Development and *in vitro* validation of a device for measuring non-shunt cardiac output by nitrous oxide throughflow

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Abstract—*A system has been developed for measuring non-shunt cardiac output by the throughflow technique, using nitrous oxide in patients undergoing general anaesthesia. The throughflow measurement technique is a non-invasive method based on inert gas throughflow theory.* In vitro *validation of the measurement system was performed using a lung gas exchange simulator. The accuracy and precision of the throughflow measurement system was assessed by comparing measured and target values for five simulated values of non-shunt cardiac output, from 2.88 to 9.86 l min^{-1}. This showed an overall mean bias of −0.03 l min^{-1} (range −0.00 to −0.10 l min^{-1}), with a mean coefficient of variation of the difference of 1.39% (1.20–1.93%). These results indicate that the measurement system is suitable for monitoring the non-shunt cardiac output in patients undergoing general anaesthesia using nitrous oxide throughflow.*

Keywords—*Cardiac output, Pulmonary blood flow, Inert gas throughflow, Anaesthesia, Nitrous oxide*

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1 Introduction

CARDIAC OUTPUT measurements are valuable throughout the process of anaesthesia and enable the calculation of many indices that reflect the status of the entire circulatory system (MORGAN and MIKHAIL, 1999). Current clinical techniques of cardiac output measurement such as the direct oxygen Fick and thermodilution methods, are relatively accurate but are highly invasive (GUYTON *et al.*, 1973). In contrast, techniques such as Doppler ultrasound and thoracic bio-impedance are non-invasive but are less accurate or precise and/or require considerable specialist training to use (PRYS-ROBERTS, 1996). Thus it would be desirable to develop a cardiac output measurement technique that is non-invasive, automated and accurate.

Methods using inert gas exchange by the lungs, such as indirect Fick-based methods, have two outstanding advantages: no invasive cannulation is required, and they can be adapted to give instantaneous measurements of the blood flow through the gas-exchanging areas in the lung (BUTLER, 1970).

A major limitation of these methods has been that the mixed venous partial pressure of the inert gas cannot be measured non-invasively. This problem was overcome by assuming zero mixed-venous inert gas concentration and measuring the cardiac output before the re-circulation time, but the technique was suitable only for single or occasional measurement of cardiac output (AYOTTE *et al.*, 1970; CANDER and FORSTER, 1959; HENEGHAN and BRANTHWAITE, 1981; KROGH and LINDHARD, 1912; PETERSON *et al.*, 1978; SACKNER *et al.*, 1975; STOKKE *et al.*, 1986; TEICHMANN *et al.*, 1974; TRIEBWASSER *et al.*, 1977; ZEIDIFARD *et al.*, 1976). Other methods to calculate the mixed venous partial pressure of nitrous oxide required special breathing techniques, such as breath-holding, single-breath and rebreathing or partial rebreathing (CAPEK and ROY, 1988; GEDEON *et al.*, 1980; BINDER and PARKIN, 2001), which limit the frequency of measurement.

We have developed and validated a measurement system based on the 'throughflow method', a new technique for the measurement of non-shunt cardiac output $\dot{Q}_C$, utilising inert soluble gas exchange, that will allow continuous measurement of $\dot{Q}_C$ during general anaesthesia (ROBINSON, 2002). Throughflow is based on the principle of synchronous but independent ventilation of the two lungs with different concentrations of an inspired inert gas. This is achieved by functional separation of the two lungs by means of a double-lumen endobronchial tube, of the type routinely used during anaesthesia for thoracic surgery. Continuous measurement of differential gas exchange in each lung allows mixed venous blood gas content (and thus $\dot{Q}_C$) to be calculated continuously, without the need for invasive sampling of mixed venous blood (ROBINSON, 2001). Unlike previous methods using soluble gas exchange, throughflow does not require any perturbations in delivery of inspired gas to the lung to make a measurement. It employs ongoing

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measurement of gas exchange and thus allows continuous blood flow measurement, potentially on a breath-by-breath basis.

2 Throughflow theory

Most soluble inert gas techniques are based on the modification of the Fick principle (BORSTEIN, 1910). This principle states that $\dot{Q}_C$ is calculated from measured exchange by the lung ($\dot{V}_G$) of an inert gas G, and the difference between the fractional content of gas in end-capillary blood leaving the lung ($C_{c'_G}$) and that entering the lung in mixed venous blood ($C_{\bar{v}_G}$)

$$\dot{Q}_c = \frac{\dot{V}_G}{C_{c'_G} - C_{\bar{v}_G}} \tag{1}$$

If there is functional separation of the two lungs by means of a double-lumen endobronchial tube, a pair of simultaneous equations of the form of (1) are generated. In these equations, the suffixes L, left lung, and R, right lung, are attached to the terms, except for the mixed venous term $C_{\bar{v}_G}$ that is common to both lungs. Transposing (1) for the left and right lungs allows us to eliminate $C_{\bar{v}_G}$ and to calculate $\dot{Q}_c$ non-invasively.

