CARDIAC OUTPUT USING THROUGHFLOW OF ISOFLURANE

by

Rebecca A Bailey

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Department of Engineering

School of Engineering and Mathematical Sciences

Science, Health and Engineering

La Trobe University

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Abstract

Cardiac output indicates how strongly the heart is working and allows early detection of patient deterioration. However, due to safety considerations and the complexity of the numerous existing techniques, it is not part of standard care in the anaesthetic environment

Ideally, monitors would provide non-invasive, accurate, and continuous measurement, with only a small delay between changes in blood flow and detection. Gas-exchange techniques have evolved and can now provide continuous, non-invasive monitoring. Alongside advancements in measurement technologies and simulation techniques, we can demonstrate accurate, repeatable and reliable monitoring of cardiac output in a simulated environment.

The delivery of nitrous oxide to the left lung (using a dual-lumen endotracheal tube) has previously been shown to enable measurement of nitrous oxide flow uptake, which could be used to estimate cardiac output. This thesis explores the throughflow of isoflurane from the left to the right airway to determine the breath-by-breath cardiac output. Isoflurane is delivered to only the left lung; this is achieved by using individual breathing circuits to the left and right ports of a dual-lumen tube.

Isoflurane can be measured at much lower concentrations than nitrous oxide, and allows more flexibility in the delivery of fresh gas to an anaesthetised patient. The size of uptake, and quick response to change due to the blood-gas coefficient of isoflurane, makes it an ideal choice.

The availability of complex simulators enables thorough testing of new gas-exchange techniques before *in vivo* studies. This thesis includes the development of a simulator capable of producing independent, bi-directional isoflurane gas-exchange in the left and right lung. The simulator was used to prove throughflow of isoflurane can measure breath-by-breath cardiac output using direct measurement of gas flows and end-tidal

concentrations in isolated (by way of separate breathing circuits) airways. Simulated measurements are supported by theoretical models.

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$A - a = Arterial - alveolar$

$C_{a_G} = Fractional\ content\ of\ gas\ 'G'\ \ in\ arterial\ blood$

$C_{a_{O_2}} = Fractional\ content\ of\ oxygen\ arterial\ blood$

$C_{C'_G} = Fractional\ content\ of\ gas\ \ 'G'in\ pulmonary\ end - capillary\ blood$

$C_{C'_{O_2}} = Fractional\ content\ of\ oxygen\ in\ pulmonary\ end - capillary\ blood$

$C_{\bar{v}_G} = Fractional\ content\ of\ gas\ \ 'G'in\ mixed\ venous\ blood$

$C_{\bar{v}_{O_2}} = Fractional\ content\ of\ oxygen\ in\ mixed\ venous\ blood$

$d\dot{V}_G/d\dot{Q} = Rate\ of\ change\ in\ \dot{V}_G\ with\ change\ in\ \dot{Q}$

$E' = End - tidal\ gas$

$\mathrm{E'}_G = End - tidal\ gas\ 'G'$

$\bar{E} = Mixed\ expired$

$F_{E'_G} = Fractional\ concentration\ of\ end - tidal\ gas\ 'G'$

$F_{\bar{E}_G} = Fractional\ concentration\ of\ mixed\ expired\ gas\ 'G'$

$F_{F_G} = Fractional\ concentartion\ of\ fresh\ gas\ 'G'$

$F_{I_G} = Fractional\ concentartion\ of\ mixed\ inspired\ gas\ 'G'$

$F_{I_{Iso}} = Fractional\ concentartion\ of\ inspired\ isoflurane$

$F_{I_{N_2O}} = Fractional\ concentartion\ of\ inspired\ nitrous\ oxide$

$F_{I_{O_2}} = Fractional\ concentartion\ of\ inspired\ oxygen$

$F_{\bar{X}_G} = Fractional\ concentration\ of\ mixed\ exhaust\ gas\ 'G'$

$F_{\bar{X}_{O_2}} = Fractional\ concentration\ of\ mixed\ exhaust\ oxygen$

$I = Mixed\ inspired$

$L.O.A. = Limits\ of\ agreement$

$\log SD = \ Log_e\ stanard\ deviation\ of\ the\ distribution\ of\ blood\ flow$

$MAC\ Minimum\ alveolar\ concentration$

$PAC \quad Pulmonary\ artery\ catheter$

$P_{A_G} = Partial\ pressure\ of\ aveolar\ gas\ 'G'$

$P_{a_G} = Partial\ pressure\ of\ arterial\ gas\ 'G'$

$P_{A_{O_2}} = Partial\ pressure\ of\ aveolar\ oxygen$

$P_B = Partial\ pressure\ of\ gas\ G'in\ end - expired\ gas$

$P_{c'_{O_2}} = Partial\ pressure\ of\ oxygen\ in\ pulomary\ end - capillary\ blood$

$P_{E'_G} = Partial\ pressure\ gas\ 'G'in\ end - expired\ gas$

$P_{E'_{O_2}} = Partial\ pressure\ oxygen\ in\ end - expired\ gas$

$PEEP \quad Positive\ end\ expiratory\ pressure$

$P_{I_G} = Partial\ pressure\ of\ inspired\ gas\ 'G'$

$P_{I_{O_2}} = Partial\ pressure\ of\ inspired\ oxygen$

$P_{L\ A_{CO_2}} = \ Partial\ pressure\ left\ alveolar\ carbon\ dioxide$

$P_{R\ A_{CO_2}} = \ Partial\ pressure\ of\ right\ alveolar\ carbon\ dioxide$

$P_{L\,A_{Iso}} = \ Partial\ pressure\ left\ alveolar\ isoflurane$

$P_{R\,A_{Iso}} = \ Partial\ pressure\ of\ right\ alveolar\ isoflurane$

$\dot{Q} = Pulmonary\ blood\ flow\ (pefusion\ or\ cardiac\ output)$

$\dot{Q}_c = Non - shunt\ or\ effective' pulmonary\ blood\ flow$

$\dot{V}_{AI} = Inspired\ alveolar\ ventilation$

$\dot{V}_{AE} = Expired\ alveolar\ vntilation$

$\dot{V}_{AE_{tot}} = Expired\ alveolar\ ventilator\ across\ all\ lung\ compartments$

$\frac{\dot{V}_{AE} - \dot{V}_{DA}}{\dot{V}_{AE_G}} = Ratio\ of\ ventilation\ of\ perfused\ alveoli\ to\ expire\ alveolar\ ventilation$

$\dot{V}_{DA} = Dead\ space\ ventilation$

$\dot{V}_E = \ Expired\ flow$ or *minute ventilation*

$\dot{V}_F = \ Fresh\ flow$

$\dot{V}_{F_G}$= *Flow of fresh gas 'G'*

$\dot{V}_G = \ Flow\ gas\ 'G'$

$\dot{V}_I = \ Inspired\ flow$

$\dot{V}_{L\,F} = \ Left\ fresh\ flow$

$\dot{V}_{L\,CO_2} = \ Uptake\ Left\ Carbon\ Dioxide$

$\dot{V}_{L\,Iso} = \ Uptake\ Left\ Isoflurane$

$\dot{V}_{L\,O_2} = \ Uptake\ Left\ Oxygen$

$\dot{V}_{L\,\bar{X}} = \ Mixed\ left\ exhaust\ flow$

$\dot{V}_{R\,F} = \ Right\ fresh\ flow$

$\dot{V}_{R\,CO_2} = \ Uptake\ of\ Right\ Carbon\ Dioxide$

$\dot{V}_{R\,Iso} = \ Uptake\ Right\ Isoflurane$

$\dot{V}_{R\,O_2} = \ Uptake\ of\ Right\ Oxygen$

$\dot{V}_{R\,\bar{X}} = \ Mixed\ right\ exhaust\ flow$

$\dot{V}_{O_2} = \ Oxygen\ uptake$

$\frac{\dot{V}_{O_2}}{\dot{V}_{L\,O_2}} = Inverse\ Ratio\ of\ Left\ Oxygen\ Uptake\ Rate$

$\frac{\dot{V}}{\dot{Q}} = Ventilation\ to\ Perfusion$

$\dot{V}_X = \ Exhaust\ flow$

$\dot{V}_{\bar{X}_G} = Flow\ of\ mixed\ exhaust\ gas\ 'G'$

$\bar{X} = Mixed\ exhaust$

$z_G =$ *Gaussian noise for gas 'G'*

$\lambda_G =$ *Blood-gas partition coefficient or Ostwald blood-gas coefficient for gas 'G'*

$\lambda_{Iso} =$ *Blood-gas partition coefficient for isoflurane*

Statement of Original Authorship

This thesis includes work by the author that has been published or accepted for publication as described in the text. Except where reference is made in the text of the thesis, this thesis contains no other material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma. No other person's work has been used without due acknowledgement in the main text of the thesis. This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

Signature

Date: 3rd September 2017

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Chapter 1 Introduction

1.1. Background

Cardiac output measurement provides valuable information about the physiological health of patients; it is one of the earliest indicators of deteriorating patient condition.

Naturally, all existing cardiac output measurement methods have limitations. Such techniques include those that use pressure, imaging, gas uptakes (blood or lung gas) or dilution.

The goal of all modern cardiac output monitoring is to provide continuous measurements: latency varies between physical and measured changes in cardiac output. Latency can be incurred when sequentially selecting the gas sample locations used in calculations which may then influence the rate of measurement and detection of change.

The technology used for cardiac output measurement continues to evolve. Pulmonary artery catheter insertion is declining; Pinksy and Vincent(2005) identified the following hazards:

- Complicated vascular access
- Generation of arrhythmias
- Catheter knotting
- Valve damage
- Pulmonary thrombosis and infarction
- Pulmonary artery rupture
- Bacteremia

These risks are not unique to pulmonary arterial catheterisation: thermal or dye dilution methods can use central venous catheterisation, and share several of these drawbacks.

> The *"risks of PAC* [pulmonary arterial catheterisation] *insertion are similar to those for central venous catheterization, making the decision to insert a PAC in the setting*

> *of central venous catheterization primarily one concerning the need for PAC- specific data for the management of the patient."* (Pinsky and Vincent 2005)

Non-invasive and minimally-invasive measurement techniques are becoming more common, reducing the risks associated with central and pulmonary arterial catheterisation.

The Australian and New Zealand College of Anaesthetists (ANZCA) is one group which recognises that it may be valuable to utilise different techniques.

> *"considering the type of NI-CO* [non-invasive cardiac output] *monitor, coupling of devices may be important. If two monitors rely on the same signal, eg. an arterial trace, then the ability to detect a problem would be reduced compared with having two monitors using two separate signals."*

(ANZCA 2010)

Critical care clinicians use pressures, heart signals and blood oxygen content from a combination of catheters, ECG and other sensors to make diagnostic and treatment decisions.

Techniques based on airway gas manipulation and the interaction of these gases between the bloodstream and the body's cells through the alveolar-arterial membrane provides a non-invasive method for measuring cardiac output. These techniques all use the measurement of uptake and/or elimination of airway or anaesthetic gases.

Some consideration with the current methods are:

- How closely they match true cardiac output
- Usefulness
- Invasiveness
- Speed of repeat measurements
- Specialist expertise

1.2. Context

During general anaesthesia, many of the normal physiological responses that indicate deteriorating physiological conditions are masked due to the sedation, paralysis, and analgesia applied to patients. In the majority of these patients, breathing is machine-controlled; this makes possible the manipulation of delivered fresh gas concentrations, delivery mode, tidal volumes, respiratory rate and other parameters.

Previous studies (Kennedy and Baker 1993, Kennedy and Baker 2001, Kennedy and Baker 2001a, Kennedy and French 2002, Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003) have shown links between the uptake of anaesthetic agents and airway gases, and changes in cardiac output in benchtop simulations and clinical studies. Robinson has shown that cardiac output can be measured using nitrous oxide throughflow. This thesis investigates whether substituting nitrous oxide with isoflurane could also produce reliable measurements. Uptake measurements in Robinson's research used the Haldane technique, and was based on the assumption nitrogen is not taken up by the body.

Advances in measurement technologies and simulation techniques have improved the accuracy, repeatability and reliability that can be achieved using throughflow. The ability to accurately measure small changes in anaesthetic vapour uptakes and concentrations warrants another look at their use in the determination of cardiac output. Throughflow cardiac output may provide accurate measurements in patients undergoing general anaesthesia, with only a small latency between physical changes and recorded measurements.

The thesis explores the following central hypothesis:

1.2.1. Null Hypothesis

The throughflow of isoflurane (using its uptake rate and end-tidal concentration measurements) does not measure change in cardiac output as reliably as does nitrous oxide.

1.2.2. Alternative Hypothesis

Isoflurane uptake and end-tidal concentrations allow the near-continuous measurement of cardiac output using gas throughflow from the left to right lung.

1.3. Purpose

Throughflow cardiac output measurement originally used nitrous oxide (Vartuli, Burfoot et al. 2002) but rapid advancements in clinical practice and technology have occurred since that initial work; these have included faster acquisition rate of measurements, and greater accuracy and precision of continuous flow measurement and gas concentrations.

Nitrous oxide during surgery is declining in usage and has been replaced with volatile anaesthetic agents. In blood and body tissue, the lower solubility of anaesthetic agents means they quickly reach steady-state, have shorter washout times, fewer side effects, and quicker recovery times.

Isoflurane was selected as the volatile anaesthetic agent in this case study because it is readily available and not associated with significant toxicities or side effects.

The current throughflow technique for measuring cardiac output was based on throughflow of nitrous oxide; large concentrations were needed, which limited the ability to customise fresh gas flows. By substituting isoflurane for nitrous oxide, smaller concentrations can be used, which enables a much larger choice of flow mixtures.

Using lower isoflurane concentrations in the left fresh gas means isoflurane uptakes and end tidal concentrations are smaller, which makes the system sensitive to fluctuations in their measurement.

Similarly, changes in the oxygen ratios can affect the measured cardiac output. Two alternatives to increase measurement stability are: 1) using a fixed oxygen ratio or 2) using a long moving-average for the oxygen ratio.

Technology for measuring gas flows has improved, and direct flow measurement has been used as the primary method for calculating flows. The Haldane technique for calculating flow has been used as an alternative, and both methods will be compared to target values obtained using an *in vitro* simulator. Direct flow measurement is superior because it remains unaffected by small errors in gas composition that may be introduced in bench simulations. The assumption of zero uptake of nitrogen during benchtop simulations is not valid, because small uptakes, or production of nitrogen, is likely to occur.

This thesis examines the suitability of using isoflurane uptake and end-tidal concentrations in the body to predict cardiac output based on Robinson's nitrous oxide throughflow method (Robinson, Peyton et al. 2003).

The relationship between sampling positions, cycling, and averaging of gases are explored to determine the optimum rate for gas sampling, while at the same time producing an accurate cardiac output measurement that is responsive to changes and variability.

The following questions are addressed:

- Can uptake of volatile anaesthetic agent be used to determine cardiac output?
- Can end-tidal concentrations of anaesthetic be used as a substitute for taking blood gas measurements?
- Using throughflow of gas during anaesthesia, is breath-by-breath measurement possible?
- What is the optimum trade-off between instantaneous single-breath averaging versus moving averages: which provides an acceptable response rate, without producing an exaggerated response to small changes in oxygen?

Kennedy and Baker (2001a) observed that end-tidal concentrations appeared to exhibit changes in hemodynamic status for blood pressure and pulse rate – this is worthy of further investigation.

1.3.1. Scope & Delimitation of Study

Different methods of cardiac output measurement suit different purposes. This thesis reviews cardiac output through the lens of an anaesthetist during surgical procedures using an anaesthetic machine for ventilation and fresh gas delivery.

The diffusion of gas across membranes and into the blood enables transport of gas in blood around the body. The uptake and excretion of gases by the body allow determination of respiratory and circulation system effectiveness (Ward, Ward et al. 2010). This makes the further exploration of the throughflow technique utilising isoflurane vapour a valuable proposition for measuring cardiac output.

> *"Patient populations in which CO monitoring is important need to be studied within the range of values that would dictate the need for clinical intervention"*

(Feldman 2009).

This is difficult to achieve during clinical trials which provide limited opportunities to produce cardiac output changes outside of normal limits. The use of *in vitro* simulation provides the opportunity to test measurement techniques over a wide range of physiological-realistic cardiac outputs.

Cardiac output using the throughflow of isoflurane is investigated for cardiac outputs of 2, 4, 6, 8 and 10 litres per minute. These cardiac output rates include values that require clinical intervention.

It is widely appreciated that clinical trials are subject to rigorous ethical considerations, and participants are chosen based on selection criteria that commonly exclude clinically-unstable patients. In addition, changes in cardiac output are physiological responses, and

occur outside the controlled environment that can be obtained in simulations. Thus, the use of bench-top and computerised simulation allows repetition of physiological updates and end-tidal concentrations that lead to cardiac outputs where intervention is necessary.

The nature of the throughflow method requires physical isolation of the left and right lung gases, this is achieved with a dual-lumen endo-tracheal tube. A commercial simulator which produced an accurate and realistic exchange of respiratory and anaesthetic gases could not be identified. Similarly, simulators described in the literature were either unable to incorporate the uptake and elimination of anaesthetic agent, or required complicated setup.

This thesis includes the description of the design and testing of a simulator which could produce realistic patient gas uptakes (including anaesthetic vapour) and end-tidal concentrations. This simulator was used to test the ability of the throughflow of isoflurane method and the ability of the system to measure accurate patient lung gas uptakes, and end-tidal concentrations. Advances in technology have allowed the automation of much of the simulator, which has a software interface and can simulate rapid changes in gas uptake and production.

1.3.2. Contributions to Knowledge

1 Isoflurane can be used as a substitute for nitrous oxide in the throughflow cardiac equation. The rapid uptake of isoflurane, in the body and by the simulator, make it an ideal choice which expands the options for fresh gas flow mixtures.

2 Although anaesthetic agents are convenient options due to their low solubilities, the small uptakes and end-tidal concentrations make them susceptible to any measurement fluctuations. Thus trending, rather than absolute measurement, is likely to be of more value.

3 Oxygen uptakes, and thus oxygen uptake ratios, vary from breath to breath. This is a combination of normal inter-breath variation along with a combination of any errors present in both oxygen concentration measurement and averaging tidal breath flows, whose instantaneous flows vary between 0 and 20 litres per minute. A long moving-average

of oxygen uptakes can be used to counteract such compounding error, but this means when a large change in oxygen uptake does occur, or where measurement is interrupted (due to necessary circuit disconnection), the system takes a long time to recover. This makes the use of fixed oxygen uptake ratios an attractive choice, particularly if we consider that the fixed ratio is a good fit for subjects with normal lungs.

4 Isoflurane, when compared with nitrous oxide, is not affected to the same degree by ventilation-perfusion scatter. However, it is possible to compensate for dead space by using a multi-compartmental model that was previously employed for nitrous oxide throughflow (Peyton 2004).

1.3.3. Haldane Technique

This thesis refers to the Haldane technique. It is based on the assumption that nitrogen is neither produced nor absorbed by the body. Fresh gas flow is easily identified either through direct measurement or recording fresh gas flow settings on the anaesthetic machine. If nitrogen uptake is zero, and its concentration is measured in both fresh and exhaust gas flows, then the change in concentration can be used to determine the exhaust gas flow without using direct measurement. A more detailed description can be found in Chapter 3.

1.4. Thesis Outline

The thesis outline follows and explains the rationale for choosing to investigate the use of inhaled isoflurane to measure cardiac output.

Chapter One in this chapter, I introduce general anaesthesia and what happens in the anaesthetised body, and contemporary physiological measurement techniques. This leads to a brief introduction of throughflow using Isoflurane and broad aims/hypothesis of the thesis, followed by an outline of original contributions: selection of fixed oxygen ratios, long term averaged oxygen ratios, instantaneous ratios, the importance of uptakes and end-tidal concentrations, how frequently these need to be sampled, and how accurate they need to be.

Chapter Two explains the characteristics of cardiac output measurement in critical care, and considers the main existing techniques for analysis. Following this is a discussion of the role of gas exchange in determining non-invasive cardiac output, the use of partial rebreathing of carbon dioxide, and the throughflow of nitrous oxide. This leads to examination of the association between the development of new models and the creation of new gas exchange simulators. Finally, existing physical simulators that produce lung simulations will be reviewed, and the merits of these methods are discussed.

Chapter 3 describes the reason isoflurane was chosen as the vapour to replace nitrous oxide for measuring throughflow cardiac output. This includes the setup for the anaesthetic machine, modified ventilator and breathing systems, as well as the measurement system (placement of flow meters, and gas analyser sample locations. As described in Chapter 2, physical lung simulators are often developed alongside new measurement techniques, as was adopted in this was done in this thesis. This is followed by a description of a new physical simulator and how it enables the testing, improvement and validation of using isoflurane throughflow to determine cardiac output. The selection and testing of five clinical scenarios will be presented for a range of isoflurane uptakes, then the effect of changing respiratory rate, and introducing positive end-expiratory pressure (PEEP), will be discussed.

Chapter 4 reviews the potential sources of measurement error from physiological variation, as well as the lack of shunt measurement. Previous modelling by Peyton (2004) based on the throughflow of nitrous oxide showed that the technique benefited from applying a multicompartmental model to compensate for dead space and measure shunt flow. This modelling will be repeated for isoflurane.

In **Chapter 5** the limitations of the method will be tested using a computer simulation to see what variability in the measured parameters can be tolerated. This will assess the usefulness of moving-average filters. The likelihood of these values occurring will be considered in relation to the results of the physical simulator in chapter 6.

Chapter 6 provides results from the benchtop simulator for five cardiac output values between two and ten litres per minute. Results are presented so that individual uptakes, end-tidal concentrations and the final cardiac output measurements can be seen, using directly measured exhaust flow and Haldane-derived exhaust flows. The use of direct measurement of oxygen uptake ratios in the place of an assume oxygen uptake ratio is also presented.

Chapter 7: The **Discussion** reviews the results of Chapter 6 and examines the accuracy and precision of the measurement system, the implications of measuring exhaust flow directly versus using Haldane-derived exhaust flows, the system responsiveness, and the ability of the system to measure cardiac output and track changes. Finally, the effect of changing mechanical ventilation factors such as PEEP and respiratory rate, is discussed.

Chapter 8: Reviews this thesis in light of the research hypothesis and primary aims; this will be done with reference to the discussion of the simulated and modelled results. It also summarises the original contributions and suggests future opportunities for further research.

Chapter 2 Cardiac Output Measurement Techniques and Lung Gas-Exchange Simulation

2.1. Introduction

Parts of this chapter have been published as:

> Bailey, R., Junor, P., (2015) Cardiac Output in General Anaesthesia and Critical Care: Present State & Future Direction, *Australian Biomedical Engineering Conference (ABEC) November 22-25 2015, ISBN: 978-1-922107-64-0*

Major surgery causes 'considerable physiologic insult that can be associated with significant morbidity and mortality' (Navarro, Bloomstone et al. 2015) and is typically combined with general anaesthesia which induces paralysis and analgesia and eliminates conscious awareness of the surgical procedure. Paralysis affords many surgical advantages but makes it necessary to control patient respiration. However, paralysis is also accompanied by the loss of many indicators of patient deterioration and strengthens the need to monitor physiological variables closely.

Cardiac output measurement during general anaesthesia is unique; it is typically characterized by a short but critical period where clinical management affects longer-term care and length of stay. Australian clinical guidelines outline the minimum requirements during all anaesthesia, and require that cardiac output monitoring be available during general anaesthesia (ANZCA 2008).

Cardiac output is an indicator of work being performed by the body; it is a measurement of the volume of blood pumped through the left ventricle each minute. In 1870 Adolf Fick described the heart as 'gas pumps' and proposed a method for measuring work, based on oxygen consumption and carbon dioxide elimination (Fick 1870). At the time, his theory could not be used because of the lack of suitable technology, but it is now the basis of most methods for measuring cardiac output.

Interest prevails in the concept of cardiac output as an early indicator of deterioration, and as a measurement that can assist fluid optimisation and improve patient care. Despite international support for fluid optimisation, there is a lack of structure, standardisation, procedures and policies at international, national and institutional levels as to how this should occur (Navarro, Bloomstone et al. 2015) and how cardiac output could be used to improve optimisation.

The range of available techniques reflects the difficulty of finding a single method that is accurate, reproducible and clinically suitable. We will review techniques which fall into five groups: dilution (in the blood), pulse pressure contour analysis, bio-impedance, imaging, and pulmonary gas exchange. The first four of these methods (dilution, pulse pressure contour analysis, bio-impedance and imaging) are commercial techniques that have been used for over 40 years in clinical practice, although over time some adaptations have been made to improve accuracy, precision and usability.

This will be followed by a discussion of pulmonary gas-exchange measurement. Gas-exchange provides a non-invasive method for determining cardiac output from the measurement of pulmonary blood flow. A range of gases and techniques have been reviewed to provide insights into measuring continuous, noninvasive cardiac output using gas flow uptakes.

Finally, the integral role of simulators (and their development) in the improvement and investigation of gas-exchange based methods will be examined.

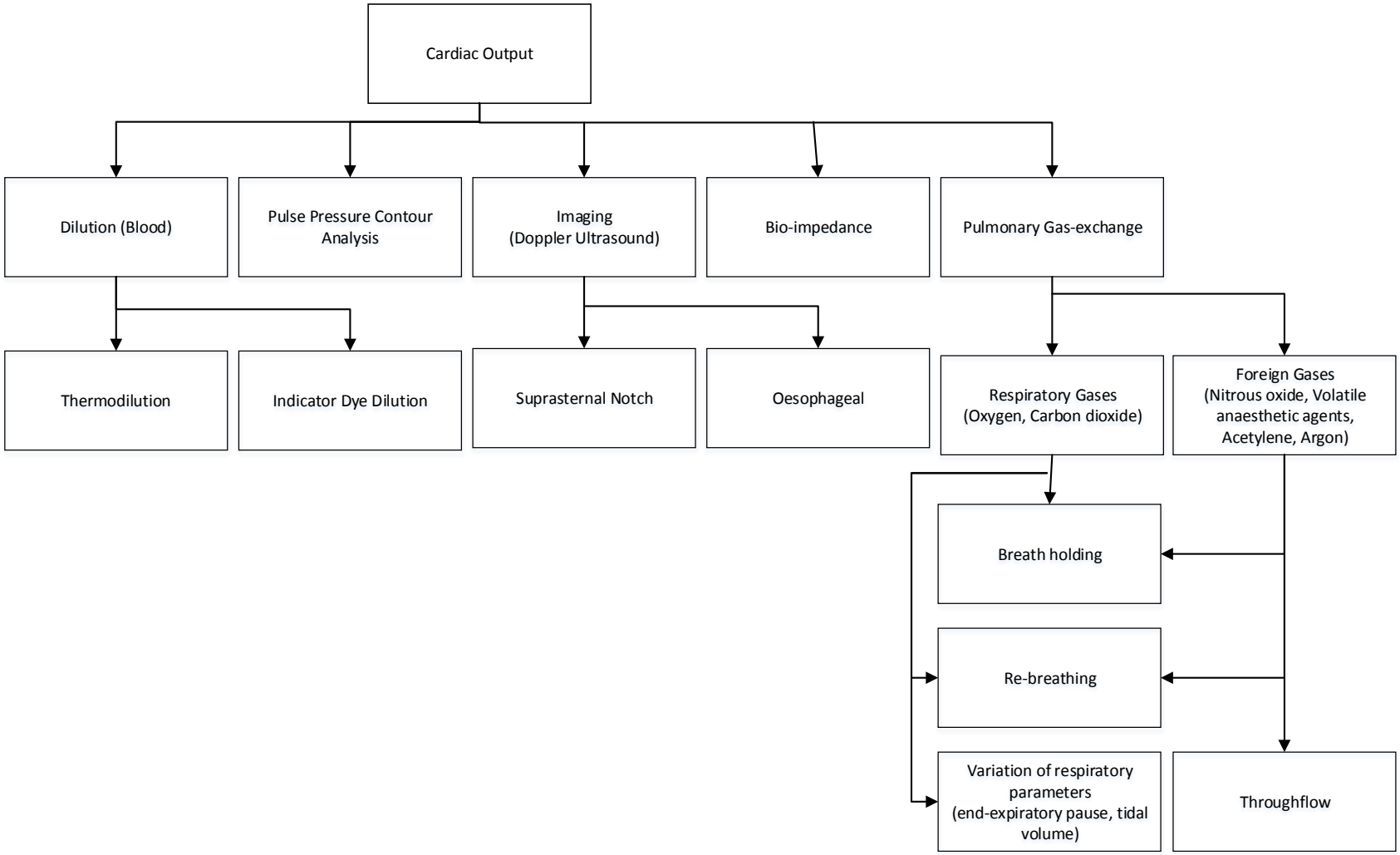

Figure 1 Review of cardiac output measurement techniques

2.2. Indicator Dilution Techniques

Thermodilution was introduced in the 1950s and was widely accepted into clinical practice. Dilution methods (thermo- and indicator-dye) remain trusted techniques; thermodilution is the de-facto gold- standard for clinical measurement of cardiac output. All dilution methods are based on the Stuart-Hamilton principle: the theory that if a known quantity of solution is injected into an unknown volume, the flow can be calculated from the time course of the concentration change downstream. This holds true when the selected solution does not interact with the body through cellular exchange, and where the flow rate is high enough that the measurements do not lose resolution (for example above two litres per minute).

Thermodilution uses a bolus of cold or room-temperature saline (or another isotonic solution); alternatively, indicator-dye dilution can be employed: indicator dyes bind with blood-borne protein and have a short half-life so that they can be removed from the body, allowing measurements to be repeated. Cardiac output is measured by intermittently introducing fluid boluses (5-10 mL) into the central venous circulation via a catheter. Right-heart thermodilution utilises placement of a pulmonary artery catheter (PAC) to measure the temperature change in the pulmonary artery flow (the traditional measurement point used in clinical practice in cardiac surgical patients). Cardiac output is then determined by measuring the area under the curve of the resulting thermal waveform. Newer adaptations of the technique use measurement in a systemic artery via an arterial blood pressure monitoring catheter (transpulmonary thermodilution), which is less invasive than a PAC but can cause some complications, for example, local haematomas, thrombosis and ischaemia (Monnet and Teboul 2017).

Despite their popularity, dilution measurement methods have several limitations:

- The fluid bolus can be cumbersome to prepare
- They need to be timed carefully to avoid re-circulation of blood so that the resultant waveform is clear and has a single peak
- Bias can occur due to thermal decay during passage through the tissues, particularly at the low flow rates.

- They are discrete and need to be repeated intermittently - and between three and five times to determine an average value for greater precision

2.2.1. Pulmonary Arterial Catheters

The location of pulmonary arterial catheter positioning is associated with several complications, including 'PA [pulmonary artery] perforation, pulmonary infarction, catheter knotting, local or systemic infection, cardiac arrhythmias, and heparin-induced thrombocytopenia' (Kowalak 2009). These complications have restricted the use of dilution methods using this anatomical site, to people who are critically ill and in the surgical, and medical intensive care settings.

The justification for using pulmonary artery catheters was tested by Guyatt (1991). He reported an 'absence of trends in favour of RHC [right heart catheterisation] in any of the measures of outcome' and queried the use of pulmonary arterial catheterisation 'it is uncertain that patients benefit from it, and it is possible they are being harmed' (Guyatt 1991). His study was influenced by the small sample size and the clinical confidence in thermodilution measurements, which meant that some participants were instrumented with a pulmonary artery catheter simply because the treating clinician believed it was 'ethically mandated'.

2.2.2. Peripheral Placement of Catheter

The use of peripheral measurement sites (away from the pulmonary artery) was pioneered by early researchers such as Hanson (1964) and is now widely accepted. Trans-pulmonary thermodilution sites measure temperature change in a systemic artery; while it still suffers from being a discrete measurement, it is 'easier to set up' and has been adopted as a calibration technique for other continuous measurement methods such as pulse pressure approaches (Monnet and Teboul 2017).

2.3. Pulse Pressure

Pulse pressure contour analysis, developed in the 1970s, uses measured arterial pressure to determine the stroke volume and then calculate cardiac output. Vascular resistance and compliance affects pressure and can vary between patients, this is problematic because it is necessary either to calibrate measurements against a discrete reference technique (for instance trans-pulmonary thermodilution) or to make assumptions about these variables. Commercial pulse pressure techniques may be calibrated periodically (Berton and Cholley 2002) against a discrete reference method (for example trans-pulmonary thermodilution) or use patient demographics in proprietary algorithms to improve estimation of cardiac output.

Pressure measurements are popular in critical-care settings: the necessary placement of catheters for systemic blood pressure monitoring in these environments has led to the popular adoption of this technique. In addition to cardiac output measurement, pulse pressure contour analysis measurements include arterial pressure, pulse rate, stroke volume, and stroke volume variation: these additional parameters increase the diagnostic value of the methods. The choice of calibration of the pulse contour device using a reference standard or a proprietary algorithm is reduced to a value proposition: is the absolute value of cardiac output more important than the trend?

If the absolute value is considered essential, then periodic re-calibration with a reference standard is required; otherwise, the use of an algorithm based on patient demographics may be sufficient. However, no existing method for measuring cardiac output is perfect, and limits of agreement of +/- 45% between methods are considered realistic.

2.5. Bio-impedance

Electrocardiograms are accepted in clinical practice and have been recognised as a valuable diagnostic tool since the 1930s. Given the non-invasive, continuous nature and simple application of electrocardiograms, it is unsurprising that this technique was explored to determine cardiac output from the 1960s.

Bio-impedance works using an electrode placement modified from that of a standard ECG. A known 70kHz signal current is applied to electrodes across the chest, across which voltages measured with respect to the current can enable determination of changes in bio-impedance through different axes, which occur as pulmonary blood volume changes with the delivery of each stroke volume from the ventricle. The use of modified electrode placement and the introduction of current does not prevent the measurement of electrocardiograms, although additional filtering is required, and the altered electrode placement needs to be considered.

Unfortunately, despite being noninvasive and continuous, bio-impedance has its drawbacks. It may produce inaccurate measurements when cardiac arrhythmias or cardiac deformities are present (Singer and Webb 2009), if suctioning is being used, if the patient is intubated (with an endotracheal tube), or if dressings are present (Barry, Mallick et al. 1997). This means it might not be suitable for patients in a critical condition.

2.6. Imaging (Doppler Ultrasound)

A decade after the introduction of bio-impedance, new methods for measuring continuous cardiac output noninvasively were still being derived. Imaging techniques which included the use of ultrasound started to be explored in the 1970s.

The combined measurement of the cross-sectional area of the aorta and the blood velocity using sonography is used to determine stroke volume and thus cardiac output. This method (because it views the left side of the heart) is advantageous because it is less affected by cardiac shunts. Most modern noninvasive cardiac output techniques exclude measurement of cardiac shunts.

2.6.1. Suprasternal Notch

Ultrasound measurements can be performed externally using insonation through the suprasternal notch, a site which benefits from being able to be located readily, and which can be employed in an emergency environment. The disadvantage of measurement is that the ultrasound probe is hand-held and is thus this is a temporary method not suitable for sustained cardiac output measurement.

2.6.2. Oesophageal Probes

In contrast, an oesophageal probe can remain in position after being introduced. This means that cardiac output can be measured continuously over a longer period. However, the probe needs to be located at the correct depth and is affected by any encountered ‘electrical cautery’ (Pugsley and Lerner 2010).

Both techniques are comparably rapid but require considerable operator skill and attention to measure cardiac output accurately.

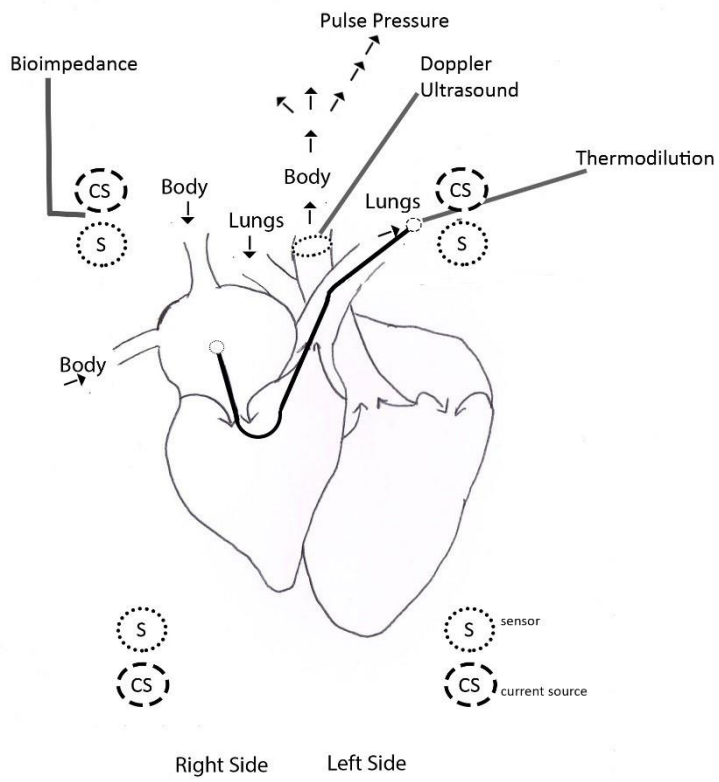

Figure 2 The sites for measurement of dilution, pulse pressure, imaging and bioimpedance. Adapted from Bailey, Junor (Bailey and Junor 2015)

2.8. Pulmonary Gas-exchange

Initially, gas-based techniques were explored because it was difficult and dangerous to perform blood-based measurements. Modern adaptations of these techniques facilitate accurate and precise measurement that can be used with increased control of airway gases. These methods are safer than invasive techniques, require less operator skills than imaging technologies, and do not have the clinical or surgical restrictions of impedance-based techniques. The invasiveness, and thus the risk, of any measurement technique, needs to be considered from the standpoint of

1) risk/invasiveness of all supporting equipment to the method
2) the additional risk/invasiveness as compared to the general care of the patient

Since Fick suggested in 1870 that gases could be used to determine the work of the heart, respiratory and foreign gases using a range of delivery methods have been investigated to measure cardiac output (Grollman 1932, Defares 1958, Gan, Nishi et al. 1993, Robinson, Peyton et al. 2003, Robinson, Peyton et al. 2004).

$$\dot{Q} = \frac{\dot{V}_{O_2}}{C_{a_{O_2}} - C_{\bar{v}_{O_2}}}$$

Equation 1 The original Fick equation based on the consumption of oxygen using the uptake rate of oxygen ($\dot{V}_{O_2}$), and fractional concentrations of arterial oxygen ($C_{a_{O_2}}$) and mixed-venous oxygen ($C_{\bar{v}_{O_2}}$)

The original Fick equation is based on oxygen gas exchange and requires the measurement of mixed venous oxygen content. Oxygen can be suitably replaced by another gas '*G*' if that gas:

- lacks toxicity
- provides direct and precise responsiveness to changes in cardiac output
- is environmentally sound
- is non-flammable

- is chemically inert (does not interact with instrumentation and tubing)
- is preferably low cost

$$\dot{Q} = \frac{\dot{V}_G}{C_{a_G} - C_{\bar{v}_G}}$$

Equation 2 Fick equation for gas 'G'

The Fick equation is complicated because it has two significant unknowns the cardiac output or pulmonary blood flow ($\dot{Q}$) and the fractional content of gas 'G' in the mixed venous blood ($C_{\bar{v}_G}$). Thus, to calculate cardiac output the fractional content of gas 'G' in the mixed venous blood needs to be measured. The use of any foreign gas in an inspired mixture will create changes in arterial and mixed venous blood content of gas 'G', which makes the re-circulation of blood a limiting factor in most gas based systems, because mixed venous blood concentration needs to reach a steady-state before measurements can be repeated.

Pre-1932, acetylene, carbon dioxide, ethylene, ethyl iodine and nitrous oxide were actively being investigated, and their various benefits and shortcomings were hotly contested by different research groups. Nevertheless, the active research in this period led to the identification of several useful gases (nitrous oxide, acetylene and carbon dioxide), and techniques including breath-holding, half-expirations and re-breathing techniques (Grollman 1932). Recent developments and novel techniques have meant that cardiac output, hitherto a discrete measurement, can now be measured continuously.

2.8.1. Carbon Dioxide – Re-breathing and Breath Holding

Carbon dioxide has had a long history of being used to determine cardiac output through breath-holding or re-breathing experiments. The use of re-breathing and breath-holding to determine the carbon dioxide concentration in the venous blood was investigated by Defares (1958), who selected re-breathing because it was quicker and allowed measurements to be collected before blood re-circulation. Despite the difficulty of obtaining an accurate carbon dioxide end-expiration plateau to determine venous concentrations, Defares challenged the suggestion that it was not possible to reach a plateau before re-circulation was attained. He demonstrated an exponential relationship between the venous

blood samples and the end-expired concentration samples collected in a Douglas bag prior to a plateau being reached after several breaths. Derived venous carbon dioxide concentrations were then used with oxygenated carbon dioxide dissociation curves to approximate cardiac output.

Notwithstanding limited technology, Defares revealed remarkable insight into the difficulties and challenges in determining both venous carbon dioxide concentration and cardiac outputs. Improvements in techniques and medical devices have made the measurement of continuous and instantaneous lung gas concentrations possible and reduced the need for complex assumptions and precise collection timing to determine end-expiration concentrations. Despite his self-identified limitations in the study, including the absence of a comparison technique, Defares' work demonstrated that carbon dioxide-based techniques could determine cardiac output.

The interest in using carbon dioxide to measure cardiac output in closed respiratory circuits introduces new challenges because in-line soda lime is used to absorb carbon dioxide to minimise gas wastage, to reduce the size of fresh gas flows, and to minimise anaesthetic vapour costs. Consequently, carbon dioxide needs to be measured before removal, or alternative patient circuits (for example, Bain circuits) need to be used. Ongoing investigations into carbon dioxide techniques have seen continual improvements as a result of technology developments in gas delivery and measurement systems.

Prior to 1980 the implementation of the Fick equation was affected by the relative errors in arterio-venous difference measurement and complicated experimental setup in ventilated patients, Gedeon (1980) demonstrated that changes in end-inspiratory pause could be used instead of re-breathing and manual breath holding manoeuvres. Changing the length of end-inspiratory pause (hyper- to hypo-ventilation) caused measurable changes in carbon dioxide elimination and end-tidal concentrations, without affecting the mixed venous blood gas concentration for carbon dioxide. This means mixed venous blood-gas concentrations can be eliminated from calculations. Cardiac output was determined using the basal carbon dioxide elimination and end-tidal concentrations, in conjunction with the measured change in these values as a result of changing end-inspiratory pause length. Non-invasive cardiac output could be recalculated at 15-minute intervals.

The work by Gedeon demonstrated non-invasive measurement of cardiac output using carbon dioxide without the need for direct blood-gas measurement, and was extended by Capek and Roy (1988). Instead of using changes in end-inspiratory pause they implemented intermittent (30 second) intervals of partial rebreathing employing an increase in circuit dead space of 170ml that was automated using a three-way solenoid. They validated their assumption that mixed venous concentrations remained constant between periods of rebreathing and normal breathing in an animal study using comparison with mixed venous blood samples. Similarly to Gedeon, they used the relatively large variation in carbon dioxide elimination and end-tidal concentrations between periods of normal and partial-rebreathing to determine the non-invasive cardiac output. However, the use of the partial-rebreathing technique meant that measurements returned to steady-state more rapidly and cardiac output measurements could be repeated at 3-minute intervals.

The introduction of changes in inspiratory gas composition through re-breathing and non-rebreathing techniques means that two Fick equations can be solved simultaneously; if the fractional concentration of mixed venous gas 'G' is at steady-state during these measurements it can be eliminated.

$$\dot{Q} = \frac{\dot{V}_{G_1} - \dot{V}_{G_2}}{x\,(P_{a_{G_1}} - P_{a_{G_2}})/P_B}$$

Equation 3 The differential Fick Equation eliminates the need to measure the fractional concentration of mixed venous blood. The term 'x' refers to a factor that relates the measured partial pressure to the fractional concentration of arterial gas (P_{a_G}).

The measurement of the differential Fick can be further simplified by using the partial pressure of end-tidal gas 'G', ($P_{E'_G}$), in the place of arterial gas measurement. The commercially available Novametrix NICO(2001) measures flow and carbon dioxide concentration and uses the differential Fick method to produce intermittent, non-invasive cardiac output that is corrected for shunt (Figure 3). A baseline measurement is made during normal ventilation, this is followed by fifty seconds of carbon dioxide re-breathing (via a respiratory loop that is incorporated into the breathing circuit through activation of a re-breathing valve) followed by a period of stabilisation. The utilisation of partial

rebreathing eliminates the need to measure mixed venous carbon dioxide, while pulse rate is used to calculate stroke volume and oxygen saturation allows correction for shunt.

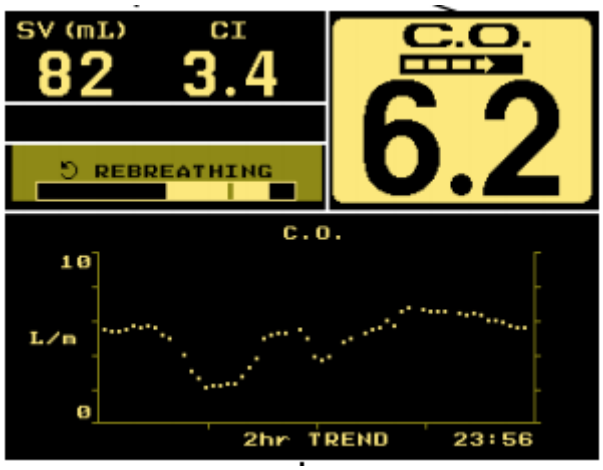

Figure 3 Novametrix NICO Model 7300 (2001)

2.8.2. Carbon dioxide – Breath-by-Breath Measurement of Cardiac Output

The problems associated with gas recirculation in blood still need to be overcome, and several techniques including variations to end-expiratory pause and tidal volume have been investigated to produce a breath-by-breath pulmonary blood flow measurement free from these problems. Peyton (2006) examined the use of simultaneous measurements of carbon dioxide uptake and end-tidal partial pressures in response to step changes in tidal volume, a method which he termed 'capnodynamics'. Paired measurements, taken from different halves of a 12-breath respiratory cycle which differed by 200ml in tidal volume, were used to track cardiac output through a series of three expressions named 'calibration', 'capacitance' and 'continuity' (Peyton, Venkatesan et al. 2006). The calibration equation was used at the time of the tidal volume step change, while capacitance equations occurred during steady-state when end-tidal concentration measurements were constant. Where end-tidal concentrations indicated a period of instability, the continuity equation was used to track changing cardiac output. The application of a continuity equation improved capnodynamics from an intermittent steady-state reference technique to a continuous method capable of measuring the change in cardiac output.

The method can be expected to track very low cardiac outputs because “a sudden reduction in cardiac output during anaesthesia (will) cause an abrupt reduction in end-expiratory P_{CO2} ” (Lumb 2005). This was supported by Peyton’s capnodynamic study that showed comparable measurements when compared with an indwelling probe. A delay of thirty seconds was measured following each intravenously-induced cardiac arrest in the animals; the initial drop in cardiac output was followed by a 2-minute delay in the recovery response. The thirty-second delay in response to cardiac output will not significantly affect clinical management, and all measurement methods need to accommodate the potential for a lag in the detection of change following an interventional response to a change in cardiac output. Unsurprisingly, it is easier to measure change following stability, rather than after a period of instability. Thus, the capnodynamic method is an attractive and potentially modular method for measuring cardiac output during anaesthesia or intensive care ventilation.

This system is valuable in anaesthetic, and intensive care settings where ventilation parameters are controlled, and adjustment of settings can be tolerated by the patient. However, unlike other re-breathing techniques, it is not suitable for subjects breathing spontaneously.

One problem with many gas-exchange based techniques is that they frequently alter fresh gas delivery to the lung: this can be either through changing the inspired gas concentrations, or the mechanical characteristics of ventilation (increasing tidal volume or end-expiratory pause). This means that complex solutions need to be used, and assumptions of constant pulmonary blood flow, either within a breath or sequence of breaths, may be necessary. Furthermore, blood re-circulation times can be critical, because this might introduce time limitations to measurements

2.8.3. Foreign Gases – Dual-inert technique

The use of foreign gases has also benefited from technology improvements: a non-rebreathing mathematical model for cardiac output determination, based on two inert gases in the spontaneously breathing patient, was developed by Gan (1993). This used acetylene, along with the relatively insoluble gas argon to determine alveolar volume.

Cardiac output could be updated every two breaths (in practice, more breaths will lead to improved accuracy). As with other techniques, the breaths needed to occur during a period of stable pulmonary blood flow.

Gan and co-workers recognised that measurement noise and respiratory variations were 'inevitable', and integrated them into the mathematical simulation using a Gaussian noise model applied to volumes and end-expiratory concentrations. To estimate noise, they measured the peak-to-peak magnitude of volumes and inspired gas concentrations. The use of dual inert gases was intended to compensate for the variations in tidal volume, but it does not eliminate measurement noise in the end-expiratory concentrations: this still needed to be addressed.

