Evaluation of Thermodilution Catheters Using Both in-vitro and in-vivo Models

YANG, Xiaoxing

A Thesis Submitted in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy in Anaesthesia and Intensive Care

The Chinese University of Hong Kong

July 2011

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

Thesis Committee

Professor Tony Gin (Chair)

Professor Lester Critchley (Thesis Supervisor)

Professor Gavin Joynt (Thesis Co-supervisor)

Professor Irwin Michael G (External Examiner)

ACKNOWLEDGEMENTS

First of all, I would like to give my great appreciation to my supervisor Professor Critchley, who gave me the constant encouragement and guidance during the three years of my PhD study.

Then, I would like to say to my father, and my mother who has been in Heaven for three years: you are always the best for me!

I would also like to thank my fiancée Du Yingzi who has supported me for the past three years.

I would like to thank Professor Gavin Joynt, who gave me great help as a co-supervisor. I would also like to thank the great guys Dewi, Kenny and Theo who helped me with the pig experiment in the LASEC. I appreciated my colleagues Zhu Fang, Tian Qi, Li Jiawei who gave me great help and support during my research. Thanks Mak Kafai for the schematic diagram and Chen Jiangang for designing the electronic board for the vitro model.

I acknowledge the direct grant from the Medicine Panel that was used to purchase the pulmonary artery catheters and pigs.

I am also deeply grateful to all the professors and colleagues in my department. I will always remember the time we spent together during my time in Hong Kong.

ABSTRACT

Thermodilution cardiac output, measured using a pulmonary artery catheter and cardiac output monitor, is the reference standard against which all new methods of cardiac output measurement are judged. There has been a recent decline in the use of pulmonary artery thermodilution cardiac output in favour of less invasive methods. When validating these new methods comparisons are made using Bland and Altman analysis with single bolus thermodilution as the accepted reference method. 95% confidence intervals and percentage errors are generated that rely on a precision of ±20% (Stetz et al (1982)) for thermodilution measurements. However, this precision is now being questioned as it is based on data collected over 30-years ago. Lack of precision of this reference standard, and uncertainty about its true values, causes difficulty when validating new cardiac output technology. Thus, the aim of this thesis was to reappraise the error of thermodilution by testing currently available catheters in both in-vitro and in-vivo settings.

For the in-vitro model, a test rig through which water circulated at different rates with ports to insert catheters into a flow chamber was assembled. Flow rate was measured by an externally placed transonic flow probe and meter. The meter was calibrated by timed filling of a cylinder. Arrow and Edwards 7Fr thermodilution catheters, connected to a Siemens SC9000 cardiac output monitor, were tested. Thermodilution readings were made by injecting 5 mL of ice-cold water. Measurement error was divided into random and systematic components, which were determined separately.

Between-readings (random) variability was determined for each catheter by taking sets of 10 readings at different flow rates. Coefficient of variation (CV) was calculated for each set and averaged. Between-catheters systems (systematic) variability was derived by plotting calibration lines for sets of catheters. Slopes were used to estimate the systematic component. Performances of three cardiac output monitors were compared: Siemens SC9000, Siemens Sirecust 1261, and Philips MP50. After the constant rate model, I also developed a pulsatile model and did a similar evaluation.

For the in-vivo model, ten domestic pigs, weight 27-32kg, were anaesthetized with propofol and ketamine infusion. The aortic flow probe was surgically placed via a left thoracotomy. A pulmonary artery catheter sheath was inserted in the right internal jugular vein. Both Arrow and Edwards catheters were used. A 10 ml, room temperature, saline injectate was used and cardiac output was calculated using the Seimens SC9000 monitor. Sets of cardiac output readings were taken over 5 minute intervals of stable haemodynamics. Catheters were frequently changed and cardiac output increased (e.g. Dopamine and Adrenaline) and decreased (e.g. Trinitrate and Beta-Blocker) using drug infusions. Baseline (e.g. no drug intervention) and drug treatment data were analyzed separately.

Based on data from my in-vitro investigation in the non-pulsatile flow test rig, my best estimate for the random (inter-reading) error was ±10.0% (95% c.i.) for single and ±5.8% for triplicate readings and the systematic (between catheters) error was

±11.6%. Thus, the overall error was ±15.3% for a single, and ±13.0% for triplicate readings.