$$C_{\bar{v}_G} = C_{c'_{G_{(L)}}} - \frac{\dot{V}_{G_{(L)}}}{\dot{Q}_{c_{(L)}}} = C_{c'_{G_{(R)}}} - \frac{\dot{V}_{G_{(R)}}}{\dot{Q}_{c_{(R)}}} \tag{2}$$

If we temporarily disregard $C_{\bar{v}_G}$ rearranging and multiplying through by $\dot{Q}_c$ yields

$$\dot{Q}_c = \frac{\dot{V}_{G_{(L)}} \cdot (\dot{Q}_c/\dot{Q}_{c_{(L)}}) - \dot{V}_{G_{(R)}} \cdot (\dot{Q}_c/\dot{Q}_{c_{(R)}})}{(C_{c'_{G_{(L)}}} - C_{c'_{G_{(R)}}})} \tag{3}$$

Measurement of $\dot{Q}_c$ is now possible using variables measured non-invasively, if the inverse proportions (not absolute values) of blood flow in the left ($\dot{Q}_c/\dot{Q}_{c_{(L)}}$) and right ($\dot{Q}_c/\dot{Q}_{c_{(R)}}$) lungs are known. If near optimum (or equal) oxygenation of both lungs can be assumed, the ratio of blood flow will approximate the ratio of oxygen (O_2) uptake ($\dot{V}_{O_2}$) by each lung, given the flatness of the haemoglobin—O_2 dissociation curve in the arterial range. Therefore

$$\frac{\dot{Q}_c}{\dot{Q}_{c_{(L)}}} = \frac{\dot{V}_{O_2}}{\dot{V}_{O_2(L)}} \tag{4}$$

$$\frac{\dot{Q}_c}{\dot{Q}_{c_{(R)}}} = \frac{\dot{V}_{O_2}}{\dot{V}_{O_2(R)}} \tag{5}$$

$\dot{V}_{O_2}$ can be readily measured simultaneously with $\dot{V}_G$.

If we apply the indirect Fick principle, the variables in the denominator can be approximated by fractional end-tidal gas concentrations ($F_{E'_G}$) multiplied by the Ostwald solubility coefficient λ_G, which characterises the relative solubility of an inert gas in blood at a specified temperature.

$$\dot{Q}_c = \frac{\dot{V}_{G_{(L)}} \cdot (\dot{V}_{O_2}/\dot{V}_{O_2(L)}) - \dot{V}_{G_{(R)}} \cdot (\dot{V}_{O_2}/\dot{V}_{O_2(R)})}{\lambda_G \cdot (F_{E'_G(L)} - F_{E'_G(R)})} \tag{6}$$

Under idealised circumstances, such as in a physiological lung simulator, the end-tidal tension of G is assumed to equal its hypothetical tension in the end-capillary blood in each lung. Thus, for the purposes of benchtop validation,

$$C_{c'_{G_{(L)}}} = \lambda_G \cdot F_{E'_{G_{(L)}}} \tag{7}$$

$$C_{c'_{G_{(R)}}} = \lambda_G \cdot F_{E'_{G_{(R)}}} \tag{8}$$

A fully automated system was developed for the measurement of $\dot{Q}_c$ by throughflow from (6), using nitrous oxide (N_2O), and validated *in vitro* as described below. The system is capable of measuring uptake and end-tidal concentrations of N_2O and uptake of O_2 with sufficient accuracy and precision and is suitable for use in patients under general anaesthesia. For the purposes of simulation, λ_{N_2O} was assumed to have a constant value of 0.47 (its value in blood at 37°C).

3 Methods

3.1 *Throughflow measurement system*

The throughflow measurement system (Fig. 3) consists of a modified anaesthetic delivery unit (Fig. 1), anaesthesia ventilator with dual bellows and associated breathing circuits (Fig. 2), multi-gas analyser, sample gas multiplexer, throughflow data module and personal computer with solenoid driver and analogue input boards (see below).

3.1.1 *Fractional gas concentration measurements:* All fractional gas concentrations for O_2, carbon dioxide (CO_2), N_2O and volatile anaesthetic agents were acquired from the analogue output data of a Capnomac *Ultima* multi-gas analyser*. This gas analyser measures O_2 using a fast differential paramagnetic O_2 sensor. CO_2, N_2O and anaesthetic agents are measured by infrared absorption. The analogue data available from the output of the gas analyser were digitised into a personal computer for storage and processing. All concentrations were measured in fully mixed gas streams (fresh gas and mixed exhaust gas) to avoid inaccuracy due to tidal changes in gas concentrations. Gas mixing in exhaust gas was achieved using a 4.5 m length of mixing tubing between patient and sampling point.