Following the mathematical model, Gan demonstrated that the dual inert technique tracked well against thermodilution using intravenous drug infusion to increase cardiac output in anaesthetised and ventilated animals. A human clinical trial in spontaneously breathing subjects was conducted next, but this was complicated because thermodilution was not appropriate in this patient population. Instead, Gan repeated a series of work-load challenges in two spontaneously-breathing trained volunteers who were allocated to breathe either an acetylene or dual inert fresh gas mixture on one day, and then the alternative gas on the subsequent day. This method is not an ideal reference because it assumes that individuals will respond analogously on consecutive days to identical work-load challenges. It is hard to compare some non-invasive cardiac output measurement techniques to a reference method in clinical studies: this may be because of the level of invasiveness of a reference technique, or because the specialist nature of the novel method makes it difficult to find a compatible technique for simultaneous reference. Despite the difficulties that can be encountered when validating a new paradigm, many of these methods have made significant contributions to our understandings. For instance, the dual inert gas technique demonstrated that manipulation of fresh gas during patients' spontaneous breathing can be used to calculate physiological variables (including alveolar dead space, and lung volumes) and that these calculations can be used to produce more stable cardiac output measurements.

More recently, it has been demonstrated that:

- volatile anaesthetic agent uptake is strongly affected by changes in cardiac output (Kennedy and Baker 2001, Kennedy and Baker 2001a), making the use of volatile agents in gas-based techniques attractive;
- The functional airway separation with the independent delivery of fresh gas to the left and right lungs also demonstrated the feasibility of providing breath-by-breath estimation of non-shunt cardiac output using throughflow of nitrous oxide (Robinson, Peyton et al. 2003).

Both techniques indicate the potential for using throughflow of anaesthetic vapour to determine cardiac output. Evolving gas exchange methods have predominately used carbon dioxide, acetylene and nitrous oxide, and are well-described by Laszlo (2004). The early research into gas exchange involved various gases and techniques t. This identified the importance of testing assumptions, knowing chemical interactions between gases, tissues and instrumentation, and accounting for gas storage in the tissues. This knowledge has been built on to develop newer techniques such as the use of acetylene with argon (Gan, Nishi et al. 1993) and nitrous oxide throughflow (Robinson 2003).

2.8.4. Choice of Ideal Inert Gas for Cardiac Output Measurement

Kennedy and Baker highlighted that uptake of anaesthetic vapours are affected by cardiac output. The relationship between these was expanded by Peyton (2004) based on differentiation of the mass balance Fick equation (Equation 2). He developed models for both single and multi-compartmental systems to demonstrate the relationship between the maximum sensitivity of alveolar-capillary gas exchange to changes in pulmonary blood flow ($d\dot{V}_G/d\dot{Q}$) for agents with different blood-gas partition coefficients (λ).

Peyton describes that for any gas *'G'*, in a single lung compartment, $d\dot{V}_G/d\dot{Q}$ is at a maximum when

$$\lambda = \frac{\dot{V}_{AE}}{\dot{Q}(1 - F_{I_G})}$$

Based on this he modelled the $d\dot{V}_G/d\dot{Q}$ as a function of blood-gas solubility for alveolar-capillary uptake of an inert gas. This showed that as the cardiac output increases, the ideal

blood-gas solubility decreases (Figure 4). In contrast, Peyton demonstrated using a multiple compartmental model that as $\dot{V}/\dot{Q}$ inhomogeneity or scatter worsens, the ideal solubility increases for any overall $\dot{V}/\dot{Q}$ ratio.

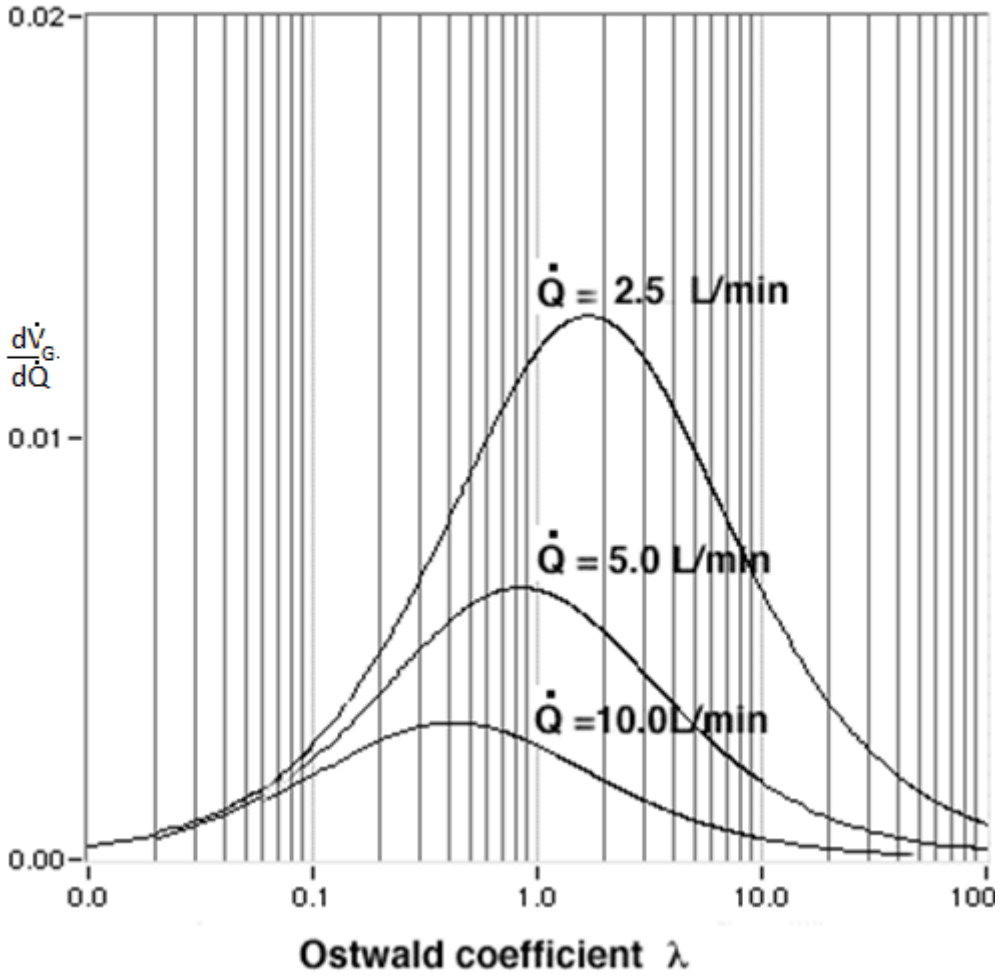

Figure 4 $d\dot{V}_G/d\dot{Q}$ versus the Ostwald blood-gas coefficient for cardiac outputs of 2.5, 5.0 and 10.0 L min^{-1} .

(Peyton 2004)

He then plotted (Figure 5) the ideal blood-gas solubility (where maximal $d\dot{V}_G/d\dot{Q}$ occurs) versus increasing $\dot{V}/\dot{Q}$ inhomogeneity. The worsening $\dot{V}/\dot{Q}$ scatter was measured by increasing natural-log standard deviation (log SD) of the distribution of ventilation and blood flow.

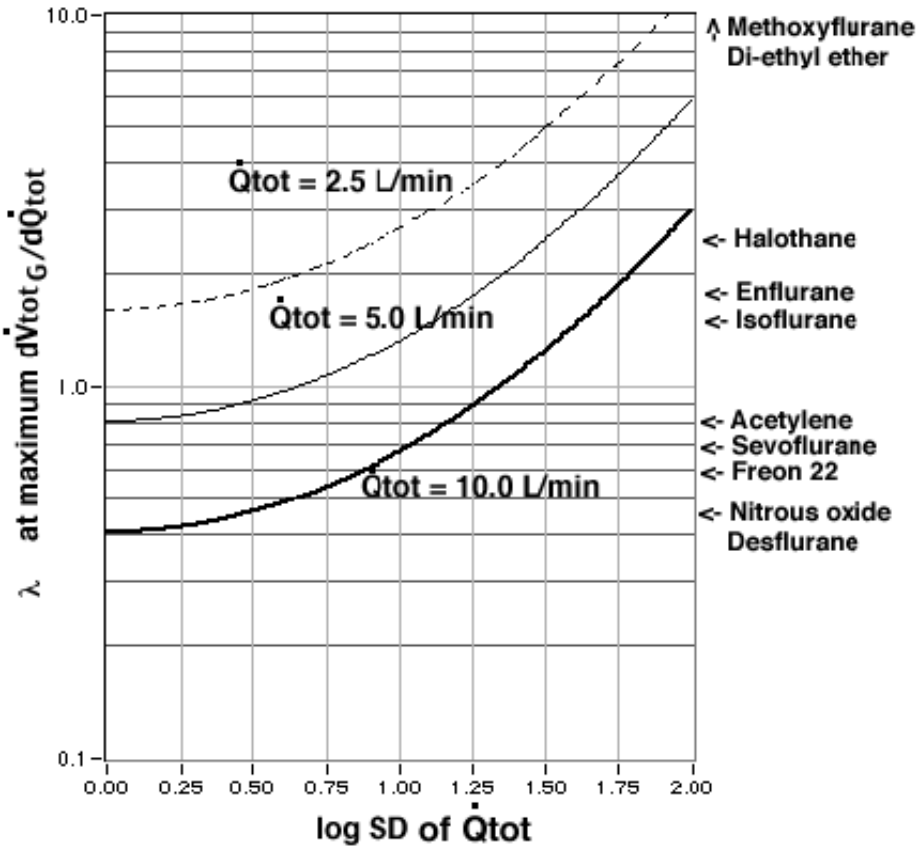

Figure 5 Ideal λ (at maximal $d\dot{V}_G/d\dot{Q}$) as a function of inhomogeneity (log SD of $\dot{Q}$) at F_{IG} of 0.01. For cardiac outputs for 2.0, 5.0 and 10.0 L min^{-1}.

(Peyton 2004)

Figure 5 shows that for typical anaesthetic log SD value (between 0.75 and 1.5), nitrous oxide is towards the lower limit of useful gases across the range of cardiac output values typically encountered in the anaesthetised patient. In contrast, volatile anaesthetic agents such as enflurane, halothane and isoflurane, which have higher solubilities, are preferable. This supports the findings of Kennedy and Baker (1993).

2.8.5. Throughflow of Nitrous Oxide – Breath-by-Breath Measurement

Advancements in the development of continuous methods using paired gas exchange measurement techniques have occurred. This concept can be paired with the use of foreign inert lung gases that has previously been used for gas exchange based methods (Grollman 1932, Gan, Nishi et al. 1993) to produce new techniques that could avoid limitations associated with re-circulation. One alternative included delivering different lung gas

mixtures to the functionally-separated left and right lungs. In this technique, nitrous oxide was supplied only to the left lung, and it is taken up in the left lung and is excreeted by the right lung causing a “throughflow” of gas from the left to right lung (Robinson, Peyton et al. 2003). This enables continuous measurement as mixed venous gas concentration is common to both lungs and eliminates drawbacks associated with re-circulation that occur when a single fresh gas mixture is used to ventilate to both lungs. End-expiratory lung gas concentrations were used to estimate the arterial blood concentration: this technique is common and has also been utilised by Gan(1993) and Peyton(2006).

The derivation of the throughflow equation was presented by Vartuli (2002) and is included here because its understanding is essential to the throughflow method. Similar to other differential methods it is based on the Fick equation (Equation 1)

Throughflow is an adaptation of the differential Fick equation which is based on separate equations for the left and right lung, with a common mixed-venous blood. Thus, the Fick equation can be rearranged and a pair of simultaneous equations for the left and right lung are generated where suffixes ‘L’ and ‘R’ are used to designate left and right lungs.

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

Equation 4 Left and right simultaneous equations for fractional concentration of mixed venous

This leads to the equation

$$\dot{Q}_C = \frac{\dot{V}_{G_{(L)}} \times (\dot{Q}_C/\dot{Q}_{C_{(L)}}) - \dot{V}_{G_{(R)}} \times (\dot{Q}_C/\dot{Q}_{C_{(R)}})}{C_{c'_{G_{(L)}}} - C_{c'_{G_{(R)}}}}$$

Equation 5 Cardiac output calculation using throughflow of gas 'G'. Left and right end-capillary and the proportion of blood distributed to the left and right lung are required.

To measure cardiac output ($\dot{Q}_C$) non-invasively, the inverse proportions of blood flow in the left and right lungs need to be known, along with the end-capillary blood leaving the lung.

Vartuli explains that if optimal (or near-optimal) lung oxygenation is present, then the proportion of left and right oxygen uptake can be used in the place of pulmonary blood flow ratios:

$$\frac{\dot{Q}_C}{\dot{Q}_{C_{(L)}}} = \frac{\dot{V}_{O_2}}{\dot{V}_{O_2(L)}} \text{ and } \frac{\dot{Q}_C}{\dot{Q}_{C_{(R)}}} = \frac{\dot{V}_{O_2}}{\dot{V}_{O_2(R)}}$$

Equation 6 Assumption of optimal (or near optimal) oxygenation allows the ratio of oxygen uptake ratios to be substituted for left and right pulmonary blood flow.

Similarly, under ideal circumstances, the end-capillary blood in the left and right lung is equal to the end-tidal concentration in each lung, multiplied by the Ostwald blood-gas partition coefficient (λ_G).

$$C_{c'_{G_{(L)}}} = \lambda_G \times F_{E'_{G_{(L)}}} \text{ and } C_{c'_{G_{(R)}}} = \lambda_G \times F_{E'_{G_{(R)}}}$$

Equation 7 Ideally end-capillary blood gas concentration can be estimated from end-tidal gas concentrations and the Ostwald partition coefficient.

Substitution of Equation 4 and Equation 5 into Equation 3, enables non-invasive cardiac output determination.

$$\dot{Q}_c = \frac{\frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_L}}} \cdot \dot{V}_{G_L} - \frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_R}}} \cdot \dot{V}_{G_R}}{\lambda_G (F_{E'_{G_L}} - F_{E'_{G_R}})}$$

Equation 8 Non-invasive calculation of cardiac output using gas 'G'.

The advantage of functional separation of the left and right lung eliminates the effect of blood recirculation times because the throughflow of gas 'G' means that in the left and right lungs it goes in opposite directions.

Robinson (Robinson, Peyton et al. 2003) used two methods for determining the pulmonary blood flow distribution between the two lungs. The first assumed 'near-optimal (or equal)' oxygenation of both lungs, allowing the use of oxygen uptake ratios as an estimate of left and right pulmonary blood ratios, the second used a fixed ratio for left to right distribution.

These two methods compared favourably with thermodilution when used in nine patients during pre-cardiopulmonary bypass cardiac surgery. Robinson hypothesised that fixed ratios work well because an underestimation of distribution for the left-side is compensated by the overestimation on the right.

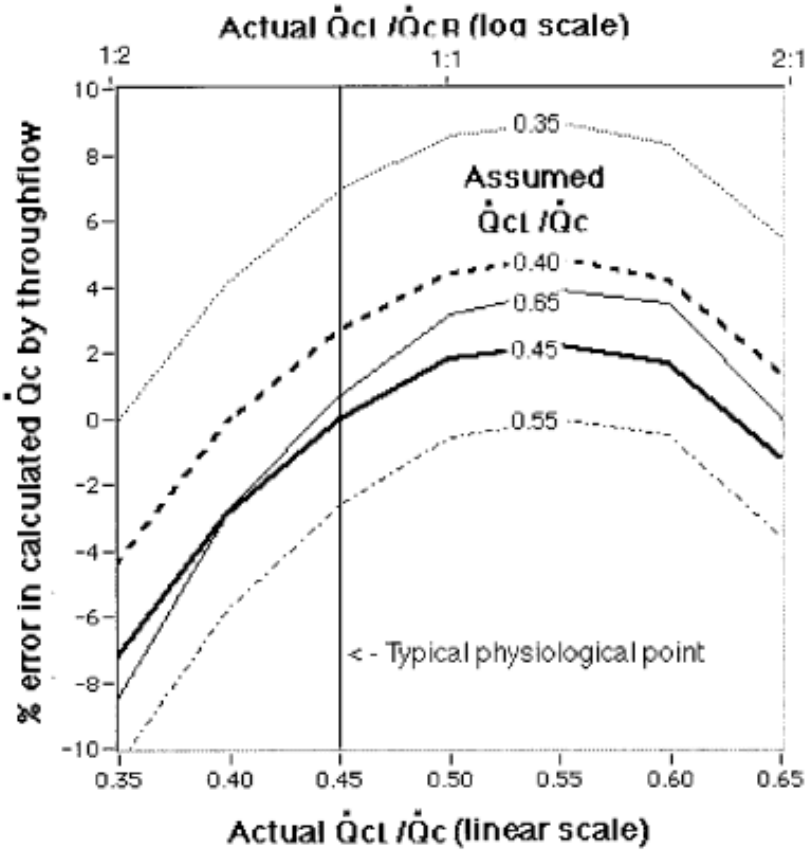

Figure 6 Incorrect assumption of the proportion of blood flow to left lung $\dot{Q}_{c\,L}/\dot{Q}_c$ affects measurement of pulmonary blood flow ($\dot{Q}_C$).

Reproduced from Fig. 3 (Robinson, Peyton et al. 2003)

As with the other gas exchange-based determinations, Robinson's approach measures the pulmonary blood flow and needs to be adjusted for the shunting fraction of blood flow. The throughflow of nitrous oxide showed significant potential for establishing responsive and accurate cardiac output. Benefits include the ability to measure continuous breath-by-breath measurements.

However, a drawback of the technique was the necessity to maintain a minimum fresh nitrogen flow so that the Haldane Transformation could be used to determine exhaust flow and thus gas uptakes in each lung. This limitation could, in theory, be overcome by using direct flow measurement in fresh and exhaust gas streams; alternatively, substitution of nitrous oxide with a volatile agent would allow nitrogen composition in the fresh gas to be increased.

2.8.6. Breath-by-Breath Gas Exchange

Measurement of continuous throughflow cardiac output requires accurate measurement of lung gas uptake flows and end-tidal concentrations. Both lung gas exchange, and the identification of breath commencement can be determined using several different techniques (Robinson, Peyton et al. 2004, Stuart-Andrews, Peyton et al. 2004, Cettolo and Francescato 2015). A breath defines a unique period of changing lung compliances, volumes and flows in the airways, and is traditionally identified by the start of inspiration. However, the exact time of the initiation of the breath is not as important as the need for it to be consistently and robustly identified as having occurred; this is particularly the case when breath-by-breath lung gas uptake flows are determined.

Kennedy's(2001a) model, identified 'that the best volatile respiratory agents to detect changes in cardiac output would have blood/gas solubilities around 1.5-2.5' and the 'ability of an agent to detect these changes is primarily determined by blood solubility.' They found that low blood-gas solubilities produced rapid rates of rise in expired concentrations; while high solubility increased the magnitude of change. This means the ideal respiratory gas/anaesthetic-agent for measuring cardiac output must balance a rapid response (to change) with the magnitude of change: because the value of measurement is lost if it detects the change slowly, or if the measured change it is too small to recognise.

2.8.7. Comparison of Techniques

Method	Location	Attributes	Shortcomings	Tech. Est.	Comments
Dilution: Saline, Isotonic Solution, Indicator Dye	PAC	I, NC	PA Perforation, Pulmonary infarction, Catheter knotting, Infection, Arrhythmias, Bleeding	50's	De-facto gold standard
Pulse Pressure Contour Analysis (Arterial Waveform)	Arterial Line	I,C	Calibration against Existing Techniques/ Proprietary algorithms	70's	Can use existing arterial IBP line
Imaging (Cross Sectional Area Artery & Blood Velocity)	Oral / External	M/NI,C	Operator skill, Time to Learn	70's	Oesophageal Probe / Suprasternal Notch
Bio-impedance (Chest Wall)	Electrodes	NI,C	Affected by Arrhythmias, Deformities, Chest drains, Endotracheal tubes & Wound dressings	60's	
Re-breathing & Breath Holding	Airway, CO_2	NI, NC	Requires open breathing circuit, not-compatible with soda-lime use	'58	Various methods

Dual-inert Foreign Gas	Airway, Acetylene & Argon	NI, C	Offline analysis required	'93	
Breath-by-breath CO_2	Airway, CO_2	NI, C		'05	Paired measurements, requires step change to tidal volume or end-expiratory pause
Breath-by-breath throughflow	Airway, N_2O	NI, C	Functionally-separated lungs	'03	Use of Haldane technique requires min. concentration of N_2 in fresh gas

Key: Invasive (I), Minimally Invasive (MI), Non-invasive (NI), Continuous Measurement(C), Non continuous measurement (NC)

Table 1 Comparison Cardiac Output Measurements(Bailey and Junor 2015)

2.9. Simulating Lung Gas Exchange

Despite the facility to test gas-based techniques in animal and human models, lung gas simulator improvement has become an integral part of developing new techniques for measuring lung gas exchange, because of the range of realistic physiological variables that can be replicated (Vartuli, Burfoot et al. 2002, Rosenbaum, Kirby et al. 2007). Unlike manikin-style simulators that are connected to virtual machines, the lung gas simulators described are connected to complex medical equipment and necessarily linked to the measurement environment. Even the few manikin-style simulators that provide realistic lung gas composition do not extend further than oxygen and carbon dioxide. Simulated blood may be drawn from them, but results are fed into a virtual display, and they are not interfaced with measuring equipment.

The development of lung gas exchange simulators has been closely associated with the development of new techniques for measuring both lung gas exchange and cardiac output; this is due to the many difficulties in achieving a wide range of uptake values in human and animal studies. Ideally, cardiac output measurement techniques should be proven over a clinically relevant range of 2-10 L min^{-1} (Peyton 2004). This is very difficult to achieve in live models where cardiac output at rest is typically between 4-6 L min^{-1}, while low cardiac output (2-4 L min^{-1}) could be a result of blood loss (surgery) or heart failure. In contrast, higher cardiac outputs are rare and in the anaesthetised patient are most likely to be a result of sepsis or more uncommon pathological conditions such as liver failure or malignant hypothermia.

There have been several attempts at producing realistic patient gas exchange simulators. Techniques for gas uptake measurement have been closely associated with both the Haldane technique to determine secondary flows, and the development of lung gas simulators to allow these new techniques to be measured robustly (Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003, Rosenbaum, Kirby et al. 2004, Peyton, Ramani et al. 2005, Rosenbaum, Kirby et al. 2007). Despite suggestions that the Haldane technique can be used only in situations where the composition of nitrogen is above 50% of the total mixture, this has been reconsidered, and concentrations as low as 29% have been used (Peyton,

Ramani et al. 2005). A concentration of around 30% appears to be the limit before measurements are compromised. The acceptance of digital flowmeters means that it has become possible to eliminate the need for nitrogen in fresh gas, although, given the historical importance of the Haldane technique in flow measurement, nitrogen concentrations that allow comparison are often used.

Similarly, in the absence of suitable and robust commercial simulators, it has been necessary for researchers to design their simulator systems, and so the development of new research simulators has been closely associated with the development of new uptake techniques.

2.9.1. Single-compartment, Multi-gas 'Apparent' Lung Simulator

Vartuli (2002) developed a single-compartment simulator which relied on the Haldane Transformation to produce 'apparent' gas uptakes. This simulator was supplied with enriching and diluting gases to produce fractional concentrations equivalent to physiologically realistic values; the use of the Haldane technique to determine exhaust flow meant that the 'true' large exhaust gas flows were of little consequence. The simulator has been used to demonstrate the effectiveness of the Foldes-Biro equation to measure oxygen uptake, and continuous indirect calorimetry (Stuart-Andrews, Peyton et al. 2004, 2006). The simulator described by Vartuli was remarkable because it demonstrated a system that could produce 'apparent' uptakes for oxygen, carbon dioxide, nitrous oxide and isoflurane. The disadvantage of this simulator was the inability to use modern measurement techniques and anaesthetic systems (including direct flow measurement) because of the high exhaust gas flow.

2.9.2. Alcohol Combustion Simulator (Oxygen and Carbon Dioxide)

Shortly after Vartuli's work, Rosenbaum (2004), as part of an investigation into a more accurate method of measuring uptakes, described a precise simulator that produced both oxygen and carbon dioxide uptakes using alcohol combustion (Rosenbaum, Kirby et al. 2007). Both Rosenbaum and Vartuli used a commercial adult hinged bellows to replicate realistic volumes, resistance and compliance, and to provide realistic fresh gas flows with concentrations of nitrogen that allowed the use of the Haldane technique. The Rosenbaum simulator enabled measurement of real rather than 'apparent' gas uptakes and produced

exhaust flows that were harmonious with inspired flows. However, because of its dependence on the chemical conversion of ethanol to carbon dioxide and water, it cannot replicate uptakes of other gases.

2.9.3. Multi-gas, Single-compartment Realistic Lung Gas Simulator

Extending on from the simulator produced by Vartuli (2002), Peyton, Ramani, Stuart-Andrews, Junor and Robinson (2005) introduced pressure controlled suctioning through a fine-bore flow resistor to produce exhaust gas flows equal to fresh gas flows. The introduction of suction complicates the calculation of simulation gas in-flows required to produce realistic simulated uptakes. To determine the amount of gas which needs to be removed, the system dead space needs to be determined. However, once the dead space is calculated using the method described in their paper it remained relatively constant throughout all scenarios.

Peyton (2005) developed and described a precise multi-gas lung simulator that replicates realistic uptakes of oxygen, nitrous oxide and isoflurane, as well as the production of carbon dioxide. The simulator was ventilated with a pre-determined fresh gas appropriate for the uptakes that would be produced for described scenarios. All fresh gas mixtures included a minimum of 29% nitrogen so that the Haldane Transformation could be used, although this was increased to 50% nitrogen when uptakes of nitrous oxide and isoflurane were eliminated.

The bellows were ventilated with a single fresh-gas mixture. The selection of constant fresh gas flow, tidal volume and respiratory rate was maintained through various scenarios: this meant that the functional dead space remained constant, simplifying the insertion and removal of gases. The simulator simultaneously extracted mixed lung gases and inserted pure gas flows to replicate uptake and excretion of anaesthetic gas. Gas flow was controlled using pressure-regulated bottled gas or pressure-regulated wall suction through pre-calibrated fine-bore tubing. Prior to data collection, each subsystem was calibrated with a 1-litre syringe to determine the pressures required to produce desired flow rates.

The simulator described by Peyton successfully replicated a variety of scenarios; the first of these included only oxygen and carbon dioxide uptakes equivalent to the functionality of

the alcohol-based simulator (Rosenbaum, Kirby et al. 2004, 2007). However, Peyton also demonstrated that his simulator could include nitrous oxide and isoflurane, something that an alcohol combustion simulator cannot replicate. Although Vartuli (Vartuli, Burfoot et al. 2002) had previously demonstrated uptake of gas flows beyond oxygen and carbon dioxide, he had not achieved this while maintaining realistic exhaust flows. This was only possible because Vartuli used the Haldane Transformation rather than direct flow measurement to determine total mixed exhaust flow based on the conservation of nitrogen in the system; true exhaust gas flow increases significantly due to the addition of gases without the corresponding removal.

Where simultaneous removal and insertion of gases occurs as in Peyton's simulator, it is necessary to maintain no overall nitrogen uptake, because any deviation will produce a variation between true exhaust gas flow and the Haldane measured flow. The need to preserve a zero-net uptake of nitrogen to use the Haldane Transformation increases the complexity of the simulator and requires that gas insertion and removal be error-free. This is difficult to achieve and requires careful monitoring of the pressure set on gas bottles and suction systems: Peyton achieved this by continuously monitoring gas pressures, but manual variable control pressure regulators do not provide the precise control that can be achieved using modern digital technology.

Peyton identified that low uptakes of nitrous oxide and isoflurane increased the observed mean bias from 5%, to 16% and 10% respectively in simulated target values. Isoflurane uptake was only simulated in three of the six scenarios: these scenarios used uptakes flows of 6.7 and 10 ml min^{-1}. The simulator produces isoflurane uptake in only one direction because the lung is ventilated with a single fresh gas mixture. The calculation of cardiac output using only the throughflow of isoflurane requires the measurement of isoflurane flows between 0.9 and 8.6 ml min^{-1}.

Peyton reported that the Haldane method for calculating exhaust gas flow is relatively stable in the face of minor fluctuations observed in breathing mechanics in the simulated environment, although these should be minimal when fresh gas and all ventilatory parameters are held steady. However, the method is not ideal, because it relies on the simulator to maintain a zero-nitrogen uptake.

For the six scenarios which were described, Peyton's simulator nevertheless demonstrated the realistic simulation of physiologically-realistic uptake and gas production of oxygen, carbon dioxide, nitrous oxide and isoflurane.

2.10. Summary

Monitoring of cardiac output needs to be able to respond rapidly to changes in cardiac output. While beat-to-beat or breath-by-breath measurement is ideal, continual small variations can make measured changes in cardiac output difficult to interpret, and it may be necessary to incorporate some filtering in the displayed cardiac output.

Despite improvements in cardiac output measurement, (and the desirability and usefulness of measurement), it is still not routinely monitored anaesthetised patients. The complexity, variability of accuracy and delays in response times have impacted on the routine clinical use of cardiac output monitoring, which is further complicated because not every technique is suitable in all situations (for example, exercise studies, complex surgery, and paediatrics). In Australia, routine cardiac output monitoring is predominately performed in cardiac and liver transplant surgery and traditionally utilises pulmonary arterial catherisation (PAC) which is the de-facto clinical standard. The invasiveness and risk of a PAC is justified in these settings because clinicians are required to make important decisions about fluid management and inotropic support (ANZCA 2010).

Blood dilution methods using pulmonary artery catheterisation require injection of fluid boluses and provide discrete cardiac output measurement. Nevertheless, they are widely used as a reference standard, despite known risks. Recent research has shown that peripheral measurement provides acceptable results and is easier to use, and this is commonly employed instead of PAC as a reference standard in critical care.

Pressure pulse contour analysis provides a continuous method for measuring cardiac output. It can make use of the routine use of blood pressure measurement in critical care patients, but relies on proprietary algorithms, or requires calibration against a discrete and more invasive measurement technique (often blood dilution methods).

In contrast, Doppler ultrasound techniques do not require calibration and can be rapidly performed, but they are heavily reliant on operator technique and variability. Insonation through the suprasternal notch can be used only as a temporary measurement, and Oesophageal Doppler can be affected by electrical cautery.

Bio-impedance makes use of the acceptance of electrocardiograms in critical-care patient monitoring. These measurements can be affected by arrhythmias and endotracheal tubes which make it impractical for use during surgical procedures where an anaesthetic machine provides respiratory support.

The above techniques all focus on quantifying cardiac changes using estimated blood flow. An alternative method is to examine pulmonary gas-exchange and how it can be used to estimate pulmonary capillary blood flow and therefore cardiac output. Many such techniques have been explored using a range of gases: acetylene, argon, carbon dioxide, and nitrous oxide (Grollman 1932, Defares 1958, Gan, Nishi et al. 1993, Robinson, Peyton et al. 2003, Laszlo 2004, Peyton, Ramani et al. 2005, Cettolo and Francescato 2015). These gas-exchange techniques vary in complexity and set-up and consist of both discrete and continuous methods.

Following on from these considerations of historical and contemporary work, two areas that I believed warranted further investigation were:

- Throughflow of nitrous oxide, which eliminated problems associated with blood re-circulation times associated with re-breathing, and, in a small pilot trial, has been demonstrated to be capable of tracking cardiac output accurately when compared with thermodilution;
- Kennedy's (2001) identification of the association between cardiac output and anaesthetic uptake and his nomination of a blood-gas solubility range of between 1.5 and 2.5 seemed ideal for use in cardiac output measurement (2001a).

The relationship between anaesthetic agent uptake and cardiac output supports the suggestion by Robinson that uptake of a more soluble volatile anaesthetic agent could be considered as a substitution for nitrous oxide in throughflow cardiac output. The commonly-used agent isoflurane (with a blood-gas solubility of 1.4) is close to the ideal blood-gas solubility identified by Kennedy, which makes it a potential substitute for nitrous oxide in the throughflow measurement of cardiac output.

Gas-exchange techniques can be well-tested using simulated uptakes produced using physical gas simulators. Indeed, the development of newer gas exchange methods have

been supported by the simultaneous evolution of gas exchange simulation. So far, production of isoflurane and a simulator that can replicate different lung gas exchange in each lung have not been described. However, such a simulator is required to test the suitability of replacing throughflow of nitrous oxide with isoflurane. Peyton's simulator (Peyton, Venkatesan et al. 2006) will be used as the basis for a new simulator which can replicate the throughflow of isoflurane. The most fundamental of changes is the integration of a vaporiser to allow insertion of isoflurane. The simulator could also be improved by automating gas insertion with the use of individual flowmeters, rather than relying on manual adjustment of input pressures through the variable gas flow regulators and pre-calibrated fine bore tubing.

The new simulator, which is described in Chapter 3, adds and removes gas using digital flow-regulation to provide precise control that can rapidly respond to change. Suction is difficult to digitally control, particularly when an active gas scavenge system is used.

Chapter 3 Method – Measurement & Simulator Design

3.1. Introduction

Chapter 2 reviewed the evolution of gas-exchange-based cardiac output techniques and the role they have in accurate, responsive and precise measurements. The throughflow of nitrous oxide technique provided a novel solution which avoided the effects of blood recirculation times (which complicates gas-based measurements) and when compared to thermodilution in a pilot study(Robinson, Peyton et al. 2003), demonstrated accurate cardiac output measurements.

Nitrous oxide throughflow has not been introduced into clinical practice as a cardiac output measurement technique. The reasons for its rejection include:

- that 45% nitrous oxide restricts choice of left fresh flow
- the potential adverse effects associated with nitrous oxide use such as postoperative nausea and vomiting
- the previous suspicion of (recently-resolved) postoperative complications (Myles, Leslie et al. 2014)
- the increased technical complexity in the gas delivery and measurement required to adapt current anaesthesia machines to incorporate the parallel gas delivery.

The availability of anaesthetic vapours and intravenous drugs that offer similar sedation and analgesia at lower concentrations has led to a reduction of nitrous oxide use in general anaesthesia. The minimum requirements of the parallel gas delivery system are fixed, but alternative gases and vapours may provide greater flexibility for the delivery of left and right fresh gases.

Anaesthetic	Blood-Gas Coefficient at 37˚C
Desflurane	0.45
Nitrous oxide	0.47
Sevoflurane	0.65
Acetylene	0.85
Isoflurane	1.4
Enflurane	1.8
Halothane	2.5
Carbon Dioxide	2.9

Table 2 Blood-gas coefficients for common anaesthetic gases and vapours - adapted from Miller, Table 5-1 (2005) and (Kennedy and Baker 1993, Robinson, Peyton et al. 2004)

Anaesthetic vapours are a practical substitute for nitrous oxide because vapour uptake also behaves comparably to changes in cardiac output. The responsiveness of a gas or vapour to changes in cardiac output can be predicted from its blood-gas solubility. Vapours and gases with Ostwald blood-gas partition coefficients between 1.5 and 2.1 provide an ideal balance between a rapid response and a relatively-large gas uptake in response to changes in cardiac output (Kennedy and Baker 2001a). Isoflurane, enflurane and halothane all have blood-gas solubility coefficients which are close to the identified range. Of these, isoflurane remains widely available and seems a practical choice, furthermore halothane is associated with hepatotoxicity while enflurane is associated with nephrotoxicity. Isoflurane was selected to demonstrate the measurement of cardiac output using throughflow: this choice was made

because modelling by Kennedy and Baker (2001) have shown that isoflurane is better than enflurane as an indicator of cardiac output change. The exploration of gas-based cardiac output measurement remains popular because it is non-invasive. Continuous (or near-continuous) cardiac output measurement is feasible because lung gases respond rapidly to changes in pulmonary blood flow. Continuous measurement relies on avoiding the consequences associated with blood recirculation; this can be acheived via functional-gas isolation of the left and right lung (throughflow technique) or manipulating ventilator mechanics to provide respiratory changes whilst avoiding re-breathing of gas.

System design is critical to successful cardiac output measurement, particularly when multiple parameters are used. During his acetylene study, Gan (1993) demonstrated the importance of measurement design. His use of 0.7% acetylene, in the fresh gas, produced relatively low uptake rates and end-tidal concentrations of acetylene; these are similar to the left fresh isoflurane concentration (1%) used in the modified throughflow method. He showed the importance of incorporating data filtering when analysing small concentrations.

All gas-based cardiac output measurement techniques require modification to conventional ventilation mixtures or mechanical characteristics. The measured gas exchange response to these changes is used to estimate cardiac output. In anaesthesia and intensive care, gas-based techniques are practical because ventilator parameters, respiratory rates and inspiratory flows can be tightly controlled.

3.1.1. Throughflow Cardiac Output Using Isoflurane

The proof of throughflow cardiac output was originally for nitrous oxide and was discussed in Section 2.8.5. However, as described above, isoflurane is known to be responsive to change in cardiac output and will be used in the place of nitrous oxide as gas '*G*'.

$$\dot{Q}_c = \frac{\frac{\dot{V}_{O_2}}{\dot{V}_{O_2{}_L}} \cdot \dot{V}_{Iso_L} - \frac{\dot{V}_{O_2}}{\dot{V}_{O_2{}_R}} \cdot \dot{V}_{Iso_R}}{\lambda_{Iso}(F_{E'_{Iso_L}} - F_{E'_{Iso_R}})}$$

Equation 9 Non-invasive calculation of cardiac output using isoflurane.

A physical simulator (providing oxygen, carbon dioxide and isoflurane gas exchange) has been used to model the throughflow method; this replicates a patient's physical lung mechanics, as well as uptake rates and end-tidal concentrations.

3.1.2. Measurement Setup and Simulator Design

This thesis contains three main practical components:

Gas Delivery

Individual fresh gas mixtures (dialled up on rotameters) are delivered to the left and right lung using separate Bain circuits. A modified ULCO EV500 ventilator is used to deliver different volumes of fresh gas synchronously (to each lung), while maintaining separation between the left and right patient circuits. See

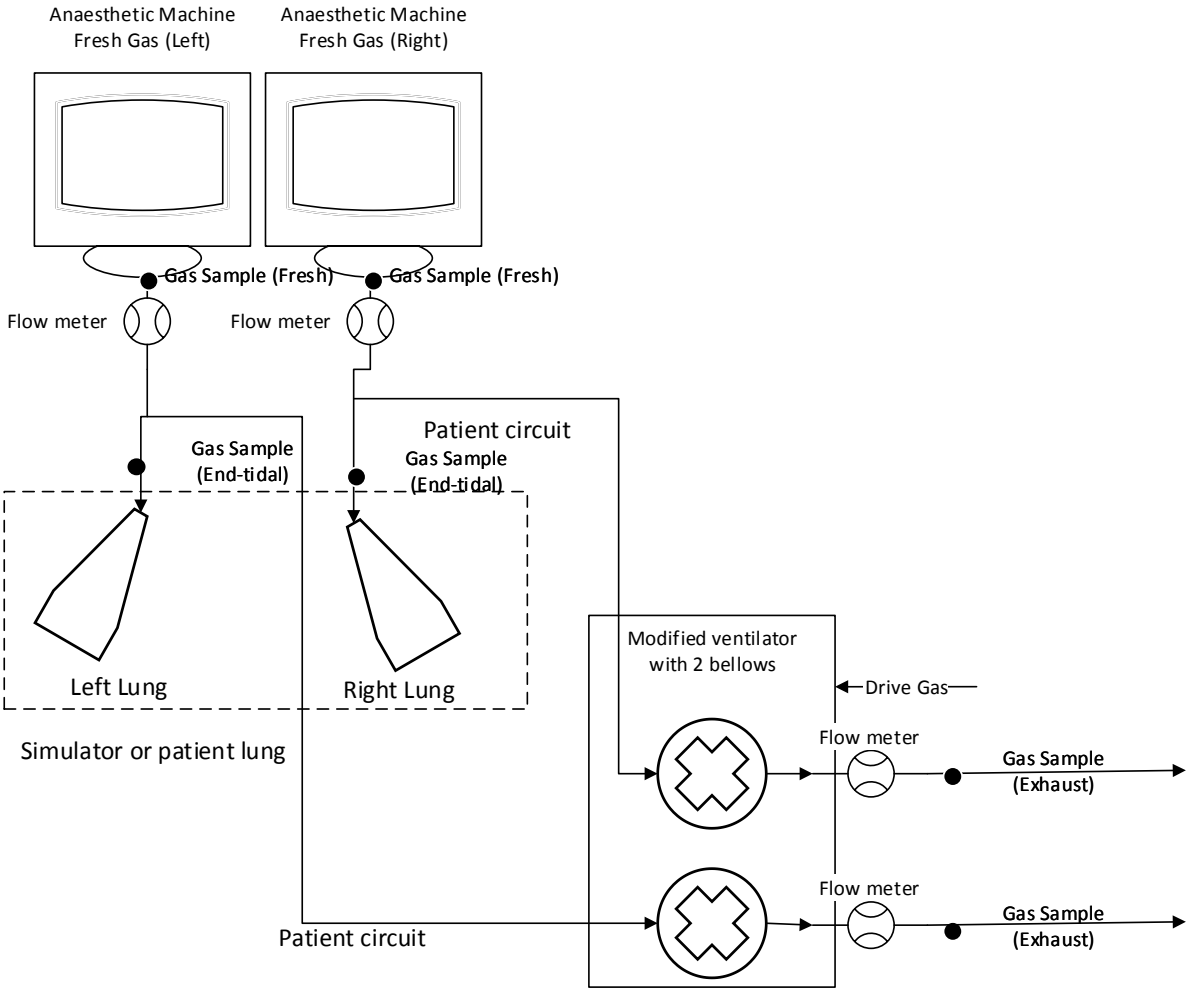

Figure 9 and Figure 10.

Measurement System

The measurement system continuously monitors fresh and exhaust gas flows in the left and right patient circuits, in conjunction with sequential analysis of gas composition, to allow the calculation of individual fresh and exhaust gas flows delivered in the left and right patient circuits. This is accompanied by cyclic measurement of left and right end-tidal gas composition, which is used in place of invasive blood gas measurements. A dedicated anaesthetic gas analyser is used for each patient circuit (left and right). See

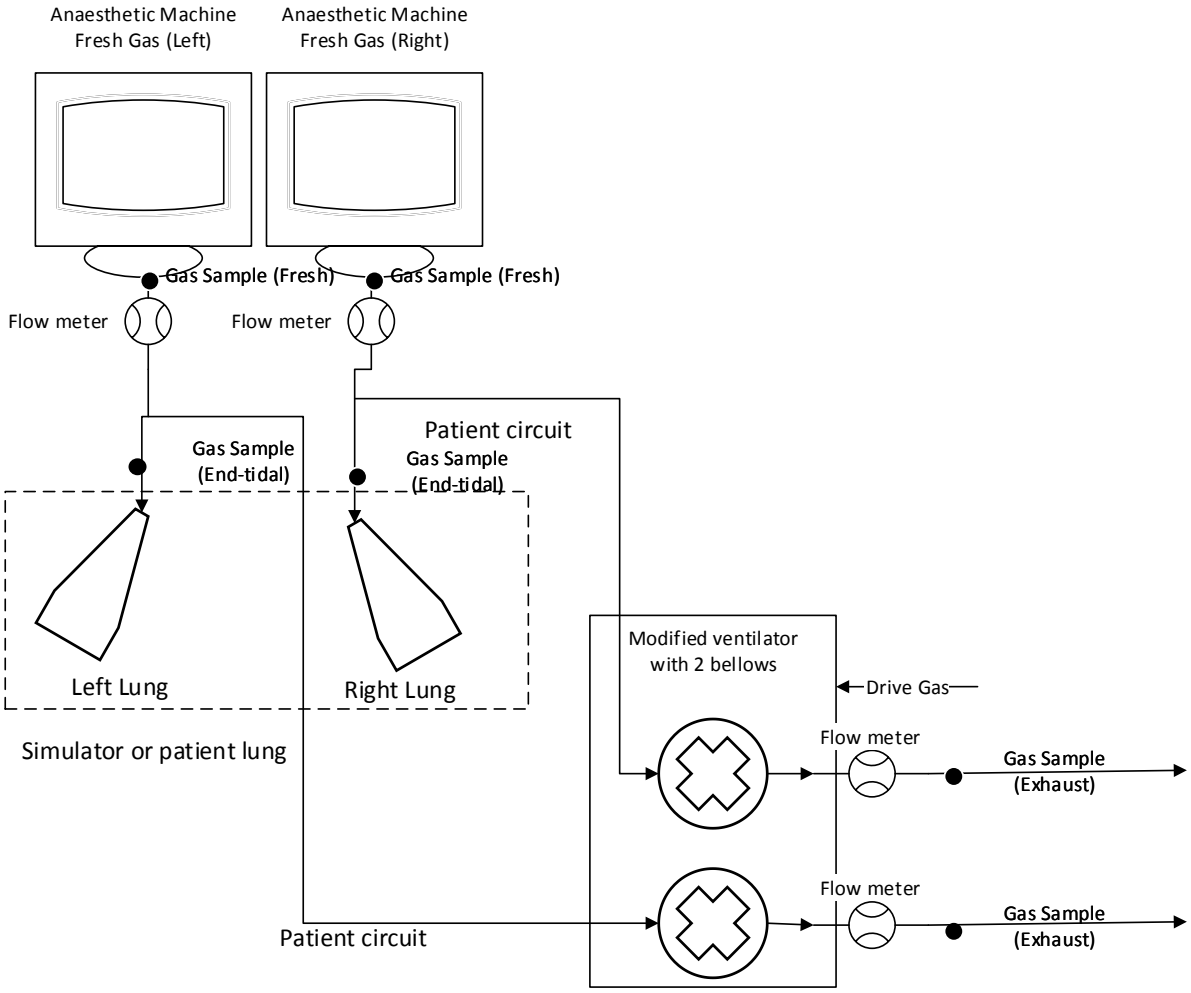

Figure 9 and Figure 10.

Dual-lung gas simulator

Simulation of gas-exchange required the development of a dual-lung simulator. Mixed gas is suctioned from the left and right lungs (physically simulated with mechanical bellows) by individual suction regulators. Replacement gas is managed

digitally, using individual gas flow controllers which are supplied with medical-grade bottled gas, and an isoflurane vapouriser (right side). These gases are then combined in a manifold before being re-inserted into a dual-lung mechanical bellows which has the mechanical characteristics of an adult lung. See Figure 15.

Anaesthetic machines are becoming more complex and integrated as technology develops, with ever-increasing leak-detection measurement systems, making it difficult to access exhaled gases without modifying these medical devices. Thus, the decision has been made to measure exhaust rather than expired gas. The use of exhaust-gas in place of expired-gas measurement will remain necessary to ensure the safety of anaesthetic machines until future developments enable real-time continuous gas concentration and flow measurements to be readily extracted from these devices.

3.2. Process of Gas Exchange

Gas exchange involves a number of mechanisms, from the bulk gas flow through the upper airway (actively driven by contraction and relaxation of the diaphragm) to the diffusion across the alveoli-capillary membranes and finally the exchange between blood and body tissues at a cellular level. The respiratory system begins at the nose and mouth, and respiratory gas travels down the trachea, where it separates into right and left bronchus stems; further separations of the bronchi lead to respiratory bronchioles that contain alveoli (where gas exchange occurs). The left and right lungs have slightly different size and anatomy, with the typical left to right distribution in a healthy conscious patient being 0.47:0.53 (Lumb 2005).

3.3. Functionally Separated Lung

The throughflow method for measuring ‘apparent’ cardiac output relies on the functional separation of ventilation and gas delivery to the left and right lungs. This can be done using a dual-lumen endotracheal tube of the type used clinically for lung isolation in thoracic surgery. For the purpose of throughflow, this enables different gas mixtures to be delivered to each lung, and thus individual gas uptake rates can be measured on the left and right sides. The cardiac output is based on the estimation of arterial blood gases from end-tidal

gas concentrations, and does not include blood that is shunted from one side of the heart to the other. Shunted blood flow is not measured, because it has not participated in the gas exchange across the alveolar-capillary membrane in the lung. In contrast, cardiac output including shunt is measured by peripheral techniques such as pulse contour analysis, or imaging of the aorta or left ventricle.

The throughflow of isoflurane is illustrated in Figure 1, which depicts gas exchange in the functionally-separated lung; oxygen is taken up by both left and right lungs, while isoflurane is delivered and taken up on the left side. As blood is transported through the body, oxygen and isoflurane are absorbed, and carbon dioxide is removed; when blood returns to the lungs, we see a net elimination of carbon dioxide and isoflurane on the right, and carbon dioxide on the left.