For the pulsatile model, the best estimate for the random (inter-reading) error (95% c.i.) was ±16.7% for single and ± 9.7% for triplicate readings and the systematic (between catheters) error was ±21.1%. Thus, the overall error was ±26.9% for a single, and ±23.2% for triplicate readings.

I set out to evaluate in the pig model two types of measurement errors, random and systematic errors, which I defined using the test rig in-vitro, the coefficient of variation (CV) was ±2.8% (95% c.i.), with random error (95% c.i.) of ±5.5%. But if the ranges of cardiac output was widened, the error was increased to ±19.3% . The systematic component of the error (95% c.i.) was ±20.0%.

There was a good linear regression relationship between the two methods (e.g. thermodilution and flow probe). The mean correlation coefficient was 0.95 (0.9-0.99, 95% c.i.) based on data from 8 pigs'. However, there were significant systematic errors due to calibration of the measurement systems between pig experiment and catheter testings. By eliminating the systematic errors based on the calibration line corrections, I was able to draw modified Bland and Altman plots for the 8 pigs. The bias was eliminated and become 0 L/min. The limits of agreement or percentage errors of this analysis, were within the ±30% limits.

When testing in haemodynamically unstable conditions (e.g. high and low flow states), the percentage error was increased by about ±15% in the treatment groups comparing with baseline group data. This finding was in agreement with the growing world opinion that thermodilution may not be as accurate as originally thought, in extreme haemodynamic conditions, such as hypovolaemia or high cardiac output states.

中文摘要

使用肺動脈漂浮導管的溫度稀釋法測量心輸出量，是評價很多新的心輸出量測量方法的標準方法。但近年來使用肺動脈漂浮導管溫度稀釋法測量心輸出量的實例卻大大減少，主要原因是由於其有創性高。也正因此，很多微創或無創的新方法湧現出來。但是這些新方法的準確性和精確性評價，仍然要依靠標準方法，即溫度稀釋法。溫度稀釋法的精確度在±20%左右。但是這個數值是來源於 30 年前的文獻，並不是很新近的結果。如果作為參考的標準方法準確度都不清楚，那麼新的要評價的方法的結果肯定也會受影響。於是，本論文的目的就是分別在體內和體外實驗中，評價肺動脈漂浮導管-溫度稀釋法這一基本方法的準確度和精確度。

在體外實驗中，我們建立了一個用膠管運載的模擬心臟迴圈的體外水迴圈模型系統，通過測量其中的水流量來評測我們的方法。我們用了兩種方法測量，一種作為標準參照，即用超聲探頭夾在膠管上來獲得流量，這個方法要通過基本的量筒測量法來校正之後，方可使用。另外一個方法就是我們要評測的溫度稀釋法。我們用了 Arrow 和 Edwards 兩種品牌的導管，和西門子，飛利浦兩種品牌的監控儀來進行測量，5 毫升冰水作為注射介質。精確度分為隨機精確度和系統精確度，分別進行測量。隨機精確度是通過一根導管，在不同流量每個取 10 組資料來進行計算得出，由變異係數來表達。系統精確度是用不同系列的導管，通過計算出每根導管的回歸線，並對其每個斜率進行比較而得出。另外，我們對不同的監控儀對精確度的影響也進行了分析。

在體外模型中，我們共用了 10 頭重約 30kg 的豬作為動物模型。豬都經全麻，然後進行左胸切開術，在升主動脈上夾上超聲探頭測出心輸出量的參考值。與此同時，肺動脈導管也經右側頸內靜脈插入到肺動脈，然後通過注入 10ml 生理鹽水來進行溫度稀釋法的心輸出量測量。我們也是用了 Arrow 和 Edwards 兩種導管，和西門子的監控儀。對於血流動力學狀況，我們要求穩定在 5 分鐘以上再進行之後的測量。我們在實驗過程中更換了不同導管，同時也用了不同藥物調高或者調低心輸出量，從而得到更廣泛的數值進行分析。

對於體外實驗，我們得到隨機精確度，在一次測量值的情況下為±10.0%，三次測量值的情況下為±5.8%，而系統精確度為±11.6%。綜合得知，總精確度在一次測量值的情況下為±15.3%，三次測量值的情況下為±13.0%。