3.1.2 *Multiplexing of gas samples in multi-gas analyser:* Gases were sampled from eight points: fresh, mixed exhaust and end-tidal gas on the left and right sides, and two calibration gases (Entonox and room air). A gas multiplexer was constructed to allow the gas mixture from each sample point to be directed into the inlet of the gas analyser sequentially. This consisted of eight tubes, each from a sample gas line, leading via its own three-way miniature solenoid† into a common manifold, similar to a setup reported elsewhere (SEVERINGHAUS, 1985), connected to the inlet of the gas analyser. Alternate gas sampling was achieved by the switching of the solenoids by a custom-made solenoid driver board under software control. Additional suction was applied to the common manifold such that, when any one of the sample lines was being sampled (solenoid on), the other seven (solenoids off) were flushed with the same gas mixture in a retrograde fashion to eliminate contamination of the sampled gas mixture with prior mixtures.

3.1.3 *Measurement of gas flow and gas exchange:* The fresh gas flow into the system was measured by an air dilution method that employed a known flow of reference gas (nitrogen (N_2) in medical air). The expiratory gas flow was estimated using the Haldane transformation (NUNN, 1993), and gas exchange was the difference between the two.

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†Type 3-132-900, General Valve Corporation, USA

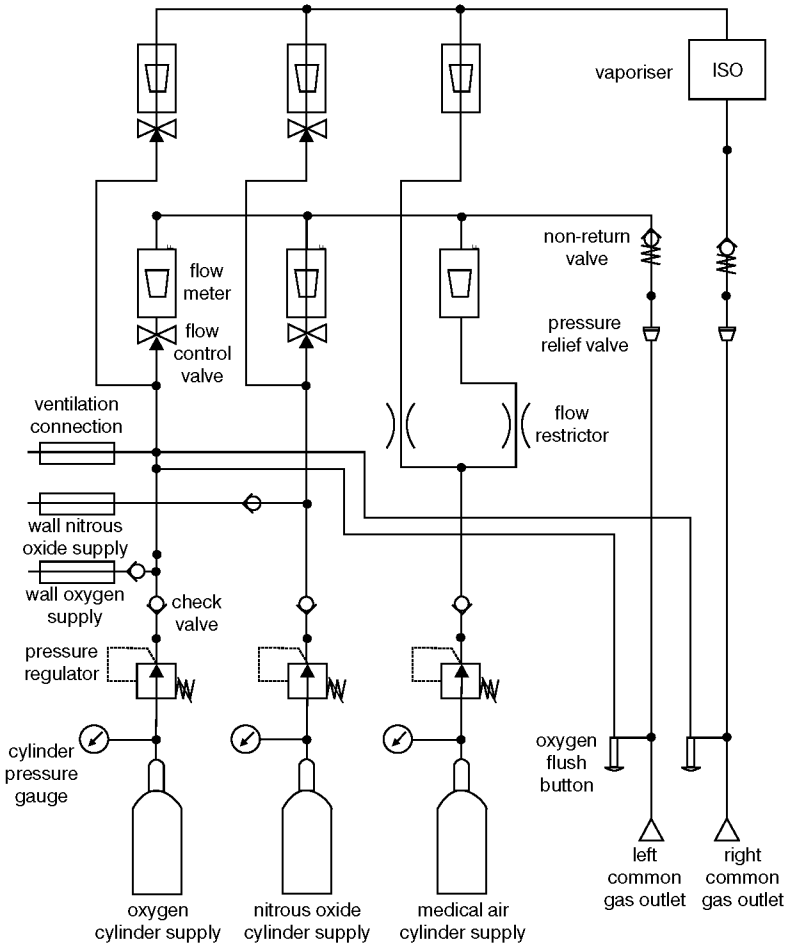

Fig. 1 *Anaesthesia delivery unit*

Fresh gas flow measurement: The reference gas flow was monitored continuously from gas supply pressure at the high-pressure gas source and the previously determined pressure–flow characteristics of a gas flow resistor. The high-pressure gas source used was a cylinder of compressed medical air in conjunction with a variable pressure regulator, delivering a pressure of 430–460 kPa. The pressures were measured using solid-state pressure transducers[‡] with associated signal conditioning circuitry and instrumentation amplifiers. The analogue outputs of these circuits continuously fed to the computer.

The reference gas flow resistor used was a 100 mm length of stainless steel tubing of 0.7 mm internal diameter. This was previously calibrated against a volumetric technique using water displacement, with appropriate corrections for temperature, water vapour and ambient pressure (BURFOOT, 1999). Thus the reference gas flow rate could be calculated continuously by measuring the upstream pressure at the fixed resistor. The downstream pressure, which was negligible in comparison, was not measured but was assumed to be the mean of the breathing circuit pressure. The pressure–flow relationship of the resistor was assumed to be linear over the narrow operating range.