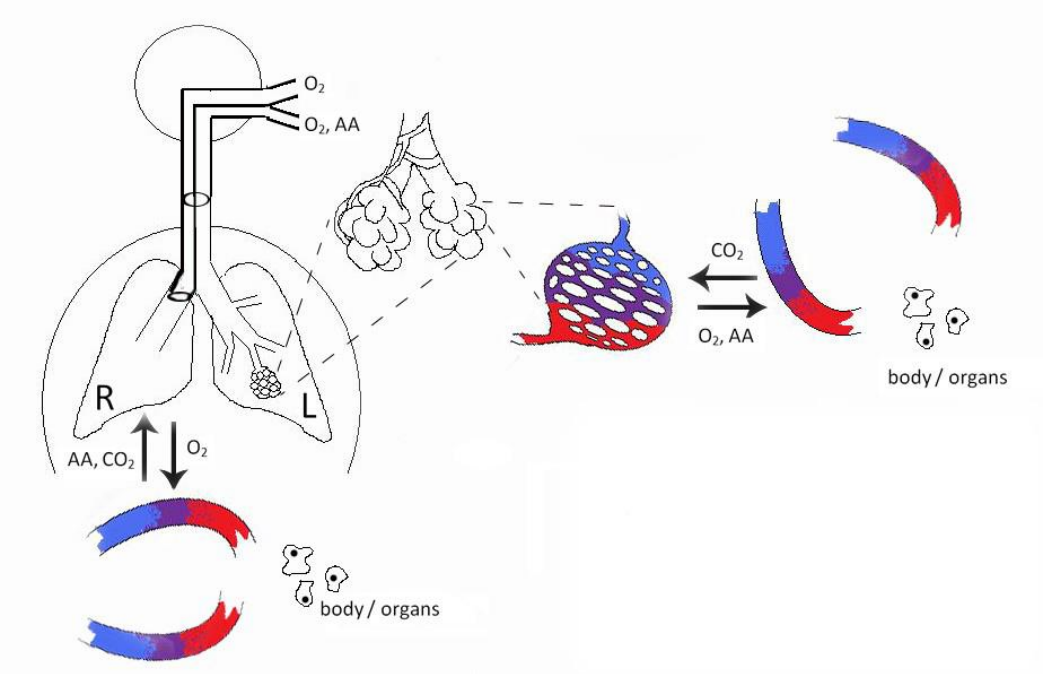

Figure 7 Gas exchange in functionally-separated lungs: the anaesthetic agent (AA) is inhaled by the left lung, flows through the body and is removed in the right lung.

The isoflurane uptake rates, and end-tidal concentrations are employed to calculate cardiac output, using Equation 9. The fractional end-tidal concentrationcs in the separated lungs, when combined with the Ostwald isoflurane blood-gas coefficient, approximates partial

pressures in pulmonary end-capillary blood leaving each lung. The effect of error arising from an end-tidal to end-capillary partial pressure difference in each lung has been considered for nitrous oxide throughflow by Robinson and Peyton (2004), and is examined in Section 4.3.

3.4. Fresh Gas Delivery and Anaesthetic Breathing Circuit Setup

The introduction of an anaesthetic ventilator and associated breathing circuits increases respiratory dead space, which consists of instrument dead space from the breathing circuit, anatomical dead space (the upper airways) and physiological dead space (alveoli that are poorly perfused).

The throughflow method for measuring cardiac output described in Section 2.8.5 requires the measurement of gas uptake rates and end-tidal concentrations. Modern anaesthetic devices determine and display these values using internal gas composition and flow measurements. However, they also deliver a single fresh gas mixture to both lungs: this is not suitable for the throughflow method, which requires delivery of different fresh gas compositions to each lung.

The calculation of oxygen uptake rate relies on gas flow and oxygen concentration measurements. Anaesthetic gas analysers must provide the ability to measure gas concentrations over the full range of possible fresh and exhaust gas concentrations. The measurement range for oxygen is 0 to 100% and the difference between fresh gas and exhaust gas concentrations is generally 2-3% in a high-flow system like the Mapleson D; this is naturally associated with poorer resolution in gas exchange measurement for oxygen than other gases that have a smaller measurement range (carbon dioxide 0-10%, isoflurane 0-5%). The Mapleson D breathing system was also used in the original throughflow design because it is a high-flow system, and this improves the system response time. Given the high fresh gas flow oxygen concentrations (left 72.9% and right 73.6%) and the relatively low left and right uptake percentage (4.0% and 4.1% respectively) the measurement of oxygen is more prone to measurement errors.

3.4.1. Anaesthetic Machine and Ventilator System

The delivery of a distinct fresh gas mixture to each lung requires several adaptations to typical gas delivery for the anaesthetised patient. The left and right fresh gases are delivered as steady continuous flows, and in this system, are connected to independent Bain anaesthetic breathing circuits.

The ventilator limb of each Bain circuit connects to a modified positive-pressure time-cycled ventilator[1]. Inspiratory time, respiratory rate and positive end-expiratory pressure (PEEP) are controlled by the ventilator, which has been modified to allow synchronous ventilation of independent fresh-gas mixtures and tidal volumes (Table 3). The ventilator's driving-gas supplies two bellows synchronously (Figure 9); the tidal volume is controlled with inbuilt plungers. Exhaust gas flow and concentrations are measured immediately after exiting from the bellows, before being removed using the hospital scavenge system.

Respiratory Rate*	10 breaths min^{-1}
Inspiratory: Expiratory Ratio	1:30
Left Tidal Volume	270 ml
Right Tidal Volume	310 ml
Positive end expiratory pressure (PEEP)*	0 cmH_2O

*Table 3 Ventilation Parameters. *Respiratory rate and PEEP will be adjusted in some scenarios.*

3.4.2. Choice of Fresh Gas Mixtures

The fresh gas delivered to the left and right breathing systems remains constant in the system described: isoflurane (1%) is supplied only to the left lung and is absent from the right fresh gas. If the left and right fresh gases both contain oxygen-air mixtures, these are provided from the flowmeters on two standard anaesthetic machines (Setup 1); this means that exhaust flows can be measured directly, or calculated using the Haldane Transformation. Setup 2 (the alternative) could be employed if directly-measured exhaust flow proves to be as robust as the Haldane-derived exhaust flow (because nitrogen could be

[1] ULCO EV500 ventilator

eliminated from the fresh gas). If pure oxygen is substituted for the oxygen/air mixture in the right fresh gas, the auxiliary oxygen outlet can be used: this will simplify the system and eliminate the second anaesthetic machine (Setup 2 - Alternative).

Setup 1 **Enables use of Haldane Transformation**	**Left Fresh Gas Flow**	**Right Fresh Gas Flow**
	Oxygen (2210 ml min^{-1})	Oxygen (2652 ml min^{-1})
	Nitrogen (790 ml min^{-1})	Nitrogen (948 ml min^{-1})
	Isoflurane (1%)	
Setup 2 (Alternative) Easier Clinical setup if elimination of Haldane-derived exhaust flow is feasible.	Left Fresh Gas Flow	Right Fresh Gas Flow
	Oxygen (2210 ml min^{-1})	Oxygen (3600 ml min^{-1})
	Nitrogen (790 ml min^{-1})	
	Isoflurane (1%)	

The independent fresh gas flows are delivered using two Mapleson D (Bain circuit) anaesthetic breathing systems that can be connected to the corresponding branch of a dual-lumen endotracheal tube.

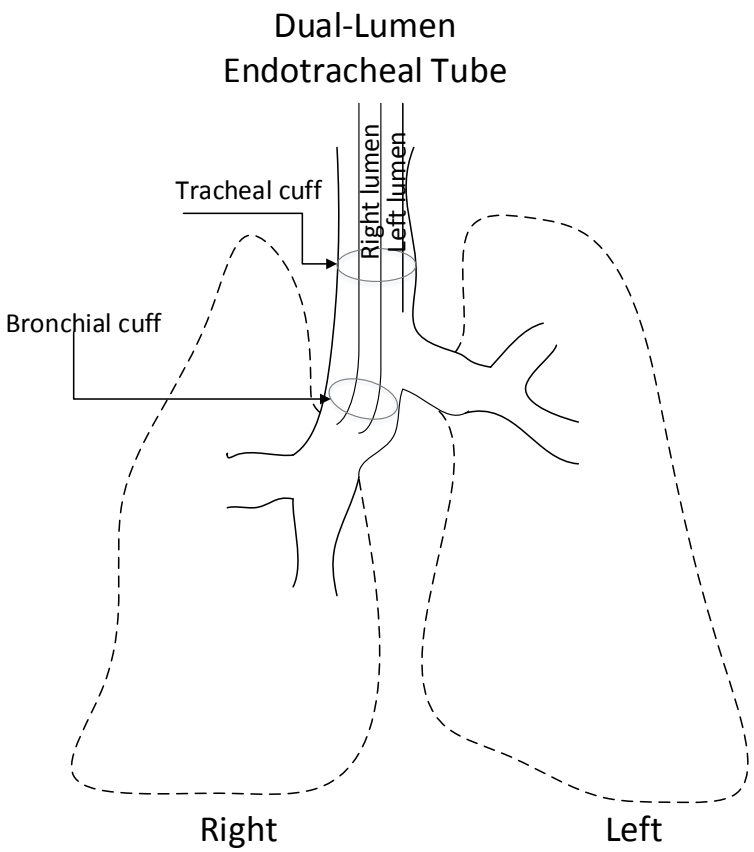

Figure 8 Example of a dual-lumen endotracheal tube, separating the left and right lung. The dual-lumen tube has two inflatable cuffs, one inflates around the tracheal tube, and the second inflates around the longer bronchial tube.

3.5. Measurement System

The isoflurane uptake rates and end-tidal concentrations vary in size and direction when isoflurane is delivered only in the left fresh-gas supply. Levels of right lung isoflurane uptake rate between -3.5 and -0.9 ml min^{-1}, and left lung uptake rates between 5.9 and 9.5 ml min^{-1} are expected to simulate a cardiac output range of 2 to 10 L min^{-1}: the negative uptake in the right lung indicates the excretion of isoflurane inhaled by the left lung.

The expected isoflurane uptake rate includes values that are smaller than those simulated by Peyton (2005). Because the right-side gas concentrations are close to the limits of the gas

analyser[2] resolution, the best method for determining uptakes and end-tidal concentrations needs to be considered. Left-side isoflurane uptakes are similar to those used in Peyton's simulator, which produced flows within 10% of target values. The acceptable relative tolerance of the target right-side uptake rates and end-tidal concentrations needs to increase as the isoflurane measurement concentration decreases (specifically for cardiac outputs between 2 and 4 L min^{-1}). The simulator described by Peyton also needs to be modified so that isoflurane can be inserted, and not just removed in the right lung of simulator, to allow simulation of a range of right-lung excretion rates.

Fresh and mixed exhaust gas flows in both the left and right breathing circuits are measured using in-line flow meters.[3] Measuring fully-mixed exhaust gas concentrations avoids the difficulty in obtaining direct access to inspiratory and expiratory gases, and greatly simplifies the measurement of expired gas flows for each gas species. Since tidal gas concentration variations seen at the level of the mouthpiece are eliminated, this allows easy integration of tidal bulk gas flow measurements and gas concentration waveforms, without the need for precise synchronisation. Synchronisation presents considerable technical difficulties when a side stream gas sampling system is employed, due to the accompanying variable waveform sampling delays. Exhaust gas mixing was achieved successfully by sampling mixed exhaust gas distal to the left and right ventilator bellows.

The measurement system can calculate mixed exhaust bulk gas flows on each side in two ways:

- Direct flow measurement using a thermal mass flowmeter; or
- The Haldane Transformation (if nitrogen is present in both fresh gas mixtures).
    - The assumption of nitrogen conservation means that the flow rate of nitrogen in the fresh and exhaust flows are equal. Similarly, an individual flow of any gas '*G*' can be

[2] Datex-Ohmeda A-S3, gas analyser with analogue output

[3] TSI Model 4040, thermal flow sensor 0-300 Standard L min^{-1}

determined by multiplying the measured gas concentration '*G*' by the total flow rate.

Thus, the total mixed exhaust flow is determined by:

$$\dot{V}_{\bar{X}_T} = \dot{V}_{F_T} \times \frac{F_{F_{N_2}}}{F_{\bar{X}_{N_2}}}$$

Equation 10 Calculation of mixed exhaust flow using principle of nitrogen consumption

The two independent exhaust gas flow measurements are used to calculate the left and right gas uptake rates. Direct flow measurement has several advantages over the Haldane-derived flow because it eliminates the assumption of zero nitrogen uptake. The Haldane Transformation is disadvantageous because:

- Gas analysers typically do not measure nitrogen concentration: it is calculated in the described measurement system by subtracting all other gas species fractional concentrations from unity, but unfortunately this combines the errors from all gas species measurements
- the choice of fresh gas composition is restricted: to avoid unacceptable error in calculated exhaust gas flow', it must contain around 30% nitrogen (Robinson, Peyton et al. 2004)
- any error in the volume of reinserted nitrogen[4] during simulation will lead to inaccuracies in Haldane-derived exhaust flow measurement.
- assumption of nitrogen conservation is not valid in all clinical situations, for example when fat is exposed to room air (Robinson, Peyton et al. 2004)

Because the fresh gas flow and composition remains constant, fresh gas composition can be sampled less frequently: increasing the time available to sample end-tidal and exhaust gas where changes affects measured cardiac output. Using a dedicated gas analyser[5] for each

[4] To produce realistic gas flow uptakes, the simulator removes mixed gas. This results in some gases being removed inadvertently. Re-inserted nitrogen refers to the replacement of nitrogen gas which is maintained in the system with zero net uptake.

[5] Datex-Ohmeda A-S3, Anaesthetic gas analyser with analogue output

anaesthetic breathing circuit increases the effective frequency of sampling at each location, which is cycled automatically every nine breaths. The measurement design and sample locations - the common gas outlet (fresh), mouth (end-tidal), and after exiting the bellows (exhaust) - are shown in Figure 9.

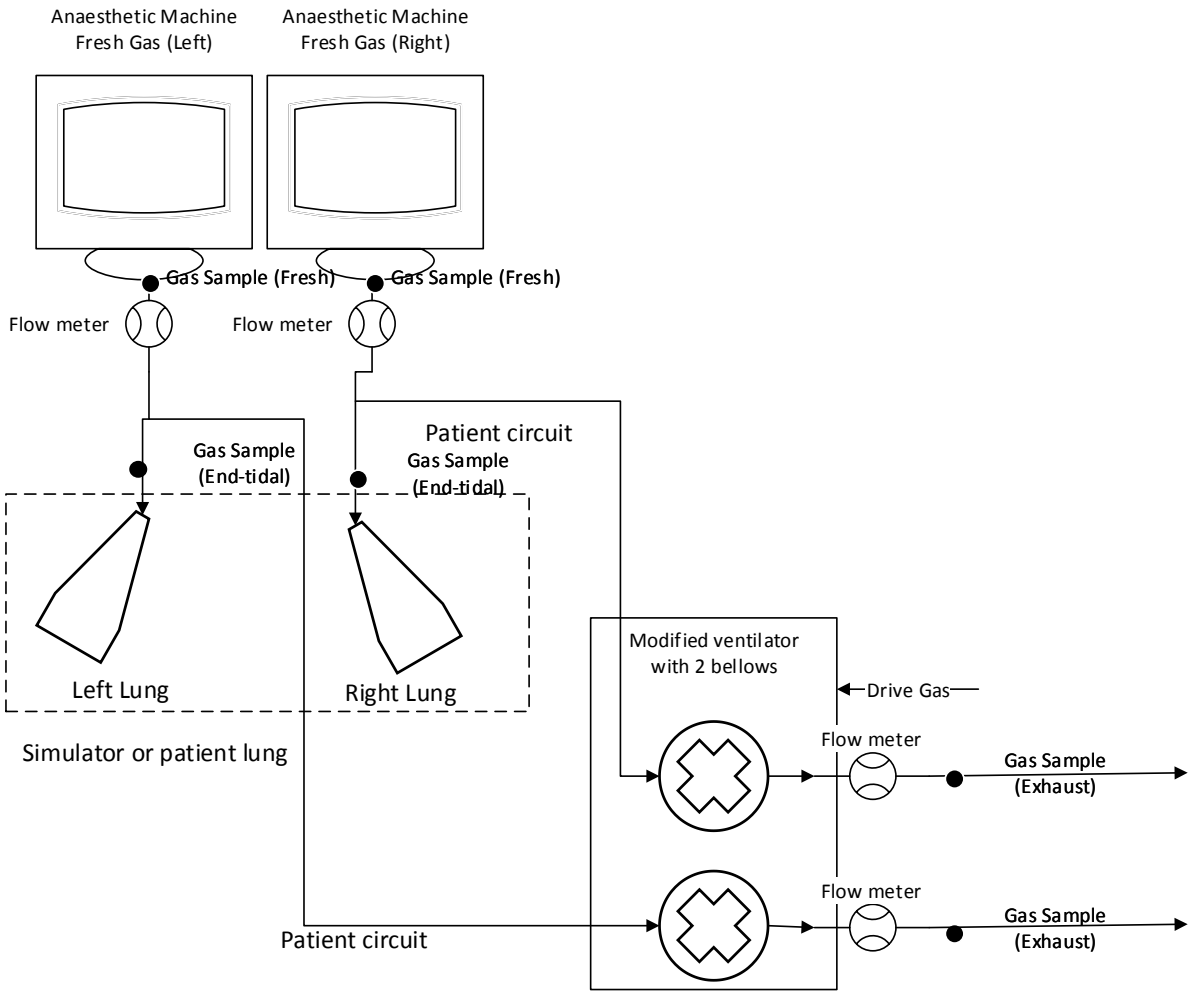

Figure 9 Measurement system for throughflow of isoflurane cardiac output

Fresh gas flows in the left, and right lung are 3.03 and 3.60 L min^{-1} respectively; this included nitrogen flows of 790 (left) and 948 mL min^{-1} (right). When different quantities of nitrogen are removed, and replaced (in the simulator), the Haldane Transformation-derived measurement is affected.

The common gas outlet of an anaesthetic machine provides a constant left fresh gas flow (oxygen, air and isoflurane), while a second machine/system provides the right-side fresh gas flow (oxygen and air). A portable trolley has been set up to include the measurement system and the ventilator (Figure 10). The ventilator uses the constant left and right fresh gas flows and provides synchronous tidal ventilation.

Figure 10 Ventilator setup and measurement trolley. (For clarity, the interconnections between components have been omitted).

The measurement system software was written using the National Instruments LabVIEW package (Version 9.0.1) installed on a laptop (DELL Latitude E6410) and mounted on a trolley (Figure 10). The programs written in LabVIEW determine breath-by-breath measurements and integrate serial measurement devices. A serial connection to a National Instruments data acquisition board (USB-6229) was used to connect analogue hardware

(used for flow and concentration measurements) and to drive the solenoids at the rear of the trolley.

The instantaneous direct flow measurement is achieved inline using TSI 4040 thermal mass flowmeters in the fresh and exhaust gas streams. Gas concentration is measured using two Datex Ohmeda A3 anaesthetic gas analysers, one for each patient breathing circuit (left and right). The measurement range of the gas analyser is oxygen: 0 to 100%, carbon dioxide: 0 to 10%, isoflurane: 0 to 5%; the resolution for isoflurane when below 1% is to two decimal places. The sample location was driven by the laptop through the data acquisition unit and cycled between fresh, end-tidal and exhaust sample locations using a three-way solenoids[6] in a switching manifold.

3.5.1. Calibration and Measurement

The measurement system is turned on (without the simulator), and flows are measured for three minutes; the user is then prompted to enter the left and right fresh flows, to which the fresh and exhaust flows are calibrated. This is followed by a further three minutes to verify accurate flow measurement and to confirm the uptake rate is zero. If necessary, individual uptake measurements can be adjusted at this stage.

Gas concentrations can be calibrated using a separate software program that uses three different gas mixtures (air, calibration gas, and pure oxygen) to calculate the coefficients of a quadratic calibration equation, these are then manually coded into the measurement system.

3.5.2. Lung gas uptakes

At the start of inspiration, a rapid downstroke in exhaust flow is observed (Figure 11); the breath is detected when the flow rate falls and remains below a pre-defined threshold. Left and right, fresh and exhaust flows are continuously monitored in real-time, and the average flow at the end of each breath is calculated. The gas concentrations in the fresh and exhaust

[6] General Valve Corporation Model:3-1329CC

flows are used to calculate breath-by-breath uptakes using direct flow measurement and the Haldane Transformation.

The breath ends five samples after the flow drops below the end-flow threshold. At this stage the flow rate is zero, making the average-flow calculation more robust.

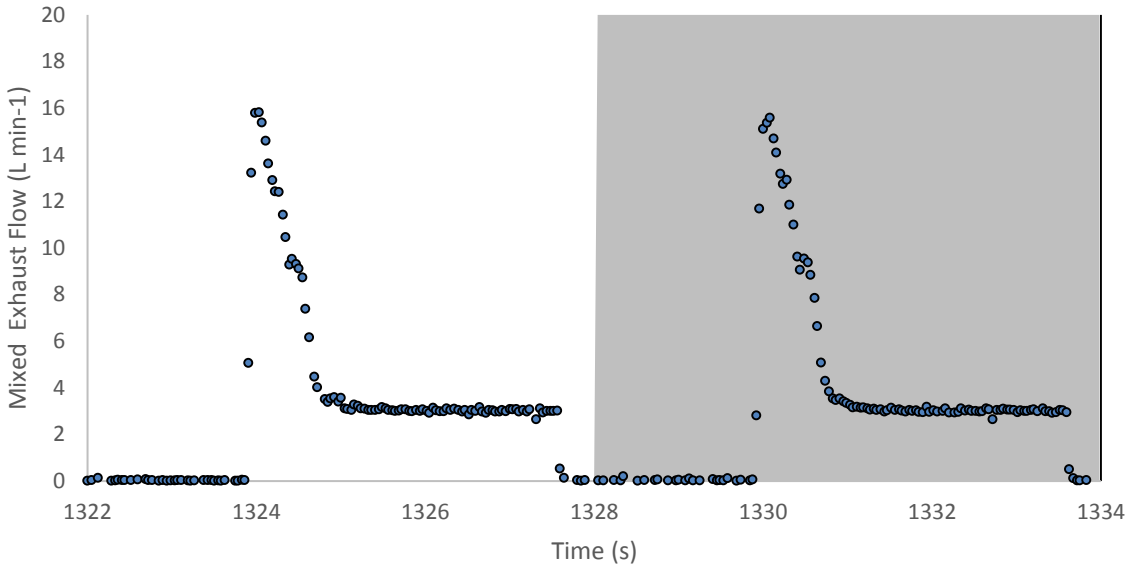

Figure 11 Simulated exhaust flow from two consecutive breaths: the shading identifies individual breaths.

The average fresh and exhaust flows are calculated by averaging the instantaneous flows over the number of measurements (Equation 11).

$$\dot{V}_{X\,avg} = \frac{\dot{V}_{X1} + \dot{V}_{X2} + \cdots + \dot{V}_{Xn}}{n} = \sum_{i=1}^{n} \frac{\dot{V}_X}{n}$$

Equation 11 Calculation of average breath exhaust flow; this equation can be modified to calculate average fresh gas flow

$$\dot{V}_{gas} = (\dot{V}_{X\,avg} \times F_{X_G}) + (\dot{V}_{F\,avg} \times F_{F_G})$$

Equation 12 Calculation of individual gas flows

The exhaust and fresh gas flows are then combined with concentration measurements to calculate individual gas uptakes.

3.5.3. *Oxygen* Uptake

In the throughflow theory, inert gas uptake in the two lungs is scaled by the proportion of blood flow to each lung (Equation 7). Oxygen uptake values are used as a substitution for the measurement of left and right pulmonary blood flow (Equation 9), based on the assumption of near optimal oxygenation (Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003).

In the presented simulations, all scenarios used tidal volumes of 270ml (left) and 310ml (right), maintaining a typical physiological left-right distribution. Despite keeping oxygen uptake rates constant, random variability in oxygen uptake measurement causes small variation in steady-state cardiac output measurement.

Two options investigated for counteracting oxygen uptake rate fluctuations were:

1. A 200-breath moving average of oxygen uptakes: justification provided in Section 5.3
2. A fixed left-right ventilation distribution of 0.45 to 0.55

Because fresh gas and ventilation parameters remain constant, fixed oxygen uptake rate ratios can be substituted for measured oxygen uptake rate ratios.

Preliminary modelling, described in Chapter 5, demonstrated that both methods were effective when left to right distribution was held constant. Both approaches are used for benchtop validation.

3.5.4. *Isoflurane Uptakes*

Due to the greater accuracy of isoflurane measurement (from the gas analyser), uptake rates of isoflurane are more accurate than oxygen measurements. Isoflurane has a relatively high rate of uptake compared with its 1% inspired concentration even though they have small concentration differences and uptake rates. In the right lung, the precision is further improved because isoflurane is absent from the fresh gas. A six-breath moving average filter is used to reduce the small breath-by-breath fluctuations that occur.

Gas concentration is sampled cyclically; the location (fresh, end-tidal, exhaust) is changed after nine-breaths (one cycle). Each breathing circuit has a dedicated gas analyser, and the

system was designed to maintain constant fresh-gas flows. As such, the need to sample fresh gas concentrations is reduced, and they are sampled periodically to ensure that the fresh gas composition has not changed. Using a control box, each of the six sample locations is switched automatically to either the left or right gas analyser as appropriate. Cyclic sampling focuses on end-tidal and exhaust gases; fresh gas is sampled every ninth cycle. The increased frequency of end-tidal and exhaust sampling improves the system responsiveness, and enables rapid detection of changes. Modelling and justification of cycle length and averaging are discussed in Chapter 5. The volume lost from periodic gas sampling (200 mL min^{-1}) is compensated for in the calculation of measured bulk gas flow rates.

3.5.5. Nitrogen Measurement

Nitrogen is not commonly measured: its uptake is typically negligible, and it does not currently assist clinical diagnostic decisions. If direct measurement of flows (rather than the Haldane technique) is used, then its measurement becomes superfluous. This study used a common anaesthetic gas analyser not capable of nitrogen measurement. The accuracy of other measured gases, and the assumption of zero net nitrogen uptake, means that calculation of nitrogen percentage can be performed by subtracting the fractional concentration of the measured gases from unity (as is standard practice).

3.6. End-tidal Concentration

Left and right non-invasive, end-tidal gas measurements are used to estimate pulmonary end-capillary blood partial pressures. However, end-tidal to end-capillary blood partial pressure differences due to variation ("scatter") of ventilation and blood flow ratios in the lung ($\dot{V}/\dot{Q}\,\mathrm{scatter}$) are expected for any gas. The conventional understanding of $\dot{V}/\dot{Q}$ scatter is based on the Riley model which describes the lung as having three basic compartments: an "ideal" alveolar compartment that is uniformly ventilated and perfused, alveolar deadspace that is ventilated and not perfused; and shunt that is unventilated but perfused. The accuracy of this estimate relies on the suitability of the Riley model, which is based on the assumptions that lungs are homogeneous and that there is minimal ventilation/perfusion inequality or shunting. These assumptions can be tested using a variety of techniques described by Wagner (2015), but such approximations are irrelevant to the benchtop simulation, where physiological $\dot{V}/\dot{Q}$ scatter does not exist.

During clinical anaesthesia, the lungs are not homogeneous, and if the ventilation to perfusion ($\dot{V}/\dot{Q}$) scatter increases, the fractional end-tidal to end capillary difference will also increase. The presence of ventilation-to-perfusion scatter gives rise to errors in the throughflow of nitrous oxide; traditionally this has been corrected using the Riley model (which assumes a linear relationship between nitrous oxide and carbon dioxide) this reduced the bias observed in Peyton's clinical measurements from -12.6% to -5.2% (Peyton 2004). Peyton suggested that the relationship was non-linear and that it also varies depending on the gas; using his A-a gradient model reduced the bias of measurements to -1.6%.

An example of the simulated left and right, carbon dioxide and isoflurane concentrations from benchtop simulation taken at the mouth-end (end-tidal position) of the breathing circuit is shown in Figure 12.

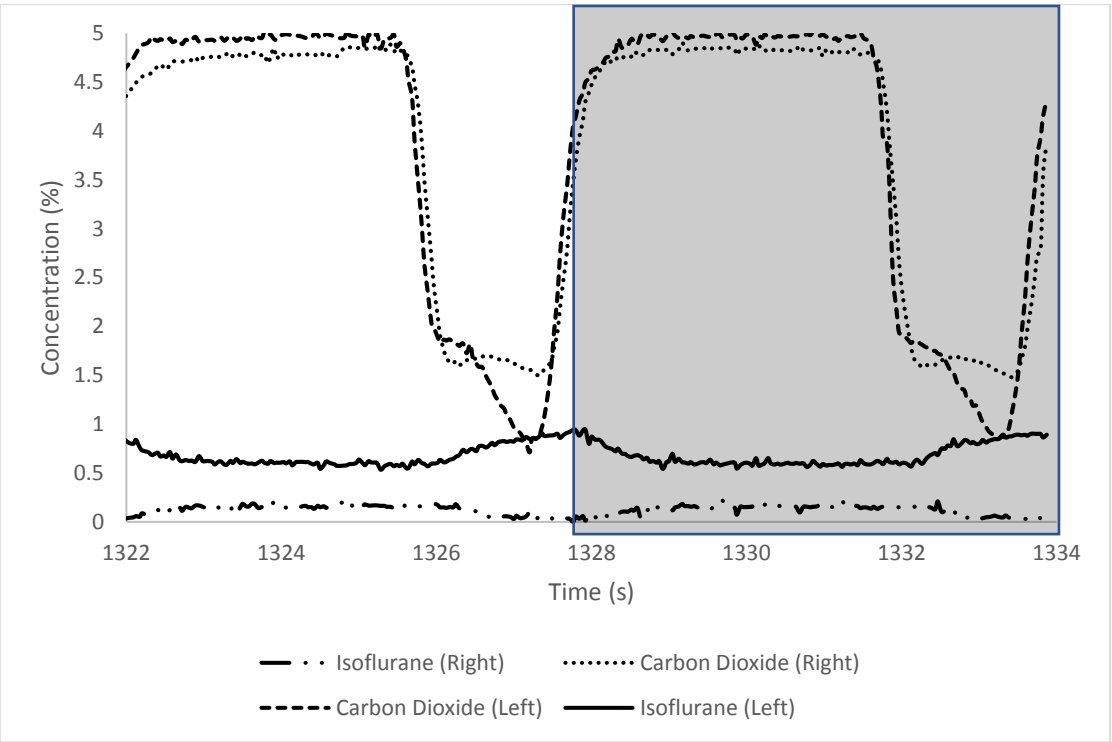

Figure 12 Continuous carbon dioxide and isoflurane concentrations at the end-tidal sampling position; shading identifies individual breaths.

The left and right capnography waveforms in Figure 12 are typical of those observed during ventilation with a single inspired gas mixture. The absence of isoflurane from the right inspired gas means it has the same orientation as carbon dioxide does, as is typical in clinical practice during anaesthetic emergency and gas washout. In contrast, on the left-side the typical pattern seen in the maintenance phase of anaesthesia is present.

To ensure accurate identification of individual end-tidal concentrations, several methods for measuring end-tidal concentrations from the raw instantaneous data were considered: filtering, measurement of the slope, timing and maximum/minimum identification.

3.6.1. End-tidal Isoflurane

Isoflurane throughflow cardiac output is sensitive to errors in both end-tidal position selection, and the measured concentration. This is due to the small magnitude of these values, and their position in the denominator of the cardiac output equation (Equation 14). Left and right end-tidal concentrations were chosen independently because waveform shapes may vary as a result of dead space and simulator gas-exchange in each lung.

The denominator of Equation 13 relies on small differences of volatile anaesthetic agent concentration during end-tidal measurement.

$$\dot{Q}_c = \frac{\frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_L}}} \cdot \dot{V}_{iso_L} - \frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_R}}} \cdot \dot{V}_{iso_R}}{\lambda_{iso}(F_{E'_{iso_L}} - F_{E'_{iso_R}})}$$

Equation 13 Isoflurane throughflow cardiac output.

The throughflow isoflurane concentrations are of a comparable scale and have similar measurement error to acetylene concentration measured in studies by Gan (1993), and they also require processing to reduce measurement noise. A six-breath moving average filter was used to address the sensitivity of the end-tidal measurement to noise in the instantaneous gas concentrations. This also assisted with accurate selection of the end-tidal value using 'End-tidal method 1'.

The denominator of the throughflow cardiac output is isolated in Equation 14. As can be seen, the blood-gas solubility for isoflurane (Ostwald coefficient, λ=1.4) is used to estimate the end-capillary concentrations. Clinically, these estimates can be adjusted using measured end-tidal to end-capillary differences determined from the A-a gradient after measuring carbon dioxide in arterial blood-gas samples.

$$\boldsymbol{\lambda_{iso}\left(F_{E'_{iso_L}} - F_{E'_{iso_R}}\right)}$$

Equation 14 Denominator of throughflow isoflurane cardiac output equation

End-tidal Method 1

The measurement system detects and defines a breath using the exhaust flow waveform as shown in Figure 11. Continuous gas concentrations are recorded during sampling at the end-tidal location in the breathing circuit (Figure 9). A six-point moving filter is applied to measurements before an initial end-tidal concentration is selected based on the peak/trough value; the five filtered instantaneous gas concentrations before and after this value are selected (approximately 0.45 sec of data), the chosen values sorted, and the four most-central points averaged.

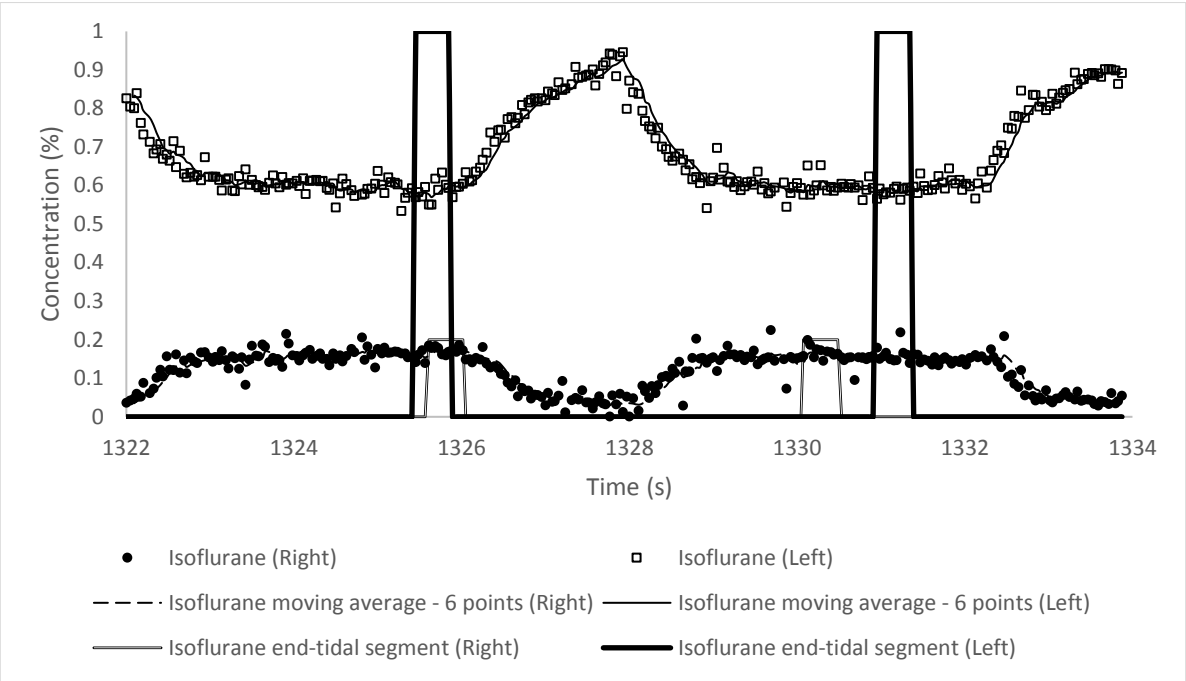

Figure 13 Isoflurane concentrations measured in end-tidal location. The square columns indicate isoflurane samples that are used to determine the end-tidal concentration.

Selection	Sorted	Average
0.158951	0.158951	
0.162973	0.162973	
0.169884	0.168411	
0.172829	0.169657	
0.171016	0.169884	
0.174415	0.170903	0.170804
0.171583	0.171016	
0.170903	0.171413	
0.168411	0.171583	
0.169657	0.172829	
0.171413	0.174415	

Table 4 Shows the selected right isoflurane segment for the first breath. Selected values are sorted, and then the four central values are averaged. This averaged value is used as the end-tidal concentration.

This method reliably determines end-tidal concentrations in the benchtop simulations and is utilized for the results in Chapter 6.

End-tidal Method 2 (Alternative)

Clinical studies may introduce more variation during instantaneous sampling in the end-tidal location, so a second method of detecting the end-tidal concentration using the smoothed waveform, but not based on defining a breath, should be considered. This could identify end-tidal points in an array, looking for peaks or troughs (as appropriate)

End-tidal concentrations were updated in breaths 2 to 7 of the end-tidal sampling interval and the end-tidal location. At all other times the average of the six breaths was used. The average end-tidal values during the sample period were stored and used during fresh and exhaust gas sampling.

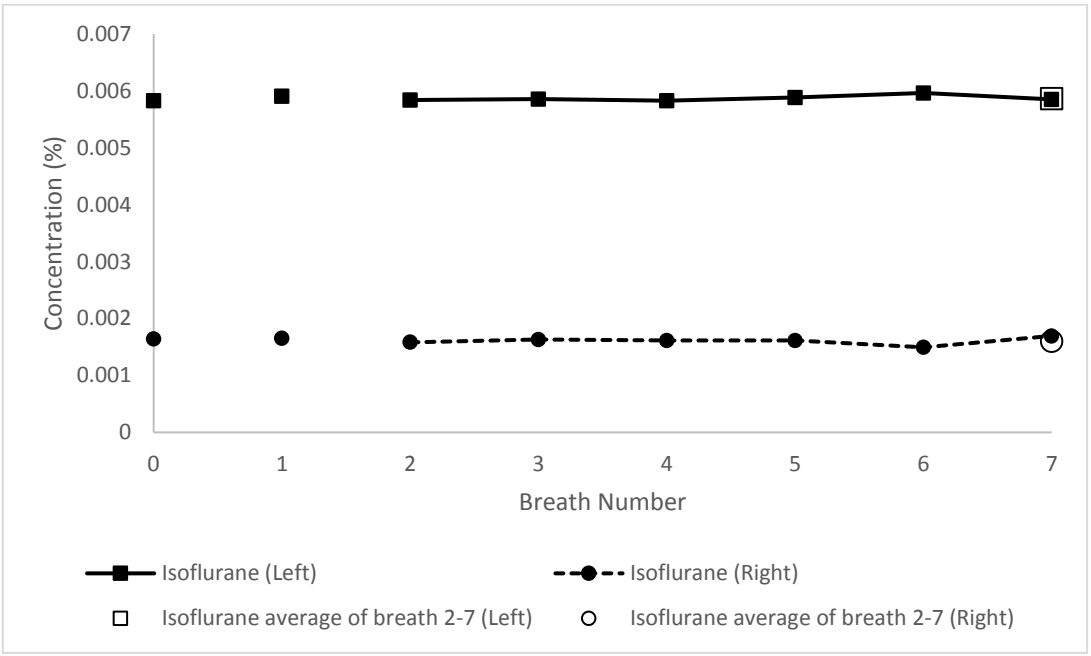

Figure 14 Example of end-tidal concentration measurements during end-tidal sampling. Solid and dashed lines indicate values used to determine the end-tidal average which is used during fresh and exhaust sampling. Large open circles or squares indicate the average end-tidal values used during fresh and exhaust sampling.

3.7. Data Storage and Display

The uptake rates, oxygen ratios, end-tidal concentrations and cardiac output are recorded and displayed using the various calculation methods. Additionally, all raw instantaneous data and calculated breath-by-breath parameters were stored in data files.

The real-time LabVIEW display shows trend measurements graphically, alongside the current numeric value (to one decimal place). This presentation format was informed by research conducted by Kennedy (2009, 2011), which demonstrated that presentation of trend data (either graphic or numeric) improved the speed and accuracy of change identification.

Although detection of changes could be further improved if trends were tracked using a statistical tool to provide feedback to the subject (Kennedy and Merry 2011), this was not implemented. The recognition of cardiac output change is beyond the scope of this thesis, which is delimited to the ability of throughflow isoflurane cardiac output to respond rapidly to change.

3.8. Simulator

As examined in Chapter 2, simulators are often developed to test new measurement systems or models, and their design must match the requirements of those models. Here this is the case: a precise patient simulator was constructed to investigate and validate the effectiveness of the isoflurane throughflow technique for measuring cardiac output. The simulator needs to produce physiologically realistic and interdependent left and right lung gas exchange to simulate the expected exchange for any given value of pulmonary blood flow: these were then used in developing and refining breath detection and end-tidal identification algorithms to ensure that measurements are robust, reliable and efficient.

The throughflow method of measuring cardiac output is unique in its functional separation of the left and right lung gases; blood flow and diffusion of gas across the alveolar-arterial membrane connects the two lungs. The separation of the left and right airways precludes the use of existing simulators (either commercially available, or those described in the literature). The use of two simulators would overcome this limitation, but still could not simulate throughflow (simultaneous uptake and excretion) of isoflurane.

This simulator developed here is modifiable in real-time and demonstrates the effects of a nominated profile of gas uptakes (oxygen, isoflurane and carbon dioxide) on alveolar gas composition and exhaust gas flow rates for each gas species. The simulator replicates the left and right lung of an anaesthetised patient and was used to validate the measurement system through five cardiac output scenarios. The two simulator lung bellows receive independent but synchronous positive-pressure ventilation from a modified ventilator. Each lung bellows has independent compliance and airway resistance, and is ventilated with different tidal volumes.

The key features of the simulator described are:

- The ability to control many inputs digitally.
- Replication of realistic anaesthetised-patient gas exchange.
- Incorporation of the insertion and removal of isoflurane (the anaesthetic vapour chosen for this system).

Lung gas exchange is simulated using parallel inputs of calculated steady gas-flows directly into a compliant bellows (the 'lung'). Concurrently a similar parallel removal of the well-mixed lung gas is suctioned to produce gas exchange.

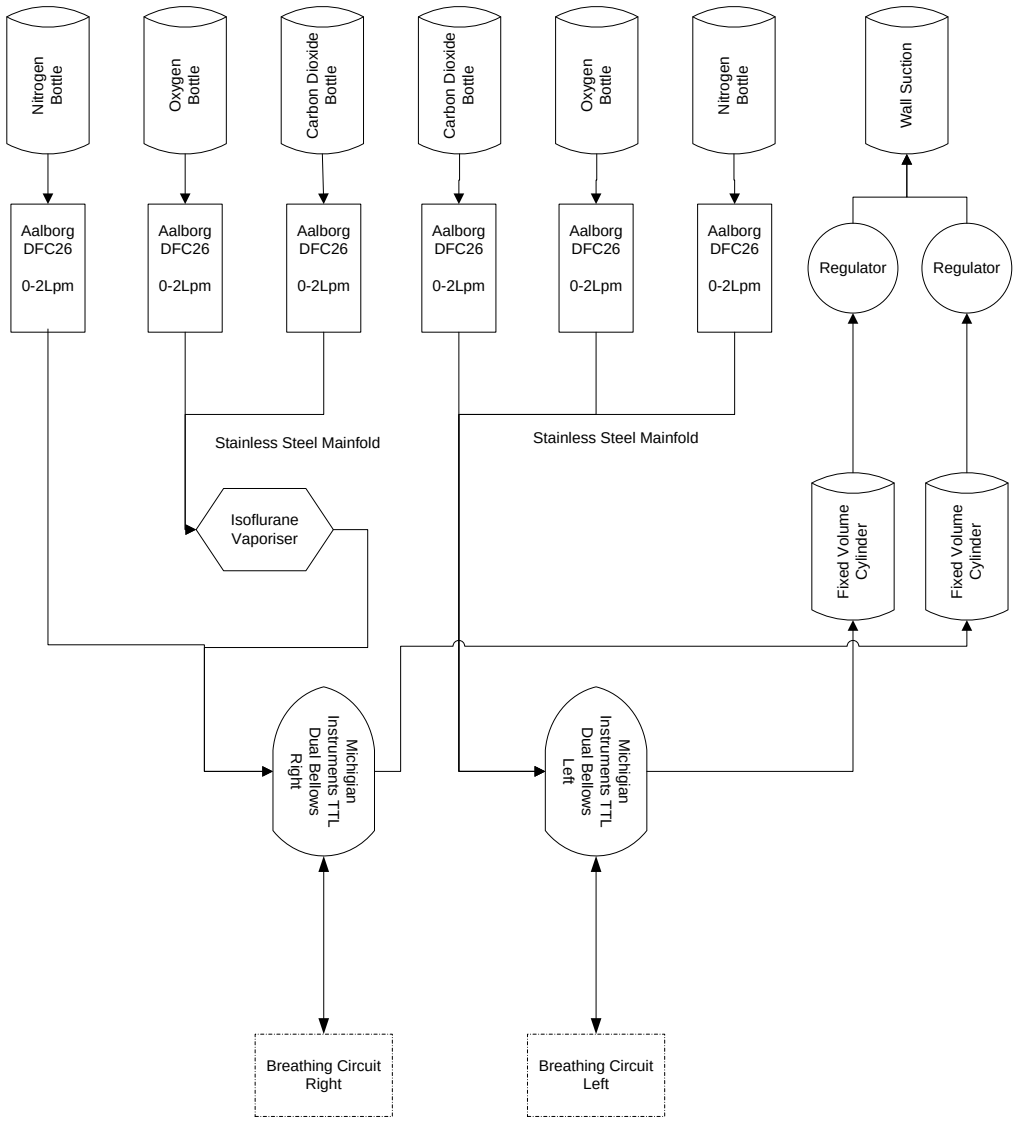

Figure 15 Dual lung simulator

Kennedy and Baker began their investigation into the association between the pulmonary exchange of anaesthetic vapour and cardiac output in 1993; using models and clinical case studies, along with French they established that a change in cardiac output could be predicted by a change in anaesthetic vapour exchange (2001, 2001a, 2002). Despite clear evidence of an association between the two variables, they concluded that a 30-40%

difference in cardiac output was required before a change in anaesthetic vapour could be detected.

Unlike Peyton's (2005) simulator, the use of digital flow controllers provides greater flexibility to simulate multiple uptake scenarios: over a shorter period, that enables real-time control. Preliminary measurement indicates that tidal movement inside the bellows is sufficient to mix gas: this simplifies the design, because the internal mixing fans can be removed.

As can be seen in Figure 15 the simulator uses six digital mass flow controllers[7] based on a program displayed in the appendices, each regulates flow of oxygen, carbon dioxide, or nitrogen. The gases merge in a stainless-steel manifold to form replacement flows for the left and right bellows[8]. The suction flow is controlled manually for each lung, using individual regulators that are connected to wall suction; this is monitored by measuring the change between fresh and exhaust flow, and adjusting as required.

The flow controllers are calibrated for individual gases; these are supplied with pressure regulated 'medical grade' bottled gas. Individual flows are computer-driven by the simulator and use electromagnetic valves to supply metered laminar flow (0-10 L min^{-1}). The set flows are accurate to within +/- 10 mL min^{-1} and respond to changes within 2 seconds. The gas mixture on the right side is diverted through a manually-adjusted isoflurane vaporiser before insertion into the right lung bellows. The left-lung bellows has isoflurane removed without replacement in all scenarios, thus an additional vaporiser is not necessary on this side.

The left- and the right-lung bellows in the simulator (Figure 15) are completely isolated, with the exception of a common wall-suction outlet. This common connection comes after the

[7] Aalborg, DFC26 0 – 200 L min^{-1}

[8] Dual Adult TTL type 1600, Michigan Instruments Inc., USA

left and right suctioned gas passes through a fixed volume cylinder (which dampens fluctuations from the hospital suction system), and independent suction regulators.

3.8.1. Scenarios

Scenarios have been designed to produce cardiac outputs between 2 and 10 litres per minute. Oxygen and carbon dioxide uptake rates were fixed at typical physiological values for anaesthetised adult patients (200 ml min^{-1} and 160 ml min^{-1} respectively). Total (net) isoflurane uptake rate was also set at a typical maintenance phase rate for a given inspired concentration of 1% in the left lung (5 ml min^{-1}). The left lung uptake and right lung excretion of isoflurane contribute to this value, and their associated end-tidal concentrations were calculated for the cardiac output nominated in each scenario.