我們同時還建立了一個搏動模型，得出隨機精確度，在一次測量值的情況下為±16.7%，三次測量值的情況下為±9.7%，而系統精確度為±21.1%。綜合得知，總精確度在一次測量值的情況下為±26.9%，三次測量值的情況下為±23.2%。

在動物模型上，我們得出隨機變異係數為±2.8%，隨機精確度為±5.5%。在更廣的心輸出量範圍裡，這個精確度會被增加到±19.3%。系統精確度為±20.0%。

超聲探頭和溫度稀釋法兩種方法的複合性非常好，從 8 頭豬的資料得出，其相關係數為 0.95（0.9-0.99,95%可信區間）。我們還通過回歸線校正之後的資料，進而排除系統誤差，得出新的一致性分析結果，其偏倚為 0，而百分誤差也在±30%之內。

當用不同藥物調節心輸出量達到高或低的水準時，我們得出的准確度比在基線水準要高出±15%。這個結果提醒我們，在臨床實踐中，對血流動力學不穩定的病人來說，其心輸出量的測量也許會存在更大的誤差。

CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

B&A	Bland and Altman
BP	Blood pressure
CO	Cardiac output
CV	Coefficient of variation
HR	Heart rate
ICU	Intensive care unit
IJV	Internal Jugular Vein
L	Litre
LASEC	Laboratory Animal Services Centre
MAP	Mean arterial pressure
Min	Minute
Ml	Mililitre
N/A	Non-available
ODM	Oesphageal Doppler monitoring

PAC	Pulmonary artery catheter
R-value	Correlation coefficients
SEM	Standard error of mean
SV	Stroke volume
SVR	Systemic vascular resistance
TD	Thermodilution
TOE	Transoesophageal echocardiography

Definitions of statistical terms used in the thesis

- Accuracy: How closely cardiac output measurements reflect the actual cardiac output.
- Bias: The offset or difference between the means of two sets of readings measuring the same variable.
- Bland and Altman plot: A method of data plotting used in analyzing the agreement between two different measurement methods.
- Coefficient of variation (CV): A measure of spread of a set of measurements of the same variable. It is a measure of variation in relation to the mean value. It is calculated as standard deviation divided by the mean.
- Degrees of freedom (df): The number of independent units of information in a sample used in the estimation of a parameter or calculation of a statistic.
- Limits of agreement or percentage error: the 95% confidence interval of the bias on the Bland and Altman plot. The percentage error is derived from the confidence intervals divided by the mean value.

- Precision: also referred to as Reproducibility, or Repeatability is defined as the ability to replicate previous readings of the same variable, such as cardiac output.

PUBLICATION

The following academic activities and publications have arisen from this research work:

Conferences attended with abstracts

(1). 20-23 March, 2010, International Anesthesia Research Society 2010 Annual Meeting, Honolulu, Hawaii, USA (Poster presentation and abstract published on Anesthesia and Analgesia).

XX Yang, LA Critchley. Determination of the precision error of thermodilution catheters by in-vitro testing.

(2). 14-16 May, 2010, 18th Hong Kong College of Cardiology Annual Scientific Congress, Hong Kong (Oral presentation and abstract published on Hong Kong College of Cardiology).

XX Yang, LA Critchley. Measurement of errors associated with using Pulmonary Artery Thermodilution Catheters.

(3). 22-25 March, 2011, 31st International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium (Poster presentation and abstract published on Critical Care)

XX Yang, LA Critchley, F Zhu, Q Tian. Performance of thermodilution catheters under control and extreme circulatory conditions in a pig model.

Publications

(1). XX Yang, LAH Critchley, G M Joynt. Determination of the Precision Error of the Pulmonary Artery Thermodilution Catheter Using an in Vitro Continuous Flow Test Rig, Anesthesia and Analgesia 2011, 112: 70-77.

(2). LAH Critchley, XX Yang, Anna Lee. Assessment of trending ability of cardiac output monitors by polar plot methodology, Journal of Cardiothoracic and Vascular Anesthesia 2011, 25(3): 536-46.

(3). Biancofiore G, Critchley LA, Lee A, Yang XX, et al. Evaluation of a new software version of the FloTrac/Vigileo (version 3.02) and comparison with previous data in cirrhotic patients undergoing liver transplant surgery, Anesthesia and Analgesia 2011, Jun 16 (Epub ahead of print).

