22 concentration normalised to He (●), SF₆ (○), and an insoluble gas of identical gaseous diffusivity (■) all as a fraction of their initial value. The value for cardiac output calculated from the diffusivity corrected slope is 4.32 litre·min⁻¹, agreeing well with the simultaneous green dye estimate of 4.48 litre·min⁻¹.

calculating the mean (95% confidence interval) of the difference between dye and soluble gas uptake estimates. All points result in a mean difference of 0.345 (0.093-0.597) litre·min⁻¹. Exclusion of points when n₉₉-He was more than 15 gives a regression equation of:

$$-0.32 + 0.92 * \dot{Q} \text{ green dye}$$

and a mean difference of 0.052 (-0.163-0.267) litre·min⁻¹. The standard deviation of the individual differences is 0.99 litre·min⁻¹ for all points and 0.75 litre·min⁻¹ excluding those with n₉₉-He >15. The upper and lower limits of agreement for individual measurements (dye - freon 22) were +3.10 and -1.54 litre·min⁻¹ for all points, +1.39 and -1.54 litre·min⁻¹ excluding n₉₉-He >15. Figure 3 plots the difference between the freon 22 cardiac output (corrected MW 86, breaths 7-13 instantaneous volume distribution) and the green dye cardiac output against the number of breaths required to reach 99% equilibration for He. Use of a sign test indicates an equal distribution of values up to n₉₉-He = 15 breaths. Beyond this value all measurements underestimate cardiac output relative to green dye. Points with n₉₉-He >15 (n = 12) have therefore been excluded from further analysis. Excluding these points, mean n₉₉-He was 9.2 (SD 2.49) breaths and n₉₉-SF₆ 13.59(3.14) breaths.

There was no significant difference between the first and second of 24 pairs of measurements made within 2 min, either for green dye (t = 0.57, p = 0.57) or soluble gas uptake (t = 0.50, p = 0.62). Neither was there a difference between green dye measurements made during a rebreathing manoeuvre and those made while the animal was being breathed by the ventilator (n = 40, t = 0.66, p = 0.51).

Figure 4 summarises the different values of cardiac output obtained by different methods of calculation. The best correlation with green dye is that in which the

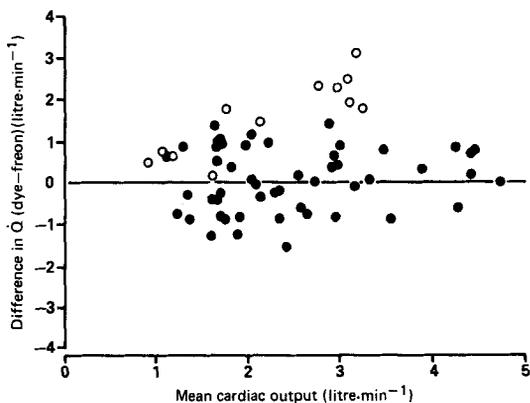


Figure 2 Plot of difference between indicator dilution and soluble gas uptake measurements (corrected for mixing, breaths 7-13, instantaneous gas volume) against the mean of the paired measurements, for all rebreathing manoeuvres. ○ represents estimates during which n₉₉-He exceeded 15 breaths.

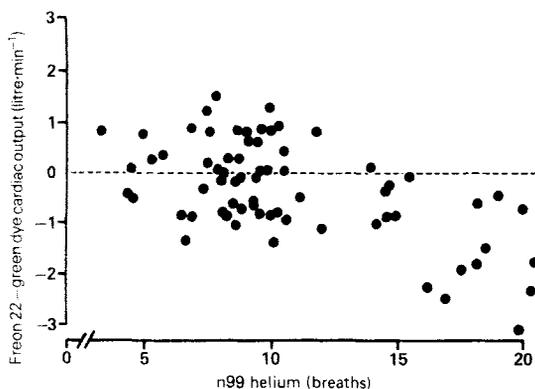


Figure 3 Plot of difference between cardiac output estimated from indicator dilution and freon 22 (corrected for mixing, breaths 7-13, instantaneous volume of distribution) against mixing efficiency (n99-He). When n99-He exceeds 15 breaths cardiac output is consistently underestimated by soluble gas uptake.