The uptake rates and end-tidal concentrations used for simulation (Table 5) were determined using an adaptation of the multi-compartment computer model, and the LabVIEW program. Peyton (2004) determined the mathematical relationship between cardiac output and the uptake of soluble alveolar gases; his model accounted for the interdependent nature of oxygen, carbon dioxide and foreign gases. He calculated the partial pressure of each inert gas (Equation 15) and the relationship between alveolar ventilation and perfusion to determine the relationship between gas uptake and cardiac output (Equation 16).

$$P_{AG} = \frac{\left(\frac{\dot{V}_{AI}}{\dot{Q}} \times P_{I_G}\right) + (\lambda \times P_{\bar{V}_G})}{\frac{\dot{V}_{AE}}{\dot{Q}} + \lambda}$$

Equation 15 Calculation of partial pressure of gas 'G' assuming that the lung compartment is an ideal compartment [Equation 19 Chapter 3 (Peyton 2004)]

and

$$\frac{\dot{V}_{A_I}}{\dot{Q}} = \frac{863\left(C_{C'_{O_2}} - C_{\bar{V}_{O_2}}\right) + P_{A_{O_2}} \times \frac{\dot{V}_{AE}}{\dot{Q}}}{P_{I_{O_2}}}$$

Equation 16 Ratio of inspired alveolar ventilation to perfusion. [Equation 20 Chapter 3 (Peyton 2004)]

Peyton's model was used as the basis for the *in vitro* and *in vivo* validations of the nitrous oxide throughflow method (Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003).

The simulation of isoflurane throughflow in this thesis uses gas uptake rates and end-tidal concentrations for target cardiac outputs of 2, 4, 6 and 8 L min^{-1} (that were derived using a model developed by Peyton (2004)). The benchtop simulator assumes a homogeneous lung, and uses an iterative process to arrive at final left and right uptake rates and end-tidal concentrations of isoflurane, carbon dioxide and oxygen. This requires the temperature, barometric pressure, haemoglobin level, left to right pulmonary ratio, left and right inspired gas concentrations, and the combined oxygen and carbon dioxide uptake rates as well as the target cardiac output, and uses a common mixed venous concentration for each gas[9]. These uptakes, flows and end-tidal concentrations were used as outputs for the benchtop simulator and employed in the calculation of throughflow cardiac output.

The removal of mixed alveolar gas in each simulator lung bellows, and its replacement with the individually-metered gases required to produce the desired uptake rates, were estimated based on system tidal volumes, respiratory rate and fresh gas flows. The simulator described in this thesis produced accurate (within +/- 10% of target) uptake rates with the simultaneous removal and replacement of oxygen, carbon-dioxide, nitrogen and isoflurane in the left and right lungs. Preliminary investigations indicated that the tidal ventilation of the bellows was sufficient to eliminate the need for additional mixing. The quantity of gas needing to be removed and replaced was mathematically estimated.

The amount of gas withdrawn from the left-lung depends on the target isoflurane uptake rate; this means that more oxygen and nitrogen is removed than necessary. Digital mass flow controllers are used for the insertion of carbon dioxide and the reinsertion of oxygen and nitrogen into the bellows. The oxygen uptake rate determines the amount of gas which

[9] Example outputs from this program are included in Appendices

needs to be removed from the right-side simulated lung, so only nitrogen and carbon dioxide need to be supplied by the gas flow controllers. Isoflurane is added on the right-side, to simulate throughflow of the isoflurane from the left to the right lung through the blood stream, by using an inline manually-controlled vaporiser; the isoflurane flow depends on the dialled concentration and the flow of carbon dioxide and nitrogen.

The ideal flows were adjusted slightly in benchtop studies to account for the difficulties manually dialling the desired suction flow rates, and the inaccuracy of the flow controllers. The accuracy tolerance of each digital flow controller and the variability of the manual suction system means that the values calculated are indicative only, and in practice they are adjusted slightly to ensure accurate system uptakes.

The Haldane Transformation-derived exhaust flow is an established method of measuring secondary flows (Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003, Robinson, Peyton et al. 2004, Peyton, Ramani et al. 2005), and was used alongside direct flow measurement to determine uptake rates in the benchtop simulator.

Cardiac output (L min^{-1})	$\dot{V}_{L\,O_2}$ (ml min^{-1})	$\dot{V}_{L\,CO_2}$ (ml min^{-1})	$\dot{V}_{L\,Iso}$ (ml min^{-1})	$P_{L\,A\,Iso}$ (mmHg)	$P_{L\,A\,CO_2}$ (mmHg)	$\dot{V}_{R\,O_2}$ (ml min^{-1})	$\dot{V}_{R\,CO_2}$ (ml min^{-1})	$\dot{V}_{R\,Iso}$ (ml min^{-1})	$P_{R\,A\,Iso}$ (mmHg)	$P_{R\,A\,CO_2}$ (mmHg)
2	90	-71	6.0	4.47	39.32	110	-89	-0.9	0.41	39.15
4	90	-71	7.3	3.76	39.28	110	-89	-2.3	1.00	39.18
6	90	-71	7.9	3.38	39.26	110	-89	-3.0	1.30	39.20
8	90	-71	8.4	3.15	39.25	110	-89	-3.4	1.48	39.20
10	90	-71	8.6	3.00	39.25	110	-89	-3.6	1.60	39.21

Table 5 Designed uptake and end-tidal values for cardiac output scenarios. Partial pressures (P_{A_G}) values based on barometric pressure of 760mmHg, experiments conducted using standard temperature and dry gas.

3.8.2. System dead space and the relationship of alveolar (end-tidal) concentration to gas uptake

For any given rate of uptake or excretion of a gas, both physiologically and in the simulator, measured end-tidal concentrations vary with different system dead space volumes. In the benchtop simulator, dead space was altered by changing the tubing volume between the lung bellows and the mouth end of the breathing circuit. Increasing circuit dead space increases the amounts of the gases excreted from the lung, and decreases those taken up. Physiological dead space makes the end-tidal concentration converge towards the inspired concentration by diluting the alveolar gas with inspired gas. This also occurs in the Bain circuit due to the relatively high fresh gas flow rate.

3.8.3. Accuracy and precision of cardiac output

Cardiac output is difficult to measure accurately. Tolerances between the novel techniques, with bolus thermodilution as a reference method, are up to 45% in clinical validation studies (Peyton and Chong 2010); in contrast, simulations should be more accurate because they can be measured against set values, and inputs can be controlled. The simulator targets the uptake rates and end-tidal concentrations to within 10% of the projected value. To measure simulated cardiac output between 2 and 10 litres per minute requires precise titration of relatively small isoflurane uptake rates (-0.9 to 8.5ml min^{-1}) and correspondingly small isoflurane end-tidal concentrations (0.04 to 4.47mmHg or 0.0 to 0.6%): a high degree of linearity and precision in the measurement response across these ranges.

A ten-percent range for uptake rate measurements in this range is small compared with the dynamic measurement range of the gas analysers used for this purpose; thus, the acceptable range was adapted to the larger of 10% or +/-0.25 ml min^{-1}: this affects only two isoflurane uptake rates in the right lung bellows: those are indicated by a '+' inside the box in Figure 16. Similarly, for end-tidal isoflurane concentration measurements, a range of +/-10% or +/-0.1mmHg (whichever was the greater) was used.

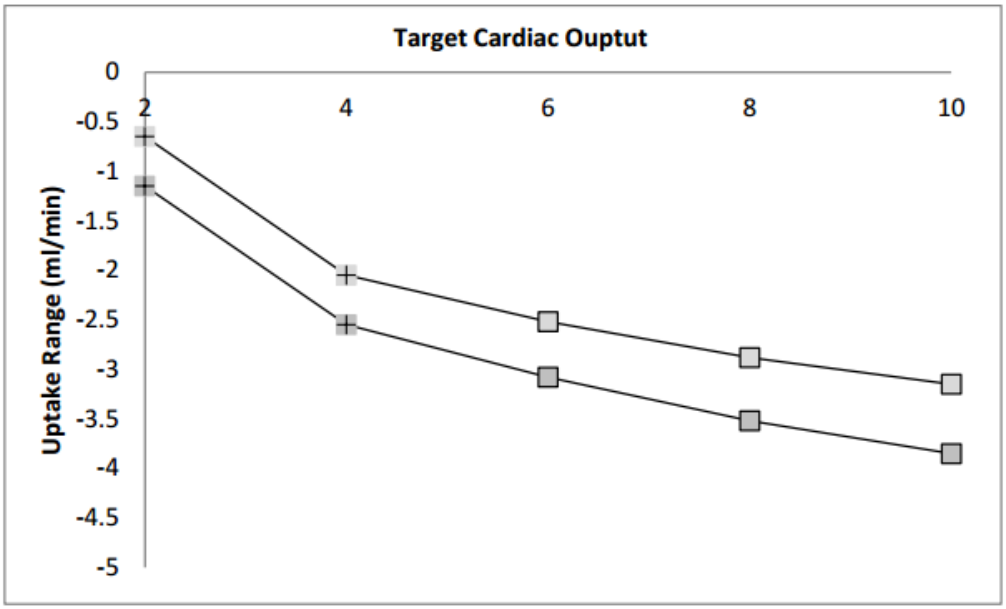

Figure 16 Right-side isoflurane uptake rates (ml min^{-1}). The crossed boxes indicate a tolerance of +/- 0.25 ml min^{-1} has been used; all other values represent +/- 10%.

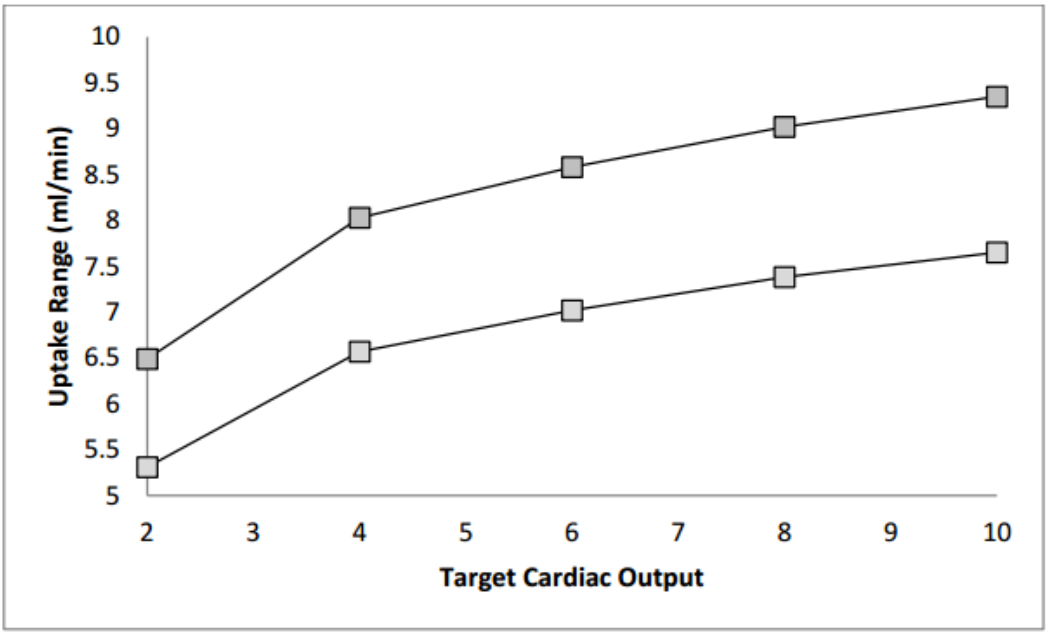

Figure 17 Left-side isoflurane uptake rates (ml min^{-1})

3.8.4. End-tidal Concentrations

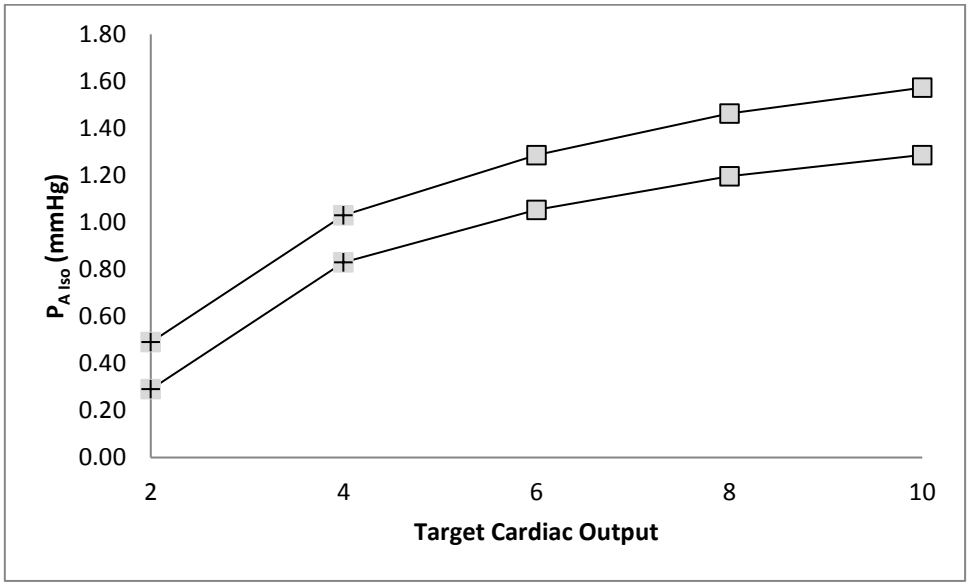

Figure 18 Right-side end-tidal isoflurane partial pressure tolerances (mmHg). The crossed boxes indicate that a tolerance of +/- 0.1 mmHg has been used rather than +/-10%.

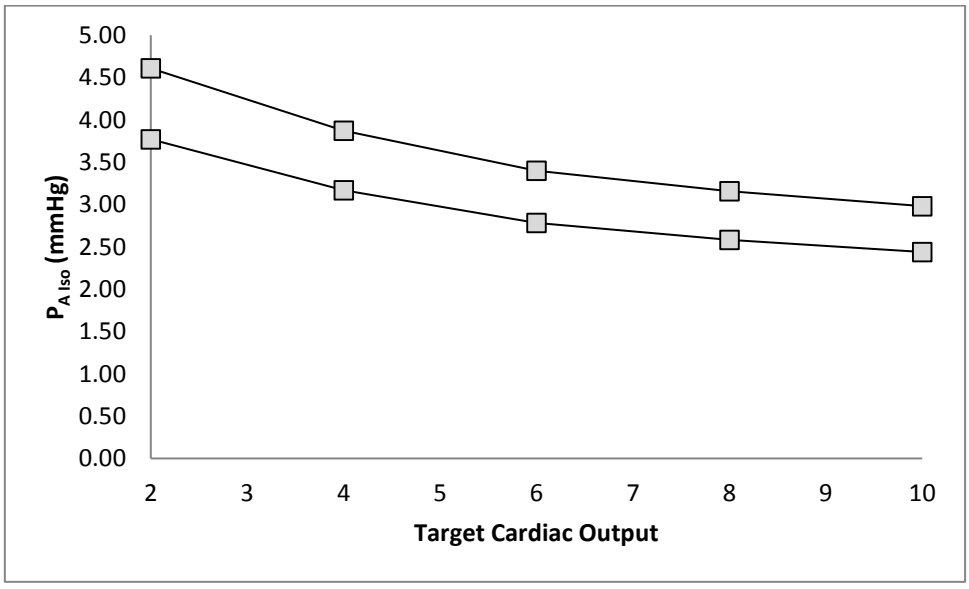

Figure 19 Left-side end-tidal isoflurane partial pressure tolerances (mmHg)

3.8.5. Accepted Range in Cardiac Output

Acceptable uptake rates and end-tidal measurement ranges were reviewed in the previous section. These ranges have a compounding effect on the cardiac output. Reviewing the throughflow equation (Equation 9), we can estimate the acceptable range, given the tolerance to uptake rates and end-tidal concentrations.

$$\dot{Q}_c = \frac{\frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_L}}} \cdot \dot{V}_{iso_L} - \frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_R}}} \cdot \dot{V}_{iso_R}}{\lambda_{iso}(F_{E'_{iso_L}} - F_{E'_{iso_R}})}$$

Equation 17 Throughflow isoflurane cardiac output

To determine acceptable tolerance, and simplifying the equation, we will for the moment fix the oxygen uptake ratios.

$$\frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_L}}} = \frac{1}{0.45} = 2.22$$

$$\text{and } \frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_R}}} = \frac{1}{0.55} = 1.81$$

Equation 18 Oxygen uptake ratios

$$A = 2.22 \cdot \dot{V}_{iso_L} - 1.81 \cdot \dot{V}_{iso_R}$$

Equation 19 Numerator of isoflurane throughflow cardiac output

$$B = \lambda_{iso}(F_{E'_{iso_L}} - F_{E'_{iso_R}})$$

Equation 20 Denominator of isoflurane throughflow cardiac output

$$\dot{Q}_c = \frac{A}{B}$$

Equation 21 Throughflow isoflurane cardiac output using terms 'A' and 'B.'

$$\dot{Q}_c \pm \Delta \dot{Q}_c$$

Equation 22 Calculation of tolerance for isoflurane throughflow cardiac output

$$\Delta A = \sqrt{2.22\left(\Delta \dot{V}_{iso_L}\right)^2 + 1.81\left(\dot{V}_{iso_R}\right)^2}$$

Equation 23 Calculation of error in term 'A.'

$$\Delta B = \sqrt{\lambda_{iso}\left(F_{E'_{iso_L}}\right)^2 + \lambda_{iso}\left(F_{E'_{iso_R}}\right)^2}$$

Equation 24 Calculation or error in term 'B'

$$\Delta \dot{Q}_c = \dot{Q}_c . \sqrt{\left(\frac{\Delta A}{A}\right)^2 + \left(\frac{\Delta B}{B}\right)^2}$$

Equation 25 Calculation of error in cardiac output equation given described tolerances

Table 5 shows the throughflow cardiac output assuming $\lambda_{iso} = 1.4$, and using tolerances for cardiac output calculated from Equation 18 to Equation 24.

Set C.O. (L min^{-1})	**Eq. C.O.** **(L min^{-1})**	**ΔC.O.** **(L min^{-1})**
10	9.9	2.1
8	8.1	1.5
6	6.0	0.9
4	4.0	0.5
2	1.8	0.2

Table 6 Acceptable tolerances for isoflurane throughflow cardiac output

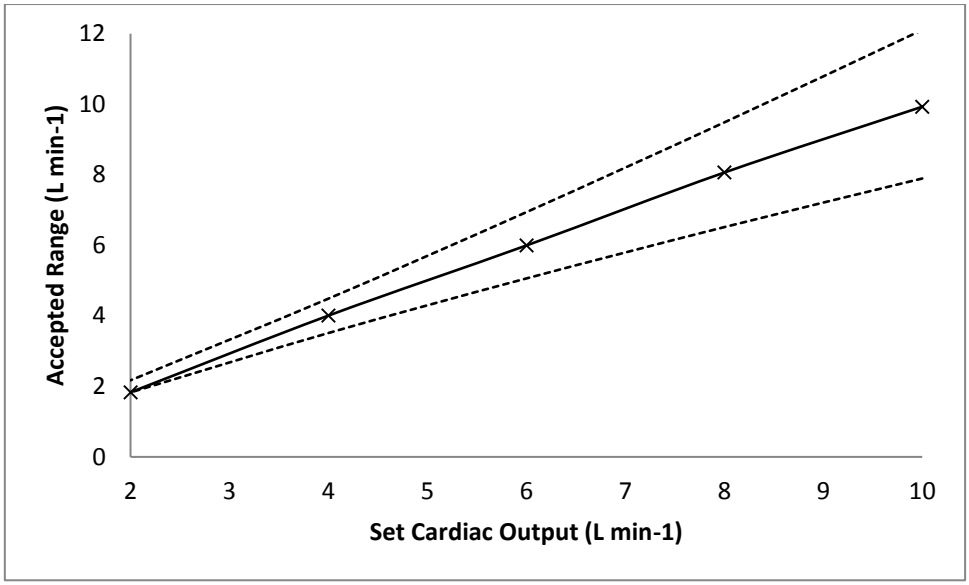

Figure 20 Set cardiac output with tolerances

This tolerance is described below

$$Tolerance = 0.0143(Cardiac\ Output)^2 + 0.0686(Cardiac\ Output) + 6 \times 10^{-15}$$

Equation 26 Calculation of tolerance for measured cardiac output based on Figure 20.

3.9. Summary

This chapter described the development of an accurate and realistic simulator, and the development of a measurement system to measure throughflow cardiac output.

It has outlined a robust measurement system that provides continuous cardiac output measurements using the throughflow technique which has been updated to use isoflurane and directly measures all flows.

The throughflow technique overcomes the limitations of blood recirculation, which prevents many other gas uptake-based techniques from being used continuously. Originally developed using nitrous oxide (Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003), the throughflow technique would benefit from using a more modern gas or vapour. The blood-gas solubility of isoflurane means that it can respond rapidly to changes in cardiac output, yet maintain relatively large variation in its concentrations, which is an important attribute given the small concentration (1%) being delivered in the left fresh gas.

Unlike a number of existing techniques, which also measure non-shunt cardiac output, the throughflow method is non-invasive. Throughflow measurement is complicated by the need to separate the lungs functionally and to measure small bidirectional isoflurane uptake rates and end-tidal concentrations. The small left-side fresh gas concentration of isoflurane means it is necessary to consider the system design carefully; this was assisted by understanding how Gan (1993) used acetylene concentrations, which also required careful filtering and selection to ensure that measurements were reliable.

The delivery of independent fresh gas mixtures requires modification of the ventilator and adaptation of the breathing circuit. Additionally, the decision to compare direct-flow measurement against the Haldane technique for validation purposes means that a minimum of 29% nitrogen must be present in the left and right fresh gas. If direct flow measurement can be used interchangeably with Haldane Transformation-derived flows, the right fresh gas could be simplified to deliver 100% oxygen using the auxiliary oxygen outlet on the anaesthetic machine.

As discussed, gas concentrations were sampled from three locations (fresh, end-tidal, and exhaust) in the left and right breathing circuit. The requirement to sample fresh gas was reduced because it was kept constant in all scenarios. Correspondingly, the rate of end-tidal and exhaust sampling enables changes in cardiac output to be detected more rapidly than otherwise possible.

The simulator developed and described replicates realistic gas-exchange for cardiac output scenarios of 2, 4, 6, 8 and 10 litres per minute. This allowed the measurement system to be tested and for its design to be refined. The simulator improves on existing systems: it can produce bi-directional isoflurane uptakes, and many of the inputs can be controlled digitally. This is done through the insertion of individually-metered gases directly to a commercial bellows lung simulator (which can alter the resistance and compliance) and by simultaneously suctioning mixed gas from the bellows. The simulator has been designed to replicate uptake and end-tidal concentrations to within +/- ten percent of target values, although it is necessary to expand this range for very low isoflurane uptakes and end-tidal concentrations (present on the right-side at cardiac output rates of two and four litres per minute).

Accuracy can be increased, and minor fluctuations reduced by filtering, averaging and careful selection of measurements. However, tradeoffs are made between the speed and complexity of designed systems; a good measurement system will provide accurate measurements that respond rapidly to real-time clinical changes. Measurement of oxygen and isoflurane uptake rates and isoflurane end-tidal concentrations were examined, and smoothing filters were applied to reduce breath-by-breath fluctuations in cardiac output readings without affecting the overall accuracy of the measurement system. The use of fixed (as opposed to measured) left or right oxygen uptake-rate ratios will also be trialled in the benchtop scenario that is presented in Chapter 6.

If the end-tidal concentration point is not selected correctly it can affect the accuracy of cardiac output considerably. This is because the left and right concentrations are small and in opposite directions. Thus, consideration was given to the best method to determine the end-tidal concentration, and two approaches were described. Method One will be used in

the result of the benchtop study (Chapter 6), but it may be necessary to use Method Two during clinical measurement.

The measured cardiac output is displayed as a continuous waveform and a single numeric. This was chosen to improve trend recognition and allow quick identification of the current cardiac output. Research by Kennedy et al. (2009) has indicated that physiological measurements should be displayed in a simple and clear format, and that trends will lead to better recognition of changes. The methods described in this chapter have been used to produce the results that will be discussed in Chapter 7.

Chapter 4 Physiological Sources of Error

4.1. Introduction

The justification for using isoflurane in the place of nitrous oxide in the throughflow techniques was discussed in Chapter 2 and Chapter 3. The physiological factors leading to systemic error associated with isoflurane measurement need to be considered; these will primarily consist of the unmeasured shunt fraction of pulmonary blood flow, $\dot{V}/\dot{Q}$ inhomogeneity (scatter), and the alveolar-arterial (A-a) difference.

The physiological modelling in this chapter has been influenced by previous work by Peyton (2004). In particular, I am grateful for the use of his multi-compartmental, continuous ventilation model which was employed to simulate the effect of alveolar dead space on isoflurane partial pressures in blood and expired gas.

The throughflow method does not measure shunt; some means of estimating the shunt fraction should be incorporated in the throughflow of isoflurane. The usual method of measuring dead space is based on arterial to expired carbon dioxide partial pressure differences using the Riley model; this model is not ideal, as evidence suggests that dead space is variable depending on the blood-gas partion coefficent of the individual gas or vapour(Landon, Matson et al. 1993). Naturally, the ideal blood-gas partion coefficient will vary further if the mismatch between perfusion and ventilation increases.

The benchtop simulator will model cardiac output between 2 and 10 L min^{-1}; it is based on an ideal single-lung compartment and thus has no inhomogeneity (log SD = 0). The log normal distribution of $\dot{Q}$ and alveolar ventilation ($\dot{V}_{AE}$) were generated with a natural-logarithm standard deviation (log SD) varying between 0 and 2.0 (representing a lung with severe homogeneity).

This means that the maximum rate of gas uptake around the measured cardiac output (pulmonary blood flow) will occur for gases with blood-gas partition coefficient (λ) of between 0.4 ($\dot{Q}$ = 10 L min^{-1}) and 1.2 ($\dot{Q}$ = 2.5 L min^{-1}). Modelling by Peyton(2004) has

indicated that if the log SD increases, the rate of gas uptake for a change in cardiac output decreases, and that the ideal blood-gas partition coefficient for detecting the change will increase. As discussed in Chapter 3, this is consistent with blood gas partition coefficients between 1.5 and 2.1 as identified by Kennedy and Baker (2001a), however they also noted that the ideal vapour will vary depending on the magnitude of cardiac output measured.

4.2. Unmeasured shunt

By definition, estimation of pulmonary blood flow from alveolar-capillary gas exchange will not measure perfusion of unventilated lung regions where no gas exchange occurs, that is, regions of pulmonary shunt. The unmeasured shunt will cause inaccurate approximation of uncorrected gas-exchange based cardiac output measurements, hence it is necessary to predict the shunt so that a correction can be applied. Shunt occurs when well-perfused alveoli are unventilated or under-ventilated; it is largest in patients with pulmonary conditions, or those that are critically ill. However, during anaesthesia and surgery, it can be a problem in normal healthy lungs. Shunt is typically determined from:

$$\frac{Q_s}{Q_t} = \frac{C_{c'_{O_2}} - C_{a_{O_2}}}{C_{c'_{O_2}} - C_{\bar{v}_{O_2}}}$$

Equation 27 Shunt equation

The fractional concentration of oxygen in arterial blood ($C_{a_{O_2}}$) can be measured relatively noninvasively, while the fractional content of oxygen in 'ideal' pulmonary end-capillary blood ($C_{c'_{O_2}}$) can be calculated from alveolar oxygen tension. However, right-heart catheterisation is required to determine the fractional concentration of oxygen in the mixed-venous blood ($C_{\bar{v}_{O_2}}$). To avoid invasive measurement, assumption or estimation of arterio-venous oxygen concentration differences have been used previously, but this also reduces accuracy.

The throughflow cardiac output technique also relies on the exchange of gas between the pulmonary and cardiovascular system, and it is necessary to incorporate an estimation of the shunt. The characteristic shunt equation is unattractive because the right-heart

catheterisation necessary to provide the mixed-venous fractional concentration of oxygen is contradictory to the advantages of throughflow.

Peyton used an another approach (Peyton 2004) based on work by Gedeon, Krill et al. (1992) and West (1997); this method relies on both pulmonary blood flow and the uptake of oxygen to estimate shunt using the Fick equation (Equation 28):

$$C_{a_{O_2}} - C_{\bar{v}_{O_2}} = \frac{\dot{V}_{O_2}}{\dot{Q}_t}$$

Equation 28 Rearranged Fick Equation

Thus,

$$\frac{Q_s}{Q_t} = \frac{C_{c'_{O_2}} - C_{a_{O_2}}}{C_{c'_{O_2}} - \frac{\dot{V}_{O_2}}{\dot{Q}_t}}$$

Equation 29 Shunt calculation using direct method

During a clinical series of thirty-eight patients by Peyton(2004), the calculation of pulmonary shunt fraction was compared using three methods: (a) invasively (using thermodilution and direct blood gas sampling), (b) estimation, and (c) direct measurement (Equation 29 deriving $\dot{Q}_t$ from either Doppler echocardiography or nitrous oxide throughflow). The direct and estimate-based techniques were compared to the invasive method using a variety of statistical techniques (t-test for paired data, Bland-Altman plots and correlation coefficients). Peyton found that the direct method (Equation 29) showed good agreement with the invasive method (in contrast to using an estimate) regardless of how the pulmonary flow was calculated (thermodilution, Doppler echocardiography or nitrous oxide throughflow).

In contrast, analysis of precision of the different methods showed that thermodilution and Doppler echocardiography varied by one-third around the average; this ruled out these two methods for determining pulmonary blood flow in the direct method. However, pulmonary blood flow which was calculated using throughflow demonstrated better precision (than Doppler and thermodilution); this was attributed to the fact the throughflow of nitrous

oxide also employs the measurement of oxygen uptake and end-capillary or end-tidal concentrations. Unfortunately, the proposed direct method still requires the fractional concentration of oxygen in the arterial blood to be measured with blood gas sampling. Peyton proposed that in the future, arterial oxygen concentration could be determined noninvasively using SpO_2 measurement instead, although the current accuracy of this technology means that this would be another source of error which would reduce the accuracy of the method to such a degree that it was no longer better than the other described techniques. The use of near-infrared spectroscopy (NIRS) or transcutaneous measurement of oxygen may offer more-accurate alternatives: these could be investigated with reference to measured blood-gases.

4.3. A-a difference and V/Q Scatter

The throughflow method uses end-tidal gas-concentration measurement; used in place of arterial blood gases, these are based on the ideal transfer of gas across the alveolar-arterial (A-a) membrane, and utilise Ostwald's blood-gas partition coefficient. However, A-a differences are a source of error in non-shunt cardiac output measurement, which is partly due to inhomogeneity of ventilation-to-perfusion ratios (expressed in terms of alveolar dead space). In throughflow we refer to the alveolar-to-end-capillary (rather than the A-a) partial pressure differences because these are quantitatively different in the two lungs where isoflurane gas-exchange occurs in opposite directions.

Unlike the carbon dioxide partial re-breathing method where physiological errors subtract out, in throughflow the alveolar-to-end-capillary (rather than the A-a) partial pressure differences are in opposite directions, so the errors are additive, and can cause underestimation of cardiac output, which needs to be addressed. A-a and end-tidal to end-capillary differences for isoflurane are due to $\dot{V}/\dot{Q}$ scatter and longitudinal diffusion gradients.

Longitudinal diffusion gradients can occur due to diffusion limitation down the airway in the presence of tidal ventilation, or across the alveolar-capillary membrane, and according to Fick's diffusion principle, are greater for heavy molecules such as volatile anaesthetic agents.

Traditionally the Riley model is used to describe and quantify physiological dead space; this is based on carbon dioxide partial pressure measurement but tacitly assumes dead space is equivalent for all gases. However, it is now known that dead space is gas-dependent and varies with different blood-gas partition coefficients (Landon, Matson et al. 1993). This is supported by Peyton's (2004) multi-compartmental modelling, which used a continuous ventilation (rather than tidal) model and utilised distributions of ventilation and perfusion, with spread defined by the log-standard deviation (log SD).

$$\lambda_{ideal} = \frac{\dot{V}_{AE_{tot}}}{\dot{Q}_{tot}(1 - F_{I_G})} e^{\frac{1}{2}(\log SD)^2}$$

Equation 30 Ideal blood-gas coefficient based on the log SD of cardiac output

Dead space for individual gases is calculated simultaneously, based on alveolar ventilation and measured partial pressures for that gas species. The ratio of total alveolar ventilation (V_{AE}) to that of perfused (non-dead space) alveoli for any gas '*G*', can be calculated from inspired, end-tidal and end-capillary partial pressures based on a derivation of the Bohr-Enghoff equation (Equation 31).

$$\frac{\dot{V}_{AE} - \dot{V}_{DA}}{\dot{V}_{AE_G}} = \frac{P_{I_G} - P_{E'_G}}{P_{I_G} - P_{C'_G}}$$

Equation 31 Ratio of ventilation of perfused alveoli to expired alveoli ventilation based on multi-compartmental modelling. This equation requires simultaneous solving for each gas. Based on the expired alveolar ventilation ($\dot{V}_{AE}$), Alveolar dead space ventilation $(\dot{V}_{DA})$ and the expired alveolar ventilation, partial pressure for the inspired gas (P_{I_G}) end-expired gas$(P_{E'_G})$ and end-capillary gas$(P_{C'_G})$.

The calculation of dead space for the throughflow of nitrous oxide required the simultaneously-run parallel copies that shared common mixed-venous blood-gas concentrations for each gas species. Although we typically describe this difference as 'A-a', in the throughflow technique the comparison is the end-tidal to end-capillary difference for the left and right lungs, because each lung is ventilated with a different mixture of gases.

Unlike the Riley model, Peyton's model shows that, the ratio of expired alveolar ventilation to ventilation of perfused alveoli for nitrous oxide increases at three times the rate of carbon dioxide. The observed left and right ratios were similar (Figure 21), which means the multi-compartmental model is still useful for the throughflow cardiac output measuring technique.

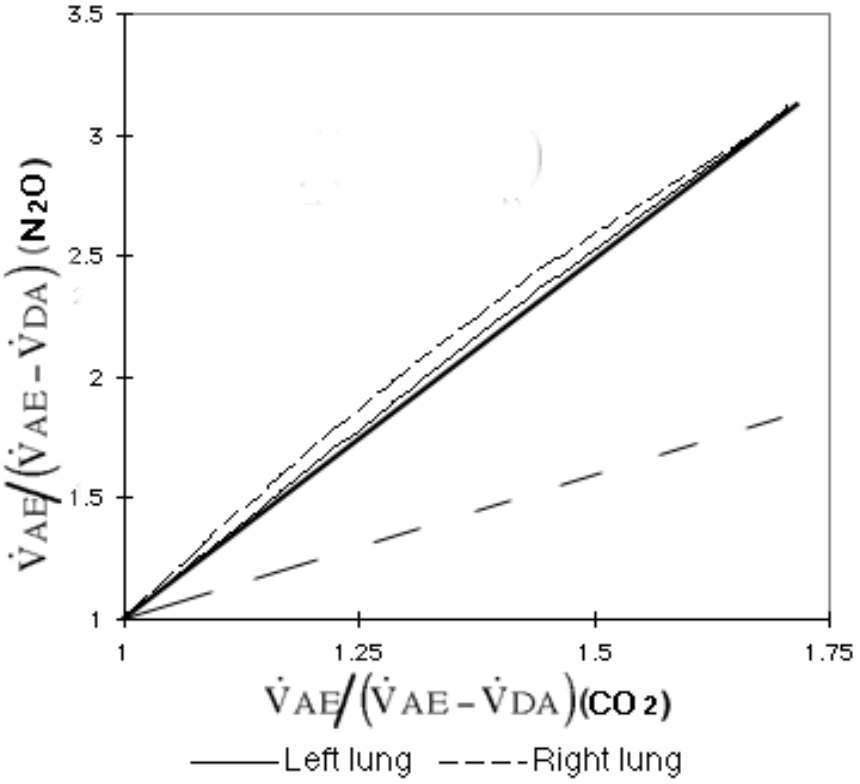

Figure 21 The inverse ratio of ventilation of perfused alveoli to expired alveoli [$\dot{V}_{AE}/(\dot{V}_{AE} - \dot{V}_{DA})$] for N_2O versus CO_2 with increasing $\dot{V}/\dot{Q}$ scatter in each lung. The lower dashed line is the line of unity. Peyton (2004)

$$\frac{P_{I_{N_2O}} - P_{C\prime_{N_2O}}}{P_{I_{N_2O}} - P_{E\prime_{GN_2O}}} - 1 = 3 \times \left(\frac{P_{a_{CO_2}}}{P_{E'_{CO_2}}} - 1\right)$$

Equation 32 Differential dead space for nitrous oxide compared to carbon dioxide Peyton (2004)

Given the different blood-gas partition coefficients of nitrous oxide (0.47), isoflurane (1.4) and carbon dioxide (2.9) it is likely that the dead space ventilation for isoflurane would be

closer to that of carbon dioxide than for nitrous oxide. Because of the error which occurs in uncorrected nitrous oxide throughflow cardiac output measurement, it is important to model the dead space behaviour of isoflurane to see the effect that dead space ventilation will have on the mismatch between alveolar and end-capillary isoflurane concentrations.

The A-a gradient modelling by Peyton was repeated to assess the error in cardiac output expected with isoflurane throughflow, and compared with that expected using nitrous oxide. A multicompartment lung was modelled with $F_{I_{O_2}} = 30\%$, $F_{I_{N_2O\,(Left)}} = 40\%$, $F_{I_{Iso\,(Left)}} = 2\%$.

For simplicity, $\dot{V}_{AE} = 4.0\ L\ min^{-1}$, $\dot{Q} = 4.0\ L\ min^{-1}$, $\dot{V}_{O_2} = 200\ mL\ min^{-1}$, $\dot{V}_{CO_2} = 160\ mL\ min^{-1}$ were divided evenly between the two lungs.

Similarly to previous work, a continuous ventilation model was used. In the left lung $\dot{V}_{N_2O\,(Left)} = 150\ mL\ min^{-1}$ and $\dot{V}_{Iso\,(Left)} = 10\ mL\ min^{-1}$, and $\dot{V}_{N_2O\,(Right)} = -100\ mL\ min^{-1}$ and $\dot{V}_{Iso\,(Right)} = -5\ mL\ min^{-1}$. The effect of increasing log SD was examined.

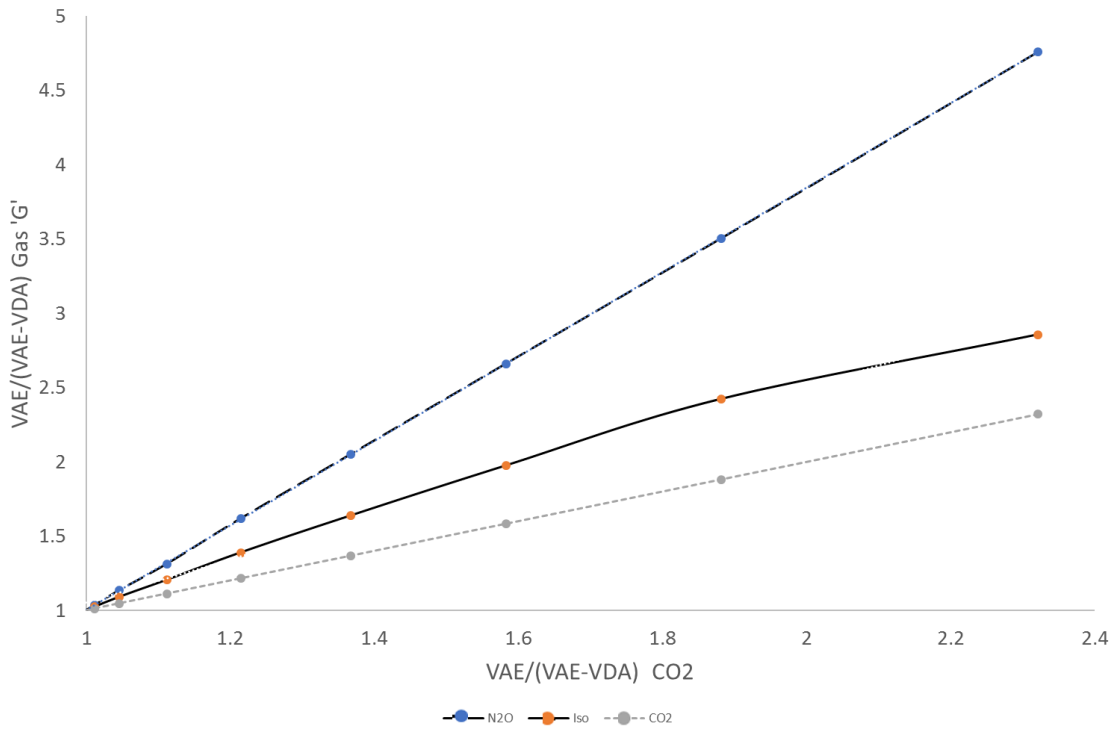

Figure 22 Left lung: $\dot{V}_{AE}/(\dot{V}_{AE} - \dot{V}_{DA})$ for nitrous oxide and isoflurane versus carbon dioxide with increasing $\dot{V}/\dot{Q}$ scatter in the lung.

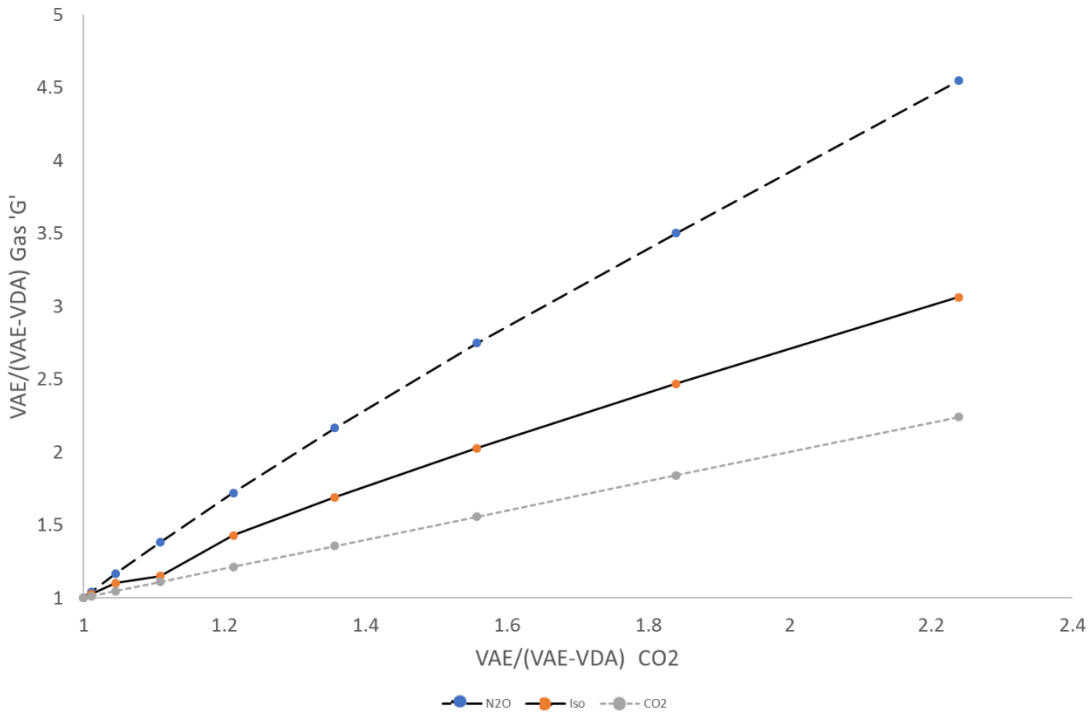

Figure 23 Right Lung: $\dot{V}_{AE}/(\dot{V}_{AE} - \dot{V}_{DA})$ for nitrous oxide and isoflurane versus carbon dioxide with increasing $\dot{V}/\dot{Q}$ scatter in the lung.

$$\frac{P_{I_{Iso}} - P_{C'_{Iso}}}{P_{I_{Iso}} - P_{E'_{Iso}}} - 1 = 1.5 \times \left(\frac{P_{a_{CO_2}}}{P_{E'_{CO_2}}} - 1\right)$$

Equation 33 Differential dead space for isoflurane compared to carbon dioxide

In Figure 22 and Figure 23 we can see the effect of end-tidal to end-capillary difference is significantly reduced for isoflurane (compared to nitrous oxide) when modelled with increasing $\dot{V}/\dot{Q}$ scatter. This suggests that the correction strategy used by Robinson et al (2004) and Peyton (2004) using an estimate of $\dot{V}/\dot{Q}$ scatter obtained from measured A-a difference for carbon dioxide, is likely to be even more successful using isoflurane throughflow than nitrous oxide.

The modelling presented above only includes the effect of $\dot{V}/\dot{Q}$ scatter and does not incorporate any effect of longitudinal diffusion limitation to A-a differences. This was not

needed in the nitrous oxide throughflow method because nitrous oxide has an identical molecular weight and similar diffusion characteristics to carbon dioxide. However, longitudinal diffusion may be a source of error for isoflurane which is a heavier molecule (Molecular Weight = 180, rather than 44 for nitrous oxide and carbon dioxide). To analyse the effect of longitudinal diffusion, a more sophisticated lung gas exchange model, incorporating tidal ventilation and diffusion limitations both down the airway and across the alveolar-capillary barrier, would need to be used. These may utilise principles described by Piiper and Scheid (1980). An assessment of the magnitude of any error in cardiac output from isoflurane throughflow resulting from this factor may be made when data from *in vivo* testing in anaesthetised patients becomes available.

4.4. Summary

Considerations of previous theoretical work on the link between $\dot{V}/\dot{Q}$ scatter and A-a differences for respired gases suggests that this might be a significant source of error for cardiac output measurement using throughflow. This was confirmed for nitrous oxide throughflow in a previous study, but successfully corrected by estimation of the severity of $\dot{V}/\dot{Q}$ scatter. This was done using a simple strategy involving arterial blood gas sampling and carbon dioxide partial pressure measurements in patients. Modelling conducted in the current study suggests that this error will be lower for isoflurane throughflow, although the effect of longitudinal diffusion needs to be assessed further. It would appear that isoflurane is also less affected than nitrous oxide for increases in $\dot{V}/\dot{Q}$ scatter, which means that correction for A-a difference might not lead to significant error in cardiac output measurement.

Chapter 5 Instrumentation Inaccuracy – Optimisation of Measurement Techniques

5.1. Introduction

Computer simulations allow precise control of measurement variables, so they are commonly used to represent physiological models. In this study of the proposed cardiac output method using throughflow of isoflurane, computer simulation was used to optimise measurement methods and test their limitations. Models can represent an ideal system, however, the aim of this model is to replicate benchtop simulation fluctuations and potential sources of measurement error that may be observed in clinical scenarios. Clinical measurement is marked by small random and systematic variations in measured variables, so it is beneficial to simulate these natural variations that can make it difficult to distinguish true changes in the endpoint of interest, that is, cardiac output.

Chapter 4 proposed a method for measuring cardiac output using throughflow of isoflurane (which is replicated here as Equation 34). The terms in this equation are direct inputs for our computer simulation. In practice, gas uptakes are derived, and cannot be measured directly.

$$\dot{Q}_c = \frac{\frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_L}}} \cdot \dot{V}_{iso_L} - \frac{\dot{V}_{O_2}}{\dot{V}_{O_{2_R}}} \cdot \dot{V}_{iso_R}}{\lambda_{iso}(F_{E'_{iso_L}} - F_{E'_{iso_R}})}$$

Equation 34 Cardiac output using throughflow of isoflurane

This chapter describes a computer simulation intended to provide realistic values for the variables in the proposed throughflow cardiac output equation.

The numerator of Equation 9 consists entirely of gas uptake rate measurements. Individual gas uptakes are measured by subtracting exhaust flow from fresh gas flow for each gas (Equation 35).

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

Equation 35 Uptake calculation for gas 'G.'

Constant left and right oxygen uptakes are nominated for scenarios used in the computer and benchtop simulations; this reflects an 'ideal' patient during steady-state respiration. The oxygen uptake ratio determines the weighting given to left and right isoflurane uptakes in Equation 9. End-tidal concentrations were identified by Kennedy (Kennedy and Baker 2001, Kennedy and Baker 2001a) as one of the early indicators of change in cardiac output. As can be seen in Equation 9 have a large influence on the determination of throughflow cardiac output. Throughflow cardiac output is inversely proportional to the fractional concentration difference between the two lungs of end-tidal isoflurane.

Unsurprisingly, gas uptake rate and concentration measurements exhibit small variations even when physiologically steady. An authentic model should incorporate this 'noise' (uncertainty) so that it characterises a true-to-life measurement system. Uncertainty originates from a diverse range of sources and includes flow variation from pressure changes in the gas delivery system, un-replaced flow from cyclic gas sampling and instrument measurement errors. Detecting change in physiological variables is difficult and increases for each variable that is added. The ability of clinicians to distinguish measurement change correctly from noise was assessed by Kennedy et al. (2009, 2011) who observed that the larger the quantity of trend data on a single parameter, the better. The research conducted by Kennedy et al. was taken into account when developing the display of throughflow cardiac output and the associated inputs in our measurement system.