CHAPTER 1

REVIEW OF CARDIAC OUTPUT MONITORING

1.1 INTRODUCTION

Haemodynamic monitoring and treatment of haemodynamic instability are fundamental tasks in managing critically ill patients. The measurement of blood pressure and cardiac output are important to assess the circulation and the effectiveness of treatment in patients with poor circulatory status. Cardiac output is defined as the volume of blood pumped by the heart per minute into the systemic circulation. During the past 30 to 40 years, cardiac output measurements have become increasingly used for managing the circulation of critically ill patients.

There are three well established clinical methods of measuring cardiac output:

(i) the Fick *oxygen consumption* method,

(ii) the dye-dilution method of Stewart-Hamilton,

(iii) the thermodilution method, using a Pulmonary artery catheter.

Of these, thermodilution is the technique that has been used most extensively in clinical practice. However, newer less invasive methods of cardiac output measurement are being developed, such as (i) bioimpedance (ii) Doppler ultrasound

(pre-cordial or oesophageal) and (iii) arterial pulse contour analysis. Although they have the obvious minimally invasive advantages, each of these new methods has its own individual limitations and merely provides an estimate of cardiac output that is subject to significant errors.

(i) Bioimpedance electrodes are easily applied and the method can provide continuous estimates of cardiac output but is sensitive to electrical interference and fragile signals. Also, its reliability is suspect in patients with sepsis, lung oedema, low peripheral resistance and cardiac arrhythmias (Critchley et al (2000 and 2005), Peng et al (2005)).

(ii) Doppler techniques detect blood flow reliably but require good beam focusing of the ultrasound beam on the aortic blood flow.

(iii) Arterial Pulse Contour analysis is a very applicable and minimally invasive method for measuring cardiac output in critically ill and anaesthetized patients as an arterial line is needed. Several different algorithms are used to estimate stroke volume from the peripheral arterial waveform. However, despite much effort and expense, no algorithm has proved to be totally reliable, when evaluated in a wide range of patient populations and conditions (Biancofiore et al (2009), Biais et al (2008), Mayer et al (2009)).

1.2 VALIDATION OF METHODS

The search for a reliable, accurate, continuous, safe and noninvasive cardiac output device that is simple to operate continues. Several newer methods appear promising, but for now thermodilution is still the standard clinical technique against which new techniques need to be compared. Validation studies for these newer technologies have always involved comparing readings from the new method with a reference method, usually thermodilution.

However, many of the reports on the performance and reliability of these new technologies have been conflicting and often limited by poor experimental design and statistical analysis (Cecconi et al (2007)). Thus, several authors have recently called for a consensus on how validation studies should be performed and analyzed (Linton et al (2002), Bein et al (2006)). Furthermore, there have been calls for authors to clearly state the precision of their reference method (Cecconi et al (2007)).

The thermodilution method was first described in 1954 by Fegler (Fegler (1954)), and gained widespread acceptance when Ganz, Swan and colleagues (Ganz et al (1971)) perfected the technique in the 1970s. And the catheter became known as a Swan-Ganz catheter. However, many factors can influence the precision of thermodilution and this has resulted in many investigations to determine these factors (Grose et al (1981), Runciman et al (1981), Bilfinger et al (1982), Nelson et al (1982), Pearl et al (1986), Renner et al (1993), Faybik et al (2004), Nilsson et al (2004)).

At present, all new cardiac output measurement technology is evaluated in the clinical setting against the thermodilution method. Therefore, it is surprising to find that up to date published data on the precision of "today's" pulmonary artery thermodilution catheters is not readily available. In fact, data collected and analyzed over three decades ago in the 1970s (Stetz et al (1982)) are still currently used to set the precision of the reference method in most recently published validation studies. However it would reasonable to suggest that catheter and measurement system technology has improved since Stetz et al's time and that the precision of thermodilution should have improved to less than the 13 and 22% that these authors suggested (Stetz et al (1982)). Such an improvement in precision has been also suggested in several other authors (Berthelsen et al (2002), Nilsson et al (2004)). Knowing the true precision of one's reference standard is also desirable when it comes to applying statistical methods and making judgments on the reliability of a new cardiac output method, especially when one is dealing with sizable errors of 10-20% (95% confidence intervals) in the reference method (Cecconi et al (2007)). Currently, limits of agreement or percentage errors (a concept popularized by my supervisor, Professor Critchley) of 28.4% that takes into account errors in both the reference and test methods are used in most journal articles when comparing two measurements to show the acceptability of a new device (Critchley and Critchley (1999)), and these limits are based on Stetz's 1982 estimates of precision for thermodilution of 20% (Stetz et al (1982)). However, this precision may be set too high, though it is favoured by the cardiac output monitoring industry because it helps

to justify the use of potentially inaccurate new monitors. More recent data suggests a 10% error may be more realistic value (Berthelsen et al (2002), Nilsson et al (2004)). Hence, clarification of the error of thermodilution is now needed, and investigating the error of thermodilution is the main focus of this thesis.