Given that air contains 79.07% N_2, the reference fresh gas flow of N_2 ($\dot{V}_{F_{N_2}}$) was calculated from the measured medical air gas flow rate ($\dot{V}_{F_{AIR}}$) in the gas flow resistor

$$\dot{V}_{F_{N_2}} = 0.7907 \cdot \dot{V}_{F_{AIR}} \tag{9}$$

The total fresh gas flow can be calculated from the measured flow of N_2 and the calculated fractional concentration

$$\dot{V}_{F_T} = \frac{\dot{V}_{F_{N_2}}}{F_{F_{N_2}}} \tag{10}$$

where $\dot{V}_{F_T}$ is the total fresh gas flow, and $F_{F_{N_2}}$ is the fractional concentration of N_2 in the fresh gas flow.

Then, for a gas G,

$$\dot{V}_{F_G} = \dot{V}_{F_T} \cdot F_{F_G} \tag{11}$$

where $\dot{V}_{F_G}$ is the flow of gas G in the total fresh gas flow, and F_{F_G} is the fractional concentration of gas G in the fresh gas flow.

Measurement of mixed tidal gas flow: The Haldane transformation assumes that the flow of the relatively insoluble gas N_2 is identical in both inspired (total fresh gas flow) and tidal gases (total mixed-tidal exhaust gas flow), as no net N_2 exchange by the lung occurs. Therefore the mixed-tidal exhaust gas flow $\dot{V}_{\bar{X}_T}$ is

$$\dot{V}_{\bar{X}_T} = \dot{V}_{F_T} \cdot \frac{F_{F_{N_2}}}{F_{\bar{X}_{N_2}}} \tag{12}$$

where $F_{F_{N_2}}$ is the fractional concentration of N_2 in the fresh gas flow, and $F_{\bar{X}_{N_2}}$ is its concentration in the mixed-exhaust gas flow. Then, for a gas G in the mixed exhaust gas flow,

$$\dot{V}_{\bar{X}_G} = \dot{V}_{\bar{X}_T} \cdot F_{\bar{X}_G} \tag{13}$$

where $\dot{V}_{\bar{X}_G}$ is the flow of gas G, and $F_{\bar{X}_G}$ is the fractional concentration of gas G in the mixed exhaust gas flow.

[‡]Type SX-100AN, SenSym, USA

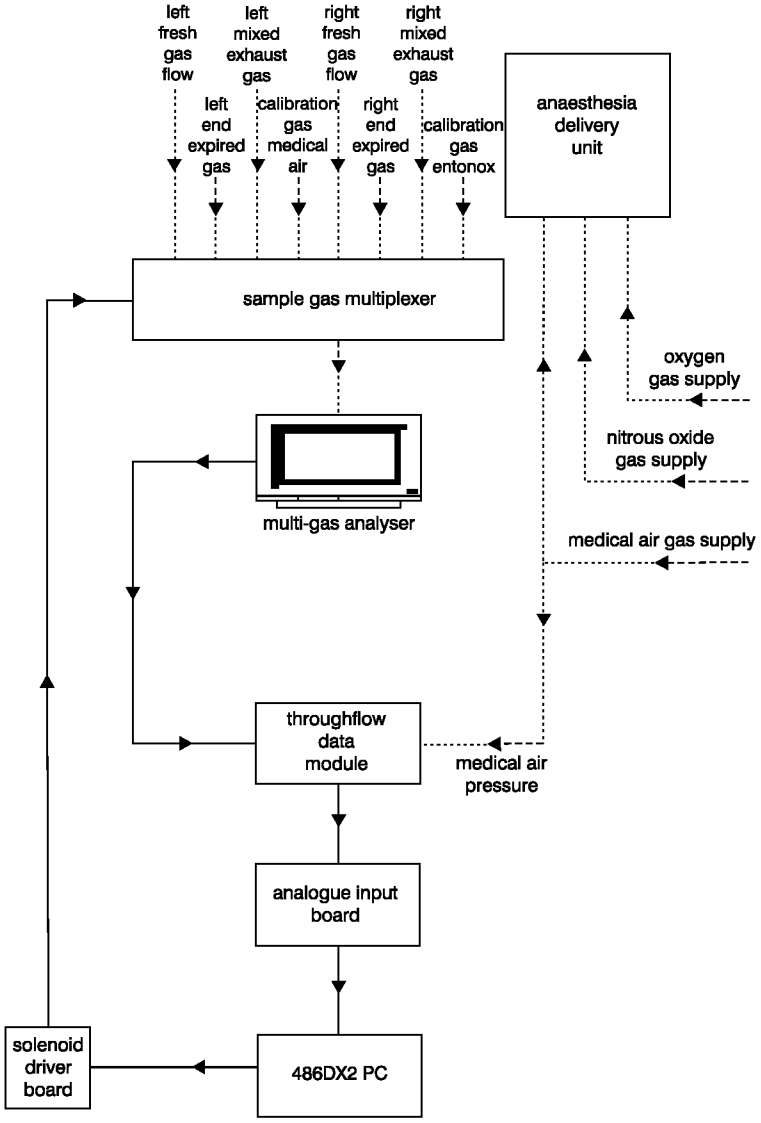

Fig. 2 *Throughflow measurement system. (- -▶- -) Gas sample; (—▶—) electrical signal*

For any gas G, the gas exchange $\dot{V}_G$ is

$$\dot{V}_G = \dot{V}_{F_G} - \dot{V}_{\bar{X}_G} \tag{14}$$

The accuracy of the Haldane transformation is affected by N_2 flux in a variety of physiological situations, including during general anaesthesia with N_2-free inspired mixtures (NUNN and POULIOT, 1962; BEATTY *et al.*, 1984), and correction for this is required for optimum accuracy *in vivo*. However, no correction was required for the purposes of benchtop validation.