The following variables were considered for improvement of cardiac output measurements using throughflow of isoflurane:

- Realistic model of throughflow parameters including noise
- Optimal averages (isoflurane and oxygen)
    - balancing response time and reduction of noise
- Selection of solenoid multiplexing rate
    - to optimise useful measurements and minimise latency
- Variation of gas uptake rates and end-tidal concentrations
    - within the tolerance range (+/-10%)
- Fixed (0.45:0.55) versus measured oxygen uptake ratios

5.2. Creating a Realistic Model

Available realistic computer models of the pulmonary system encompass different aspects of mechanical ventilation, gas exchange, pulmonary mechanics, airway modelling, accurate breath detection, physiological relationships, ventilation-perfusion inhomogentity and gas uptake rates (Stegmaier, Zollinger et al. 1998, Peyton and Thompson 2001a, Brandes and Granato 2006, Wilson, Murphy et al. 2009). However, these models primarily focus on specific aspects of these processes and the effect of changing individual variables. The model described here aims to produce realistic inputs for left and right isoflurane uptake rates ($\dot{V}_{iso_L}, \dot{V}_{iso_R}$), oxygen uptakes ($\dot{V}_{O_{2_L}}, \dot{V}_{O_{2_R}}$) and isoflurane end-tidal fractional concentrations($F_{E'_{iso_L}}, F_{E'_{iso_R}}$) for Equation 9; the calculation of realistic inputs requires incorporation of realistic values and noise.

Fresh and mixed exhaust gas-flow measurements were analysed to identify features that are relevant for breath identification and needed to be considered for measurement selection. These are used in the computer simulation to closely replicate uptake rates, so that the measurement system can be designed using proven methods to evaluate physiological variables.

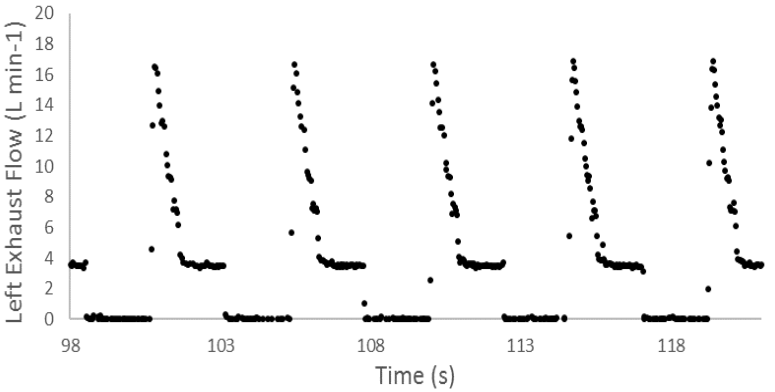

Figure 24 Sample left exhaust gas flow (breaths 3 - 7)

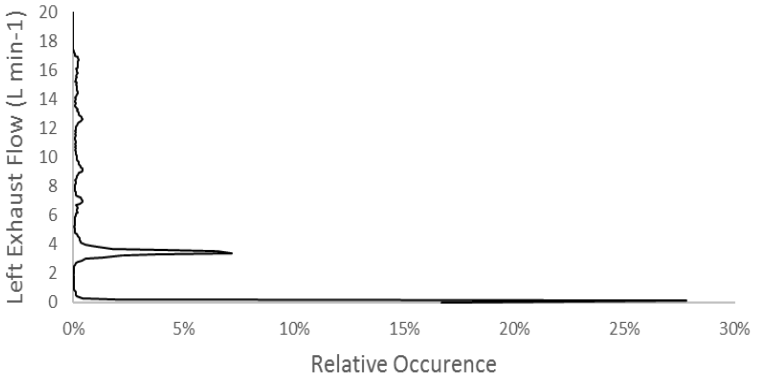

Figure 25 Left exhaust flow distribution

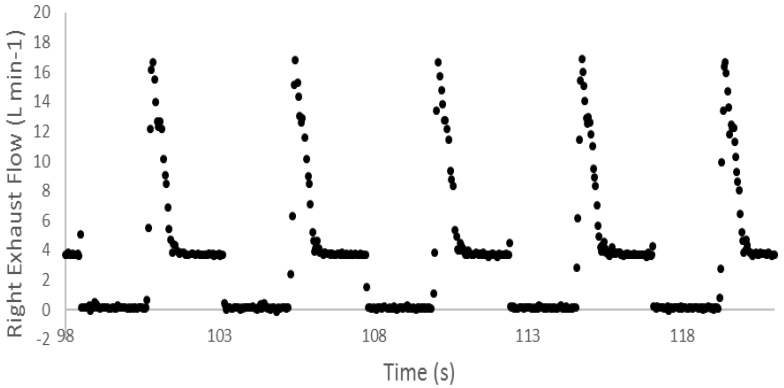

Figure 26 Sample right exhaust gas flow (breaths 3 - 7)

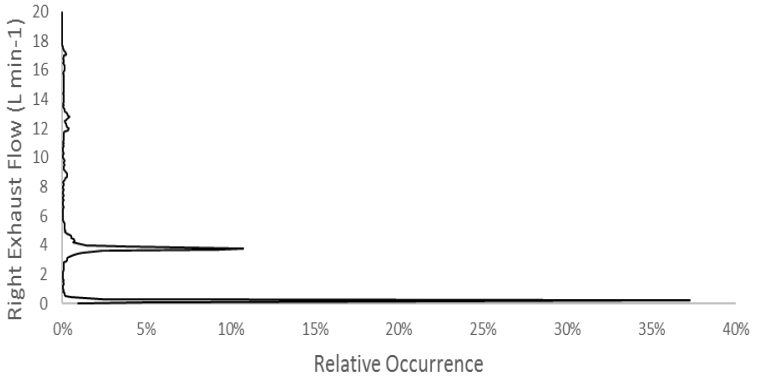

Figure 27 Right exhaust flow distribution

Figure 25 and Figure 27 use the histogram data to identify features of the exhaust flow waveforms in Figure 24 and Figure 26. The two most prominent peaks in the histogram occur during inspiration when exhaust flows have ceased (zero litres per minute) and the end expiratory pause (between three and four litres per minute) which is equivalent to the fresh gas flow settings for the left and right lung.

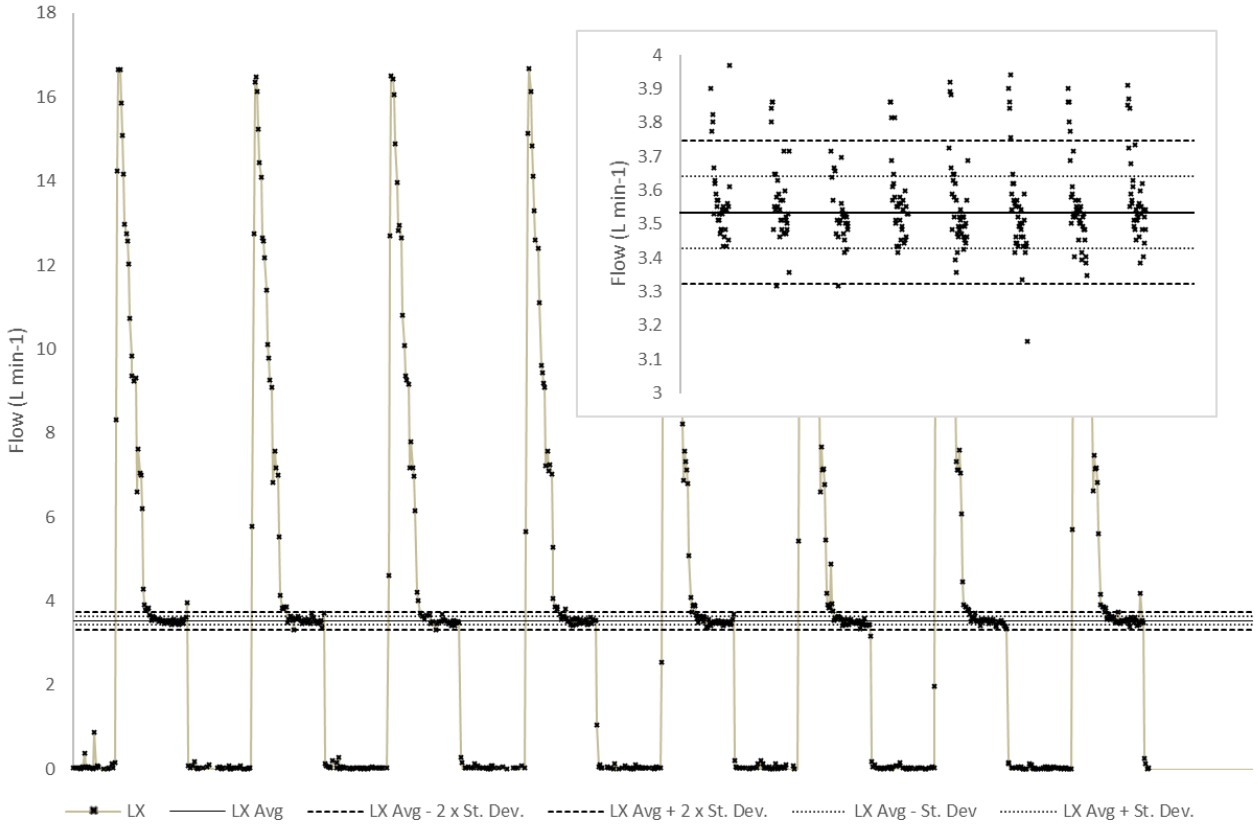

Figure 28 Sample of Left Exhaust Flow

Figure 28 shows a sample flow waveform measured in the left exhaust stream of the Mapleson D breathing system used in the benchtop study described in Chapter 3. The solid straight line in Figure 28 represents the average flow (3.5 L min^{-1}); this corresponds to the second-most significant peak in the Figure 25 histogram, which occurs when the ventilator bellows has reached maximum inflation before it empties. The largest peak occurs at zero litres per minute as the ventilator bellows are filling. A single standard deviation and two standard deviations are represented by dotted lines and dashed lines respectively. The inset in Figure 28 is enlarged and cropped along the y-axis to illustrate how individual data points fit within the standard deviation.

There is disagreement over the best location to define the beginning of a breath; traditionally it is marked by the start of inspiration. However, as discussed in Chapter 3, Cettolo (2015) argues that gas composition measurements (specifically the oxygen-nitrogen ratio at the mouth) should be used as this provided better accuracy when determining alveolar gas uptakes. In this thesis, the breath is marked by the end-expiration in the exhaust gas because it is followed by a period of zero flow; this provides a margin of tolerance if the waveform displays non-standard characteristics.

Oxygen concentration measurements typically have the lowest accuracies compared with other gases when measured by commercial anaesthetic gas analysers. Nitrogen is the exception because it is determined by subtracting all other airway gases from unity. In benchtop simulations of Chapter 6, significant amounts of oxygen will be removed and inserted from the left bellows to replicate isoflurane uptakes and carbon dioxide production. Although it is not obvious, commercial monitors typically display filtered data, because all measurements contain noise. The digitised signals produced by these monitors are more precise than the raw, unfiltered data, but do incorporate quantisation and interference noise.

Realistic physiological models should account for signal noise and its contribution to measurement accuracy and precision for component variables; there are several continuous

models available that can be chosen to model noise distribution, the selection of which can be based on analysis of sample data.

Concentration and flow data (used to determine noise for the model) could be collected during a period of constant or tidal flow; in my system data was collected during tidal flow because uptake rates and end-tidal concentrations are determined within a typical clinical tidal breathing environment. Tidal exhaust flows have been selected to demonstrate typical noise measured by this system during tidal ventilation as can be seen in Figure 25 and Figure 27.

In the computer simulation, uptake flow rate, end-tidal partial pressure, and the standard deviation of the measured noise are defined; this creates realistic inputs for throughflow cardiac output. The end-tidal partial pressures are used as the visible inputs for the computer simulator. However, these are immediately converted to fractional concentrations for use in the throughflow cardiac output calculation.

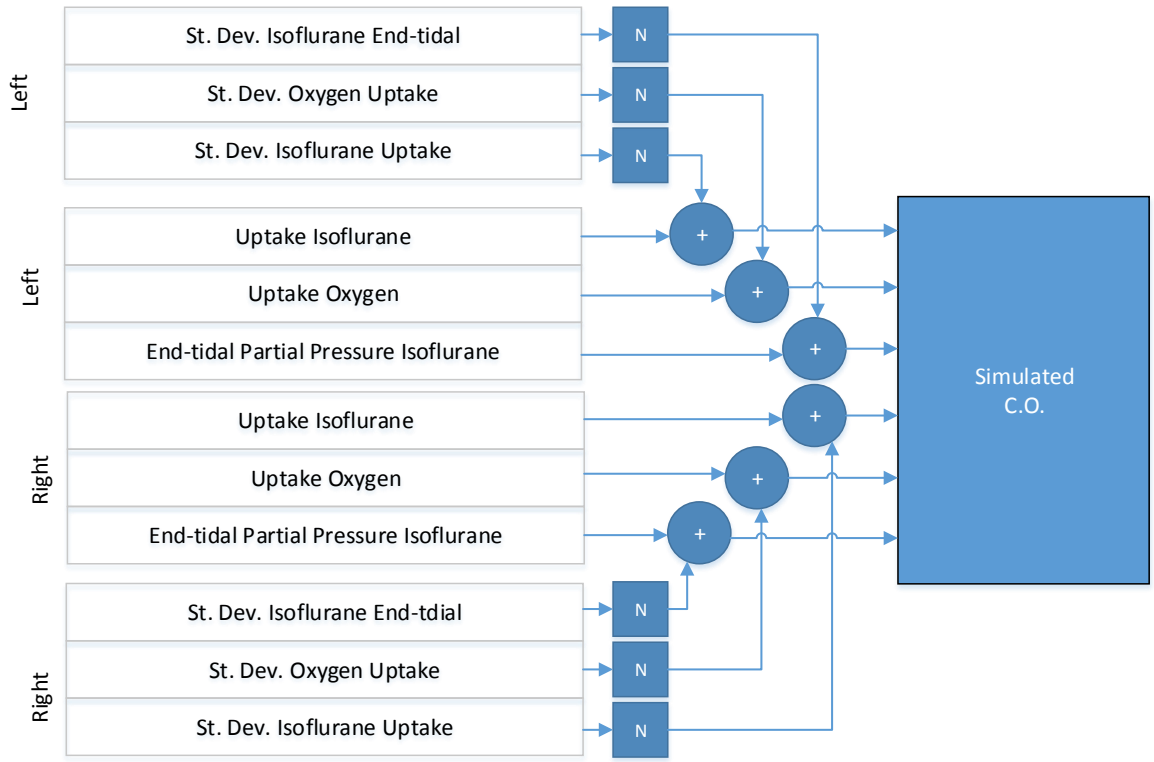

Figure 29 Computer Simulation Inputs

$$\dot{V}_{Sim_G} = \dot{V}_G \pm z_{\dot{V}_G}$$

Equation 36 Simulated uptake for gas 'G' is the predicted uptake with simulated noise applied.

$$P_{L\ Sim\ E'_{Iso}} = P_{L\ E'_{Iso}} \pm z_{P_{L\ E'_{Iso}}};\ P_{R\ Sim\ E'_{Iso}} = P_{R\ E'_{Iso}} \pm z_{P_{R\ E'_{Iso}}}$$

Equation 37 Simulated left and right end-tidal partial pressures $(P_{L\ Sim\ E'_{Iso}}, P_{R\ Sim\ E'_{Iso}})$ *for isoflurane; these are the target end-tidal partial pressures* $(P_{L\ E'_{Iso}}, P_{R\ E'_{Iso}})$ *with noise* $(z_{P_{L\ E'_{Iso}}}, z_{P_{R\ E'_{Iso}}})$ *terms applied.*

The uptake of oxygen, for example, is determined by initially calculating the average fresh and mixed exhaust flows along with the average fresh and exhaust oxygen compositions. These values are then combined so that the average oxygen flow in the mixed exhaust can be subtracted from the average oxygen flow in the fresh gas (Equation 38).

$$\dot{V}_{O_2} = \left(\frac{\sum_{i=0}^{n} V_F}{n} . \frac{\sum_{i=0}^{n} F_{F\,O_2}}{n}\right) - \left(\frac{\sum_{i=0}^{n} V_{\bar{X}}}{n} . \frac{\sum_{i=0}^{n} F_{\bar{X}\,O_2}}{n}\right)$$

Equation 38 Calculation of oxygen uptake requires calculation of the breath average for fresh and exhaust flow (for all gases) and the average fractional oxygen concentration in the fresh and exhaust gas stream.

Although individual measurements are not replicated perfectly by a Gaussian model, the central limit theorem suggests that the combination of independent and identically distributed variables will tend toward Gaussian distribution even if the original variables (concentration and flows) are not normally distributed. Accordingly, a Gaussian distribution rather (than others, such as Rician or Rayleigh) was selected to replicate the observed variations in the uptake rates. The choice of a Gaussian distribution to model the noise has also been used by other researchers replicating realistic respiratory systems (Stegmaier, Zollinger et al. 1998, Brandes and Granato 2006). Modelled noise includes a combination of digitised noise from the gas analyser and flow signals. Other measurement errors that could relate directly to benchtop simulation and can be caused by fluctuation in wall suctioning rates and gas insertion rates. In a similar way to the digital noise in flow measurements, gas concentration measurements are also affected by noise.

The flow and concentration measurements used to calculate throughflow cardiac output were analysed so they could be modelled accurately. This modelling allows the influence of noise and filtering of each of these components to be considered. Standard deviations for oxygen and isoflurane concentrations and the four flow waveforms were calculated based on preliminary benchtop simulated data, and are included in Table 7. The standard deviation of exhaust and fresh flows were determined during periods of constant flow within the tidal breath. The exhaust flow was measured during the end expiratory-pause. All concentration measurements were collected from the mixed exhaust gas.

	$\dot{V}_{L\,\bar{X}}$ (L min^{-1})	$\dot{V}_{L\,F}$ (L min^{-1})	$\dot{V}_{R\,\bar{X}}$ (L min^{-1})	$\dot{V}_{R\,F}$ (L min^{-1})	$F_{L\,\bar{X}_{O_2}}$ (%)	$F_{L\,\bar{X}_{Iso}}$ (%)	$F_{R\,\bar{X}_{O_2}}$ (%)	$F_{R\,\bar{X}_{Iso}}$ (%)
1 x St. Dev.	0.106	0.066	0.119	0.066	0.24	0.05	0.22	0.01
2 x St. Dev.	0.211	0.131	0.238	0.131	0.48	0.10	0.44	0.02

Table 7 Standard deviations calculated from preliminary benchtop simulation.

The standard deviations in Table 7 were used to derive the magnitude of Gaussian white noise required to create realistic noise in uptake and end-tidal values.

The propagation of the uncertainty in measurements was determined for nominated uptake rates because they are calculated by subtracting exhaust from the fresh gas flow (Equation 39). Equation 40 is utilised to calculate the uncertainty for the standard deviation of noise in the error for uptakes and gas compositions (Equation 41 A-D).

$$\dot{V} = V_F - V_{\bar{X}}$$

Equation 39 The total mixed exhaust flow subtracted from the total fresh gas flow gives us the overall total uptake of the system.

$$\Delta\dot{V} = \sqrt{(\Delta V_{\bar{X}})^2 + (\Delta V_F)^2}$$

Equation 40 Change in flow

$$z_{\dot{V}\ St.Dev.} = \sqrt{\left(\frac{\dot{V}_{L\,\bar{X}\ St.Dev.} + \dot{V}_{R\,\bar{X}\ St.Dev.}}{2}\right)^2 + \dot{V}_{F\ St.Dev.}{}^2} = 0.130\ \text{L}\,min^{-1} \quad \text{[A]}$$

$$z_{F_{O_2}\ St.Dev.} = \sqrt{F_{L\,\bar{X}_{O_2}\ St.Dev.}{}^2 + F_{L\,\bar{X}_{O_2}\ St.Dev.}{}^2} = 0.34\% \quad \text{[B]}$$

$$z_{F_{L\,Iso}\ St.Dev.} = \sqrt{F_{L\,\bar{X}_{Iso}\ St.Dev.}{}^2 + F_{L\,\bar{X}_{Iso}\ St.Dev.}{}^2} = 0.07\% \quad \text{[C]}$$

$$z_{F_{R\,Iso}\,St.Dev.} = \sqrt{F_{R\,\bar{X}_{Iso}\;St.Dev.}{}^{2} + F_{R\,\bar{X}_{Iso}\;St.Dev.}{}^{2}} = 0.01\% \qquad [D]$$

Equation 41 (A-D) Error Calculations for mixed flows and gas concentrations. [i]

Flow measurements dominate noise production in gas uptake measurements, so concentration errors were excluded from calculations. Noise associated with oxygen and isoflurane uptake rates were refined based on the percentage of the individual gas in the measurement. The derivation of the standard deviation for oxygen and isoflurane uptake rates is described in Equation 42 and Equation 43. The standard deviation 'z' for the total gas flow (which was derived from fresh and exhaust flows for the left and right airways) as a portion of the total left fresh flow was calculated as $\left(\frac{z_{\dot{V}\;St.Dev.}}{\dot{V}_{L_F}}\right)$; and multiplied by the fractional concentration of oxygen $\left(F_{L_{F_{O_2}}}\right)$ in the fresh left gas. This was doubled because the deviation is found in both the fresh and exhaust gas streams; finally it was multiplied by the anticipated oxygen uptake flow $\left(\dot{V}_{O_2}\right)$ of the system to give us an estimate of a reasonable standard deviation for oxygen uptakes $\left(z_{\dot{V}_{O_2}\;St.Dev.}\right)$.

$$z_{\dot{V}_{O_2}\;St.Dev.} = \left(\left(\frac{z_{\dot{V}\;St.Dev.}}{\dot{V}_{L\,F}}\right) * F_{L\,F\,O_2}\right) * 2 * \dot{V}_{O_2} = 0.007\ L\ min^{-1}$$

Equation 42 Standard deviation for oxygen uptake white Gaussian noise in a computer simulation. For simplicity, oxygen uptake rate was assumed to be 0.100 L min^{-1}.[10]

The calculation of isoflurane uptake Gaussian noise was simplified because of its accuracy and small magnitude.

[10] 130ml SD/3000 ml F gas = 0.0433*0.75 Oxygen= 0.325*2errors in both directions = 0.065 x 100ml expected uptake

$$z_{\dot{V}_{L\,Iso}\,St.Dev.} = \left(z_{\dot{V}\,St.Dev.} * F_{L\,F\,O_2}\right) = 0.001\ L\ min^{-1}$$

Equation 43 Standard deviation for left isoflurane uptake white Gaussian noise in computer simulations.

Fresh gas supplied to the right lung does not contain isoflurane. Consequently, right isoflurane uptake is calculated based on the concentration of isoflurane in the mixed exhaust gas. The standard deviation for right-side isoflurane Gaussian white noise in the computer simulations was estimated at 0.0005 L min^{-1}. This is half of its equivalent left-side value (Equation 43). Inputs for left and right end-tidal Gaussian noise standard deviations were taken from Equation 41 C-D.

Having created a model with realistic noise, it is now necessary to try to manage and filter the noise in our measurements to limit its effect. The noisier the signal, the harder it becomes to identify changes. This applies in particular when we are attempting to define changes in real-time, and do not have the benefit of determining the point of change using retrospective analysis. It is not uncommon when calculating cardiac output to be dealing with small measurements and changes, particularly when dealing with the small measured isoflurane uptake rates and end-tidal concentrations. Post- and batch-processing can also be employed for refining signals; data processed in this way often use regression analysis and modelling (these methods are difficult to implement for continuous real-time measurement). Gan (1993) when measuring breath-by-breath acetylene concentrations, was working with concentrations of similar magnitude to those we see when measuring the end-tidal concentration of isoflurane in the left and right lungs; he utilised a smoothing process for end-expiratory concentration. Similarly, Brandes (2006) used a smoothing algorithm for both a linear and nonlinear model based on a 'Kalman Filter' and 'Extended Kalman Filter' which estimates values based on the available measurements and the statistical history of previous measurements. In real-time systems that may be subject to dynamic changes, careful selection of measurements, recognition of erroneous values, and moving average filters are appropriate. Improving the signal quality through filtering techniques reduces the signal-to-noise ratio when compared with the raw signal which

assists in recognition. However, when using smoothing filters, it is essential that careful consideration is given to the potential to introduce delays, which could counteract the benefit of a cleaner signal.

5.3. Oxygen Uptake Ratios

In the designed scenarios, combined oxygen uptake was intended to be a constant 200 ml min^{-1}. Under normal physiological circumstances, the resting ventilation distribution varies between 40-48% in the left lung and 52-60% in the right lung, depending on the positioning of the patient[11] (Lumb 2005). A typical left to right lung distribution ratio was assumed to be 0.45:0.55, thus the respective left and right lung uptakes were 90 ml min^{-1} and 110 ml min^{-1}. Although small breath-by-breath variations are common, oxygen uptake rates are not expected to change significantly. If we consider the numerator used to determine cardiac output using the throughflow of isoflurane (Equation 9), it is evident that the ratio of oxygen uptake flow significantly weights the isoflurane uptakes. Likewise, preliminary benchtop simulations identified the need to reduce the effect of measurement error and noise in oxygen uptake rates because these could have a pronounced effect on the cardiac output calculated.

5.3.1. Effect of precision of cardiac output measurement

Two options which will be discussed are (a) using fixed ratios of oxygen uptake rates, or (b) apply a smoothing filter to oxygen uptake rate measurements on each lung. Using fixed ratios limits the accuracy of the system, especially when the lung physiology differs from the typical; however, it does reduce fluctuations from small changes. One drawback of using a fixed oxygen ratio is that it does not account for variations in physiological lung volumes and perfusion. In contrast, measured ratios will reflect differences from the assumed ratio, but with the application of a smoothing filter will have a delayed return to 'usual' oxygen ratio

[11] Pg. 111

after a sudden brief but significant variation in measured oxygen uptake rate. The oxygen uptake ratio indicates the distribution of lung gas uptake rates in the right and left lung. Differences from the typical 0.45:0.55 distribution could be due to differences in alveolar ventilation or capillary perfusion. This ratio is used to weight the influence of isoflurane uptake and excretion in the left and right lung. Differences in alveolar ventilation will also affect the end-tidal concentrations. We will examine the sensitivity of cardiac output to changing oxygen uptake ratios to determine the importance of this measurement. A combined oxygen uptake of 200 ml min^{-1} was used in the above computer simulations with a left to right ratio of 0.45:0.55 where 0.45 is the left oxygen uptake ratio term (LORT) and 0.55 is the right oxygen uptake ratio term (RORT).

The oxygen uptake ratio

$$LORT = \frac{\dot{V}_{L\,O_2}}{\dot{V}_{O_2}}$$

Equation 44 Left oxygen ratio

$$RORT = \frac{\dot{V}_{R\,O_2}}{\dot{V}_{O_2}}$$

Equation 45 Right oxygen ratio

The numerator of the throughflow cardiac output equation is:

$$\left(\frac{\dot{V}_{O_2}}{\dot{V}_{L\,O_2}}\right)\dot{V}_{L\,Iso} - \left(\frac{\dot{V}_{O_2}}{\dot{V}_{R\,O_2}}\right)\dot{V}_{R\,Iso} = \left(\frac{1}{LORT}\right)\dot{V}_{L\,Iso} - \left(\frac{1}{RORT}\right)\dot{V}_{R\,Iso}$$

Equation 46 Numerator of throughflow cardiac output equation. The left-hand side represents the numerator as expressed in Chapter 3 while the right side expresses it in terms of left and right oxygen ratio terms.

Isoflurane uptake rates and end-tidal concentrations were held constant at values that would produce a cardiac output of 4.27 L min^{-1} if the oxygen uptake ratio were fixed. The

suitability and size of moving averages applied to measurements with Gaussian white noise can be investigated in computer simulations.

To demonstrate the effect of using various oxygen-uptake rate moving averages on measured cardiac output, all isoflurane measurements employed in the first iteration were noise-free. Moving average filters for oxygen uptakes of 1, 10, 20, 50, 100, 150 and 200 were used to determine the ideal degree of oxygen uptake smoothing to produce reliable cardiac output measurements.

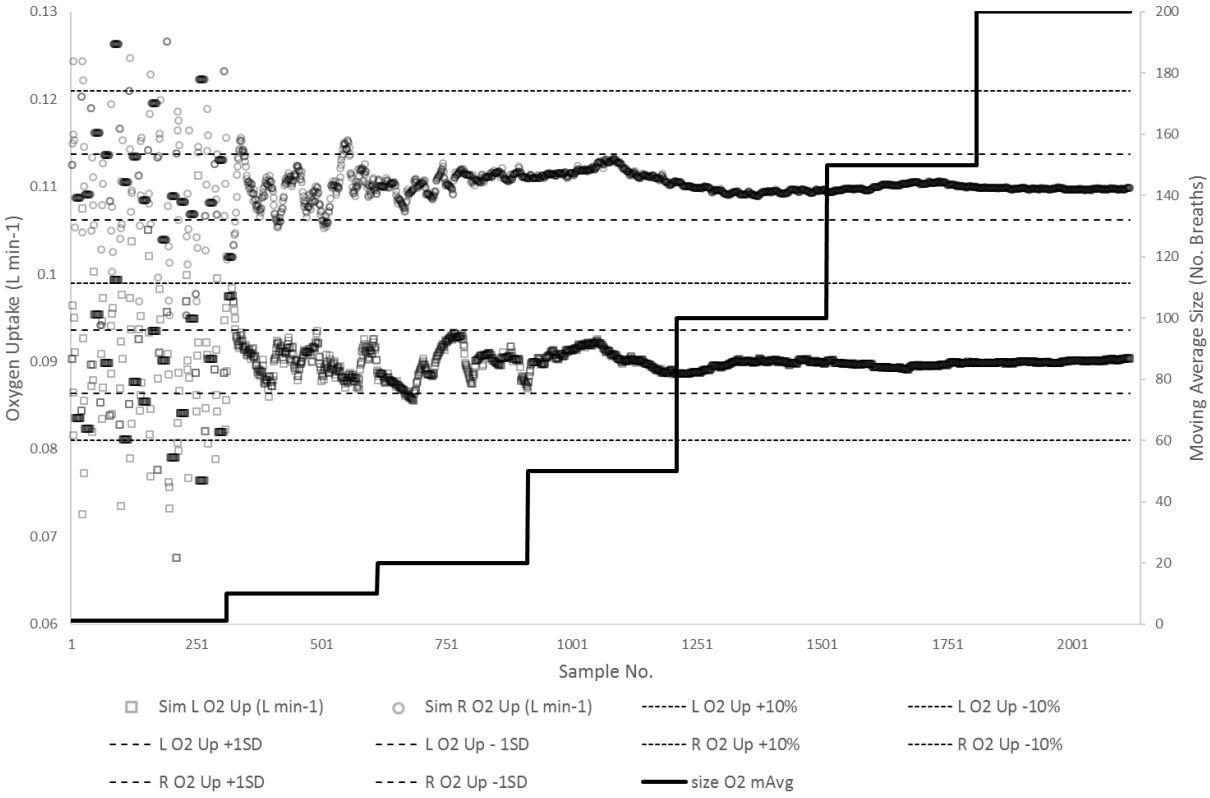

Figure 30 Predicted cardiac output of 4.27 L min^{-1}. Oxygen uptake rate with moving averages of 1, 10, 20, 50, 100 and 200 applied (no noise has been added to isoflurane measurements).

An immediate improvement in cardiac output is witnessed with the application of even a small ten-breath moving average, and it continues to be refined as the moving average size increases.

However, isoflurane measurement is not noise free, and so the isoflurane moving averages between 1 and 6 for isoflurane uptakes and end-tidal concentrations were re-applied in the next iteration of the model.

5.3.2. Effect on accuracy

The left to right oxygen uptake ratio was varied from 0.00:1.00 to 1.00:0.00 to investigate the consequence of a changing oxygen uptake ratios.

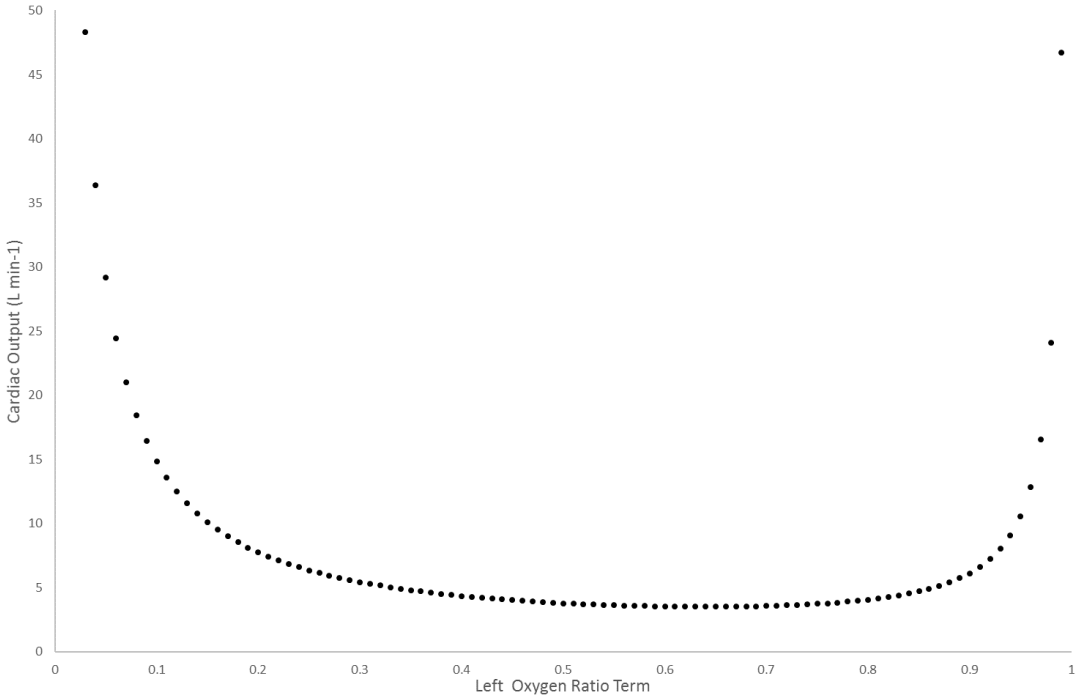

Figure 31 Cardiac output using isoflurane uptake and end-tidal concentrations to produce a cardiac output of 4.27 L min-1 (if the oxygen left to right uptake ratio were 0.45:0.55). The left oxygen ratio term is varied between 0 and 1.

Figure 31 demonstrates the effect of varying the left to right oxygen uptake distribution between the lungs. Changes in the oxygen uptake ratios influence measured cardiac output; the change is a result of adjusting the weight given to the left and right isoflurane uptake flows. Closer inspection allows the association between the left term in the oxygen uptake ratio and the measured cardiac output to be examined.

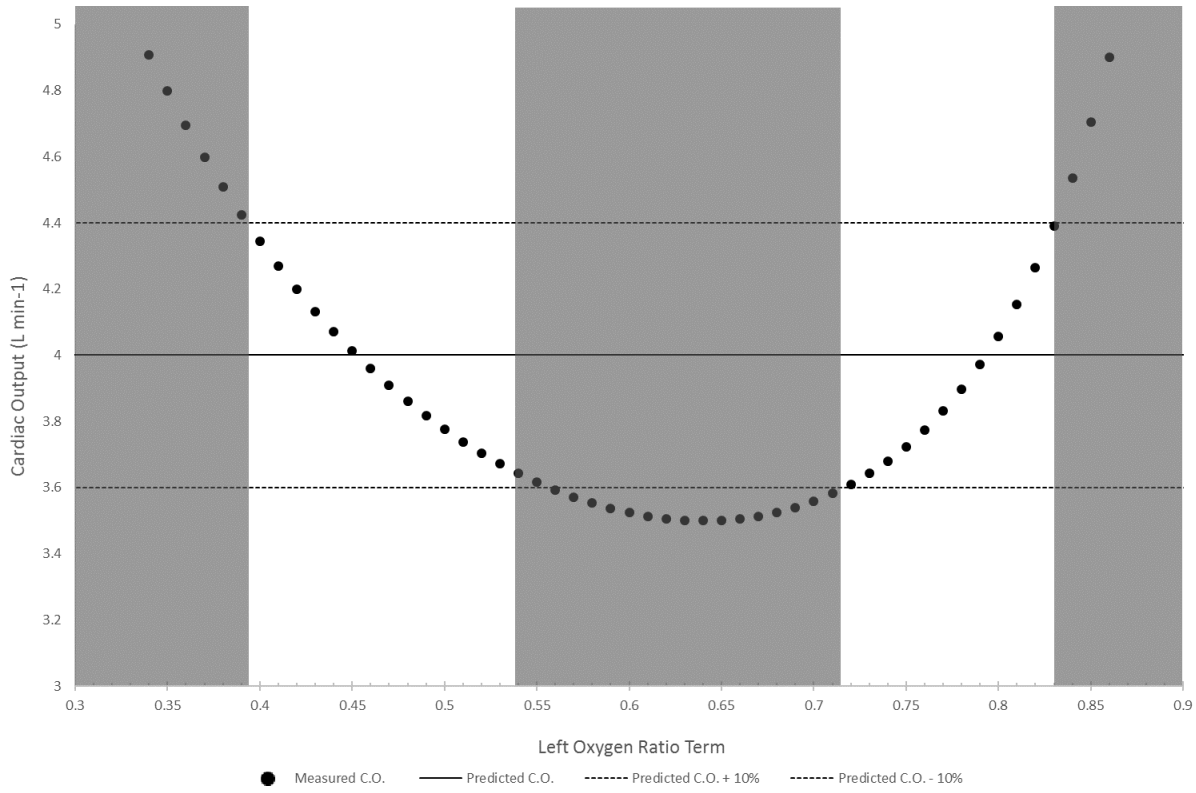

Figure 32 Subsection of C.O. using isoflurane uptake and end-tidal concentrations to produce a cardiac output of 4.27 L min-1. Grey blocks demonstrate where measured values fall outside +/- 10% of the predicted value.

Figure 32 reveals that oxygen uptake ratios of 0.40:0.60 - 0.55:0.45 and 0.72:0.28 - 0.83:0.17 maintain a cardiac output within 10% of the predicted cardiac output. The central greyed range of 0.56:0.44 - 0.71:0.29 includes the cardiac output dropping a further 3% below the 10% boundary. This demonstrates that cardiac output measurements can tolerate variations in measured oxygen uptake ratios and an estimated ratio in computer simulations but remain within plus or minus ten percent of the predicted value. This finding is consistent with that reported by Robinson et al. (2003) for modelling of throughflow using nitrous oxide. However, the suitability of using a fixed oxygen uptake ratio should be tested further using benchtop and clinical studies.

5.4. Multiplexing of Gas Concentration Sampling

Continuous cardiac output measurement is beneficial for clinical decision making in real-time; breath-by-breath measurement can be considered to be effectively continuous. However, the simultaneous measurement of gas concentrations in the fresh, end-tidal and exhaust gas sampling points to achieve this is resource-intensive, requiring multiple gas analysers. Though feasible, this presents additional challenges to accurate gas uptake and cardiac output measurement. Because gas uptake rate in the left lung, in particular, is calculated from small concentration differences between fresh and exhaust gas streams for isoflurane and oxygen, small discrepancies in calibration between analysers at each point would be expected to produce substantial measurement error in these derived variables. In contrast, simultaneous measurement of gas concentrations in the left and right breathing systems using separate analysers will be far less sensitive to this source of error.

Thus the decision was made to cycle between these three sample points using the same gas analyser, but to use separate analysers on the left and right sides. To reduce the latency of measurements, careful consideration was given to how sequential acquisition is best undertaken. Changes in cardiac output affect both isoflurane uptake rates and end-tidal concentrations, so there is likely to be an immediate response to a variation in cardiac output, but there will be a small delay before the full effect of the change is reflected in the measured cardiac output.

The duration of a single measurement state requires consideration of sample-line length, gas analyser sample rate, and how regularly mixed-exhaust and end-tidal gas concentration switching should occur. The solenoid cycle rate was calculated manually, with timing based on the number of completed breaths rather than a specific time interval. The number of breaths in a single state of the cycle is important because it limits the number of breaths that would be included when using a moving average filter on isoflurane measurements. We need to consider physical issues in sampling (line length) and analyser sample rate. To prevent errors from mislabelling and inclusion of gas from the previous sample site, the first two and the final breaths at each sample position are excluded from analysis.

The number of breaths within a measurement stage needs to balance the system response time while taking advantage of included breath data. Based on these considerations, nine breaths were included within a single stage including the three excluded breaths. Accordingly, the sample position will change every 45-67.5 seconds depending on the selected respiratory rate. A 2-metre length of sample-line tubing has been chosen to connect sample points to the solenoid multiplexer. This length was chosen over a shorter (45cm) length because it does not restrict the placement of the solenoid multiplexer. Placement of the solenoid multiplexer away from the patient circuit and closer to the gas analyser is ideal because it keeps the patient field clear. It also reduces the likelihood of electrical noise contaminating physiological measurements such as ECG. Separate gas analysers sample the left and right breathing circuits. These are connected to the left and right multiplexer outputs, resulting in a combined sample line length of 4m (~5.1 ml in total [12]). The gas analyser removes 15-27.5 ml each breath so the dead space in the sample line can be up to one-third of the breath.[13] Fresh gas flows are kept constant which reduces the required frequency of its sampling relative to the other two sampling points. Thus, fresh gas is sampled at the start of the measurement sequence and then every ninth cycle to confirm fresh gas compositions have remained steady.

[12] Sample line tubing ID 1.27mm. $V = \pi r^2 l$ = 3.14 x 0.000635m^2 x 4m = 5.1 x 10^{-6} m^3 or 5.1ml. 1 m^3 = 1000 L.

[13] Gas analyser samples 180-220 ml min^{-1}. Ventilating at 8-12 breaths per min.

5.5. Isoflurane Uptake Rate and End-tidal Concentration Measurement

The uptake rates and end-tidal partial pressures required to produce throughflow cardiac outputs were based upon previous work by Peyton (2015); these values are referred to as "set values". Solenoids automatically cycle after detecting nine breaths, the reason for using only a sub-selection of six breaths will be discussed. This results in the continuous measurement of gas concentration at either the mouth (end-tidal) or mixed exhaust location for 36 seconds in an 84 second period (assuming a respiratory rate of ten breaths per minute). The length of the moving average filter for isoflurane uptake flow and end-tidal concentration measurements was limited to between one and six breaths. This allows rapid detection of changes while sampling at a single sample point (fresh, end-tidal or exhaust). Moving average size selection is the same for isoflurane end-tidal concentration and uptake rate measurements so that both measurements have the same measurement response time to modelled changes.

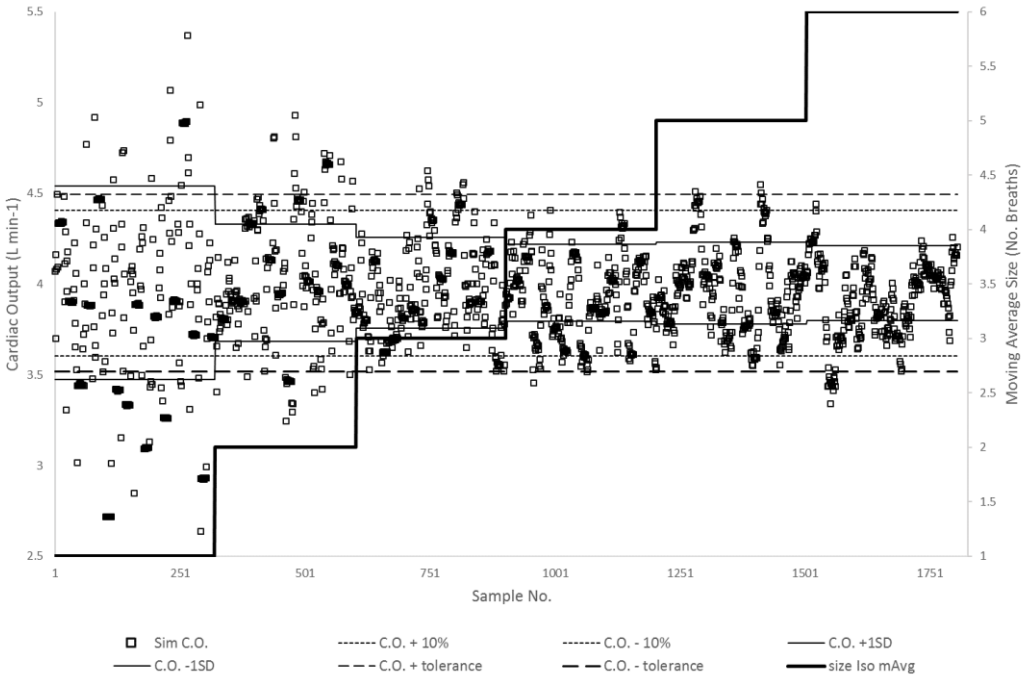

Figure 33 Predicted cardiac output 4.00 L min^{-1}. Isoflurane moving averages for uptake rates and end-tidal concentrations of 1, 2, 3, 4, 5 and 6 breaths are shown with moving average of 200 breaths for oxygen uptake rates.

The influence of increasing moving average size in single breath increments from one to six breaths was tested in Figure 33 using measured oxygen uptake rates to obtain oxygen uptake ratio in the numerator of the throughflow equation. When the cardiac output is re-modelled (Figure 33) using a six-breath moving average for isoflurane measurements, the apparent response to the increasing moving oxygen averages is reduced but not eliminated. A moving average size of six was therefore selected, based primarily on the reduction of noise for isoflurane uptakes.

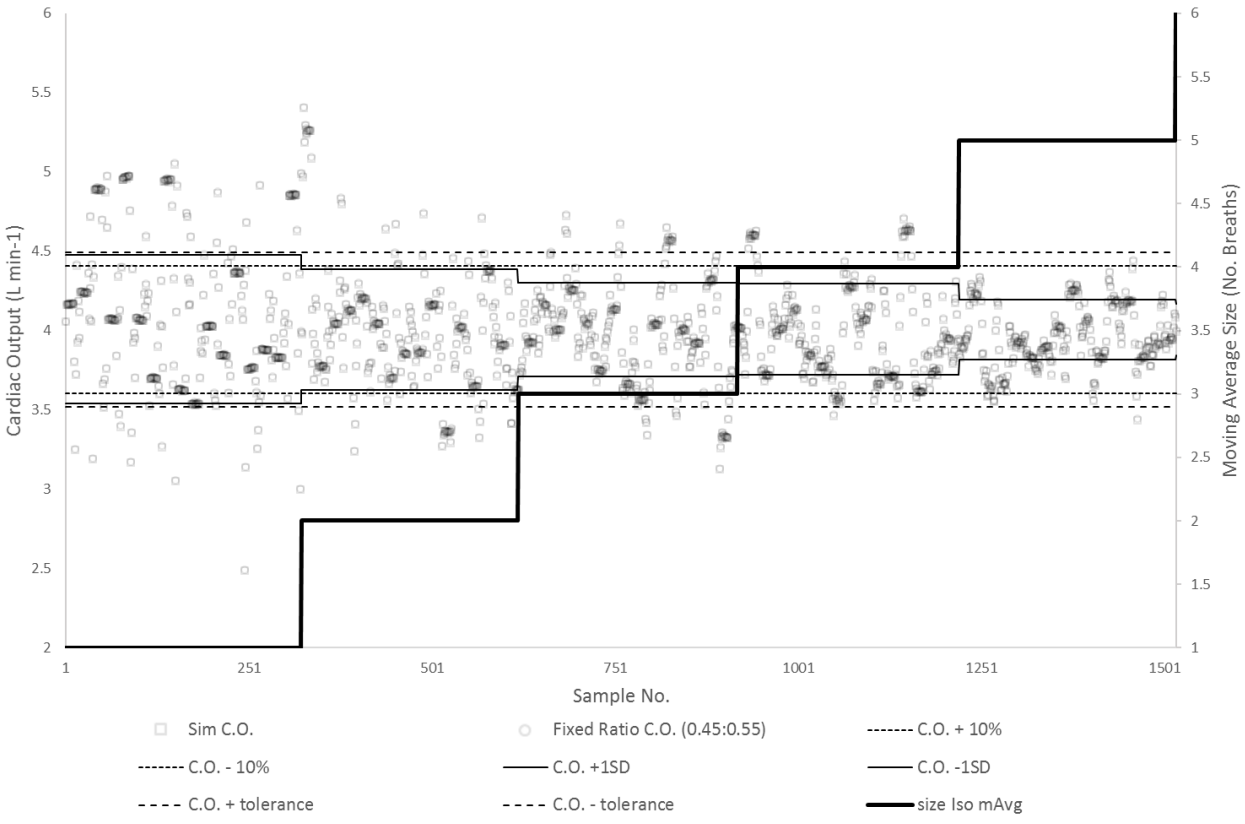

Figure 34 Cardiac output set to 4 L min^{-1}, predicted value 4.00 L min^{-1}. The graph shows the response to moving averages of 1-6 breaths. It also identifies +/- 10% predicted values and +/- 1 & 2 standard deviations of the measured value for each moving average.