As suggested by Critchley (my supervisor), the percentage error of 28.4% was derived by using a standard statistical approach of adding variances (where the variance is the square of the standard deviation) (Critchley and Critchley (1999)). The precision of thermodilution readings is assumed to be 20% and the target error for the test method should be no more than 20%. The square root of $2*20^2$ gives percentage error of 28.4% and acceptance criteria of below 28.4% (Critchley and Critchley (1999)). These limits and errors are based on 95% confidence limits, or approximately two standard deviations. Many published works on cardiac output device validation have rounded up these limits or criteria to 30%, and often referred to at meetings and by the cardiac output monitoring industry as the 30% limits.

1.3 OLDER METHODS OF CARDIAC OUTPUT MEASUREMENT

1.3.1 FICK METHOD

The Fick *oxygen comsumption* method is one of the oldest methods developed for measuring cardiac output and was based on the principle described by Adolph Fick in 1870 (Fick (1870)) in which the total uptake or release of a substance by an organ is the product of the blood flow through that organ and the arteriovenous difference in content of that substance.

Although the Fick method was often referred to as the "true gold standard" in cardiac output measurement, its use in the clinical practice has been limited because of the special needs such as haemodynamic status, large equipment and so on.

1.3.2 DYE DILUTION

Whereas the Fick method used oxygen uptake, Stewart in 1897 used a constant infusion of 2.5% saline and measured the downstream concentration to determine cardiac output (Stewart 1897). Stewart's method was later modified by Hamilton to a bolus injection technique using a dye in 1928, which used the Stewart-Hamilton equation (Hamilton et al (1928)). The method involved injecting a bolus of a marker substance into a bloodstream, and then analyzing the blood for the changing level of

marker at a point downstream to obtain a time dilution curve, from which cardiac output was calculated from the area under the dilution curve and bolus dose.

The thermodilution method is a modification of the Stewart-Hamilton method that uses a volume of cold fluid. The specific gravity and the specific heat of both blood and injectate, usually cold saline, are substituted into the Stewart-Hamilton equation. Before the thermodilution was introduced into clinical practice by Swan and Ganz in 1971 (Ganz et al (1971)), dye dilution, usually indocyanine green dye, was mainly used for measuring cardiac output in the clinical setting. Other indicators have also been tested such as, (a) bromsulphalein (Mellette et al (1958)),

(b) krypton85 (Cornell et al (1961), Sanders et al (1968)),

(c) Iodine-125 (Hobbs et al (1966)),

(d) dissolved hydrogen (Klocke et al (1968)),

(e) fiber optic (Hugenholtz et al (1969)), and

(f) ether (Bachofen et al (1971)).

However, none of these indicators were shown to be better than indocyanine green dye.

The dye dilution method has been compared with the Fick method in four studies (Reddy et al (1976), Venkataraman et al (1976), Hillis et al (1985), Nanas et al (1986)). In a meta-analysis of data from these studies more than 2000 patients were

included. Good correlation was found with the agreement falling within 10% of the regression line between the two methods (Reddy et al (1976), Venkataraman et al (1976), Nanas et al (1986)). However, there is evidence to show that when the cardiac output valves are low, the variation between the dye dilution and Fick methods deteriorates (Hillis et al (1985)). However, these studies were pre – Bland and Altman era, so the Bland and Altman analysis with limits of agreement from these studies was not provided (Bland and Altman (1986)).