3.1.4 *Anaesthesia delivery system:* The anaesthesia delivery unit** was specially modified to deliver simultaneously two independent gas mixtures, providing different inspired gas concentrations and allowing independent gas flow and concentration measurements to be made in the breathing systems to each lungs. This required construction of a second low-pressure gas delivery system into the anaesthesia machine, entailing the addition of another rotameter flowmeter bank, another common gas manifold and another common gas outlet and O_2 flush button. A separate Mapleson D system (Bain circuit) was used for the breathing system on the left and right sides. The Bain circuit is a partial rebreathing system, in which gas recirculation does not occur, and an adequate total fresh gas flow is required to prevent rebreathing (typically 70 to 100 ml/kg/min).

The anaesthesia ventilator†† provided synchronous but independent ventilation of the two lungs. Synchronous ventilation of the lungs was achieved through a bifurcating drive gas hose and the addition of a second bellows assembly. Independent adjustment of tidal volumes could be performed by adjustment of the plungers on the bellows.

3.2 *Lung gas exchange simulator*

A physiological lung simulator (Fig. 4) was constructed to simulate the gas exchange that occurs *in vivo* and, hence, to simulate particular values of $\dot{Q}_C$. The accuracy and precision of the throughflow measurement system was determined by comparing predicted or target $\dot{Q}_C$ with that measured on the simulator.

3.2.1 *Construction of the lung gas exchange simulator:* Tidal ventilation was achieved using a dual-hinged bellows device

**TM41 Anaesthetic Major Apparatus, CIG, Australia

††Type 7800, Datex–Ohmeda, USA

‡‡Dual Adult TTL type 1600, Michigan Instruments Inc., USA

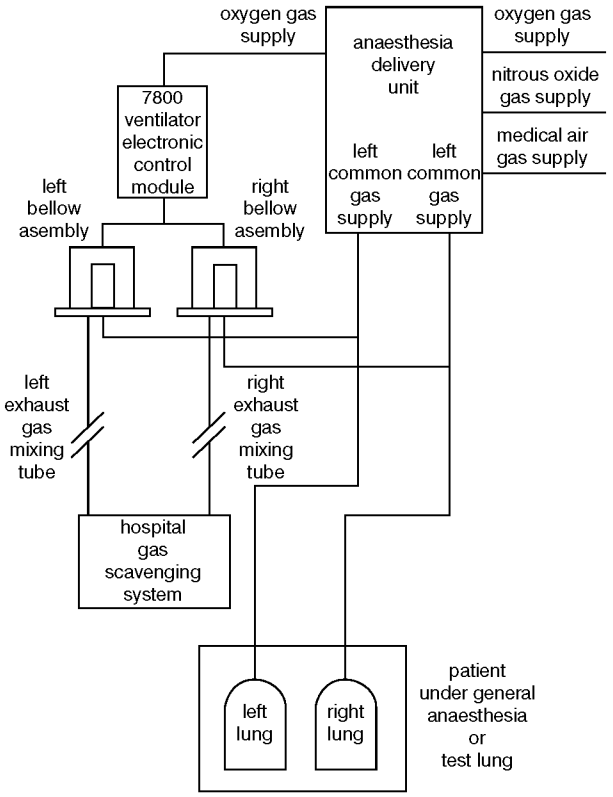

Fig. 3 *Anaesthesia delivery system including duplicate breathing systems*

('artificial lung') that simulated both left and right lungs[‡‡]. To simulate respiratory dead space, tubing with a volume of 75 ml was added to the common inlet/outlet port of each lung. Mixing of the gases within each bellows, which simulates the alveolar gas compartment of the real lung, was optimised by placing small electrically driven fans inside each bellows.

3.2.2 *Simulating gas exchange:* Uptake of O_2 and N_2O and the production of CO_2 were simulated by infusing precise flows of CO_2, N_2 and other test gases into the artificial lung. CO_2 infusion directly simulates CO_2 production. In contrast, N_2 infusion does not simulate any real physical O_2 and N_2O exchange. Rather, a difference in O_2 and N_2O concentrations produced by infusion of N_2 simulates 'apparent' uptake of O_2 and N_2O. Note that all gas uptakes simulated are 'apparent uptakes', as, in reality, the artificial lung is not able to absorb any gas species. Changing the lung gas flow rates into the artificial lung alters the exhaust gas concentrations, thus simulating different gas uptakes and different values for $\dot{Q}_C$.