Figure 34 shows the cardiac output calculated using the isoflurane uptake rate and end-tidal concentration measurements with averages between one and six breaths applied, while using a fixed oxygen ratio instead. Naturally, the standard deviation of cardiac output values improves as the moving average increases. The six-breath moving average has a variance such that two standard deviations fall within our ideal threshold of plus or minus ten

percent of the cardiac output. This limitation is important because measurement noise is only one of the measurement quality considerations.

End-tidal isoflurane partial pressures (mmHg) have been displayed due to the familiarity of this unit of measurement, but they are converted to a fractional concentration for use in the cardiac output equation. The combined effect of smoothed isoflurane uptake rates and end-tidal concentration measurements, when paired with a fixed oxygen-ratio of 0.45:0.55 on measured cardiac output, is illustrated in Figure 34.

The comparatively long (200 breath) moving average that has been selected for oxygen uptake rates is justified because the oxygen uptake rate ratio is not expected to change, and because the throughflow method is relatively tolerant to variations in the measured oxygen uptake ratio (Figure 32). In contrast, isoflurane was chosen for the throughflow method because it responds rapidly to changes in cardiac output. Thus, the usefulness of smoothing filters to reduce minor breath-by-breath fluctuations in isoflurane uptake rates and end-tidal concentrations needed to be balanced to minimise delays in response to changing cardiac output.

5.6. Summary

This chapter describes how a computer simulation was used to optimise the measurement of cardiac output using throughflow of isoflurane. This required careful consideration of how uptake rates and end-tidal concentrations were collected and processed so that throughflow could be used to provide an accurate and near-continuous real-time measurement of cardiac output. The measurement system was refined using the techniques described, and this chapter provides support for the selection of averaging techniques and sample rates that have increased the robustness of the measurement design. This is useful because the limitations to precision and accuracy in gas delivery and removal in the benchtop simulator will be expected to introduce further challenges to measurement in the throughflow system.

The exhaust flow signal was analysed using a histogram, and the frequency of instantaneous flows during a breath helped to define the key features in the waveform. Similarly, flow and gas concentrations were measured during plateau periods of the tidal waveform to calculate the standard deviation of measurements.

There are different methods for marking the beginning or end of a breath; the flow signal instead of the gas concentration was used to identify the breath. The point chosen to mark the breath is at the end of expiration as the exhaust flow approaches zero. This provides a larger tolerance to small changes in the exact position of the end of breath that is used to calculate breath averages.

To test our measurement technique adequately, it was necessary to produce realistic noise inputs for isoflurane and oxygen uptakes and end-tidal isoflurane concentrations. Noise in physiological measurements can come from various sources including subtraction errors, interference, digitisation noise and fluctuations from the bulk movement of gas in and out of patient lungs or from the bulk gas changes produced by the benchtop simulator. A Gaussian noise model was selected because the central limit theorem suggests that the more inputs involved in a measurement, the more likely it is to be Gaussian. This holds true because gas uptake is a combination of flow and gas composition measurements in the fresh and exhaust gas streams.

After replicating realistic inputs, it was necessary to determine the best method for filtering out the applied noise. Continuous real-time filtering is challenging, and many of the techniques such as retrospective and regression analysis and complex modelling that are used in offline processing are difficult to use, or inappropriate. The decision to use moving average filters required the value of a clearer signal to be balanced with an accurate and time-responsive signal. The selection of moving average size was determined separately for oxygen and isoflurane.

Even though computer and benchtop simulations have been designed to keep a constant oxygen uptake, measuring oxygen uptakes ensures true lung distribution, and perfusion is accurately reflected. Thus after analysis of averages between one and two hundred breaths, a moving average of two hundred breaths was selected. Because oxygen uptakes are unlikely to change significantly during measurements of real changes in cardiac output, the use of fixed oxygen uptake ratios was explored. After reviewing the effect of oxygen uptake ratios varying from a perfect 0.45: 0.55 left-right ratio, it was decided that both fixed oxygen ratios and a long moving average of two hundred breaths would be used for benchtop trials.

The number of breaths included in the moving average filter for isoflurane uptake and end-tidal concentrations is more challenging than for oxygen uptake because these values are expected to change in response to changes in cardiac output. In determining the number of breaths for these values, it is essential to consider the multiplexing of gas composition measurements, particularly for end-tidal and exhaust gas concentrations. It was important to consider the placement and length of the sample line, circuit delays, and the necessity to exclude breaths because of contamination of the sample-line with gas from another site to establish the best cycle length for switching between measurement positions. Given all of these considerations, a nine-breath cycle was chosen of which three breaths were excluded, leaving six breaths in which measurements are made. This meant that to reliably track cardiac output, the length of the moving average filter for isoflurane uptake and end-tidal concentrations should be limited to between one and six breaths. After analysis of the effect of using the different length, a moving average of six breaths was selected.

All of these decisions have been incorporated into the system measurement design that has been used for the benchtop measurements that will be employed in Chapter 6.

Chapter 6 Analysis

6.1. Introduction

The use of simulated gas exchange has become an essential part of testing the robustness, precision and reliability of gas exchange measurement systems and their clinical applications. This approach allows a range of gas exchange scenarios to be replicated and measured independently of the ethical considerations required for animal and clinical investigations.

The use of a gas-exchange simulator facilitates the exploration of novel gas-based cardiac output techniques. The use of the described simulator removes well-mixed gas from the left and right lung and replaces it with individually metered gas flows.

The original throughflow method (Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003, Robinson, Peyton et al. 2004) has been adapted, with nitrous oxide being replaced by using isoflurane. The blood-gas solubility of isoflurane makes it a more ideal choice for the reasons discussed in Chapter 4.

This responsiveness of measured gas exchange to cardiac output changes is important because isoflurane is delivered at only 1% in the left fresh gas (in comparison, previously nitrous oxide was provided at approximately 40%). The substitution of nitrous oxide with isoflurane would allow a larger range of delivered fresh gas mixtures. Mixed exhaust gas flows were calculated using the Haldane Transformation based on the conservation of nitrogen in the system. Chapter 3 introduced the possibility of measuring fresh and exhaust flow rates directly; this involves a brief period of calibration at the start of scenarios, to ensure fresh and exhaust gas flows in each of the left and right side respectively, measure the same flow rate.

Direct flow measurement has many advantages, including the ability to eliminate nitrogen gas from the fresh gas mixture. For the purposes of benchtop validation of the measurement system, in the current series, nitrogen has been maintained in the fresh gas

mixture to enable the comparison with gas uptake rate measurements determined using the Haldane Transformation.

The simulation of gas exchange has also been updated (as described Chapter 3): digital flow controllers have been integrated into the system to enable flexible system control and to reduce setup time.

The gas uptake rates and end-tidal concentrations required to simulate a range of cardiac outputs were described in Chapter 3. The denominator of the equation (which contains end-tidal concentrations of isoflurane and the isoflurane blood-gas coefficient) used in the cardiac output throughflow of isoflurane, is common to both the reference and comparison techniques, which are explored in this chapter.

The use of a simulator allowed the method to be tested for robustness, and for the same clinical scenario to be replicated multiple times to determine the precision and accuracy; this was done under normal physiological conditions and also at both extremes of simulated cardiac output. All described gas uptakes and end-tidal concentrations were targeted to +/- 10% of the target value. This flexibility was allowed, due to the difficulty of obtaining higher precision using the digital flow controllers and wall suctioning system.

The work in this chapter uses the Haldane Transformation to calculate exhaust gas flow rates. These flows are integral to the Haldane-derived cardiac output as they directly influence the isoflurane and oxygen flow uptakes. Exhaust flows, both directly-measured and Haldane-derived will be provided here, along with uptake rates, and calculated cardiac output. Waveforms depicting isoflurane concentrations measured in the end-tidal position, and the selection of the end-tidal point, will then be presented. This will be followed by measured isoflurane and oxygen uptake rates, and finally simulated cardiac output measurements. That will show how absorption and excretion of volatile anaesthetic agent and end-tidal concentrations can be used to determine cardiac output.

The described system updates the cardiac output measurement at the end of each breath, with a complete cycle of measurements (end-tidal and exhaust) occurring every 18 breaths. This is an improvement on the prior nitrous throughflow method, which updated cardiac

output measurements once every four minutes. The reduction of the overall cycle time is due to less-frequent calibrations, and the duplication of gas analysers.

This chapter commences with a display of oxygen concentration measurements over the complete set of scenarios of 116 minutes (7000 seconds) duration. This leads to the presentation of Haldane-derived exhaust flows, which are based on the concentration of nitrogen in the exhaust gas versus that in the fresh gas. When compared to directly-measured exhaust flows they follow the fresh gas flow better due to their dependence on the fresh gas flow measurement. This is clearly demonstrated by the overall uptake measurements which are much closer for Haldane-derived flow uptakes.

The measured oxygen uptake is presented next. These can be determined using the directly-measured exhaust flows, from Haldane-derived exhaust flows, or we can assume a value. Naturally, this choice will affect the standard deviation of the oxygen uptake flow rates.

Then we look at the end-tidal concentration measurements. It is important to select values accurately because any error in measurement can have large consequences on the accuracy of the derived cardiac output. The selection of end-tidal points with respect to the raw continuous and smoothed continuous signal is presented. Although the running data is available it is broken up into breath-by-breath values, and the selection of the end-tidal point is demonstrated and displayed over the full set of scenarios.

Having dealt with the end-tidal concentration results I present the isoflurane uptake results to show how Haldane-derived and directly measured isoflurane uptakes compare with the reference target range.

The next aspect is the presentation of simulated cardiac output. This is broken into two sections 1) using measured oxygen uptake ratios 2) using assumed oxygen uptake ratios. Initially, results are presented to display the measured and Haldane-derived cardiac output with respect to the reference target range; this is followed by an analysis using descriptive statistics and then the facility to track changes. To measure the capability to track changes, I chose to compare the directly measured values to Haldane-derived values rather than target values.

This was done using 4-quadrant and polar plots. While this is normally only used for clinical scenarios, I used it here to show compare small breath-by-breath variations.

This moves onto the need to review the system response time following a step change, and finally the effect of changing respiratory rates and positive-end-expiratory pressure on measured cardiac output is presented.

6.2. Comparison Method – Throughflow using Haldane Transformation Measured Exhaust Gas Glow Rates

Using the Haldane Transformation, the mixed exhaust gas flow is calculated relative to the measured fresh gas flow, based on the principle of nitrogen conservation throughout the system. This means that Haldane-derived exhaust gas flow rate will be expected to track the fresh gas flow rate more precisely than an independently measured exhaust flow, due to the interdependence of the two variables.

Nitrogen concentration is not measured directly by the gas analysers and is inferred by subtracting the fractional concentrations of all other measured gases from unity. This makes the Haldane measurement of exhaust flow susceptible to cumulative measurement errors by the gas analyser. In the scenarios tested, the largest component of the mixed gas in fresh and exhaust gas streams is oxygen. This means an error in oxygen concentration measurement will be proportionally larger and could have significant implications. The same gas analyser was used to measure gas composition in fresh, end-tidal and exhaust positions within an individual lung to eliminate errors that would have been introduced by using multiple gas analysers within a lung, due to misalignment of calibration between devices.

6.3. Oxygen Concentration Measurement

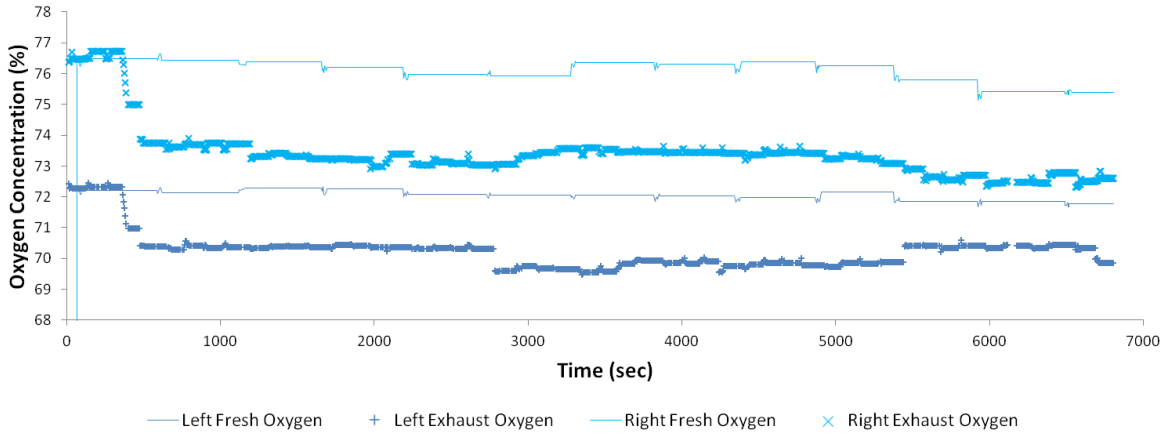

Figure 35 Oxygen concentration measurement (fresh and exhaust)

The gas analyser cycles through three sample positions fresh gas, exhaust gas, and end-tidal gas. During the non-sampling phase for each position, the average of the last sampled composition for that position is assumed for cardiac output calculation.

The initial calibration of the system (the first 300 seconds), where the oxygen composition in the fresh and exhaust gas is equal, is indicated in Figure 35 as a period of no gas uptake in the breathing system.

6.4. Directly Measured Exhaust and Haldane Measured Exhaust Flow Rates

Fresh gas flow rates are selected manually on the gas rotameters of the anaesthetic machine, and the vaporiser isoflurane flow is measured by both methods. The measured exhaust gas flow rates are calibrated to the measured fresh gas flows during a period of zero uptake flow during the first 300 seconds of system operation. This is shown in Figure 36. Fresh gas flow rates on the left and right sides were set at 3.03 L min^{-1} and 3.6 L min^{-1} respectively.

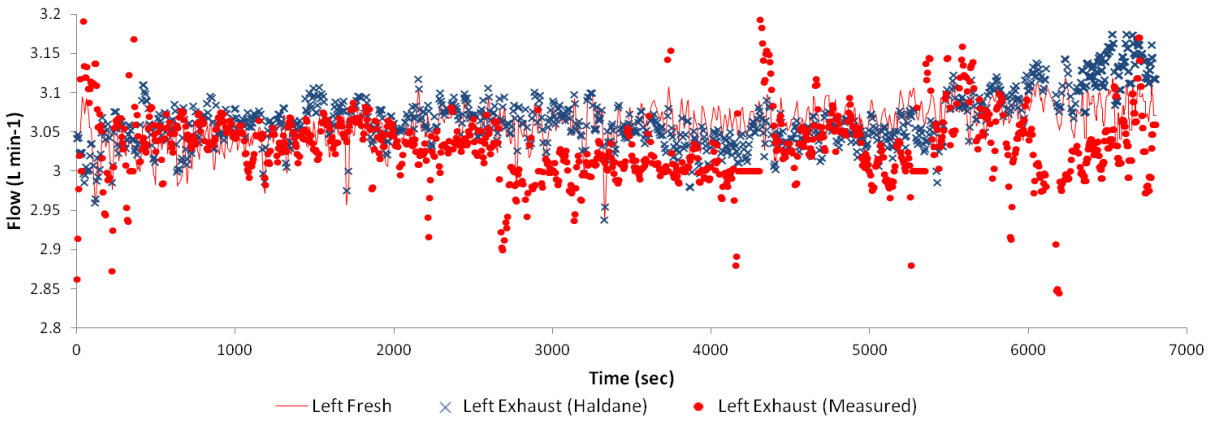

Figure 36 Exhaust gas can be measured directly or calculated from the fresh gas flow using the conservation of nitrogen (Haldane Transformation)

The left exhaust gas flow rate (Haldane) follows the fresh gas flow rate smoothly, while the directly-measured exhaust flow rate shows minor fluctuation in response to changes.

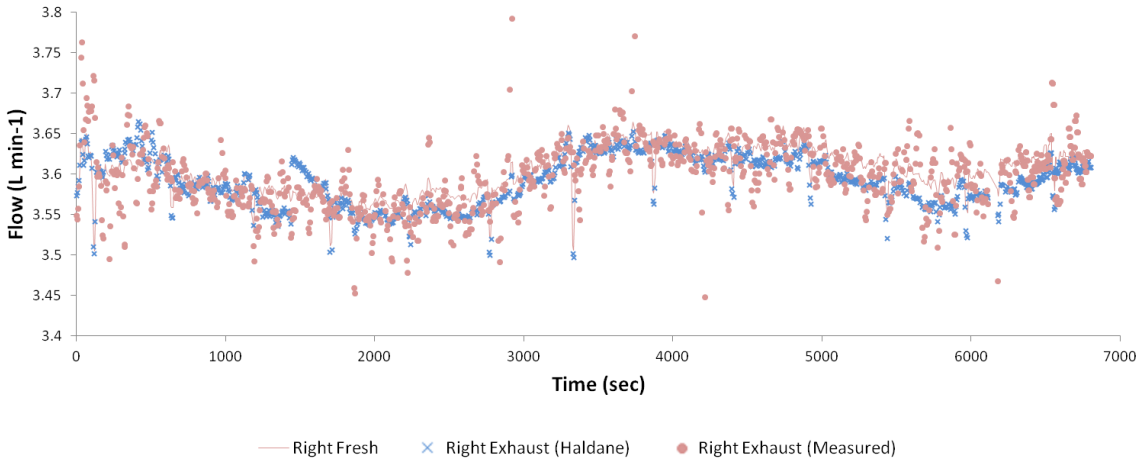

Figure 37 Right exhaust flows (Haldane and measured) graphed against fresh gas flow

The difference between fresh gas and exhaust gas flow measurements (direct and Haldane) is more consistently closer to zero on the right side than the left during calibration. This is because, on the left side of the simulator, where left lung uptake of isoflurane and oxygen is simulated, different quantities of gas are both removed and replaced for each cardiac output scenario, whereas only the concentration of isoflurane varies on the right side of the simulator.

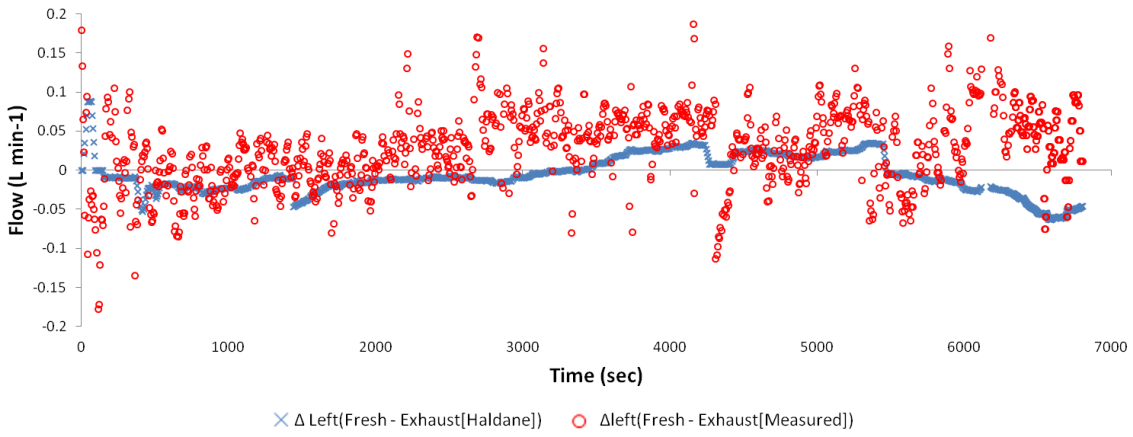

Figure 38 Left side - difference between Haldane or directly measured exhaust flow and the fresh gas

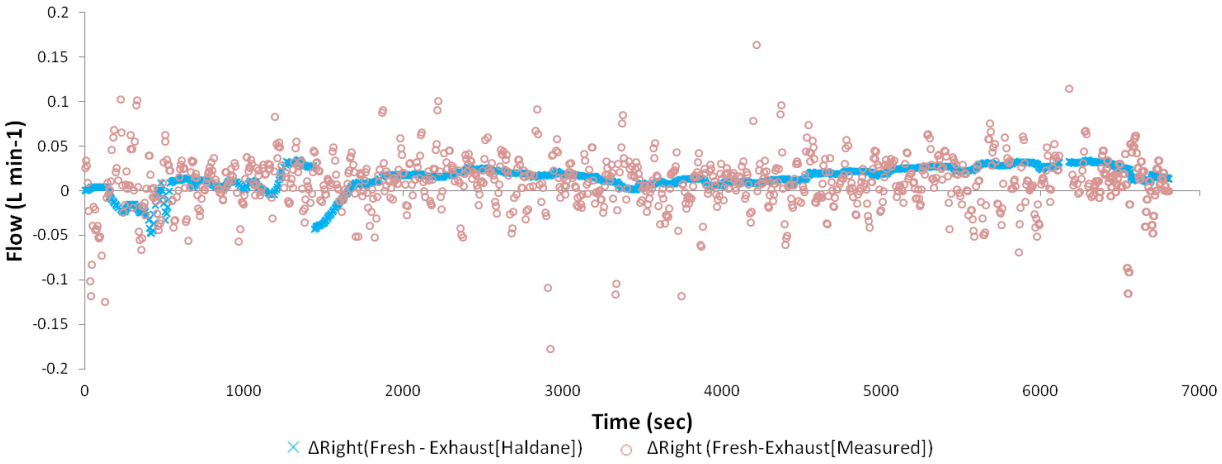

Figure 39 Right side - difference between Haldane or directly measured exhaust flow and the fresh gas

The Haldane derived exhaust gas flow rates in Figure 38, and Figure 39 are much smoother than the directly-measured flow rates. Unlike direct measurement of exhaust flow rate, the Haldane-derived exhaust flow rate is dependent on the fresh gas flow rate. This is likely to contribute to gas uptake rates with a lower standard deviation; however, this dependence will also make measured oxygen uptake rates more susceptible to errors in exhaust Haldane flow rates and oxygen concentrations.

6.5. Oxygen Uptake Rates

Calculated gas uptake rates appear in the numerator of the throughflow equation (Equation 13); they are calculated using gas composition and flow rate measurements. The oxygen uptake ratio is used to estimate the proportion of blood flowing to the left or right lung (Equation 6).

Robinson et al. (2004) and Peyton (2004) have previously suggested that an assumed proportion of blood flow to the left and right lungs could be employed instead of measuring the ratio oxygen uptake rates. They demonstrated this by graphing the percentage error in calculated nitrous oxide throughflow cardiac output for different assumed ratios (Robinson, Peyton et al. 2003). Robinson's suggestion is supported by our analysis in Chapter 5 which showed that variability of the left-to-right oxygen uptake ratio of between 0.40:0.60 to 0.83:0.17 maintained a cardiac output of within 10% of the predicted value (where no other measurement errors were present).

Oxygen uptake rates are calculated using the measured exhaust gas flow rate, the Haldane-derived exhaust gas flow rate, and also use an assumed value for the analysis. A potential benefit to including a fixed (assumed) oxygen uptake ratio is that it may improve precision in the agreement between the cardiac output measurements made by the reference and isoflurane-throughflow methods.

Left lung oxygen uptake simulation requires both removal of alveolar gas from the lung bellows by suction, and its partial replacement along with carbon dioxide and nitrogen to achieve target alveolar and exhaust gas oxygen concentrations and flow rates. In comparison on the right-side, it is only necessary that oxygen be removed. Thus the uptake rate of oxygen determines the overall amount of gas which is withdrawn from the right lung. This means that oxygen does not need to be reinserted into the lung. However nitrogen needs to be replaced, and carbon dioxide and isoflurane are inserted. The bias of simulated oxygen uptake flows can vary depending on the skill of the operator, but the standard deviation is not as likely to change. The coefficient of variation represents the magnitude of change around the measured point.

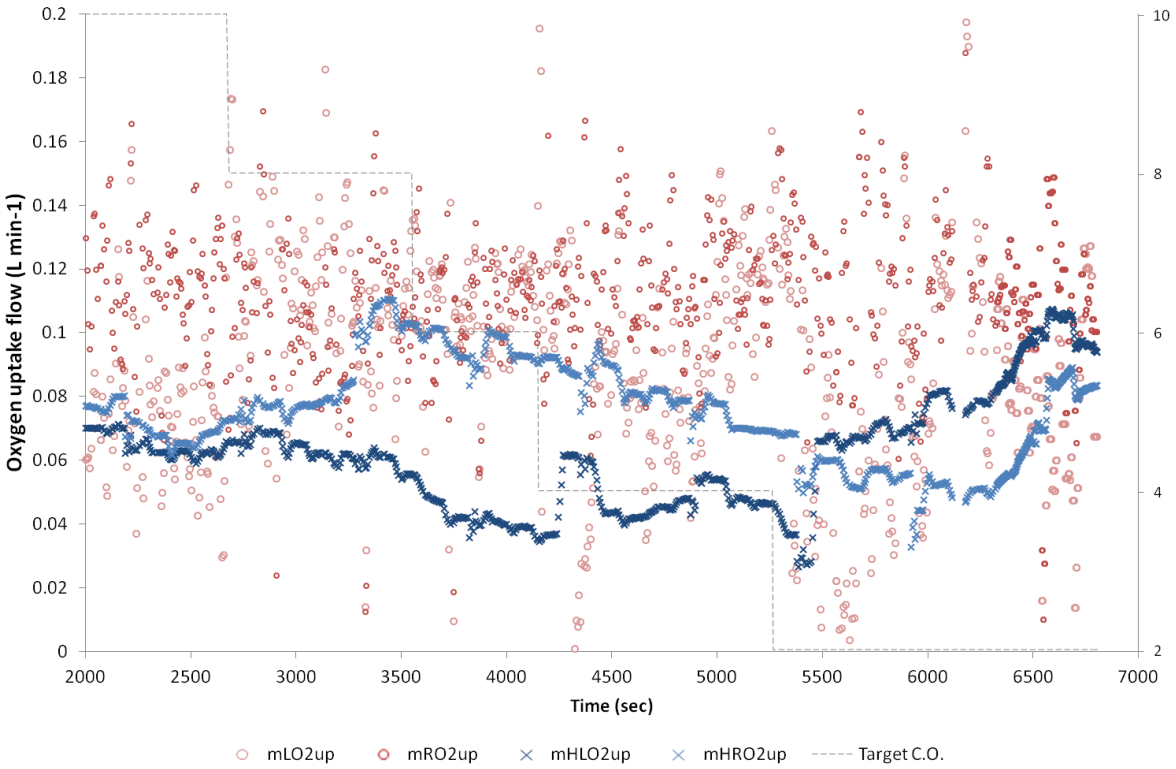

Figure 40 Oxygen uptakes using Haldane-derived and directly measured exhaust flow. Target cardiac output indicated by the dashed line.

Oxygen Uptake Flow for Target Cardiac Output of 10 L min^{-1}	Mean (L min-1)		Bias (L min-1)		Ratio Value	St. Dev (L min-1)		Coefficient of Variation (%)		Limits of Agreement (L min-1)	
	Left	Right	Left	Right	Left: Right	Left	Right	Left	Right	Left	Right
Measured	0.085	0.110	-0.005	0.000	0.44: 0.56	0.030	0.030	35.3	27.3	[0.025,0.145]	[0.049,0.170]
Haldane	0.065	0.072	-0.025	-0.038	0.47: 0.53	0.003	0.005	4.6	6.9	[0.058,0.071]	[0.062,0.081]

Table 8 Oxygen uptake flows: directly measured (M) and Haldane-derived (H)

Table 8 contains an analysis of a small section of data to give an appreciation of the breath-by-breath variability of oxygen uptake flows. The large variation of measured oxygen uptakes demonstrates the importance of using a long two-hundred breath moving average for oxygen uptakes (if fixed oxygen uptake ratios are not used). Despite the importance of accurate oxygen uptake values, it is the overall ratio of oxygen to the left or right lung that is paramount in the throughflow method.

Given the length of moving average used for oxygen uptakes, a brief circuit disconnection or flow misreading can have a significant impact on calculated uptake values. These can be filtered out using offline analysis if necessary, but these large changes are not filtered in real-time because they would indicate a problem in the measurement system, requiring immediate attention. They also may be an indicator that the simulated flows have been adjusted.

In testing of the system to calculate cardiac output by throughflow, both fixed and measured oxygen uptake rates were used and compared, alongside measured isoflurane uptake flows.

6.6. End-tidal Gas Concentrations

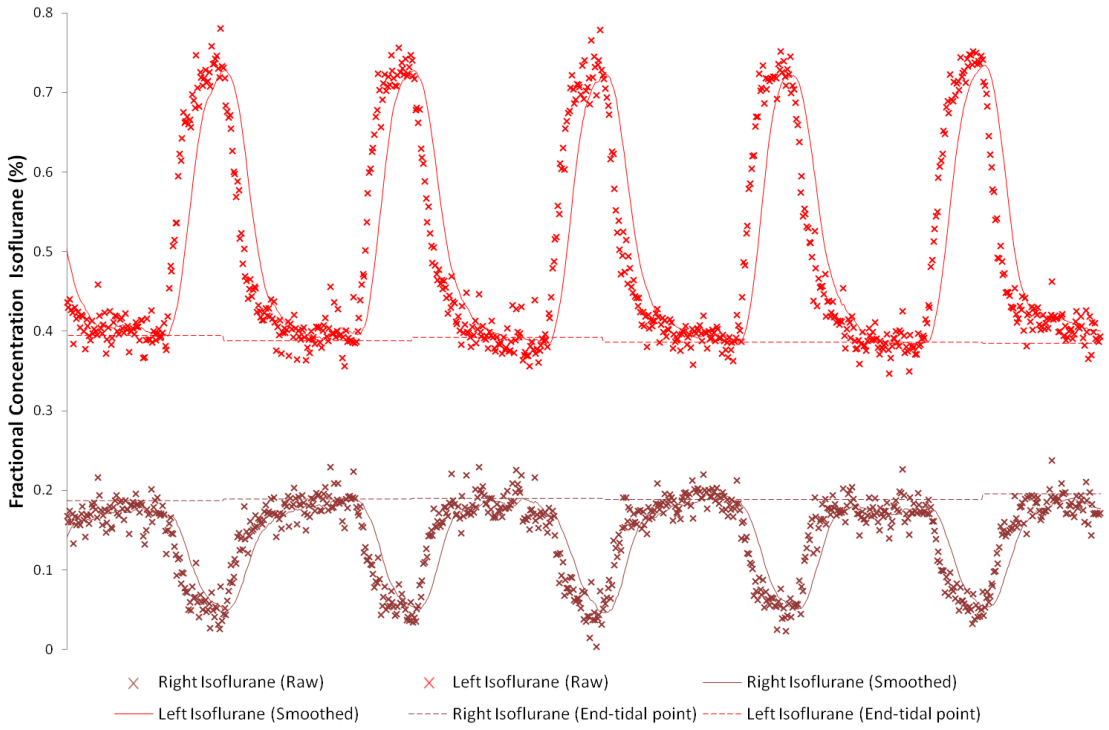

Figure 41 Isoflurane concentration measured at the mouth of the patient circuit (Raw concentration measurements, smoothed concentration and selection of end-tidal point.

Figure 41 shows the raw tidal isoflurane concentration measurements at the end-tidal gas sampling position of the patient breathing system. The concentration measurements have been smoothed, which introduces a slight delay. This is done to provide reliable identification of isoflurane concentrations at the end-tidal point of the tidal waveform. The

end-tidal point is indicated using the dashed line and is updated at the conclusion of the breath. The selection method for the end-tidal position was described in Chapter 3 at the conclusion of each breath. The selected end-tidal concentration value is used in the denominator of the cardiac output throughflow equation.

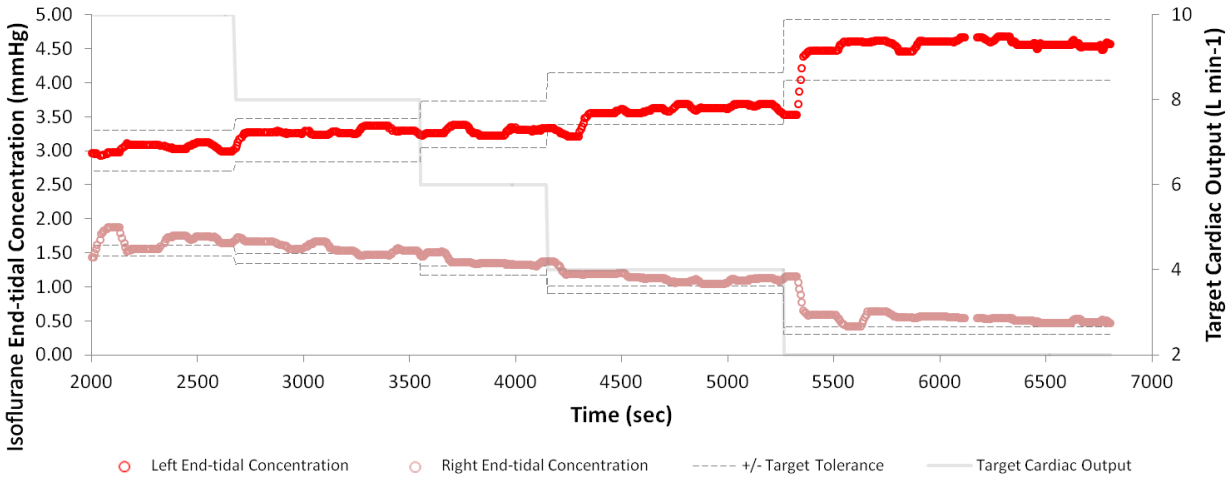

Figure 42 End-tidal measurements taken for target cardiac outputs of 2, 4, 6, 8 and 10 L min^{-1}. Dashed lines indicate the target range for values.

Figure 42 shows the measured end-tidal concentrations, which were determined using the selection process described in Chapter 3 the dashed line indicates this in Figure 41. Figure 42 gives the target tolerance for these values for each of the different target cardiac outputs in each scenario. How well cardiac output measurement follows true change from one target cardiac output scenario to the next, will vary depending on where, in the collection cycle, the change has occurred. As discussed in Chapter 5 the first two and the last end-tidal concentration measurements in each cycle are removed. Also, when the change occurs, the gas concentration can be sampling in fresh, end-tidal or exhaust gas sampling positions.

6.7. Isoflurane Uptake Rates

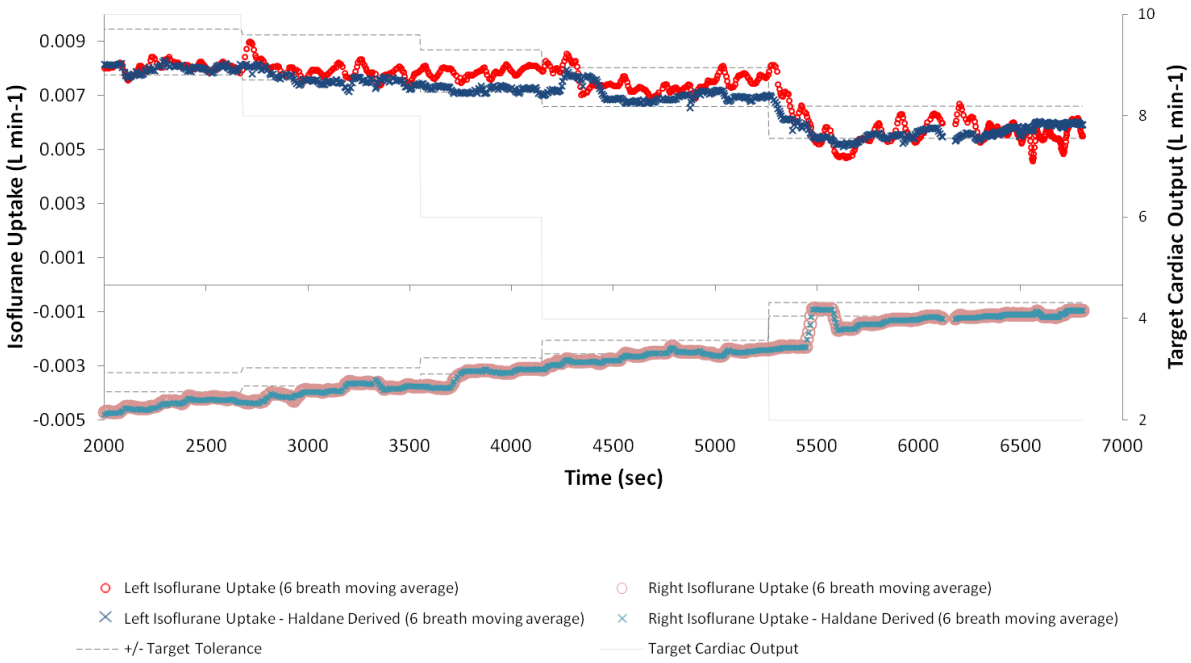

Figure 43 Isoflurane uptake (directly measured and using Haldane technique)

The Haldane and the directly-measured right isoflurane uptake rates shown in Figure 43 are very similar (and difficult to distinguish from one another). The right-side isoflurane uptakes are on the lower limit of the target tolerance.

The left-side isoflurane uptake rates track within the target tolerances; the uptake rates using direct measurement of exhaust gas flow rates shows a larger breath-by-breath variation than Haldane-derived uptake rates for the reasons discussed earlier.

6.8. Simulated Cardiac Output

6.8.1. Using Measured Oxygen Uptake Ratios

Cardiac Output (Direct Measurement of Exhaust Flow versus Haldane-derived Exhaust Flow):

All of the inputs employed in the calculation of throughflow cardiac output have now been reviewed. There is only one method used for determining the end-tidal concentration of isoflurane in the right and left breathing systems. However, we have shown two different methods for calculation uptake flow rates and have discussed the possibility of using a fixed oxygen uptake ratio rather than determining them by measurement.

The accuracy and precision of agreement calculated for cardiac output measurement by isoflurane throughflow was assessed by comparison with target values on our simulator, using both directly measured exhaust gas flow rates and those derived from Haldane-calculated exhaust gas flow rates. This was also done using both measured oxygen uptake rates and using a fixed oxygen uptake ratio.

Cardiac output measurements are updated at the end of each breath, based on uptake rate and end-tidal concentration moving averages. As described, the location which is not currently being sampled holds the last averaged position. The graph below is a sub-selection of the continuous data collected during our scenarios which shows only the 50 breaths prior to a step change in cardiac output. Values before this have been excluded to eliminate the effect of transient cardiac outputs when the suction rate was manually adjusted on the simulator.

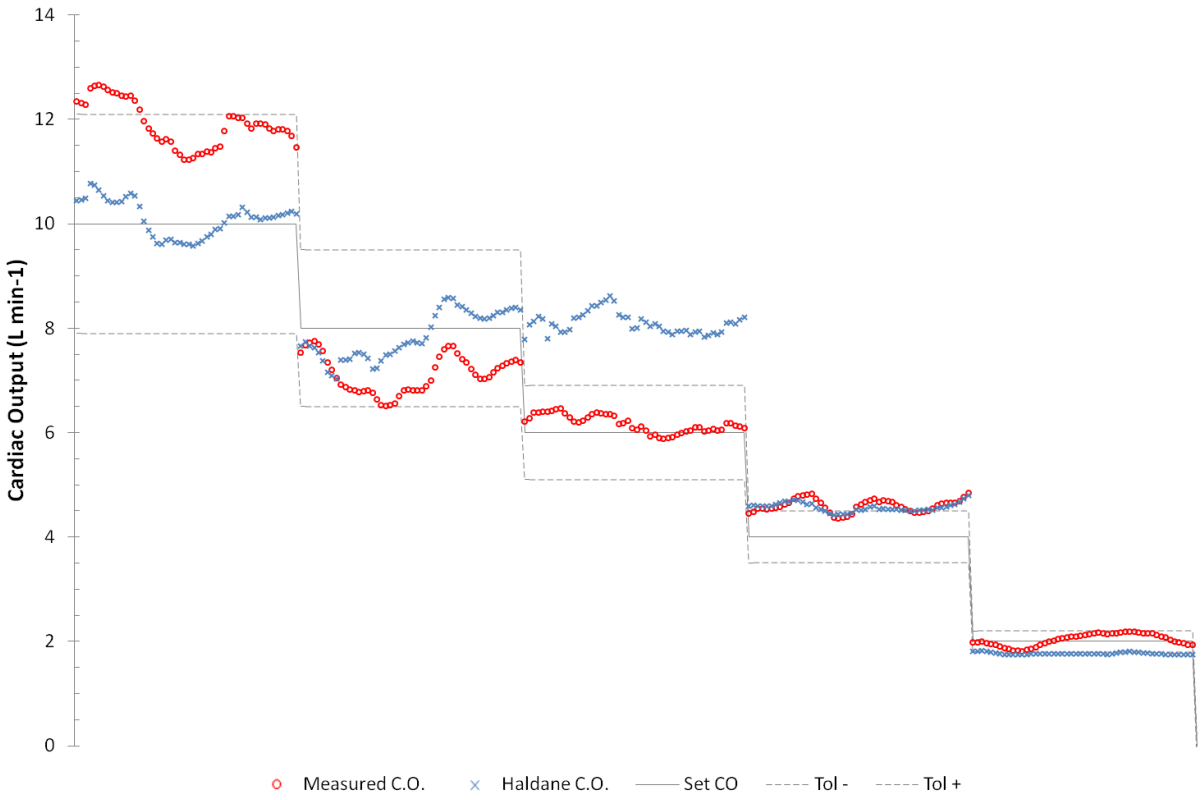

Figure 44 Cardiac output using direct measurement of exhaust flow or derived using the Haldane technique

The dashed lines in Figure 44 indicate the acceptable tolerance of cardiac output measurement (as described in Chapter 3) across six cardiac output scenarios. Both techniques show measurements within accepted tolerance, except the Haldane-derived cardiac output at a target cardiac output value of six litres per minutes. This difference will be examined in Chapter 7. Visually, the techniques seem to show a similar trend despite a bias for some values.

The cardiac outputs can be evaluated using descriptive statistics and using a range of graphical techniques (Table 9, pg. 136). The bias described in Table 9 between target and calculated cardiac outputs and between the direct and Haldane measurement varies in scale and direction. This is most likely a result of the simulation technique, the tolerances of individual flow controllers, and the difficulty in managing wall suction flows.

Cardiac Output (L min-1)	Measured (Test Method)						Haldane (Comparison Method)					
	Mean (L min -1)	Bias (L min -1)	St. Dev. (L min -1)	L.O.A. (L min -1)	Coeff. Var (%)	Error (%)	Mean (L min -1)	Bias (L min -1)	St. Dev. (L min -1)	L.O.A. (L min -1)	Coeff. Var (%)	Error (%)
2	2.03	0.03	0.12	[1.80,2.26]	6	2	1.77	-0.23	0.02	[1.73,1.81]	1	-12
4	4.60	0.60	0.12	[4.38,4.85]	3	15	4.57	0.57	0.08	[4.40,4.73]	2	14
6	6.17	0.17	0.17	[5.84,6.50]	3	4	8.09	2.09	0.20	[7.69,8.49]	3	35
8	7.12	-0.88	0.36	[6.41,7.83]	5	-11	7.85	-0.15	0.45	[6.96,8.74]	6	-2
10	11.90	1.90	0.44	[11.05,12.76]	4	19	10.11	0.11	0.34	[9.44,10.78]	3	1

Table 9 Descriptive statistics for Haldane and directly measured cardiac outputs using measured oxygen uptakes

Bland-Altman plots (Bland and Altman 1986) are commonly used in clinical comparison studies. The simulator provides target cardiac outputs, so the Bland-Altman plot has been modified to use the target value rather than a reference method. Modified plots have been used previously by Rosenbaum (2004) and Peyton (2005) in simulator studies. Results have also been presented in tabular form to show the bias and percentage error for each scenario.

The Bland-Altman plot provides an indicator of the accuracy (mean bias between paired measurements) and precision (+/- one standard deviation of the difference between paired measurement) of the two methods when compared to a reference method. In the case of the current study this was the set cardiac output for each scenario. A modified Bland-Altman plot shows how each of the two methods varies from the set cardiac output. Naturally, a larger variation is acceptable when measuring larger cardiac outputs and the target tolerance is indicated in the graphs.

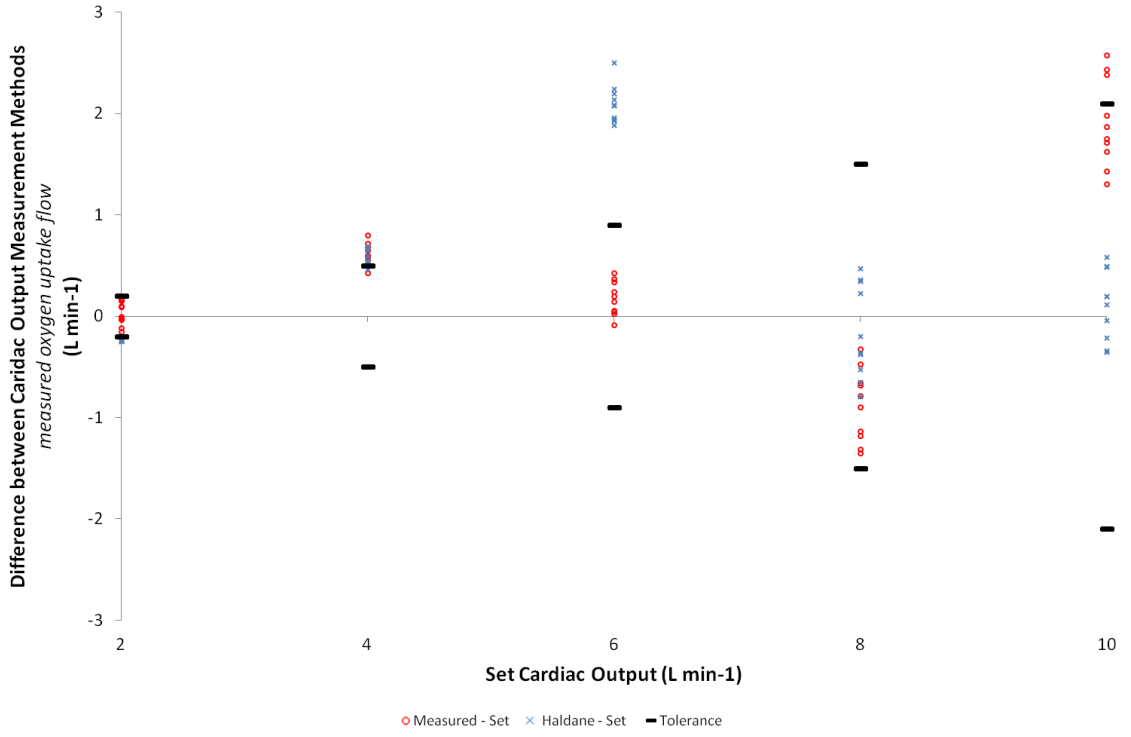

Figure 45 Modified Bland-Altman plot shows the difference between methods and the desired (set) cardiac output at each of 2, 4, 6, 8 and 10 L min^{-1}. Data is grouped into averages of 5 breaths.

The modified Bland-Altman plot Figure 45 shows that the variability between measurement increases as the cardiac output increases, however when we view this alongside the coefficient of variation percentage presented in Table 9, it is evident that this is not the case when the variation is considered with respect to the absolute measurement that is being monitored. This is likely because for larger simulated cardiac outputs a greater volume of gas needs to be removed and replaced by the lung gas exchange simulator.

Ability of Method to Track Cardiac Output Change -Comparison of Directly Measured Exhaust Gas Flows versus Haldane-derived Exhaust Gas Flows:

The Bland-Altman plot provides an indicator of the accuracy and precision of the two methods when compared to a reference method. In the case of the current study, this was the set cardiac output for each scenario. However, it does not give an indicator of how well the two approaches track changes. Scrutiny of Figure 44 suggests that the two methods track changes comparably, but this needs to be examined using an alternative method.

Although normally reserved for clinical measurement two approaches for measuring trending ability have been used. To see how closely the direct measurement of exhaust gas flow and Haldane-derived exhaust gas flows follow one another.

The four-quadrant plot has been used this indicates the size and direction of change and how it correlates between the two approaches.