1.4 THERMODILUTION METHOD

1.4.1 BACKGROUND

The thermodilution method for measuring cardiac output was first described in 1954 by Fegler (Fegler (1954)) in dogs, and became widely used in clinical practice after Ganz and Swan (Ganz et al (1971)) developed it into a clinical method. The principle behind the thermodilution method is based on indicator dilution first described by Stewart in 1897 (Stewart (1897)) and later modified to a bolus technique by Hamilton in 1928 (Hamilton et al (1928)). A known amount of a cold solution, the indicator, is injected into circulation using the proximal port of the thermodilution pulmonary artery catheter and the resulting change in temperature of the blood is measured by a thermistor at the tip of catheter placed downstream of the injectate site.

1.4.2 THE PULMONARY ARTERY CATHETER (PAC)

The PAC as we know it today was developed by Swan and Ganz, in the 1970s, who used an inflated balloon at the tip of the catheter to assist passage through the chambers of the heart and placement in the pulmonary artery (Ganz et al (1971)). In addition to thermodilution cardiac output measurement, the catheter also facilitated the measurement of right heart and wedge pressures.

A standard adult PAC is made from PVC (polyvinyl chloride) and is 7.0-7.5 Fr (e.g. French gauge) in diameter. It is about 110 cm long and has markers at 10-cm intervals

from the distal tip. A thicker black maker indicates 50 cm. The PAC has three main lumens, a thermistor near the tip, and an inflatable balloon at the tip to aid placement (n.b. flow directed). The distal lumen terminates at the tip of the catheter, and is used for measuring pulmonary artery and wedge pressures, and blood sampling. A right ventricular lumen exits 20 cm from the tip and is used for fluid and drug administration, and in some catheters as a conduit for a right ventricular pacing electrode. A proximal lumen opens 30 cm from the tip and it is used for measuring central venous pressure, for fluid and drug administration, and most significantly for injecting the fluid bolus for cardiac output determinations. Positioned 3-5cm from the distal tip is a thermistor bead which connects, via a wire, to the cardiac output monitor.

1.4.3 METHOD USE TO CALCULATE CARDIAC OUTPUT

Thermodilution cardiac output measurement is based on the conservation of heat energy. The changes in temperature of the blood are analogous to the changes in colour when using the dye dilution method. Cardiac output is calculated using the Stewart-Hamilton equation which is modified for thermodilution cardiac output determination, $Q = \frac{V1\ (Tb-Ti)K1K2}{\int_0^\infty \Delta Tb(t)dt}$, Where: Q = cardiac output; V1 = injectate volume, Tb = blood temperature, Ti = injectate temperature, $\Delta Tb(t)dt$ = change in blood temperature as a function of time, which is integrated over a set-time to provide the area under the curve; K1 = density factor, ratio of the density times the specific

heat of injectate to the density times the specific heat of blood; K2 = computation constant which takes into account units in liter per minute, catheter dead space, heat change in transit, and injection rate. This variation is catheter make specific, and provided by the manufacture prior to use.

A typical thermodilution curve is shown below (Figure 1.1).

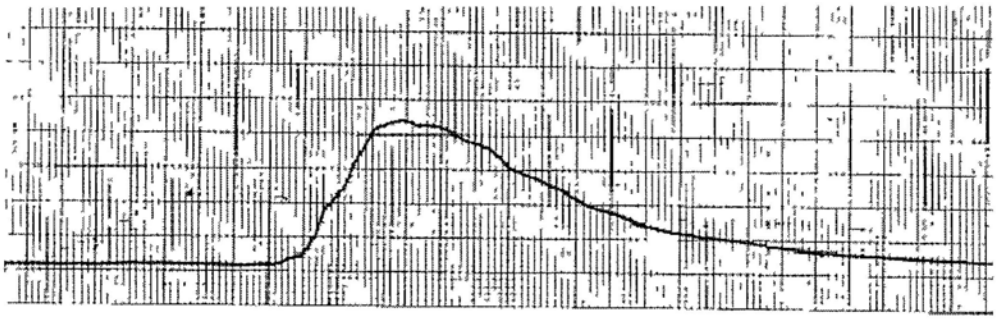


Figure 1.1. Illustration of thermodilution curve with a rapid smooth upstroke and a gradual down stroke. (Levett et al (1979)).