3.2.3 *Equipment used for gas infusions:* The gases were added to the artificial lung through gas flow resistors, similar in nature to the reference gas flow resistor described above, but of different length, depending on the required flow range for each added gas. Each gas was supplied by a variable pressure regulator attached to a high-pressure gas bottle. Each resistor was previously calibrated over a range of driving pressures. The pressure–flow characteristics of these resistors were found to be alinear over a wide range of driving pressures, and a second-order equation was obtained for each resistor using a least squares method that links flow with pressure in a way that reproduces the experimentally determined curve. In this way, continuous measurement of added lung gas flow from driving gas pressure was performed.

3.2.4 *Determination of target variables:* Target values for all flow and concentration variables were nominated. Fresh gas flows and concentrations were independent variables, whereas mixed exhaust flows and concentrations and end-tidal concentrations were arrived at by trial and error, using a computer model to achieve combinations ('scenarios') of physiologically realistic values for apparent gas exchange that predict particular values of $\dot{Q}_C$.

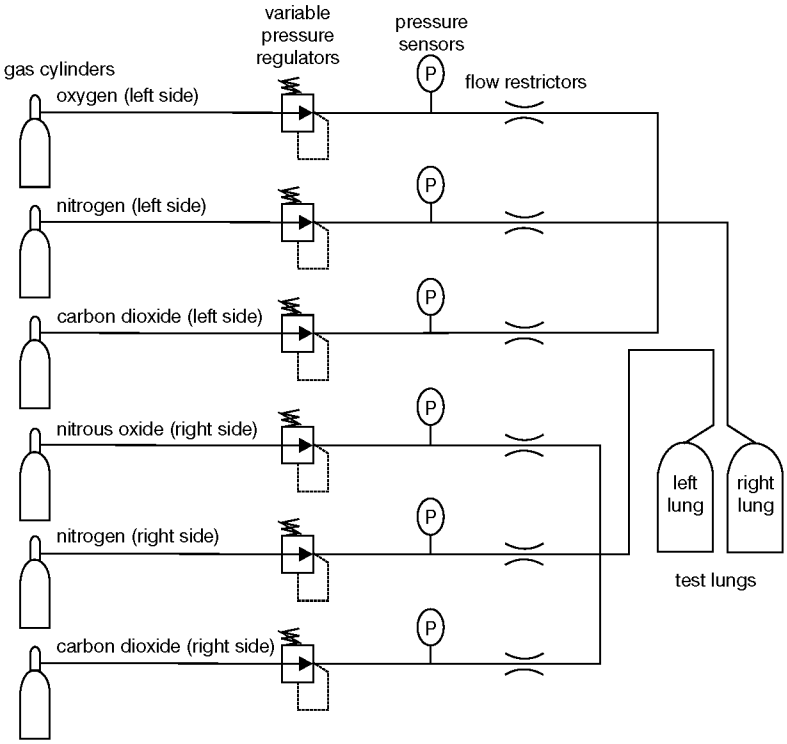

Fig. 4 *Lung gas exchange simulator*

For gas G, $F_{\bar{X}_G}$, the target concentration in mixed exhaust gas, is related by

$$F_{\bar{X}_G} = \frac{\dot{V}_{F_G} + \dot{V}_{W_G}}{\dot{V}_{\bar{X}_T real}} \quad (15)$$

where $\dot{V}_{W_G}$ is the added lung gas flow for G. $\dot{V}_{\bar{X}_T real}$ is the real total mixed exhaust gas flow and is the sum of fresh gas and all added lung gases.

Target gas exchange for G was calculated (using (13) and (14)) from $F_{\bar{X}_G}$ from (15). Apparent gas exchange for G, measured by the throughflow measurement system, was calculated from $F_{\bar{X}_G}$ measured by the rapid gas analyser, and a similar process was followed for each gas species present.

Determination of predicted partial pressures of end-tidal gas: As the calculation of the target $\dot{Q}_C$ from (6) also required target end-tidal N_2O concentrations to be determined beforehand, it was necessary to know the precise relationship between target end-tidal $(F_{E'_{N_2O}})$ and mixed-exhaust $(F_{\bar{X}_{N_2O}})$ concentrations of N_2O for both the left and right sides of the artificial lung. This is determined by the functional respiratory dead space of the breathing system and the artificial lung. The term 'functional respiratory dead space' includes, not only the 75 ml of conducting tubing, but also an amount of further dead space known as 'apparatus dead space' (NUNN, 1993). As this arises partly because some fresh gas mixes with tidal gas without entering the conducting tubing, apparatus dead space is not clearly bounded and is unable to be predicted accurately.