freon 22 slope is corrected to an insoluble gas of MW 86 using the instantaneous volume of distribution, over breaths 5-11 or 7-13. The mean difference between normalisation to He and to SF₆ was 1.21 (SD 0.72) litre·min⁻¹ (breaths 5-11) and 0.86(0.56) litre·min⁻¹ (breaths 7-13). The mean instantaneous gas volume over breaths 5-11 was 0.824(0.188) litres for He, 0.77(0.179) litres for insoluble gas MW 86, and 0.751(0.177) litres for SF₆. Over breaths 7-13 instantaneous gas volumes were 0.896(0.199) litres for He, 0.846(0.191) litres for insoluble gas MW, 86 and 0.829(0.190) litres for SF₆. Equilibrium volume was 1.163(0.231) litres.

Use of the uncorrected slope resulted in a mean overestimation of Q_c of 2.69 litre·min⁻¹ (breaths 5-11) and 1.31 litre·min⁻¹ (breaths 7-13). A combination of the freon slope corrected to MW 86 with the equilibrium volume resulted in an overestimation of Q_c of 1.2 litre·min⁻¹ for breaths 5-11 and 0.76 litre·min⁻¹ for breaths 7-13.

Tissue volume as drained lung weight obtained in two dogs was 10.79 and 9.28 g·kg⁻¹ body weight. Wet/dry ratios from four regions of each lung were similar, the range being 4.61-5.05. An estimated value for tissue volume of 10 g·kg⁻¹ body weight was used in the other three dogs.

Discussion

VALIDATION OF CARDIAC OUTPUT MEASUREMENTS

Several comparisons have been made between pulmonary capillary blood flow measured by soluble inert gas uptake and other techniques such as indicator dilution,³ and direct or indirect Fick.² These reference methods are also subject to inaccuracies. The indicator dilution method used for validation in this report has itself a variability of ±15% when compared with direct Fick for oxygen.¹³ In this series of experiments the repeatability of green dye estimates was similar to that

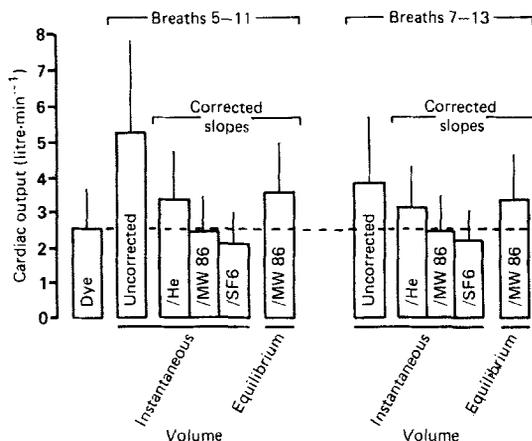


Figure 4 Histogram of mean cardiac output calculated from soluble gas uptake, slopes measured over breaths 5-11 and 7-13. Uncorrected slopes are compared with those corrected to He, SF₆, and the interpolated insoluble gas of identical gaseous diffusivity (MW 86). The effect of using different volumes of distribution is also shown, instantaneous volume being the mean volume of distribution over which the slope was measured. Cardiac output estimated by indicator dilution is shown for comparison. Standard deviation bars are included.

for the soluble gas uptake. It therefore seems probable that the methods have a similar degree of precision in these dogs. Validations carried out using large tidal volumes cannot be applied to patients who will be unable to perform the test in the same manner as in the original evaluation. This may lead to serious errors. Our method has been designed for clinical use in patients with heart and lung disease and our validation has been carried out with this in mind. The scatter of the data points in fig 2 is not surprising in view of the low tidal volumes (deliberately chosen) and substantial mixing delays (n99-He >15 breaths) in some cases. In patients, n99-He rarely exceeds 14 breaths and in normal subjects and in cardiac patients n99-He averages seven breaths.