When compared to Fick or dye dilution methods, thermodilution is more simple to perform, as it requires only one catheter to be inserted into the subject and there is no need to withdraw blood during the measurement. Also measurements are minimally affected by the recirculation of the indicator and hence can be repeated many times, which is a problem with repeated dye dilution measurement. Any heat deficit from the cold injectate is rapidly corrected. Hence, thermodilution became the preferred clinical method of measuring cardiac output. However, use of a PAC is not without its risks, the most serious being pulmonary artery thrombosis and rupture, and sepsis (Runciman et al (1981)). Furthermore, the use of the PAC in critically ill patients on

the intensive care unit has not been shown to improve outcomes, as originally believed. A number of major clinical trials failed to show any benefit and the morbidity and mortality associated with its use was not insignificant (Connors et al (1996), Sandham et al (2003)). Today, the use of PACs has declined, and been replaced to some extent by Transoesophageal Echocardiography and minimally invasive methods of cardiac output measurement, such as Arterial Pulse Contour analysis, Doppler and the Transpulmonary thermodilution method.

1.4.4 FACTORS THAT INFLUENCE THERMODILUTION MEASUREMENT

Since its introduction in 1970's, a number of important factors have been discovered that affect the accuracy and reliability of thermodilution measurement.

a. patient position and catheter position

Positioning of the patient may affect the reliability of the thermodilution measurements, and two studies with conflicting outcomes have been published. Doering et al (Doering et al (1988)) compared readings from 51 patients using three different positions, supine, right lateral and left lateral, and found significant differences in reading between the three positions. In contrast, Grose et al (Grose et al (1981)) found that position did not affect readings. Therefore, it is unclear whether patient position affects the reliability of thermodilution measurement. Therefore, it is

recommended to use the same patient position, usually supine, to control for any possible position related variation.

b. injectate temperature and volume

There are two common choices for the temperature of the cold injectate, zero degrees using ice water and room temperature. Ice cold injectate provides a great thermal challenge (0 to 37℃) compared to room temperature injectate (22 to 37℃). When using 0℃ the amplitude of the change in the thermodilution curve is approximately twice the size of when using room temperature leading to greater accuracy. However, in the clinical setting this advantage is offset by other potential sources of error, and room temperature has theoretical advantage of reducing the effect of any temperature differences between the injectate and the fluid in the catheter dead space (Reuter et al (2010)).

Usually, the volume of cold indicate chosen is either 5 or 10 ml. Theoretically, 10 ml has a greater thermal load and thus is more accurate compared to 5 ml. However, using a larger injectate volume has the disadvantages of a longer duration of injection, more uneven delivery recirculation and increased patient cooling. Injection's time should be restricted to less than 4 seconds.

The effects on accuracy of temperature and volume of the injectate have been well described. Bilfinger et al (Bilfinger et al (1982)) found that the indicate volume (3, 5, or 10 ml) had little influence on the reproducibility of thermodilution measurement.

Shellock et al, Faybik et al (Shellock et al (1983), Faybik et al (2004)) found that room temperature was as acceptable as iced injectate in clinical practice. Some authors have suggested using a dual thermistor catheter with a second thermistor placed proximally at the exit for the cold injectate. The use of two thermistors catheter reportedly provides highly accurate temperature data requiring no correction for temperature change if a room temperature injectate is used (Berthelsen et al (2002)). The consensus view is that 10 ml of iced injectate is most accurate, but 5 ml of iced or 10 ml of room temperature injectates are also accecptable in clinical practice (Elkayam et al (1983); Pearl et al (1986); Renner et al (1993)).

c. delivery of injectate

An injection time of less than 4 seconds is normally required for thermodilution measurement by most monitors. Otherwise, cardiac output measurements will be unreliable due to poor quality thermodilution curves, which are flat and spread over many seconds. Normally, cold saline is injected manually, but this may affect timing and eveness of the curve, so automated injectors have been used. Nelson et al studied the use of automated injectors but were unable to show any advantage over manual injections (Nelson et al (1982)). However, in order to maintain the consistency of injection, the same operator should perform all the measurements.

d. dead space effect

When performing thermodilution measurements, the injectate passes down the lumen of the PAC which has a volume of 0.7 to 1.0 ml, depending on the type of catheter, before entering the blood (Reuter et al (2010)). The fluid contained in the catheter lumen is not at the same temperature as the injectate, and can vary quite considerately, however it contributes to the injected volume and is referred to as "dead space". Furthermore, the temperature of the cold indicator is affected by the temperature of the catheter and the surrounding blood, as it passes through this lumen and is warmed.