Functional respiratory dead space was measured empirically with each measurement cycle using a derivation of the Bohr equation (NUNN, 1993). This relates dead space to tidal volume and end-tidal, mixed-exhaust and fresh gas partial pressures for CO_2 thus

$$\frac{\dot{V}_D}{\dot{V}_T} = \frac{P_{\bar{X}_{CO_2}} - P_{E'_{CO_2}}}{P_{F_{CO_2}} - P_{E'_{CO_2}}} \quad (16)$$

where $\dot{V}_D$ is the minute deadspace ventilation, $\dot{V}_T$ is minute ventilation, $P_{\bar{X}_{CO_2}}$ is the partial pressure of gas CO_2 in the mixed-exhaust gas flow, $P_{F_{CO_2}}$ is the partial pressure of gas CO_2 in the fresh gas flow, and $P_{E'_{CO_2}}$ is the partial pressure of gas CO_2 in the end-tidal gas. The true $\dot{V}_D/\dot{V}_T$ was followed empirically from (16) using measured values of $P_{\bar{X}_{CO_2}}$ and $P_{E'_{CO_2}}$ from the left and right sides. CO_2 was found to be a suitable reference gas for this purpose in the simulator, as it is *in vivo*, because its inspired partial pressure is zero, which simplifies (16). In addition, the precision of CO_2 measurement for the multi-gas analyser is superior to that of other gas species.

From (15), the mixed exhaust concentration of a gas is a function only of the combined flows of the gases into the artificial lungs. Hence a change in $\dot{V}_D/\dot{V}_T$, due for example to a change in ventilation pattern or of total flows of gas into the artificial lung, will change only end-tidal concentration. Using this principle, a change in $P_{E'_{CO_2}}$ can be used to track changes in $\dot{V}_D/\dot{V}_T$ and thus the expected change in end-tidal partial pressure for another gas. The expected end-tidal partial pressure of N_2O $(P_{E'_{N_2O}})$ was calculated from the reciprocal of the measured $\dot{V}_D/\dot{V}_T$ by transposing (16) for N_2O

$$P_{E'_{N_2O}} = \frac{P_{\bar{X}_{N_2O}} \cdot (\dot{V}_T/\dot{V}_D) - P_{F_{N_2O}}}{(\dot{V}_T/\dot{V}_D) - 1} \quad (17)$$

where $P_{F_{N_2O}}$ is the fresh gas, and $P_{\bar{X}_{N_2O}}$ is the mixed-exhaust partial pressures of N_2O. Partial pressures were converted to concentrations at measured ambient barometric pressure (no correction for the presence of expired water vapour was necessary in the simulator) to allow calculation of $\dot{Q}_C$ from (6).

3.3 *Protocol for validation*

To test the measurement system over a physiologically relevant range, five different scenarios were drawn up, simulating five different target values for $\dot{Q}_C$ (2.88 l min^{-1}, 4.20 l min^{-1}, 5.50 l min^{-1}, 7.68 l min^{-1} and 9.86 l min^{-1}). For each of these, the measurement system was tested for 40 consecutive measurements, over a period of approximately 4 h.

3.4 *Statistical analysis*

For each scenario, the target value for $\dot{Q}_C$ was compared with the mean measured simulated value, and the standard deviation of the difference between them was calculated. The statistical significance of the measured mean difference (bias) was calculated using the t-test. Two standard deviations on either side of the mean difference were expressed as the upper and lower limits of agreement between target and measured values. One-way analysis of variance (ANOVA) was used to determine the strength of the relationship between scenario and both measured values and measurement difference, and also to determine whether there was a relationship between measurement difference and the passage of time (indexed by the ordinal value of the measurement from 1 to 40).

4 Results

Fig. 5 shows the raw data for the measured simulated values of $\dot{Q}_C$ for each of the 40 measurements (in order of determination) in the five scenarios. The target value for each scenario is also plotted. One-way ANOVA showed that there was a strong relationship between scenario and measured $\dot{Q}_C$ ($p<0.0001$).

Mean difference (bias) between target and measured values (and its statistical significance) are given in Table 1. Table 2 lists results for standard deviation and limits of agreement between measured and target values. ANOVA showed a strong relationship between scenario and bias ($p<0.0001$). However, the mean bias was never worse than 1% of the target value, and the limits of agreement remained within 4% of the target value in all scenarios. Furthermore, ANOVA revealed no significant relationship between measurement difference and ordinal value of the determination ($p>0.999$), suggesting that the system provided very stable measurement throughout the

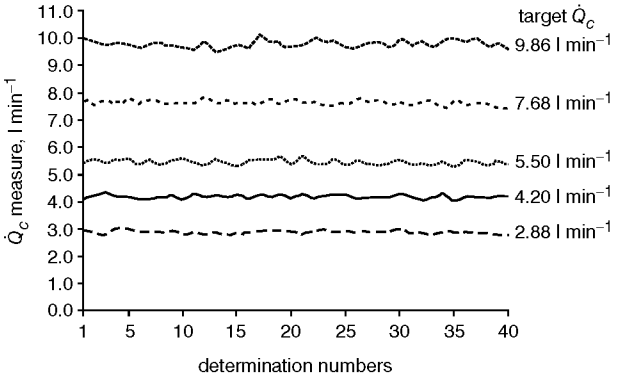

Fig. 5 *Raw data for simulated $\dot{Q}_C$ measurements for five scenarios, each of 40 determinations*