EFFECT OF GAS MIXING

The rebreathing method with soluble gases involves three separate phases. As described by Teichmann *et al.*,² in phase 1 the gas mixes between bag and lung, in phase 2 there is an exponential fall in soluble gas concentration dependent on pulmonary blood flow, and in phase 3 recirculation of soluble gas back to the lungs occurs. In our rebreathing system for humans the bag volume is typically 20% of the patient's functional residual capacity,¹⁴ whereas most other studies have used rebreathing volumes greater than 2 litres.^{2 7-9 15} Not surprisingly, gaseous mixing takes longer than with larger volume breaths.¹¹ In the extreme, recirculation of soluble gas will occur before gaseous mixing is complete. In the dogs, the mean number of breaths to reach 99% equilibrium for a gas of identical diffusivity to freon 22 was 10 breaths when

rebreathing 300 ml of test gas. This volume is equivalent to 700 ml for humans (in terms of the ratio between functional residual capacity to rebreathing volume) and is one which most patients can rebreath more than 10 times before recirculation occurred. In the absence of equilibration some correction must be applied to the soluble gas concentration to differentiate between fall in concentration due to gas mixing and fall in concentration due to gas uptake by the blood.

CORRECTION FOR GAS MIXING

Point by point correction of soluble gas uptake by normalisation to simultaneous He concentration was applied by Sackner *et al.*,⁸ but only data points occurring after He was effectively mixed were used for calculation of pulmonary capillary blood flow. The rebreathing volume in that study was 3.5 litres and so only the first two or three breaths had to be eliminated from analysis. Kallay *et al.*¹⁶ calculated the rate of uptake over a range of tidal volumes, again correcting soluble gas to He, but including all breaths in the analysis, the first being corrected for the effect of anatomical and instrumental deadspace using the equation of Petrini *et al.*⁴ Gaseous mixing limitation due to diffusion of gases can be considerable, especially in disease. Even in seated normal subjects, mixing for He and SF₆ has been shown to be significantly different during rebreathing of small volumes.⁵ The correction of soluble gases for mixing by normalisation to He is therefore inappropriate if diffusion limitation is present. This effect becomes more important the higher the molecular weight of the soluble gas. Thus for acetylene (MW = 26) the error introduced is small, but for freon 22 (MW = 86) the error will be greater. Nevertheless, the non-explosive, non-toxic nature of freon 22 at concentrations which can be monitored accurately by mass spectrometers make its use attractive.⁹

The addition of SF₆ to the rebreathing mixture allowed us to interpolate a mixing curve for an insoluble gas with the same molecular weight as freon 22, to which the soluble gas itself was normalised. The difference between normalisation to He, SF₆, and this hypothetical gas was at maximum 2.7 litre·min⁻¹. Obviously, the discrepancy in the values depends on the magnitude of the He-SF₆ mixing differences, which in these animals was not as great as has been shown in normal subjects in the lateral decubitus posture.⁵ The minimisation of errors will also be important if tissue volume is measured by the method introduced by Sackner *et al.*⁸ using carbon monoxide (CO) to define time zero; CO (MW = 28) and freon 22 can each be normalised to an appropriate interpolated insoluble gas.¹⁴

VOLUME OF DISTRIBUTION (GAS)

The appropriate volume of gas distribution from which the soluble gas is taken up by pulmonary capillary

blood flow requires careful thought. In the multiple breath holding studies of Cander and Forster,¹⁷ the alveolar dilution volume calculated from the inspired/expired He concentrations was used. These breath holds were at total lung capacity and in healthy normal subjects probably closely approximated the true alveolar volume. In the situation where mixing is taking place throughout a rebreathing manoeuvre, the appropriate volume of distribution is less clear. The volume of distribution is varying throughout the measurement. If the rate of uptake of soluble gas is constant in all regions of the lung, the appropriate volume of distribution would be the total system volume, bag volume plus lung gas volume, and tissue volume including capillary blood. This is the volume used by most authors.^{2-4 9 15 16} Thus the initial rate of uptake of the soluble gas, multiplied by the total volume of distribution at equilibrium would yield the most accurate estimate of blood flow. It is clear from our data that the use of the equilibrated system volume overestimates blood flow relative to green dye by a considerable amount (about 1 litre·min⁻¹, fig 4). In addition, the overestimation is greater using a combination of the equilibrium volume and the slope measured over breaths 5-11 than over breaths 7-13. Two conclusions may be drawn from this observation. Firstly, the rate of uptake is not monoexponential, and secondly, that the rate of uptake is higher in areas of high ventilation. This is not altogether surprising as both Wagner *et al.*¹⁸ and West *et al.*¹⁹ have demonstrated stratified distribution of blood flow in the lungs. Kallay *et al.*¹⁶ point out that this phenomenon tends to minimise variability of blood flow estimates with different breathing patterns. In our study, the closest correlation with the green dye estimates of blood flow was obtained using the mean slope of corrected freon 22 uptake over either breaths 5-11 or 7-13 with the instantaneous gas volume measured over the same breaths, despite the mean difference of 80 ml between these two gas volumes.