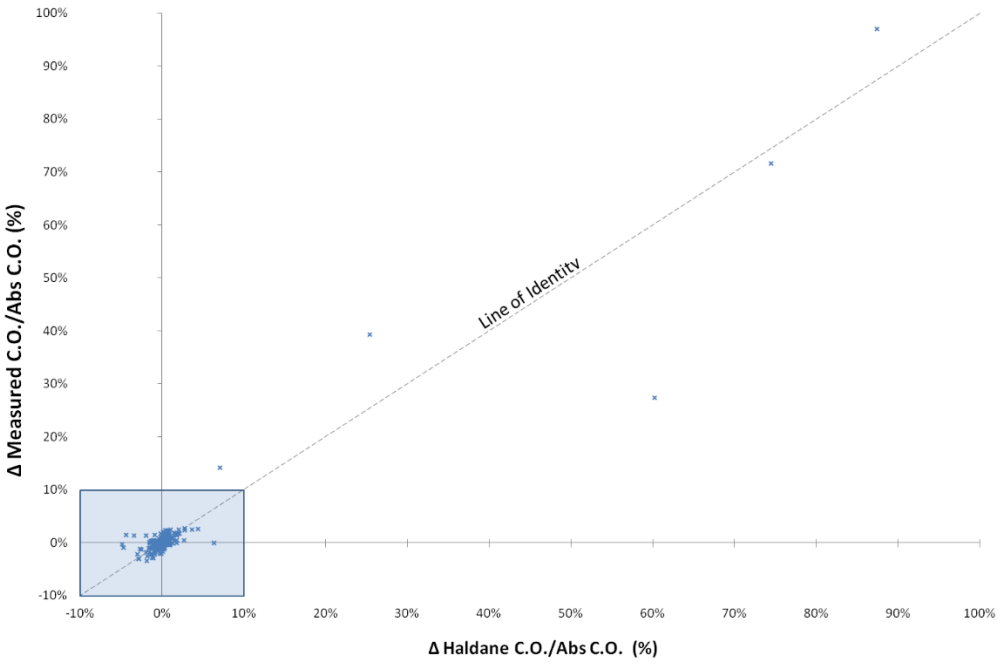

Figure 46 Four-quadrant plot showing the relationship between changes in measured and Haldane derived cardiac output

To allow the comparison of cardiac outputs at the five values (2, 4, 6, 8 and 10 L min^{-1}) the measured change was divided by the absolute cardiac output. Where a step change occurred, the larger of the two cardiac outputs was used. The inset box indicates an exclusion zone of 10%; this is used because small variations in uptakes are not expected to follow using the two different methods. This leaves only five changes which are large enough to be included. Concordance was calculated with the exclusion zone at 100%, although this reduced to 68% when all values were included.

Concordance rates have been ranked as follows: Good >= 92%, 88% < Acceptable <92%, Poor <=88% (Critchley, Lee et al. 2010).

The use of four-quadrant plots will provide basic information about trending, but it does not indicate how closely two methods correlate. Critchley (2010, 2011) suggests polar plots could indicate how well two techniques compare.

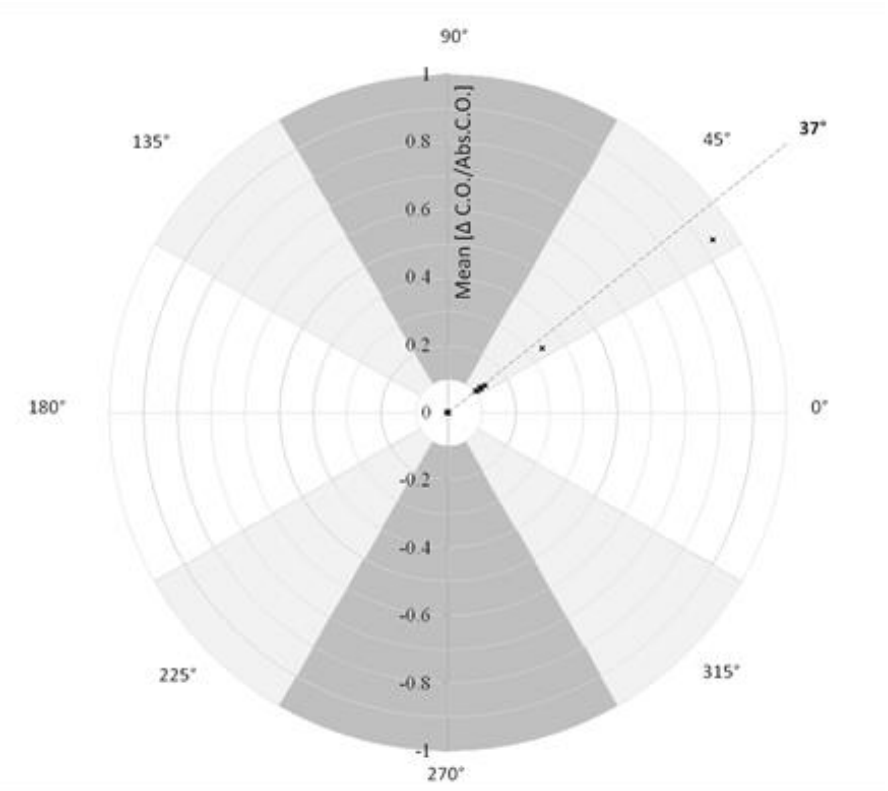

Figure 47 Polar plot of Measured and Haldane derived cardiac output

The polar plot in Figure 47 describes how closely two methods agree in measurement of change in cardiac output. Similar to the four-quadrant plot I have incorporated a 10% exclusion zone. Each point is derived from the mean difference between two cardiac outputs divided by the absolute cardiac output measurement, and the how the angle of the two cartesian plots is related to the identity line (45˚) which has been shifted clockwise to 0˚. Ideally, points will be as close to 0˚ as possible. However, I have split the regions into equal portions as follows:

Good 0-30 ˚, 150-210 ˚, 330-360 ˚

Acceptable 30-60 ˚, 120-150 ˚, 210-240 ˚

Poor 60-120˚, 240-300˚

Using this criterion, the 37˚ angle suggests an acceptable correlation between the Haldane and directly measured techniques when using measured oxygen uptake flows.

6.8.2. Using Fixed (Assumed) Oxygen Uptake Ratios

Cardiac Output (Direct Measurement of Exhaust Flow versus Haldane-derived Exhaust Flow)

These analyses have been repeated using fixed (rather than measured oxygen) ratios of 0.45:0.55.

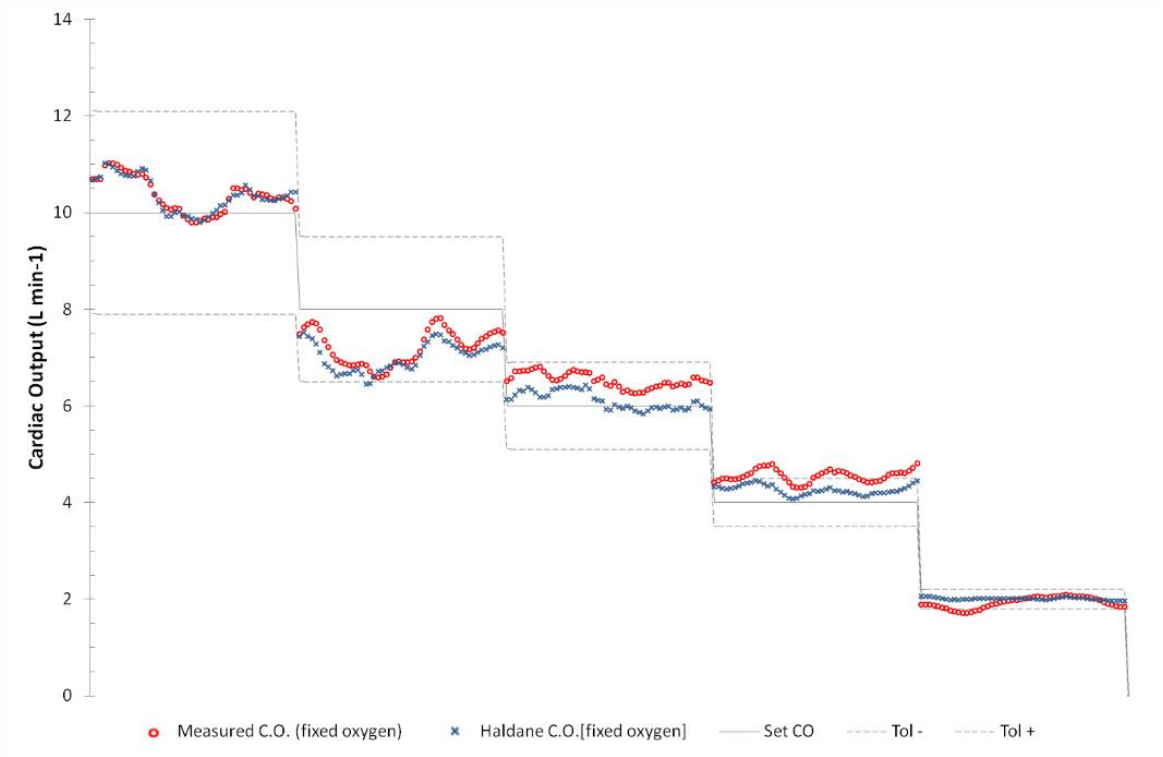

Figure 48 Cardiac output using fixed oxygen ratios

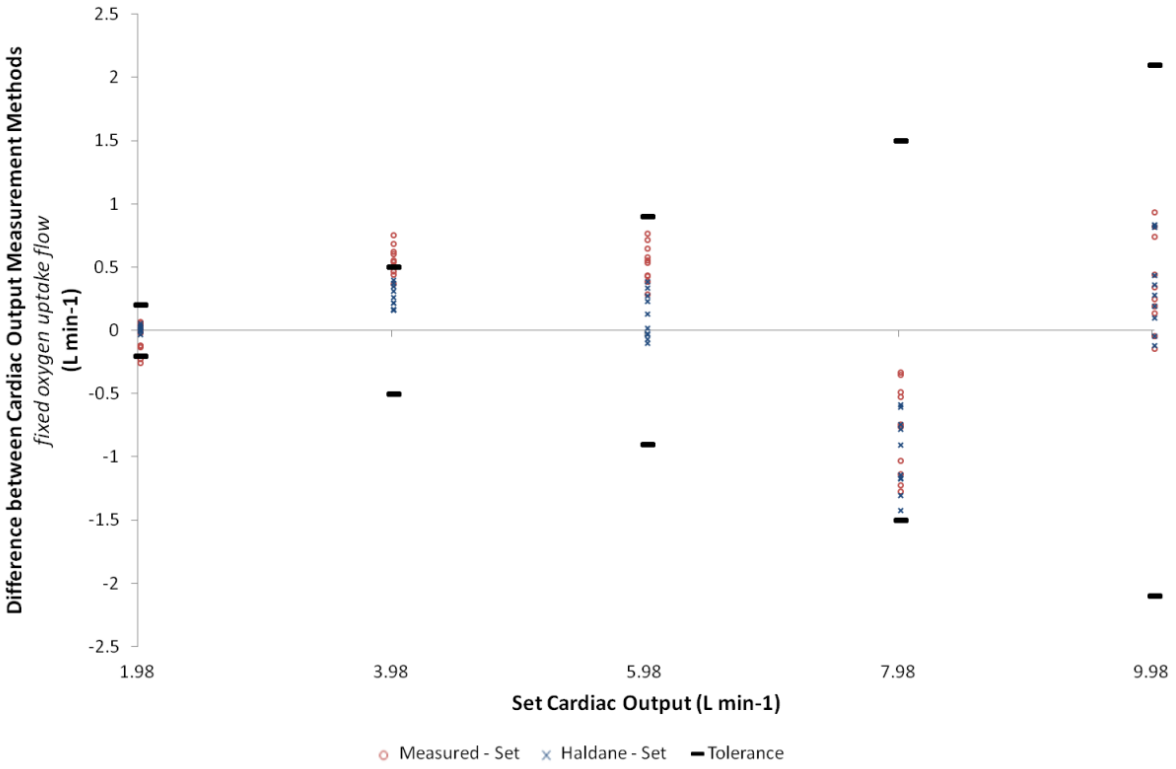

Figure 49 Modified Bland-Altman plot for cardiac output measurement using fixed oxygen ratios. Data is grouped into averages of 5 breaths.

Cardiac Output (L min-1)	Measured						Haldane					
	Mean (L min -1)	Bias (L min -1)	St. Dev. (L min -1)	L.O.A. (L min -1)	Coeff. Var. (%)	Error (%)	Mean (L min -1)	Bias (L min -1)	St. Dev. (L min -1)	L.O.A. (L min -1)	Coeff. Var. (%)	Error (%)
2	1.93	-0.07	0.12	[1.70,2.15]	6	-4	2.01	0.01	0.02	[1.96,2.06]	1	0
4	4.55	0.55	0.13	[4.30,4.80]	3	14	4.26	0.26	0.10	[4.07,4.46]	2	6
6	6.53	0.53	0.15	[6.23,6.83]	2	9	6.11	0.11	0.18	[5.75,6.47]	3	2
8	7.21	-0.79	0.37	[6.49,7.93]	5	-10	7.02	-0.98	0.30	[6.43,7.60]	4	-12
10	10.36	0.36	0.37	[9.64,11.09]	4	4	10.37	0.37	0.36	[9.66,11.07]	3	4

Table 10 Descriptive statistics for Haldane and Measured cardiac output using fixed oxygen ratios

Ability of Method to Track Cardiac Output Change -Comparison of Directly Measured Exhaust Gas Flows versus Haldane-derived Exhaust Gas Flows

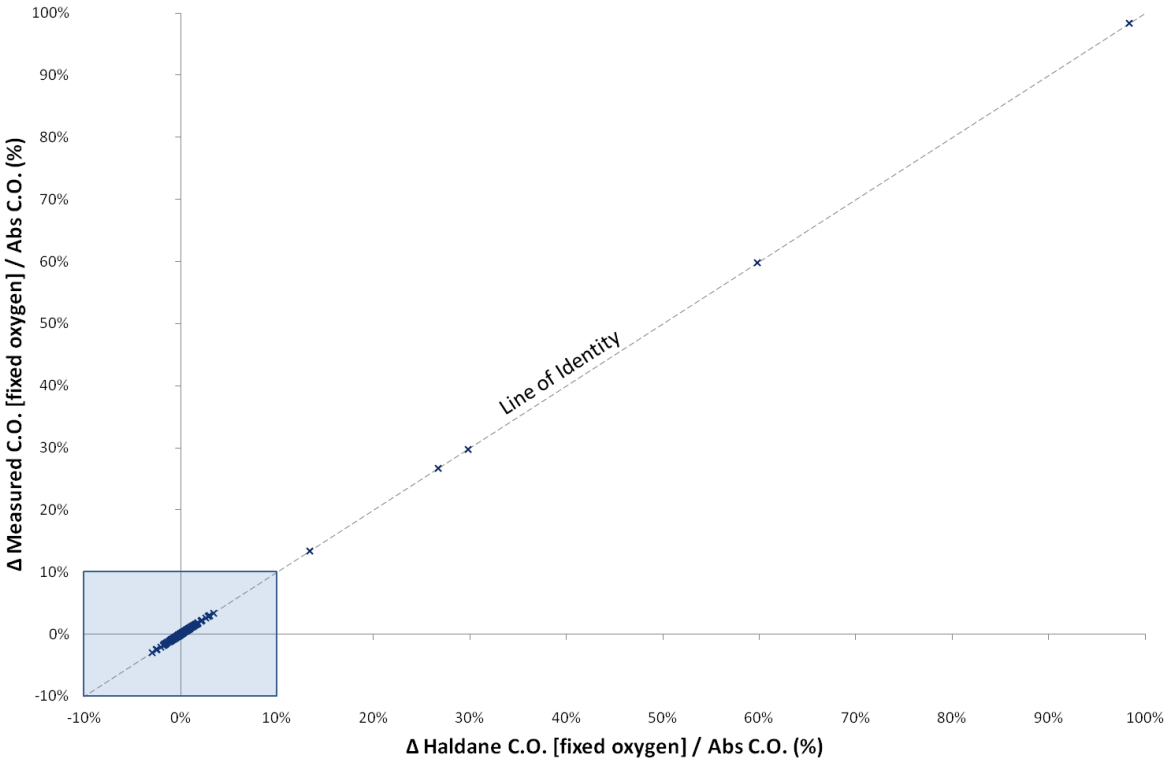

Figure 50 Four-quadrant plot cardiac output using fixed oxygen ratios

Again, the inset box indicates an exclusion zone of 10%. Regardless of the presence or absence of this exclusion zone, the concordance remains at 100%. The measured values closely follow the line of identity when fixed oxygen ratios are used.

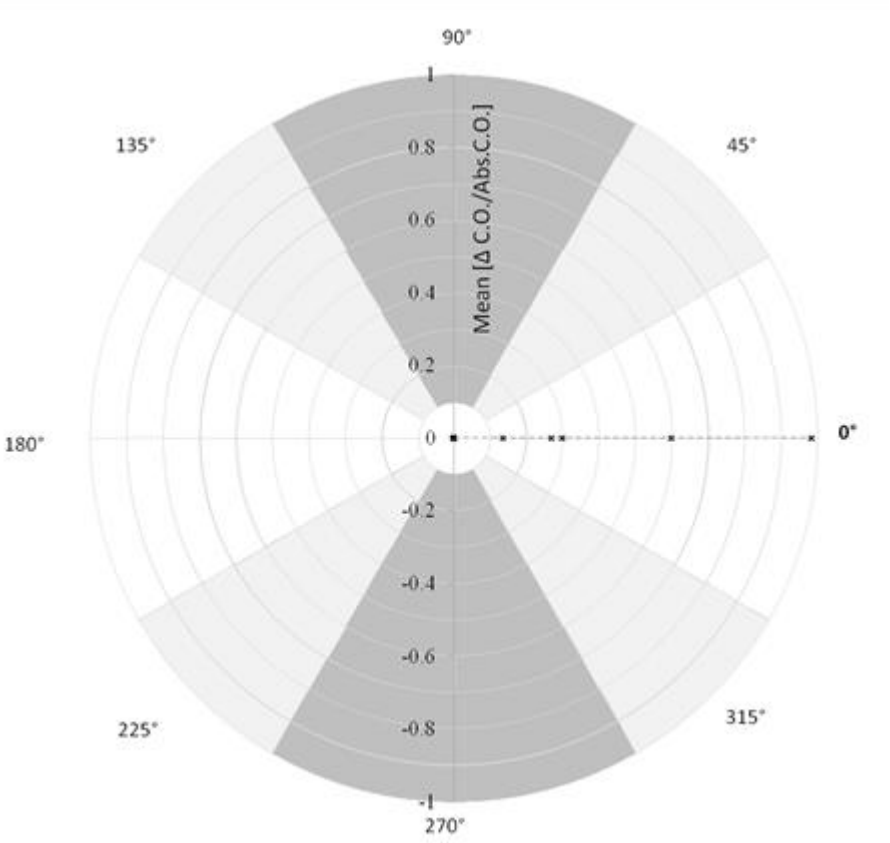

Figure 51 Polar plot for cardiac output comparison when used fixed oxygen ratios

As expected after viewing the four-quadrant plot the polar plot also indicates that cardiac output measurements using fixed oxygen ratios track the target values very closely. This is expected because the use of fixed oxygen uptake ratios means that the only difference between the Haldane and direct exhaust flow measured cardiac output is the isoflurane uptake on the left and right sides.

6.9. Detecting a Step Change in Target Cardiac Output

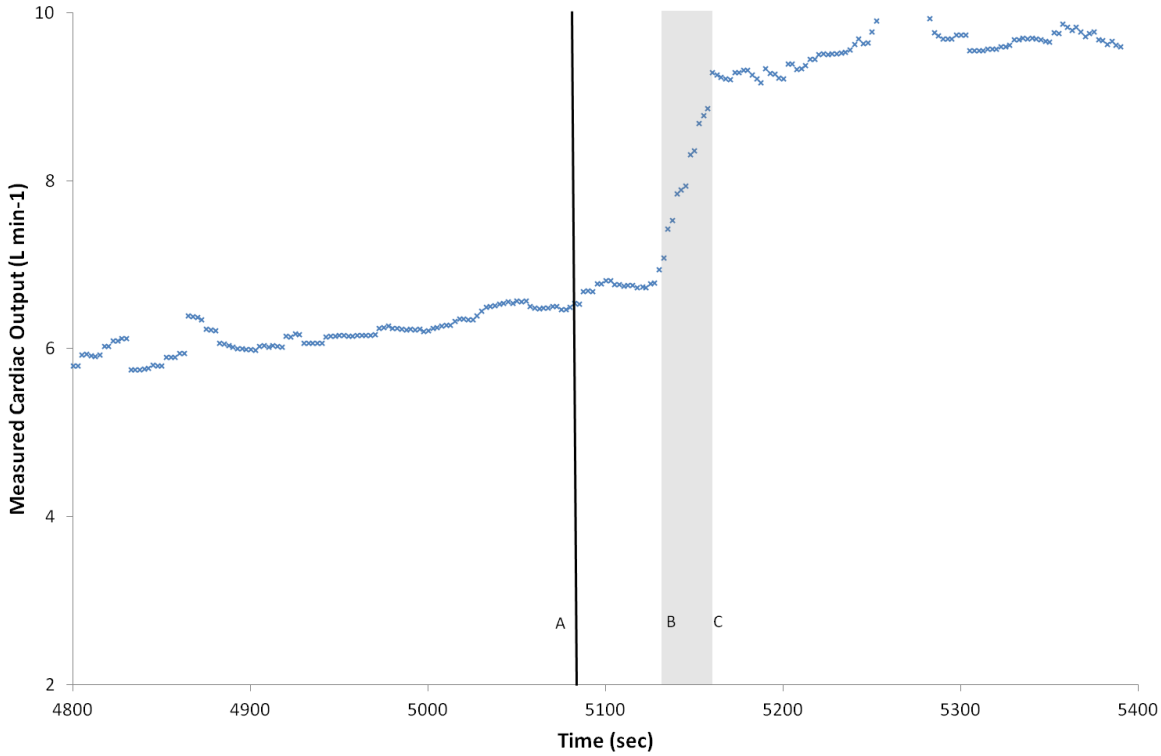

Figure 52 Response to a simulated step change in target cardiac output

	Time (sec)	Delay/Duration (sec)	Delay/Duration (breaths)
Step Change (A)	5083		
Change Detected (B)	5130	47	8
Change Complete (C)	5163	33	6

Table 11 Response to step change in target cardiac output

6.1. Changing Respiratory Rates and Introduction of Positive End-Expiratory Pressure

The effects of lung ventilation settings during anaesthesia mean that a range of respiratory rates and positive end-expiratory pressure (PEEP) variables are often used to optimise gas exchange and patient oxygenation. PEEP may be used to improve ventilation by maintaining alveolar expansion and preventing the development of lung atelectasis. Manipulating the respiratory rate helps to optimise carbon dioxide clearance and maintain normocarbia.

The use of both changing respiratory rates, and PEEP during ventilation makes it necessary to review the effect of changing these parameters on calculated cardiac output.

RESPIRATORY RATE (BREATH MIN-1)	MEAN (L MIN-1)	BIAS (L MIN-1)	L.O.A. (L MIN-1)	COEFF. VAR. (%)	ERROR (%)
MEASURED CARDIAC OUTPUT (L MIN-1)					
8	4.19	0.19	[4.04,4.33]	2	26
10	4.03	0.03	[3.83,4.22]	2	25
12	3.88	-0.12	[3.69,4.05]	2	24
HALDANE CARDIAC OUTPUT					
8	3.76	-0.24	[3.62,3.89]	2	-6
10	3.75	-0.25	[3.37,4.12]	5	-6
12	3.54	-0.46	[3.43,3.65]	2	-11
MEASURED CARDIAC OUTPUT [FIXED OXYGEN RATIO]					
8	4.29	0.29	[4.13,4.44]	2	7
10	4.12	0.12	[3.87,4.36]	3	3
12	3.96	-0.04	[3.83,4.08]	2	-1

Table 12 Changes in cardiac output in response to variation of respiratory rate

Table 12 shows that as the respiratory rate increases the calculated cardiac output decreases. No trend in oxygen or isoflurane uptake rates was observed, however as

respiratory rate increased the end tidal isoflurane concentrations showed an increase on the left and a decrease on the right.

PEEP (CM H_2O)	MEAN (L MIN-1)	BIAS (L MIN-1)	L.O.A. (L MIN-1)	COEFF. VAR. (%)	ERROR (%)
MEASURED CARDIAC OUTPUT (L MIN-1)					
0	4.03	0.03	[3.83,4.22]	2	25
6	4.18	0.18	[3.85,4.50]	4	26
10	4.28	0.28	[4.07,4.48]	2	27
HALDANE CARDIAC OUTPUT					
0	3.75	-0.25	[3.37,4.12]	5	-6
6	4.01	0.01	[3.73,4.28]	3	0
10	3.67	-0.33	[3.45,3.88]	3	-8
MEASURED CARDIAC OUTPUT [FIXED OXYGEN RATIO]					
0	4.12	0.12	[3.87,4.36]	3	3
6	4.60	0.60	[4.28,4.92]	3	15
10	4.67	0.67	[4.37,4.96]	3	17

Table 13 Changes in cardiac output in response to changes in PEEP

Table 13 shows that as positive end-expiratory pressure increases the calculated cardiac output -using measured exhaust gas flow decreases, however, the same trend was not observed in the Haldane derived exhaust gas flow. This was associated with an increase in oxygen and isoflurane uptake rates on the left-side. No trends were observed in measured end-tidal concentrations or the right-side uptake rates.

6.2. Summary

The results and the implications of the graphs and tables presented in this chapter will be analysed in the Chapter 7. I will discuss whether isoflurane can be successfully used in place of nitrous oxide to measure cardiac output using the throughflow method, and, if direct thermal mass flow measurement can be successfully used in place of the Haldane measurement technique for exhaust gas flow rate measurement.

Chapter 7 Discussion

The measurement of lung gas-exchange provides the potential to determine cardiac output non-invasively. Historically, carbon dioxide or foreign-gas exchange techniques for measuring cardiac output have required off-line analysis and have been hampered by the need to complete measurements before these gases in the blood are recirculated. However, technology improvement and a strong focus in clinical research over the last 15 years has seen the development of continuous, real-time cardiac output measurement techniques based on lung gas exchange.

In Chapter 2 I discussed the limitations associated with the re-circulation of blood, predominately that it eliminates the possibility of continuous cardiac output measurement. Recent research has shown that manipulation of mechanical characteristics of gas delivery systems can overcome the limitations imposed by recirculation of foreign gases in the bloodstream. Robinson (2003) overcame the recirculation problem by implementing functional separation of the lungs using dual-lumen endotracheal tubes and individual left and right lung breathing systems to deliver different fresh gas mixtures to each lung, allowing and measuring the pulmonary throughflow of nitrous oxide (blood gas coefficient = 0.47). This approach uniquely permitted continuous pulmonary capillary blood flow calculation with disregard of mixed venous gas content.

Other solutions to the problem of variable mixed venous blood gas content have been explored. Introducing oscillating inspired concentrations of inert gas into the breathing system at a sufficiently high frequency to avoid producing sustained fluctuations in mixed venous partial pressure has been explored by Zwart et al. (Zwart, Seagrave et al. 1976) Following investigations by Peyton (2006), who proposed measuring the response of expired carbon dioxide flow rates and end-tidal partial pressures to continuous cyclic manipulation of tidal volume, Haljso-Sander et al. in a series of studies in a porcine model used continuous cyclic variation in respiratory rate with a periodicity of approximately a minute. This generated cyclic variations in expired carbon dioxide excretion and end-tidal partial pressure of similar periodicity, but without evidence of significant induced variations in mixed venous carbon dioxide content, thus allowing continuous cardiac output calculation

by the Differential Fick principle. This method has produced encouraging preclinical results but awaits clinical testing (Hällsjö Sander, Hallbäck et al. 2014).

The simulation of lung gas-exchange affords control of the physiological variables and allows application of step changes that cannot be achieved using *in vivo* studies, except those that utilise step changes onto a cardiac bypass machine, or drug-induced changes in animal models.

Computer optimisation and modelling in Chapter 5 enabled the determination of filtering and averaging techniques to improve the reliability of the method, and to balance system response times, reliability and accuracy of the method.

Unlike *in vivo* studies where breath-by-breath fluctuation of gas exchange is expected for a wide variety of physiological reasons (such as spontaneous effort, sighs, inadvertent physical manipulation of the external chest wall) gas-exchange simulation provides relatively constant simulated gas uptake rates and end-tidal concentrations during steady-state conditions. The *in vitro* results in Chapter 6 show fluctuations will occur in benchtop simulation models such as mine; these fluctuations particularly occurred whenever measurements were taken, regardless of the magnitude of simulated gas uptake rates or the target cardiac outputs, and were due to perturbation of the gas delivery system and gas uptake simulator by the side stream gas sampling process. The benchtop simulator this allowed the variability and sources of measurement error inherent to the measurement system to be identified and quantified separately from physiological sources of variability. This is essential to allow focus on these physiological factors in assessment of results generated by the system during subsequent use of the measurement system *in vivo*.

The use of a laboratory-simulated 'patient' thus provides reliable assessment the effectiveness of the measurement system regarding measurements of patient gas uptake rates and end-tidal concentrations. It removes the complications of physiological factors such as, for instance, alveolar-arterial gradient and $\dot{V}/\dot{Q}$ scatter discussed in Chapter 4, and models the 'perfect' patient.

The sub-stages of cardiac output measurement, the collection of data, and the implications of choices made in the measurement design, will be explored in this chapter.

7.1. Selection of Isoflurane for Throughflow Cardiac Output Measurement

Carbon dioxide is recognised as a sensitive indicator of changing cardiac output, and when used in the method described by Peyton, does not impose any restriction on the composition of fresh gas delivered to patients. A clinical case study by Kennedy (2001a) that used change in end-tidal carbon dioxide and pulse rate to infer a change in cardiac output, demonstrated that expired anaesthetic vapour concentration could predict change as well as carbon dioxide could. Kennedy estimated that a change of 30-40% in cardiac output was required to produce a measurable change in isoflurane (λ*=1.4*), enflurane (λ*=1.8*), or halothane (λ*=2.5*). However, he did not quantify the link between anaesthetic vapour uptake rate, or change in end-tidal concentration, and absolute cardiac output.

Kennedy has contributed to the understanding of uptake of anaesthetic vapour and its relationship to change in cardiac output. He identified that vapours having easily identifiable responses to changes in cardiac output had Ostwald blood-gas coefficients between 1.5 to 2.5. His model demonstrated that the best response to a step change in cardiac output from 5 to 10 L min^{-1} was observed when measuring the change in isoflurane. The ability of isoflurane to predict a cardiac output change is supported by Peyton's (2004) model of the gas uptake against a ratio of cardiac output versus $\dot{V}/\dot{Q}$ inhomogeneity at an inspired concentration of 1%.

After analysing the throughflow of nitrous oxide using computer modelling, Peyton (2004) stated that a gas more soluble than nitrous oxide, such as a volatile anaesthetic agent, could theoretically be used with throughflow. Using modelling derived from this work, a range of isoflurane uptake rates, and end-tidal concentrations were provided to simulate throughflow cardiac output values of 2, 4, 6, 7 and 10 L min^{-1} for the purposes of our project.

These models suggest that the use of lung isoflurane uptake for estimating cardiac output benefits from being as good a predictor of changing cardiac output as using carbon dioxide. However, its small concentration in the fresh gas flow means that uptake and end-tidal concentrations need to be measured with precision. The use of the throughflow technique

means the inert gas exchange occurs across the two lungs. Because isoflurane concentrations are typically low, the relative magnitude of change is relatively large compared to that of nitrous oxide and oxygen, which both have large concentrations in the fresh gas flow.

7.1.1. Measurement system accuracy and precision

By its underlying nature, throughflow possesses an additional advantage over other methods based on inert gas uptake. Because of the persistent elimination of inert gas by the right lung, the magnitude of gas uptake in the left lung is maintained at a relatively high rate, which maximises the relative precision of gas uptake measurement in the left lung. This advantage is somewhat offset by the need for separate gas exchange measurement in two lungs, with cumulative sources of measurement error. However, as discussed in Chapter 3, because inert gas is eliminated in the right lung, measurement is simpler and more precise.

In the modelled scenarios, the predicted magnitude of isoflurane uptake varies with the target cardiac output, with higher cardiac outputs corresponding to larger left-right rates of throughflow of isoflurane. All isoflurane uptake rates measurements track consistently, regardless of whether direct or Haldane-derived exhaust measurements are used for their determination. As discussed in Chapter 3, measured Isoflurane uptake rate is not subject to the same degree of breath-by-breath fluctuation as oxygen uptake rates, due to the higher rate of uptake of volatile anaesthetic agent relative to its inspired concentration compared to oxygen.

On the right (hand) side, Haldane-derived and directly measured isoflurane uptake rates are virtually indistinguishable. The similarity between the two techniques on the right-side is due to the presence of isoflurane in the exhaust gas only, and thus the similarity between measured and Haldane-derived exhaust flows. It might also be that the right-side measurements are more consistent because the performance of the lung simulator on the right side is simpler and more predictable. Suctioned and replaced gas flows in the simulator do not vary between the five simulated cardiac output scenarios - only the manual vaporiser setting does.

In contrast, the differences between Haldane-derived and directly-measured exhaust gas flow rates produce larger differences in calculated gas uptake rates on the left side of the lung simulator. The directly measured isoflurane uptake rate fluctuates and has multiple peaks and troughs, and similarly to measured oxygen uptake rates the standard deviation of isoflurane uptake rates is greater than those calculated using the Haldane technique.

Despite these differences, gas uptake rates appear to track closely and with little difference in bias relative to target values, regardless of the method used for calculation. Direct measurement of exhaust flow seems to produce calculated isoflurane uptake rates as reliable as those using Haldane-derived exhaust flows, and the two techniques could be interchanged. This is especially the case when using fixed oxygen uptake rate ratios, when using measured oxygen uptakes the bias between direct and Haldane derived measurements can be significant.

With a blood-gas partition coefficient which is almost double that of acetylene which is delivered at 0.7% in Gan's dual inert technique (1993), isoflurane is delivered at 1% in the left fresh gas mixture in our simulations. The fresh gas concentration for isoflurane in influenced by its minimum alveolar concentration (MAC) values. Through animal studies and simulations, Gan demonstrated both the necessity to include measurement noise and the effect of respiratory variations in computer modelling. He verified that measurement noise could be managed and an end-tidal value accurately selected by removing obvious data outliers and using a smoothing filter.

I successfully adopted techniques reported by Gan for the selection of isoflurane end-tidal concentrations required for the throughflow cardiac output calculation. Accurate and precise identification of the end-tidal concentration was required due to the low isoflurane concentrations being measured. For a target, cardiac output of 4 L min^{-1}, the fractional concentration of isoflurane measured at the end-tidal sample position was 0.35% (2.66 mmHg) on the left-side and 0.15% (1.14 mmHg) on the right-side.

Figure 13 in Chapter 6 depicts the raw isoflurane concentration measurements and shows that, despite relatively steady simulation conditions, there are many small variations in concentration measurements. The small size of these variations is still significant as a

proportion of the overall magnitude of the isoflurane concentration during tidal breathing. These variations are similar to the acetylene concentrations observed by Gan (1993). His observations and techniques were adopted in the optimisation in our system, and in the smoothing filter applied to our raw measurements described in Chapter 5. The application of a smoothing filter made it simpler to determine the end-tidal concentration by reducing variations. This was applied to the instantaneous measurements and the end-tidal point on the smoothed waveform selected at the conclusion of each breath, as described in Chapter 3. However, they have been limited enough that our method for measuring cardiac output remains valid.

It was difficult to produce simulated end-tidal concentrations on the right-side that were within the tight 10% target tolerance, with measurements in this location consistently measuring at or just above these values. Given the small maximal fractional concentration at the right side end-tidal position, these values were accepted. The inter-breath variation in end-tidal concentrations also suggests that the quantification of isoflurane uptake rates directly from concentrations measured in this position, instead of at the mixed exhuast gas concentration and flow point (distal to the ventilator bellows), could be difficult, and it was decided early in the development phase of this study that this option for gas uptake rate measurement would not be pursued.

For progression to a clinical study of isoflurane throughflow, it is necessary to consider the end-tidal to end-capillary gradient of isoflurane and its predicted effect on the accuracy of throughflow for cardiac output measurement. This has been extensively discussed in Chapter 4, where, using a multi-compartment computer model of lung gas exchange model employed previously by Peyton 2004 to examine the problem for nitrous oxide throughflow, it was shown that isoflurane is likely to be a better choice of agent than nitrous oxide, with less underestimation of cardiac output predicted. The data presented allows a simple correction for the predicted error to be made in a similar way to that employed for nitrous oxide by Robinson et al. (2004) and Peyton(2004), using an estimate of the end-tidal to end-capillary isoflurane difference in each lung obtained from end-tidal and arterial blood gas CO_2 measurement in a given patient. The success of this strategy with isoflurane throughflow awaits confirmation in a future clinical study.

7.2. Oxygen Concentration Measurement and Uptake Flow Rates

The throughflow method for measuring cardiac output requires an estimation of the relative proportion of pulmonary blood flow to each lung. Robinson(2003, 2004) used oxygen uptake rates in the left and right lung to determine the perfusion distribution in the lung.

As discussed in Chapter 5, oxygen concentration is not measured continuously from all locations, but instead, gas sampling is continuously measured cyclically for nine breaths at each site. Because each of the simulated cardiac output scenarios assume a stable fresh gas mixture to both lungs, fresh gas was delivered at a constant composition and flow rate throughout all scenarios, and fresh gas is only sampled periodically (every ninth cycle, or seventy-two breaths). If the fresh gas mixture is changed, the measurement system can be forced to sample fresh gas (or any other location) out of sequence. For simplicity, all scenarios assumed an identical oxygen and carbon dioxide exchange rate with only isoflurane exchange in the two lungs varying in response to changing the cardiac output. During measurement of gas uptakes, Robinson (2004) sampled fresh gas for 15 seconds in every 120 second period, which is about 12.5% of the time. However, because the throughflow method relies on both the measurement of gas uptake rates and end-tidal concentrations, I have reduced the frequency of fresh gas sampling. The measurement period for gas sampling in each position (fresh, end-tidal and exhaust) is equal and based on the number of breaths (rather than a specific time interval). To eliminate the potential for cross-sampling of gas from consecutive sampling positions, the two breaths at the start of a cycle and the last breath of the cycle are excluded.

Figure 35 in Chapter 6 shows the oxygen concentration measurement over 116 minutes (~7000 seconds). During this period, there is little variation in the oxygen concentration in the measured fresh and exhaust gas flows. The measured exhaust oxygen concentration does not vary significantly beyond the variations observed in the fresh gas flow, despite the *in vitro* simulation removing and replacing a large quantity of oxygen in the lung bellows on the left-side. In contrast, the right-side of the simulator was simply required to extract the calculated amount of oxygen (without replacement).

The hospital-piped oxygen was used to supply the anaesthetic machine and to drive the ventilator bellows. Replacement oxygen (for the simulator) was supplied using oxygen cylinders to remove the potential for fluctuations that could occur from the varying demands on the hospital supply, including those from the simulator gas delivery system.

The oxygen concentration is significant for two primary reasons:

- It is the largest component of all mixed gases, and any variations to measured concentration will be reflected in measured oxygen uptakes.
- The Haldane Transformation relies on the conservation of nitrogen. However, the gas analysers used in this system do not measure nitrogen directly, but by subtracting summated fractional concentrations all measured gases from unity.

Three different techniques were used for the determination of oxygen uptakes: direct measurement, Haldane-derived, and fixed oxygen uptake ratios.

In the data collected for Table 8 'Oxygen uptake flows: directly measured (M) and Haldane-derived (H)', the bias of the directly measured oxygen uptake rate (relative to the target value) was smaller than oxygen uptake rates calculated using the Haldane technique. This is despite the ten-fold increase in the observed standard deviation when using directly measured exhaust flows, which is remarkable. The larger standard deviation in the directly-measured value is a result of the large breath-by-breath fluctuations observed in directly-measured flows. This would suggest that Haldane-derived cardiac outputs will be smoother than those using direct flow measurement. Despite the potential for a smoother response, the Haldane-derived flow is also to a degree reliant on any fluctuations in the oxygen concentration measurement because these are reflected in calculated nitrogen concentrations.

The use of moving averages of oxygen uptake rate over a two-hundred breath window produces smoother calculated cardiac outputs. This assists clinical interpretation, but it also means any large temporary changes to measured oxygen concentrations or flow rates will be reflected in the oxygen uptake rate for the following thirty minutes, which would produce an unacceptable persisting error in calculated cardiac output.

Chapter 5 also examined the use of assumed oxygen uptake ratios. This indicated that a wide variation in oxygen uptakes flow ratios (0.40:0.60 to 0.83:0.17) could be utilized before the predicted cardiac output fell beyond 10% of the target value.

Given the breath-by-breath variation of measured oxygen uptake rates (regardless of method), and the long moving averages that need to be applied to reduce arbitrary fluctuations in cardiac output, it is likely that the use of an assumed ratio value will produce a more reliable and consistent cardiac output measurement that can be utilized clinically, without significantly sacrificing accuracy.

As anticipated, when reviewing measured gas flow rates, the Haldane-derived oxygen uptake rates are more precise than those using direct exhaust gas flow rate measurements; this is visualised in Figure 37 (Chapter 6), and also when reviewing the standard deviation. However, during Haldane-derived measurements, between 3400 and 4200 seconds, we observed a steady decrease in recorded left-side oxygen uptake and a step increase in right-side oxygen uptake. It is hard to see the corresponding changes that occurred in the oxygen concentration and Haldane-derived exhaust gas flow rate that produced this error, but it illustrates the effect of a small change in oxygen concentrations on the exhaust flow measurement. The result of this Haldane-derived oxygen uptake rate measurement is seen in Figure 44 where the Haldane-derived cardiac output falls outside the target tolerances.

The corresponding cardiac outputs using direct measurement of oxygen uptake rate (Figure 44) and fixed oxygen uptake ratios (Figure 48) fall within target tolerances. It would appear that the measurement of Haldane-derived oxygen uptake is challenging; this makes its use problematic for the determination of cardiac output, and reinforces the utility of using assumed oxygen uptake rates instead for cardiac output calculation. These comparisons can be repeated during future clinical testing of the method, to confirm the findings of our benchtop simulations.

7.3. Exhaust Gas Flow Measurement

The Haldane technique has commonly been used to measure exhaust gas flow rate based on the conservation of nitrogen.

Problems with this occur around the assumption of no uptake of nitrogen both in clinical scenarios where nitrogen uptake is known to occur, and in simulation because of imperfect precision of gas controllers.

It also restricts the fresh gas mixture because a minimum concentration of around 30% must be maintained in the fresh gas. This means that delivered oxygen concentrations are reduced, which may be difficult or dangerous in critical clinical situations requiring a high inspired oxygen concentration; however, it lessens the likelihood of alveolar collapse associated with absorption atelectasis, which can be a problem during anaesthesia when high oxygen concentrations are used.

With nitrogen being calculated by subtraction and with oxygen being present in such high concentrations, a difference between calculated and actual nitrogen composition can occur.

It is expected that, during target cardiac output and zero uptake scenarios, the exhaust gas flow rates using either measurement method will follow the fresh gas flow rate. Unlike direct measurement of exhaust flow rate which is independent of the measured fresh gas flow rate, Haldane-derived exhaust flow rate calculations are directly related to the fresh gas flow rate. This means the difference between measured fresh and Haldane exhaust gas flow rate (Chapter 6, Figure 38 and Figure 39) is smoother with less variation than when using direct measurement, an effect which was expected to extend to measured oxygen and isoflurane uptake rates.

The benefits of directly measuring flow rates are two-fold. Despite the increase in variation between measurements, it makes the exhaust flow measurement independent; this is expected to be associated with increased robustness. The other advantage is it removes the need to rely on the conservation of nitrogen to calculate exhaust flow rate. In gas-exchange simulations, this means that discrepancies between set nitrogen replacement flow and

actual flow have a reduced effect on measured flows and calculated uptakes. Importantly, it maximises flexibility in delivered gas concentrations to the patient in the clinical situation.

As previously discussed the dependence on accurate oxygen concentration measurements for the Haldane-derived exhaust flow rate measurement makes oxygen uptake rates calculated using this method susceptible to errors.

Scenarios were designed to deliver an exhaust gas flow rate which was between 25.0 and 27.3 mL min^{-1} (left-side) and 17.4 to 20.1 mL min^{-1} (right-side) lower than the delivered fresh gas rate, due to the net gas uptake occurring in the lung on each side. In practice, this was hard to achieve because:

- gas flow controllers (used for simulation) are accurate to +/- 10 millilitres
- three flow controllers are used for each simulated lung
- gas is removed by manual suction regulators connected to the hospital wall suction system, with limited precision of suction flow control.

Thus, the exact difference varied depending on both the amount of gas to be removed from the lung bellows and in response to the analogue and manual selection of the suction rate.

The choice of the fresh gas mixture could be widened since we have shown that cardiac output calculations using directly-measured exhaust gas flow rate measurements are as accurate as Haldane-derived measurements. This is because it would remove the need to have a minimum of 29% nitrogen in the fresh gas. It also means the method could be used clinically for surgical techniques where loss or absorption of nitrogen occurs between body tissue and atmosphere. If oxygen concentrations are increased, then this will have physiological effects and may require the introduction of positive end-expiratory pressure to maintain alveolar recruitment in the lungs.

7.4. Collection of Fresh, End-tidal and Exhaust Gas Concentrations while Maintaining System Responsiveness

Gas concentrations need to be sampled from the fresh, mouth, and exhaust locations of the left and right lungs. There are several ways that this could be done, but two major changes were made to the system for throughflow cardiac output measurement that was described by Robinson: 1) an adapted cycling gas sampling manifold and 2) a separate gas analyser for each lung.

Cyclic measurement of gas concentrations in fresh, end-tidal and exhaust locations was discussed in Chapter 5. The sampling position was changed every nine breaths: this decision was made to enable quick detection of variation in cardiac output. The fresh gas mixture was held constant during all scenarios; meaning it was not necessary to sample fresh gas as frequently as end-tidal and exhaust gases.

An accurate way of determining system response time is by observing a step change in cardiac output. This is comparatively easy to achieve in animal and simulation studies because these changes can be marked (or time-stamped) and controlled chemically (through drugs) or by making changes to simulated gas-exchange. In clinical scenarios, true step changes are rare, but may be, for example, the result of a sudden cardiac arrhythmia or arrest, or transition onto partial or complete cardiopulmonary bypass in patient undergoing cardiac surgery. Because most changes in cardiac output are more gradual, measurement delays in clinical comparison studies can be difficult to determine; they depend on a timely response by the reference method, or another indicator (for instance a change in carbon dioxide end-tidal concentrations) and can be heavily influenced by a variety of physiological factors, such as lung wash-in or washout times for changes in alveolar gas concentrations resulting from changes in alveolar-capillary gas exchange.

The ability of the measurement system to respond to changes depends on the experimental method. Robinson (2004) measured lung gas uptake rates using cyclic sampling between fresh and exhaust gas measurement over a four minute cycle (two-minute in each lung consecutively) – fresh gas was cycled for approximately 15 sec in every two-minute interval. Robinson did not discuss the elimination of any breaths due to potential contamination

(from the alternative sampling location). This technique was developed further using *in vitro* simulation by Vartuli, who instead of eliminating breaths due to potential contamination, suctioned sample lines through a common port. He flushed the system with the gas mixture that was currently being sampled (Vartuli, Burfoot et al. 2002), he also used room air and an Entonox mixture for frequent gas analyser calibration with every cycle). I adopted a similar cyclical gas sampling system; however, some breaths were excluded to avoid cross-contamination between consecutive gas sampling positions. Additional sample lines and solenoids for calibration gases were not used. Instead, the gas analysers are re-calibrated with calibration gases (as a separate process). As discussed earlier, use of separate gas analysers for the left and right sides doubled the effective cardiac output sampling rate of the system.

The cyclic collection of gases for concentration measurements does reduce the responsiveness of the system to changes in cardiac output compared to that of a system which measures continuous gas concentrations at all locations. However, the benefit of independent cyclic sampling for each lung is that it reduces the requirement from six anaesthetic gas analysers (one for each measurement location) to two (one for each breathing circuit).

Another alternative would be to determine gas uptake rates using measurements made at the end-tidal sampling location. If this produces uptakes that are equivalent to those calculated using the difference between fresh and exhaust measurements, it would reduce the requirement for multiplexing from different sample points, and improve the system response time. However, as discussed above, the challenges in achieving satisfactory measurement using this approach are great, as it involves dealing with tidal fluctuations in both gas concentrations and flow rates at the end-tidal gas sampling position, with the need for tight synchronisation of waveforms to calculate breath-by-breath flow rates and volumes of each gas species.

7.5. Cardiac Output

Nitrous oxide throughflow has previously been validated *in vitro* in a study by Burfoot (1999) and Vartuli (2002). They measured simulated cardiac output values that had a standard deviation of the difference ranging between 0.06 and 0.14 L min^{-1}, the standard deviation of the difference increasing as the cardiac output increased. They used the Haldane-transformation to calculate exhaust gas flow rates and gas uptake rates; these values were described as 'apparent' lung-uptakes because the simulator only added gases (rather than simultaneously removing them), reducing one of the potential sources of simulator system error.