Table 1 Results for mean measurement difference in relation to target values for simulated $\dot{Q}_C$. Statistical significance of mean difference from t-test is shown

Target $\dot{Q}_C$, $l\,min^{-1}$	Mean $\dot{Q}_C$ measured, $l\,min^{-1}$	Mean difference, $l\,min^{-1}$	Mean difference, %	Statistical significance of mean difference
2.88	2.87	−0.00	−0.02	$p>0.05$
4.20	4.20	−0.00	−0.01	$p>0.05$
5.50	5.46	−0.04	−0.70	$p<0.05$
7.68	7.65	−0.03	−0.36	$p>0.05$
9.86	9.78	−0.10	−0.98	$p<0.05$
overall	overall	−0.03	−0.51	$p<0.05$

Table 2 Results for standard deviation and limits of agreement between measured and target values of $\dot{Q}_C$

Target $\dot{Q}_C$, $l\,min^{-1}$	Standard deviation of difference, $l\,min^{-1}$	Coefficient of variation of difference, %	Upper limit of agreement, $l\,min^{-1}$	Lower limit of agreement, $l\,min^{-1}$
2.88	0.06	1.93	0.11	−0.11
4.20	0.06	1.34	0.11	−0.11
5.50	0.09	1.56	0.13	−0.21
7.68	0.09	1.2	0.15	−0.21
9.86	0.14	1.46	0.18	−0.38
overall	0.10	1.39	0.16	−0.23

duration of the experiment in all scenarios. Fig. 6 shows the difference between measured and target values and the limits of agreement, for each scenario and overall.

5 Discussion and conclusions

The experimental results shown here provide a direct comparison between simulated $\dot{Q}_C$ and the measurements made by the throughflow measurement system. The accuracy of the system and limits of agreement with target values remained well within clinically acceptable bounds at all levels of $\dot{Q}_C$. Thus this system has shown satisfactory levels of precision and accuracy to be tested *in vivo* within ranges of $\dot{Q}_C$ of $2.5 - 10\,l\,min^{-1}$.

The measurement system we have described is designed specifically for gas exchange and measurement of $\dot{Q}_C$ in the setting of general anaesthesia. Several components of the system, such as the inclusion of calibration gases with each measurement cycle and the technique for referencing gas flow and gas exchange measurements to a calibrated flow of a reference gas using gas supply pressure, were used to achieve optimum accuracy of $\dot{Q}_C$ measurement. Although this is important for the purposes of validation of the measurement system on the benchtop and later *in vivo*, a considerably simpler system can be envisaged for routine clinical use. However, a number of unique features of the system are fundamental to the throughflow method. These include duplicate gas delivery systems for the left and right lungs, and duplicate gas exchange measurements (either serially or using duplicate measurement devices for both gas flow and concentration).

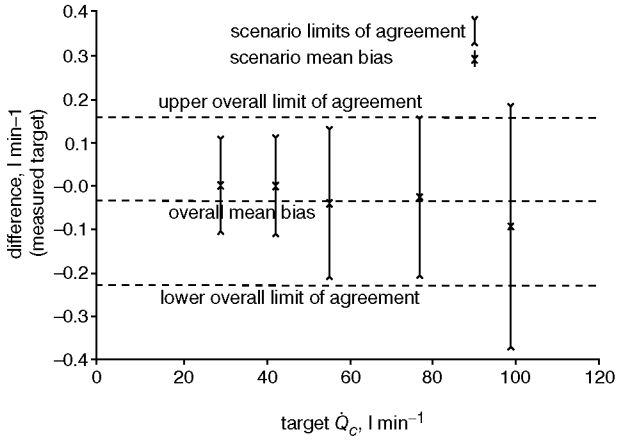

Fig. 6 *Difference between measured and target values of $\dot{Q}_C$ (y-axis) against target value (x-axis). For each scenario, mean difference and limits of agreement are shown by vertical lines. (- - - -) Overall mean difference and limits of agreement*

These logistical requirements of the throughflow method may be justified by its advantages over previous methods of measurement of $\dot{Q}_C$ from soluble gas exchange.

Most important is the rapid repeatability of measurement, as the mixed venous gas content no longer represents an obstacle to application of the Fick principle. In addition, the ability to automate the system allows a versatile and 'handsfree' measurement to take place, as manipulation of inspired gas concentration or ventilation is not required. Continuous pulmonary blood flow measurement has not previously been possible from approaches based on soluble gas exchange, but is readily achievable by throughflow.

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