VOLUME OF DISTRIBUTION (TISSUE)

Part of the volume of distribution of the soluble gas is the lung tissue volume.¹⁷ An estimate of lung tissue volume was obtained from the measurement of drained weight of the lungs of two of the dogs. During the rebreathing manoeuvre the volume of lung tissue equilibrated with soluble gas must have been increasing and must make a contribution to the fall in concentration of freon 22 during measurement of the slope. The use of a constant value for tissue volume for all calculations would lead to inaccuracies in situations with slow mixing, but the effect will be small, as the tissue volume * solubility component is only about 5% of the total volume of distribution.

INFLUENCE OF REBREATHING MANOEUVRE

Rebreathing has been shown to increase cardiac

output, especially when high tidal volumes are used.^{6,7} The absence of any significant difference between cardiac output measured by indicator dilution when the dogs were connected to the ventilator (0.25 Hz) or during rebreathing (1 Hz) may be due either to the small rebreathing volumes used in our method, or to the fact that the rebreathing in these studies was by positive pressure inflation, thus involving no effort from the animal. This contrasts with the method as used in conscious humans.¹⁴

INFLUENCE OF BACK PRESSURE

Bonde-Petersen *et al*⁹ recommend that rebreathing measurements should not be repeated within 10 min because of back pressure of soluble gas. We were unable to detect any back pressure 2 min after a rebreathing measurement. In addition repeat estimates of blood flow made within 2 min showed no tendency for the second estimate of blood flow to be lower than the first.

SUMMARY

The repeated use of invasive measurements in the study of disease progression or response to treatment is rarely justifiable. The ability to measure cardiac output non-invasively in patients with heart and lung disease is therefore of great importance. Our rebreathing method, which is tailored for use in patients, allows cardiac output to be measured non-invasively, by a 15 s rebreathing manoeuvre. The correction of the soluble gas to an insoluble gas of identical gaseous diffusivity is critical, because inhomogeneity of ventilation leading to diffusive limitation to mixing is always present to some extent, even in normal subjects. We have shown that the confidence limits of the method are similar to more invasive methods and that only in grossly abnormal mixing conditions, which can be defined by the He mixing efficiency, does the method become unreliable.

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NOTICE

World Congress on Cardiology takes place on 12-15 December 1991 in New Delhi, India. The scientific programme will cover: myocardial infarction; coronary artery disease and its evaluation; rheumatic and congenital heart disease; hypertension; congestive heart failure; electrophysiology; pacemakers; arrhythmias; cardiomyopathies. President: Dr K L Chopra, Chairman of Heart Care Foundation of India. For

further enquiries contact Miss M Passi, Committee Executive IJCP, 495 Reddings Lane, Hall Green, Birmingham B11 3DF. Tel 021 777 7933.

CORRECTION

Corr *et al*, March 1991, page 260. We regret that an incorrect legend was attached to figure 4 when the issue was

prepared for printing. The correct legend should be as follows:

Figure 4 Log cumulative relaxation-response curves to (A) noradrenaline, (B) isoprenaline, and (C) salbutamol in ring preparations of the rabbit coronary artery with the endothelium intact (solid lines) and removed (dotted lines). Preparations were pretreated with 50 $\mu\text{mol}\cdot\text{litre}^{-1}$ phenoxybenzamine. Results are expressed as percent relaxation of the KCl induced tone and are the means of data from 4-6 animals; bars = SEM. There were no significant differences between preparations with and without endothelium.