Robinson(2003) demonstrated *in vivo* the ability of throughflow of nitrous oxide to measure cardiac output using thermodilution as a reference standard method of measurement. His results showed a mean bias with a closer agreement to thermodilution cardiac output when using a fixed oxygen ratio (instead of measured oxygen uptakes); however, this was contrasted with a larger standard deviation.

Simulation of gas exchange in this *in vitro* simulation is complicated by the decision to simulate lung gas uptake by removal of mixed alveolar gas from the simulated lung bellows; this was required so that it could directly measure exhaust gas flows, and to test the measurement system with the most physiologically realistic benchtop lung gas exchange simulation available. This contrasts with the simulator described by Vartuli (Vartuli, Burfoot et al. 2002) that simulated "apparent" gas exchange using enriching and diluting gases without suctioning of a volume of mixed gas equal to that added to achieve target lung gas concentrations. As a result of these differences, and because of the range of uptake and end-tidal concentrations involved, the decision was made to have a target tolerance of ten percent[14] for all gas uptake rates and end-tidal concentrations used in the calculation of

[14] The small isoflurane flow uptakes and concentration measurements at target cardiac outputs of 2 and 4 L min^{-1} make 10% an unrealistic target. This is explained more fully in sections 3.8.3 and 3.8.4 of the thesis.

isoflurane throughflow cardiac output. The accuracy and precision of the simulated cardiac output rely on suitable estimation/measurement of oxygen, and isoflurane uptake rates, and isoflurane end-tidal concentrations. Although the numeric output of our measurement system displays the cardiac output to one decimal place, the waveforms are all presented as measured. This means that the displayed cardiac output is smoother despite greater breath-by-breath variation being apparent.

Chapter 6, Figure 44 and Figure 48 show simulated cardiac output measurements for five consecutive scenarios. The 50 breaths immediately before each change in simulated cardiac output are shown. The cardiac outputs are presented by the gas flow rate measurement method used and have been grouped into four categories: Measured, Haldane-derived, measured with fixed oxygen ratios, Haldane-derived with fixed oxygen uptake ratios. These calculated cardiac outputs are compared against the target value, but this does not provide the facility to see how well the measured cardiac output follows small changes in gas uptake rates and end-tidal concentrations. The Haldane Transformation is a common method for determining exhaust gas flow rate, and has been used previously to calculate cardiac output; it is included in this thesis to allow the determination of how well the system responds to small changes.

The tolerance of our cardiac output measurement method was calculated based on allowing a +/- 10% tolerance on each of the input variables into the isoflurane throughflow equation (Chapter 3, Equation 40 to Equation 43). The calculation steps and values for the associated tolerance in calculated cardiac output were determined in Chapter 3. For cardiac outputs of 2, 4, 6, 8 and 10 L min^{-1} we can use a polynomial equation to estimate the tolerances.

$$Tolerance = 0.0143(Cardiac\ Output)^2 + 0.0686(Cardiac\ Output) + 6 \times 10^{-15}$$

Equation 47 Calculation of Tolerance for Measured Cardiac Output

Chapter 3, Figure 9 shows measured and Haldane-derived simulated cardiac output measurements. Reviewing the raw data, both methods follow the same basic pattern apart from two instances (cardiac outputs of 2 and 6 which show variations in shape). We have already mentioned that the difference between the Haldane-derived and target cardiac output at 6 L min^{-1} is due to the effect of using Haldane-derived oxygen uptakes in the

presence of small unanticipated variations in oxygen concentration, which is not observed when using direct measurement of exhaust gas flow rate.

The difference between measured and Haldane-derived cardiac outputs at 2 L min^{-1} (Chapter 6, Figure 44 and Figure 48) was unexpected because they do not appear to follow the same general trend. This must be related to the measurement of isoflurane uptake rather than oxygen uptake rates, for it is observed in the calculated cardiac outputs using both measured and fixed oxygen uptake ratios. I expected that a cardiac output of 2 L min^{-1} would have a greater degree of susceptibility to noise because of the small isoflurane excretion rates In the right lung. However what I found was the opposite: this was actually due to the difference between isoflurane end-tidal concentrations on the left and the right sides in the denominator of the expression.

The standard deviation for cardiac output scenarios of 2 and 4 litres per minute is lower when calculated using Haldane-derived exhaust gas flow rates for both measured and fixed oxygen uptake ratios. This advantage disappeared when targeting cardiac outputs of 6, 8 and 10 L min^{-1}; this was surprising because observation of the isoflurane and oxygen uptake rate measurements suggested that Haldane-derived cardiac output measurements would be smoother. Higher cardiac outputs are simulated by larger isoflurane uptakes in the left lung. The suctioned gas contains a higher percentage of oxygen that must be replaced to maintain the target oxygen uptake. This may account for the similarity in standard deviation for these cardiac outputs regardless of the method for calculating exhaust gas flows.

The use of fixed (rather than measured oxygen) uptake ratios reduced the bias between the two methods and reduced the standard deviation for higher cardiac outputs. One of the reasons that the effect is larger at higher target cardiac outputs might be because this requires greater removal and replacement of left-side oxygen to achieve the target left isoflurane uptake rate. This would also explain why the standard deviation did not reduce at lower target cardiac outputs. A comparison of modified Bland-Altman plots comparing Haldane-derived and direct-exhaust-measured cardiac outputs for measured and fixed oxygen uptake ratios indicates that the latter provides cardiac output measurements that are more precise and accurate than those using measured oxygen uptake rates which include breath-by-breath variation. The use of fixed oxygen uptake ratios is supported by my

investigation Chapter 5. Previous work by Kennedy (2009) suggests that careful consideration needs to be made as to how data is presented so that it can provide diagnostic value; this justifies using fixed oxygen uptake ratios that eliminate some of the error arising from breath-by-breath variation. In the digital cardiac output display, it was decided to limit cardiac output to one decimal place, but this was not done in the graphed data, due to its lower visible resolution. The increased breath-by-breath variation, when using measured oxygen uptake rates, may diminish from the throughflow technique the ability to recognise changing cardiac output.

In summary therefore, simulation of cardiac output measurement using isoflurane throughflow supports the use of using direct measurement of exhaust gas flow rate to determine gas uptake rates, in combination with fixed oxygen uptake ratios in the throughflow equation. Both of these make cardiac output measurements less reliant on breath-by-breath fluctuations in oxygen uptake rate or random errors in its measurement.

The computer models designed by Peyton (2004) that showed the relationship between the pulmonary exchange of soluble gases and cardiac output, have been used in our *in vitro* work to determine the isoflurane uptake rates and end-tidal concentrations required to simulate target cardiac outputs during throughflow of isoflurane. Peyton's modelling of nitrous oxide throughflow also supports both the direct measurement of exhaust flow to determine gas uptake rates, and the used of fixed oxygen uptake ratios. Both direct measurements of exhaust gas flow rate and the use of assumed oxygen uptake ratios make cardiac output measurements more robust in the face of breath-by-breath fluctuations.

My *in vitro* measurement of cardiac output using the model developed by Peyton(2004) demonstrates that cardiac output changes of less than 30-40% can be detected using throughflow of isoflurane. This enables the measurement of cardiac output with more accuracy using isoflurane than previously hypothesised by Kennedy(2002), modelling ventilation of the lungs with a single gas mixture. The simulated cardiac outputs described in this thesis have demonstrated the ability to detect step changes of 2 L min-1 between 2, 4, 6, 8 and 10 L min-1, which represent changes of between 20% and 50%.

7.6. Trending Cardiac Output and Delay

New test methods are typically tested against an established reference technique. The Haldane-derived cardiac output was used as a comparison technique because it had been used successfully by Robinson and validated with a pilot trial to thermodilution. However, the use of a simulations means that both Haldane-derived and direct measurements were compared with the target cardiac output.

The trending ability of throughflow cardiac output was analysed using four-quadrant plots and polar plots. Four-quadrant plots indicated good concordance regardless of whether oxygen uptake ratios were measured or fixed. However, the polar plots indicated much closer agreement for fixed oxygen uptake ratios: this supported what appeared to be the case when visually comparing calculated cardiac outputs to target values.

The difference between techniques will be more relevant in clinical measurements where physiological and pathological factors occur. Clinical measurements are likely to have more variation in lung gas distribution and changes of gas flow rate measurements, as a result of variations in individual physiology and pathologies. Despite this, I anticipate the effect of moderate physiological variation of left-right perfusion-distribution in human lungs would be counteracted by the likely increased breath-by-breath variation. Comparison of these different measurement options awaits testing in the clinical environment.

7.7. Mechanical Ventilatory Factors

Respiratory rate is sometimes altered to improve lung gas uptake. If the ventilation rate is changed, it might influence cardiac output measurements. Using a target cardiac output of 4 L min^{-1}, and without introducing any changes from the standard measurement and simulator setup, the respiratory rate was increased in increments of 2 breaths, from 8 to 12 breaths per minute.

No substantial changes in isoflurane or oxygen uptake rates were observed, yet the end-tidal concentration measurements increased in magnitude, with the left value decreasing and the right value increasing. This was associated with a decrease in measured cardiac output, the size of which depended on the method used for calculation. However, the change in cardiac output is not likely to result in a major change to clinical intervention.

Positive End Expiratory Pressure is used to improve oxygenation by way of increased alveolar recruitment and maintaining expansion of alveoli. Improving oxygenation in a patient will be more practical if directly measured exhaust gas flow rate measurements are used in place of Haldane-derived flow rates because it would enable an increase of oxygen concentration in fresh gas up to 100%. Prolonged periods of high oxygen concentrations in the lung are known to be associated with deterioration and collapse of alveoli. As PEEP increases, simulated cardiac output measurements using measured exhaust gas flow rate also increases, although this did not happen to Haldane-derived values. When reviewing gas uptake rates and end-tidal concentrations, it was observed that increased PEEP was associated with increased measured gas uptake rates on the left side. Increase in PEEP corresponded to an increase in estimation of cardiac output when using direct measurement of exhaust flow; this was more apparent when the oxygen uptake was estimated (rather than directly measured).

7.8. Compensation for Physiological Errors

It is well recognised that dead space increases during surgery and anaesthesia. During a clinical trial of nitrous oxide throughflow cardiac output, it was demonstrated that the throughflow technique underestimates true cardiac output in the presence of shunt (Robinson, Peyton et al. 2004). The typical method for estimating dead space is the Riley model which is based on a one-to-one relationship between the dead space for gas 'G' and measured carbon dioxide dead space. However, Peyton's 2004 model demonstrates better correction for shunt when measuring throughflow. This model was adopted in Chapter 4 which indicates that $\frac{P_{I_{Iso}}-P_{E'_{Iso}}}{P_{I_{Iso}}-P_{C'_{Iso}}}-1=1.5\times(\frac{P_{a_{CO_2}}}{P_{E'_{CO_2}}}-1)$ (Equation 33) can be used to estimate the end-tidal to end-capillary difference for isoflurane, based on carbon dioxide blood-gas concentration measurements.

7.9. Summary

Techniques for measurement of cardiac output that use the inhalation of foreign inert gases (or re-breathed carbon dioxide) can be hindered by the effect of blood recirculation on the accuracy of the method. This means they are not suitable for continuous determination of cardiac output. A collaborative effort by Vartuli, Robinson and Peyton (2002, 2003, 2004) demonstrated that delivering different inspired gas mixtures to the left and right lung and the associated throughflow of nitrous oxide, overcame the limitations of blood re-circulation.

Computer modelling by Peyton (Peyton 2004) indicates that any inert gas with a suitable pulmonary uptake rate could be used for this purposed in the place of nitrous oxide.

Isoflurane was one of the anaesthetic vapours identified by Kennedy and by Peyton as being responsive to changes in cardiac output. The challenges that were foreseen by these authors were the low inhalation concentrations (because of the physiological potency of the vapour), and the difficulty in measuring small changes in concentration and uptake rate. The problem of detecting changes in end-tidal concentration was overcome in our study by adopting the smoothing techniques described by Gan(Gan, Nishi et al. 1993).

The simulator-derived measurements presented in Chapter 6, based on the relationship between inert gas uptake and cardiac output that was modelled by Peyton(Peyton 2004), show that measurement of the throughflow of isoflurane provides responsive, and accurate cardiac output measurement *in vitro*.

Direct measurement of exhaust gas flow rates is better than using Haldane-derived flow rates for achieving reliability in cardiac output measurement. Direct measurement eliminates the reliance on nitrogen concentration measurement and the assumption of zero net lung nitrogen uptake. In clinical studies, this will remove the need to apply correction factors and problems in clinical settings where nitrogen exchange is known to occur. The Haldane-derived exhaust gas flow measurement is further affected because many commercial gas analysers do not measure nitrogen directly, and its calculation is imprecise and reliant on accurate measurement of all other respiratory gases. Elimination of the need

for nitrogen allows maximum flexibility in the choice of inspired oxygen concentration in the anaesthetised patient.

Assuming a physiologically typical ratio of left/right lung blood flow distribution ("fixed oxygen uptake ratios" in the numerator of the throughflow equations) provides better reliability in cardiac output measurement than measured oxygen uptake rates, even after incorporating prolonged smoothing windows to minimise variability from breath-by-breath fluctuation of measured oxygen variables. Although variation is expected in clinical measurements, the degree of variability observed in our steady-state simulations was surprising but indicates the variability in measurement even in a controlled environment.

The custom-designed simulator has allowed rigorous testing of throughflow cardiac output using isoflurane. The simulator could be modified to include more gases, simply by extending the stainless-steel manifold and introducing further digital mass-flow controllers if required.

The throughflow technique seems to maintain adequate accuracy and precision when changes to respiratory rate and positive end-expiratory pressure occur, and to have a similar response time to other gas-exchange methods.

A limitation of the measurement design is that real-time instantaneous gas concentration measurements are available only during their cyclic sampling by the gas analyser on each side. The requirement for two gas analysers is another limitation, as is the need for duplicate fresh gas delivery and breathing systems, but this allowed the system response time to be effectively halved.

A further enhancement of the design and technique which was not explored would be to sample gas concentrations from the end-tidal sampling position continuously, and take all measurements from this waveform. Achieving accurate measurement of gas uptake rates from tidal gas concentrations and flow waveforms is a technical challenge that can be addressed in a future development of the throughflow method for cardiac output measurement in ventilated patients.

Chapter 8 Conclusion

8.1. Thesis Conclusions

The main limiting factor for gas-based cardiac output measurement systems are the re-circulation of blood, and the need to maintain a steady mixed-venous blood gas concentration between measurements.

Isoflurane has been identified as an anaesthetic vapour that has a rapid and identifiable response to changes in cardiac output, and can predict change as well as carbon dioxide does (Kennedy and Baker 2001a).

The original nitrous oxide throughflow method(Vartuli, Burfoot et al. 2002, Robinson, Peyton et al. 2003) is an elegant solution for measurement of cardiac output; the functional separation between the left and right lungs and throughflow of nitrous oxide means that the mixed-venous blood content can be disregarded: this overcomes the limitation of blood re-circulation.

Using a model devised by Peyton (2004) to test isoflurane gas-exchange measurements, this thesis assessed the feasibility of replacing nitrous oxide with isoflurane in five *in vitro* scenarios (Cardiac outputs of 2, 4, 6, 8 and 10 L min^{-1}). These scenarios were implemented using the simulator described in Chapter 3, which provides isoflurane uptake in the left lung, oxygen uptake oxygen in both lungs, and excretion of isoflurane by the right lung and carbon dioxide by both left and right lungs. The use of digital mass flow controllers has meant that changes in cardiac output can be made quickly and easily.

This thesis has been unable to confirm the null hypothesis (proposed 1.2.1) that '*The throughflow of isoflurane (using its uptake rate and end-tidal concentration measurements) does not measure change in cardiac output as reliably as does nitrous oxide.'* Accordingly, this thesis instead shows that the alternative hypothesis (proposed in 1.2.2) is valid '*Isoflurane uptake and end-tidal concentrations allow the near-*

continuous measurement of cardiac output using gas throughflow from the left to right lung.

In vitro modelling shows that isoflurane can be utilized successfully to measure absolute and track step changes in cardiac output regardless of if direct or Haldane-derived measurement determines exhaust flow.'

Cardiac output can be derived using a combined measurement of isoflurane uptake rates and end-tidal concentrations. End-tidal gas concentration can be used as a substitute for arterial blood gas in an *in vitro* simulation where there is no lung inhomogeneity. In a clinical setting where $\dot{V}/\dot{Q}$ scatter is increased with log standard deviations of between 0.75 and 1.5, it might be necessary to apply a correction to maintain accurate measurement of cardiac output.

Modelling of this effect was done using Peyton's continuous, multi-compartmental model (2004) which showed that throughflow of isoflurane cardiac output measurement would benefit from applying a correction factor based on arterial carbon dioxide blood gas measurement. However, this correction factor is around half the size of that which was required for nitrous oxide. Without applying a correction factor to clinical measurements, and in the presence of significant $\dot{V}/\dot{Q}$ scatter, isoflurane throughflow of cardiac output will still provide good trend measurement, although absolute accuracy might be reduced.

Similar to nitrous oxide, isoflurane throughflow provides reliable trending for cardiac output measurement. However, modelling of $\dot{V}/\dot{Q}$ inhomogeneity demonstrates that isoflurane is less susceptible than nitrous oxide to physiological error from alveolar-to-arterial gradients.

The ultimate aim of all cardiac output monitoring devices is to provide continuous measurements. Throughflow of isoflurane will update cardiac output measurements after each breath. However, it may take up to 18 breaths to converge to an accurate cardiac output measurement after a step change in cardiac output.

Lengthy moving averages are required if oxygen uptake measurements are used for the calculation of throughflow cardiac output; this reduces breath-by-breath fluctuations. The use of assumed oxygen uptakes renders cardiac output measurement less variable, but in the presence of increasing positive end-expiratory pressures, it may be worthwhile to have the ability to use measured oxygen uptakes.

The throughflow cardiac output method using isoflurane can provide an accurate and precise cardiac output indicator that responds rapidly to change, is not reliant on operator skill, and can be easily measured when implementing the described system setup.

8.2. Future Research

Multiplexing of measurement points for concentrations was used to reduce the necessity of extra hardware. This introduces delays in the correct registration of cardiac output change. Two different methods that could be used:

1) Simultaneous measurement of end-tidal, fresh and exhaust concentrations (although in the current technique, that would lead to 600ml min^{-1} of loss through suctioning by the gas analysers in the system.)
2) Modification of the throughflow method, to allow the opportunity to take all measurements from the end-tidal waveform.

Investigating the elimination of fresh and exhaust sampling, and using only the end-tidal waveform may be the more practical solution. This would reduce the need for sampling across multiple points and reduce time delays, as well as gas losses from the system.

Longitudinal diffusion of isoflurane might be a source of error in throughflow cardiac output, the magnitude of this problem needs to be assessed in future clinical pilot trials. Correction for any physiological measurement error, as a result of such longitudinal diffusion, will require the development (and application) of a sophisticated airway model that includes tidal ventilation and the diffusion limitations.

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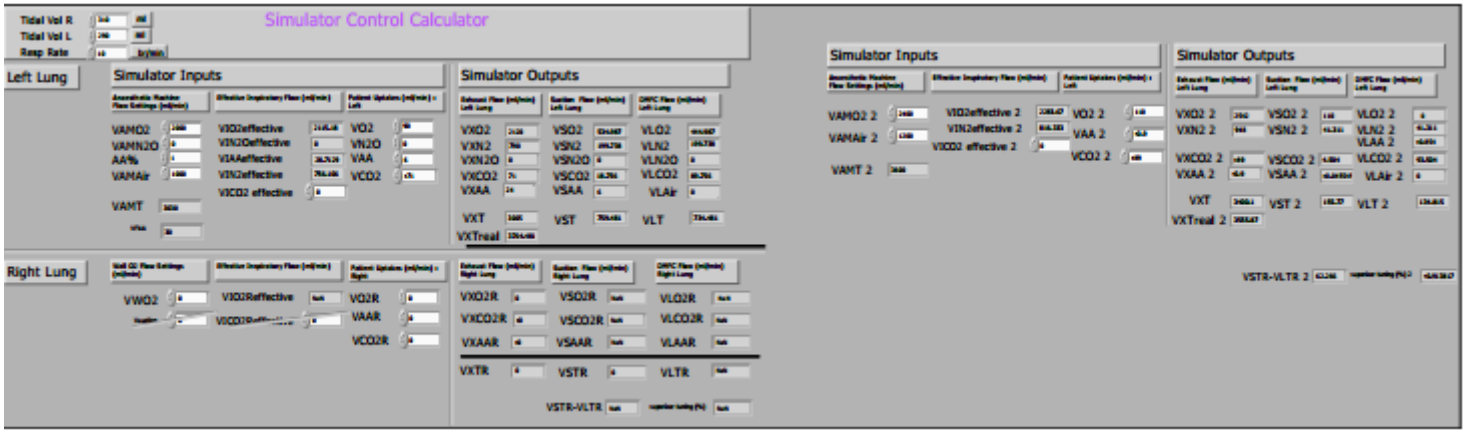
Appendices

1.1. Leak Detection

Leaks can be caused by a circuit or sample-line disconnection and inaccurate placement of the endotracheal tube. These leaks can be detected using circuit pressure, change in exhaust flow, or the carbon dioxide end-tidal waveform.

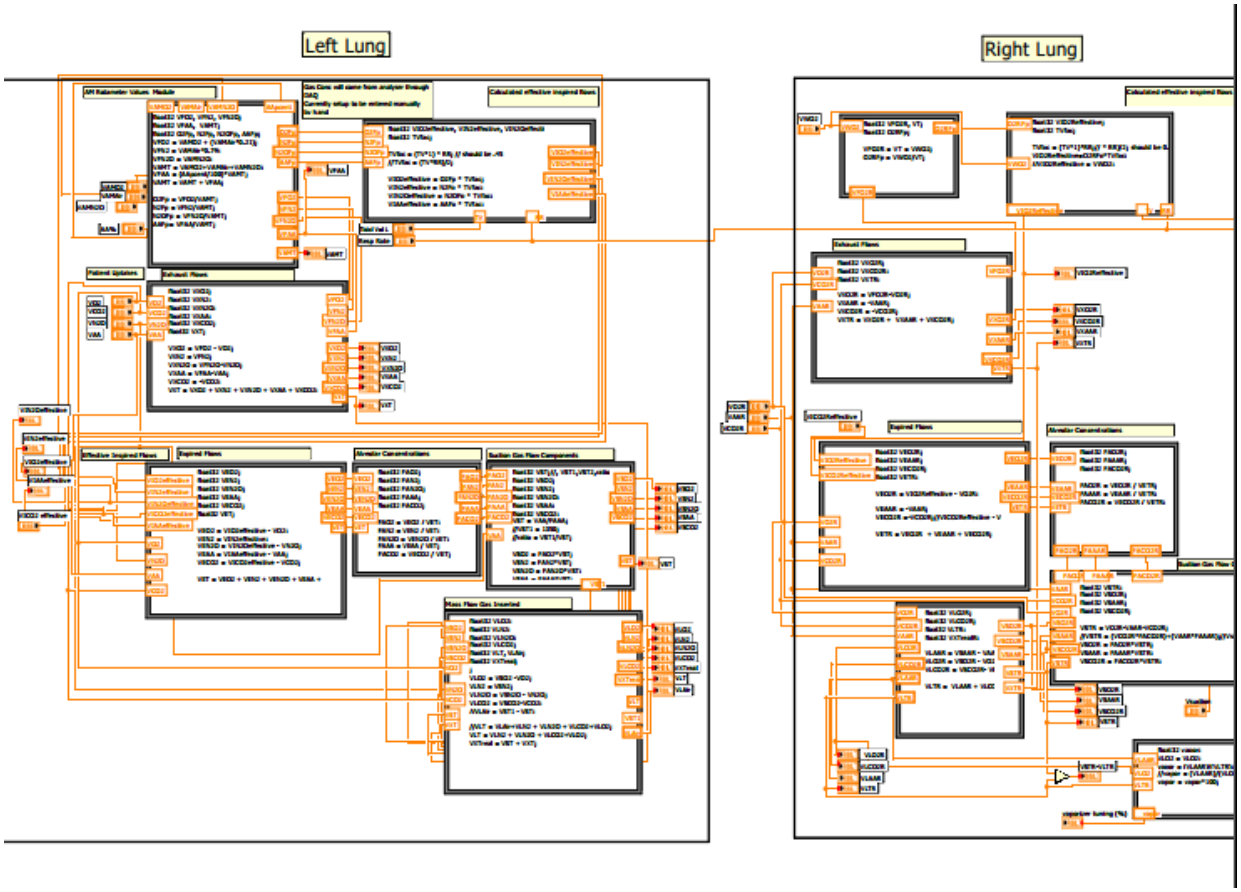
1.2. LabVIEW Code for Simulator

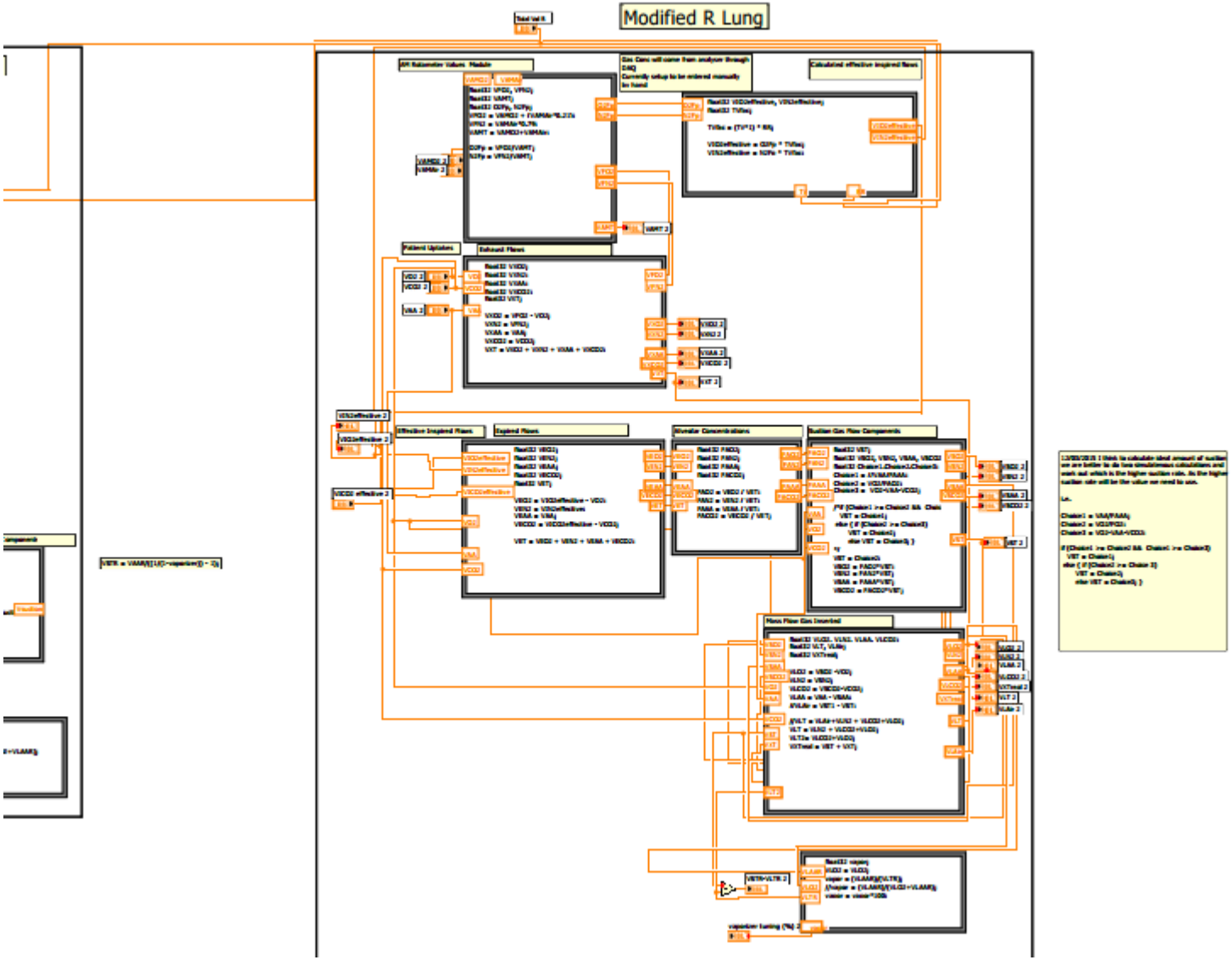
This allows the calculation of the left and right mixed suction flows, and the individual replacement gas flows an vapouriser setting.} Inputs: Left tidal volume, Right tidal volume, Respiratory Rate, Fresh gas flows rates (Oxygen, Air, Isoflurane) and target uptake gas/vapour flow rates.



1.3. Flow rate and Suction Calculator

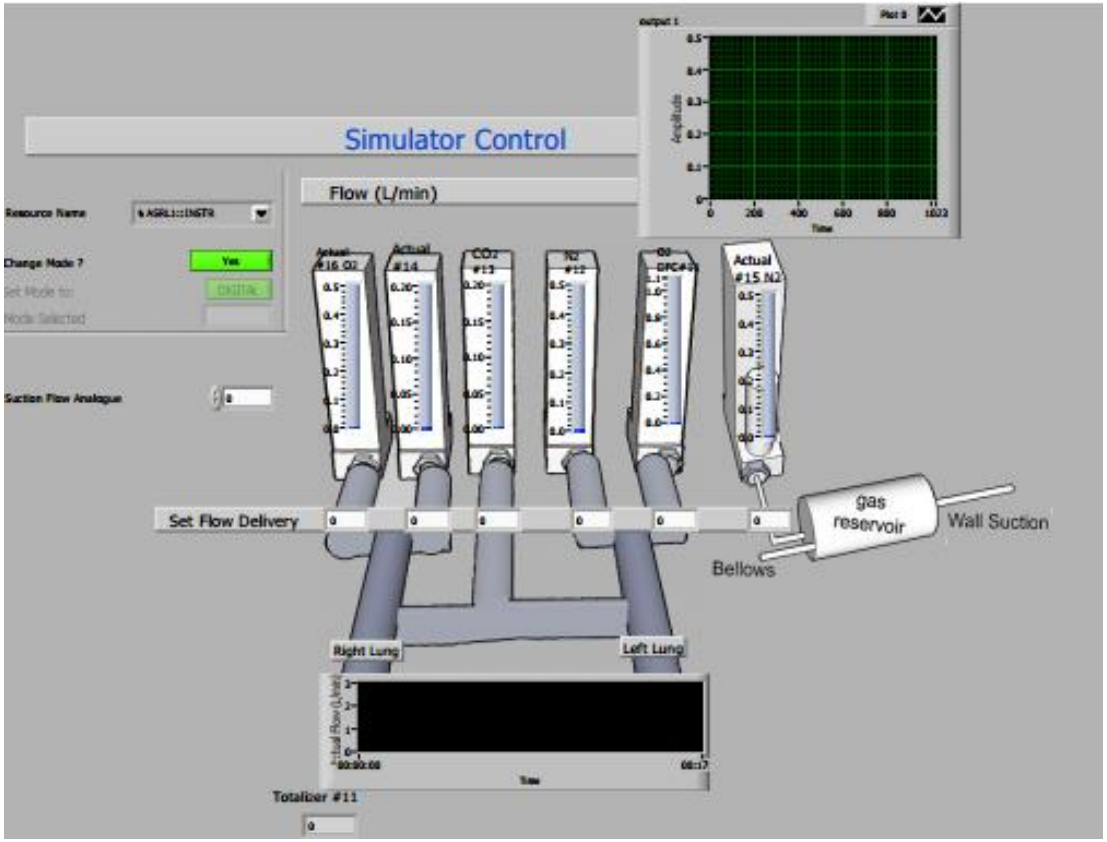
Below is the LabView code which calculates the outputs. Orange boxes indicate inputs and outputs.




Modified R Lung

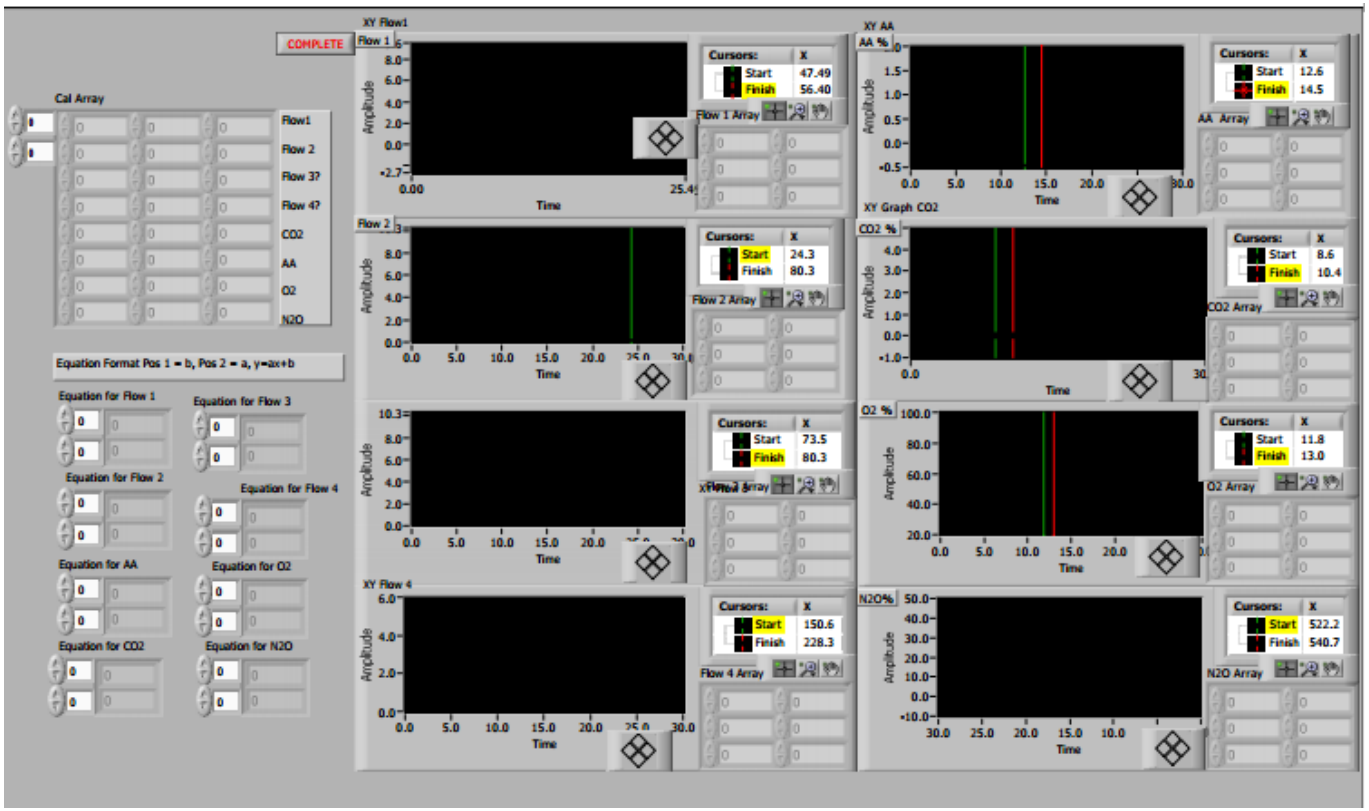
1.4. Software control of Simulator

This shows the software control for the digital flow controllers where flow rates are set, flow rates are also measured continuously and this is represented visually.



1.5. Calibration: Flow meters and Gas Analyser

The flow meters and individual gases measured by the gas analyser can all be calibrated using three points. This results of this calibration can then be used by the measurement system.

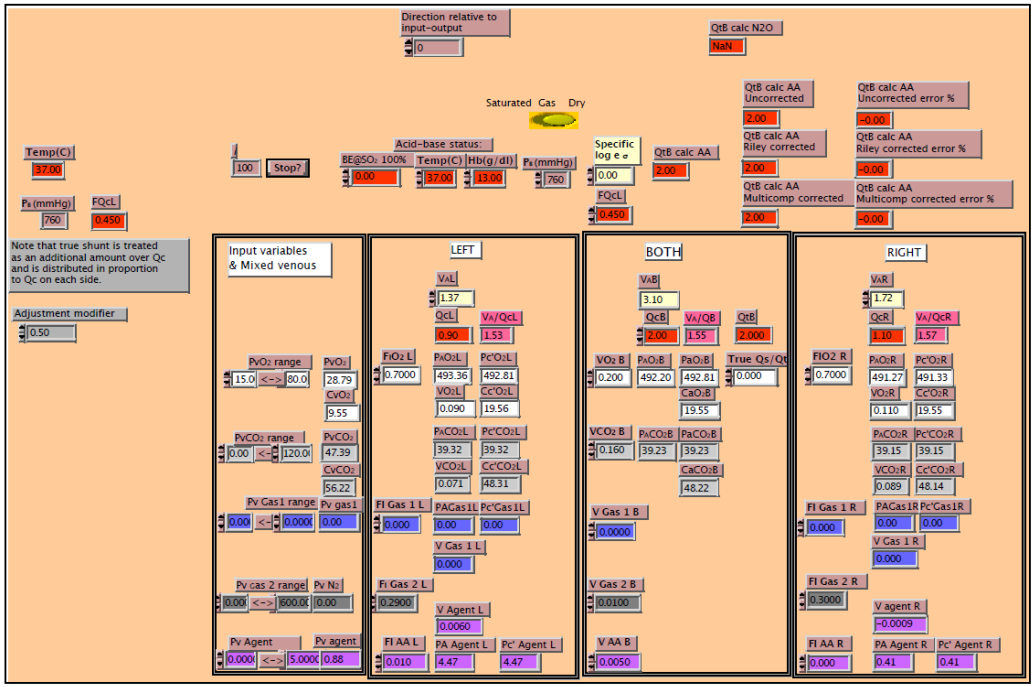


1.6. Front Panel of C.O. Measurement

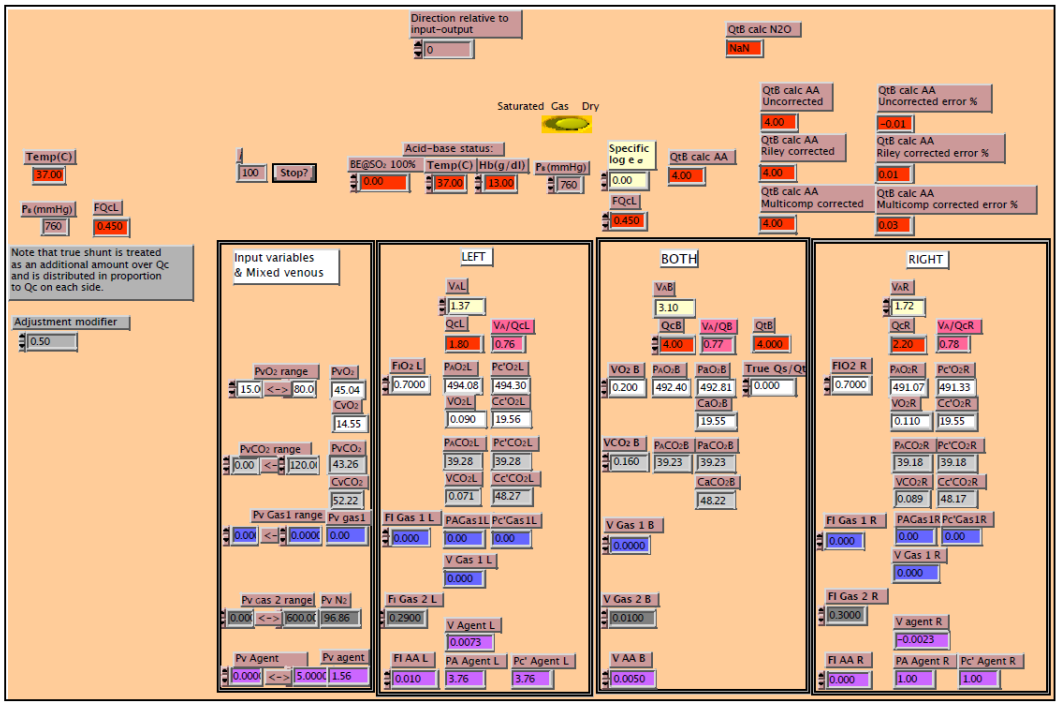
This panel shows the measurement of cardiac output calculated using direct measurement, the Haldane technique and a fixed oxygen uptake ratio. This is also accompanied by individual uptake flow rates for oxygen, carbon dioxide, isoflurane and end-tidal concentrations for isoflurane and carbon dioxide.

1.7. Scan of Scenarios

2 lung diff MIRAGE Thruflow AA.vi
Macintosh HD:Users:philippeyton1:Desktop:Rebeccå PhD:2 lung diff MIRAGE Thruflow AA.vi
Last modified on 15/7/16 at 1:34 PM
Printed on 10/4/17 at 9:14 PM



2 lung diff MIRAGE Thruflow AA.vi
Macintosh HD:Users:philipjpeyton1:Desktop:Rebeccå PhD:2 lung diff MIRAGE Thruflow AA.vi
Last modified on 15/7/16 at 1:34 PM
Printed on 19/4/17 at 10:17 AM



2 lung diff MIRAGE Thruflow AA.vi
Macintosh HD:Users:philipjpeyton1:Desktop:Rebeccå PhD:2 lung diff MIRAGE Thruflow AA.vi
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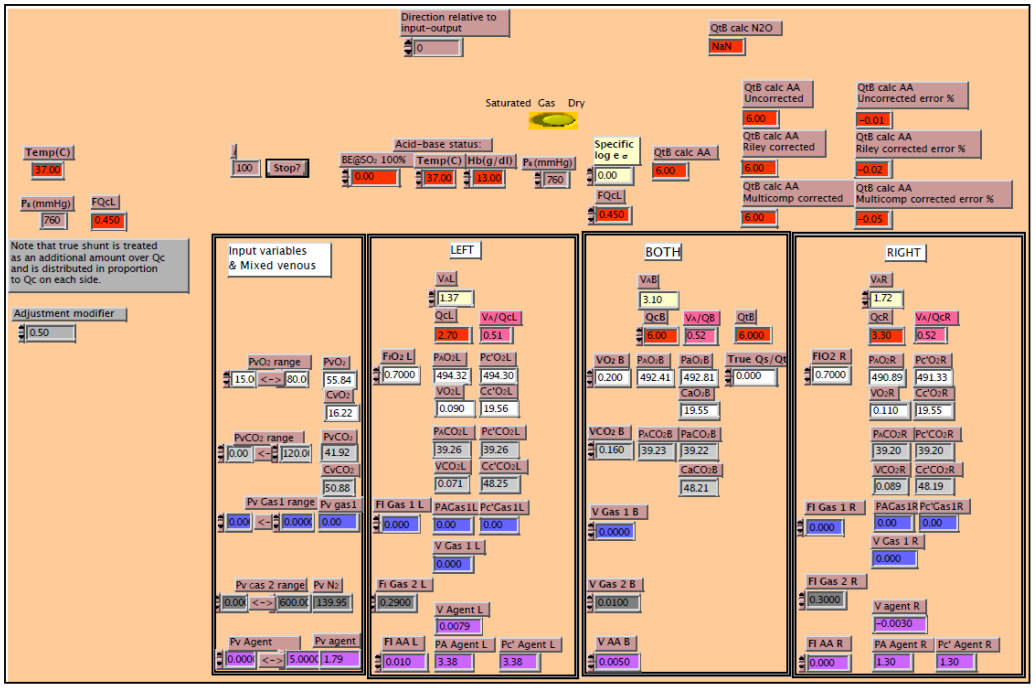

2 lung diff MIRAGE Thruflow AA.vi
Macintosh HD:Users:philipjpeyton1:Desktop:Rebeccå PhD:2 lung diff MIRAGE Thruflow AA.vi
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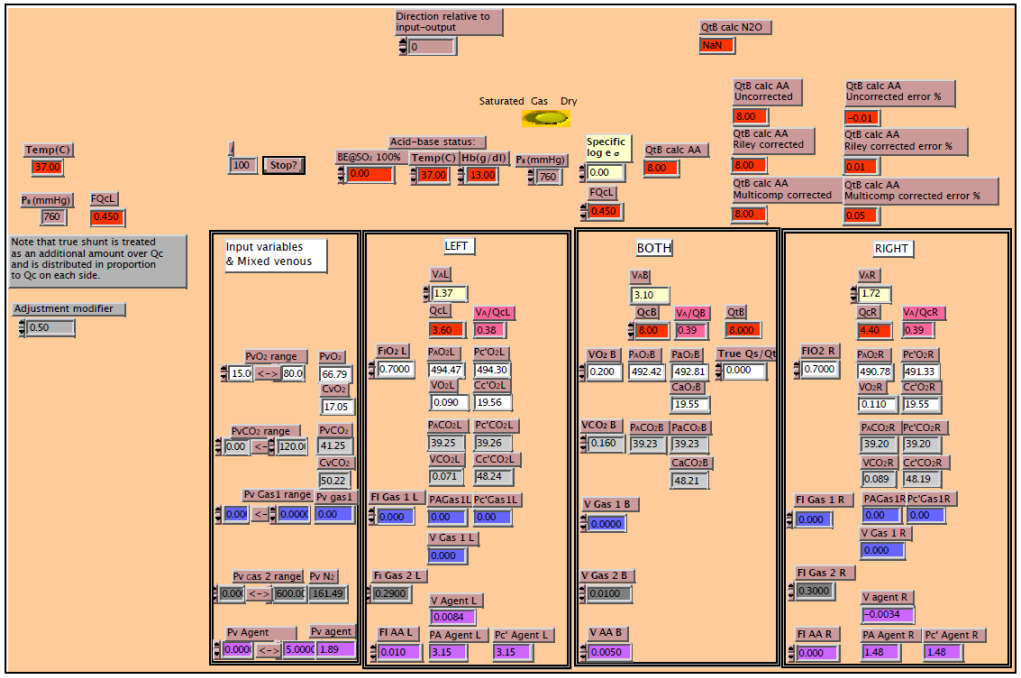

2 lung diff MIRAGE Thruflow AA.vi
Macintosh HD:Users:philipjpeyton1:Desktop:Rebeccå PhD:2 lung diff MIRAGE Thruflow AA.vi
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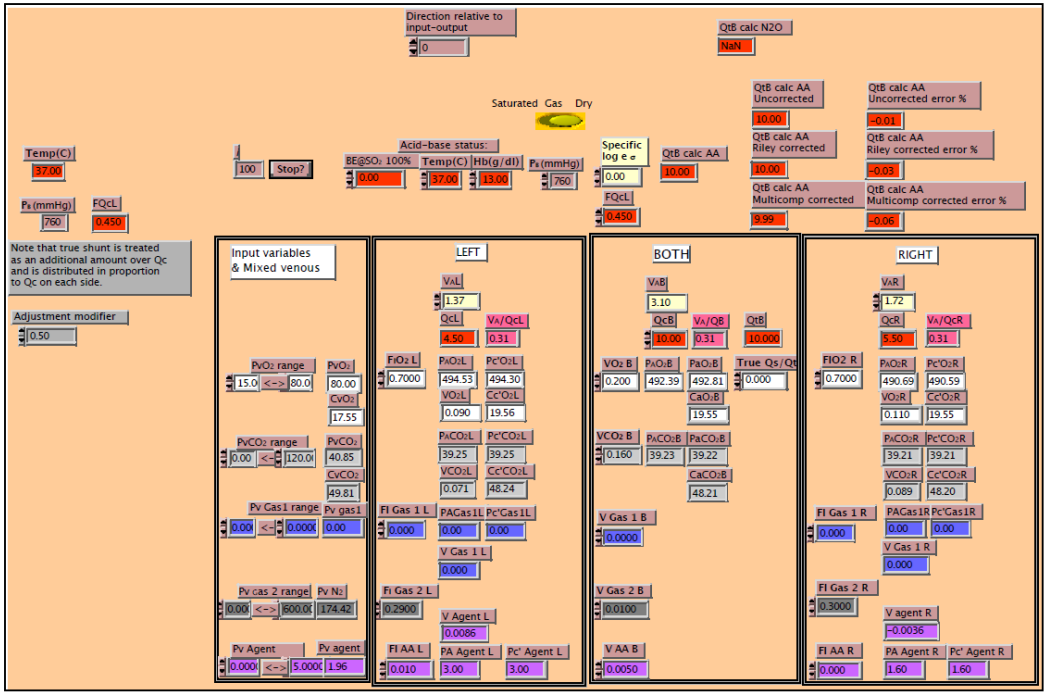

[i] Steps for Equation 41 (A-D) Error Calculations for mixed flows and gas concentrations. Calculations below are for Equation 41 A

$$z_{\dot{V}\ St.Dev.} = \sqrt{(\frac{0.106 + 0.119}{2})^2 + (0.066)^2}$$

$=\sqrt{(0.112)^2 + (0.066)^2}$

= 0.130