Thus, during the passage of the cold indicator from the injection site to the right artial delivery site, some degree of unquantified heat transfer will evitable occur. Since heat gain by the indicator is represented by a decrease in the temperature difference between blood and indicator, a correction factor may be drived as C=Tb-Td/Tb-Ti, where Td is the mean temperature of the injectate delivered into the right atrium and Ti is the temperature of the injectate measured just prior to injection. Forrester in 1972 first described this error and suggested a correction factor of approximately 0.82 to compensate for PAC heat loss due to dead space (Forrester et al (1972)).

Reuter et al (Reuter et al (2010)) have described three critical stages during performing a thermodilution measurement, (a) before the injection, (b) during injection and (c) after injection, where the temperature of the indicator may be affected. If one uses an ice cold injectate, each 1℃ increase in temperature of the injectate contributes to about a 3% error to the measurement of cardiac output (Runciman et al (1981)). From this aspect, using a room temperature injectate is better

because potential temperature change errors are less. However, compared to ice cold indicator, room temperature injectate has the smaller thermal signal which can also effect the accuracy of the measurement, as mentioned previously.

Of the three stages of injection, when the indicator passes through the catheter lumen, or dead space, the most significant heat transfer occurs across the catheter wall with the blood which is at body temperature of 37℃. In a standard thermodilution catheter the lumen used for cold indicator injection is about 118 cm long (n.b. 110cm is the standard length of the catheter and, 8cm is the length of the port) and about 1 ml in volume. This has a significant effect on thermodilution cardiac output measurements, as the injectate volume is 5 or 10ml and, 10-20% of the injected volume that reaches the thermistor starts in the dead space which is at a different temperature to the cold injectate. Thus a significant thermal heat energy deficit exists in the injected volume if left uncorrected which results in an overestimation of cardiac output. Kim et al (Kim et al (1980)) has described a 20%, and above, overestimate of cardiac output as a result of dead space warming. However, the potential effect of dead space is difficult to predict and can vary significantly. Thus much of the cost of manufacturing pulmonary artery thermodilution catheters is spent on ensuring a consistent dead space volume between catheters. The cardiac output algorithm built into the monitor is also modified to compensate for the dead space effect. By keeping the dead space a precise volume, errors in calculating cardiac output can be kept to a minimum. However, different makes and sizes of catheter require different individualized

correction factors that are input into the monitor prior to use. Failure to compensate for the dead space effect, which accounts for 10-20% of the injected volume, can result in a large measurement error. Therefore, in clinical practice it is widely recommended when performing thermodilution that the first reading is discarded, which standardizes the methodology and avoids further error due to temperature variations due to different resting times. When performing thermodilution measurements, it is also recommended to use the average of three to four serial readings, and to carefully inspect the thermodilution curves and reject any that are irregular in outline.

e. respiratory circle

Fluctuation in cardiac output due to the respiratory cycle produces variable readings if measurements are performed at random time points in the cycle. However, studies investigating this issue give conflicting conclusions. Some suggest that respiratory variations have an insignificant effect on data (Snyder et al (1982), Hodges (1975)), while others suggesting a clinically significant effect with cardiac output readings varying by as much as 50% (Stevens et al (1985)). This may reflect levels of intra thoracic pressure that may impede ventricular filling.

Two strategies have been suggested to overcome respiration variation. First, all the thermodilution measurements are taken at a fixed time point in the respiratory cycle. The other is to average three or more measurements which are obtained randomly. However, as using a fixed time point can be difficult to perform, the average of three

or more randomly taken readings is more widely used in clinical practice (Stetz et al (1982), Nilsson et al (2004)).

1.4.5 A STATISTICAL ANALYSIS OF AVAILABLE DATA

Precision, also called Reproducibility, or Repeatability is defined as the ability to replicate previous readings of the same cardiac output, while accuracy is defined as how closely do cardiac output determinations reflect the actual cardiac output. Both are important when making clinical decisions based on cardiac output measurements and reflect the quality of thermodilution measurements of cardiac output (Stetz (1982)). Since thermodilution has become the principle method for measuring cardiac output clinically, many experiments have been conducted to evaluate both its reproducibility and its accuracy. These experiments include (a) in-vitro experiments (bench work), (b) in-vivo experiments (animal laboratory) and (c) clinical studies. Stetz et al in 1982 reviewed a series of papers based on experiments performed in the 1960's and 1970's which defined the reliability and accuracy of the thermodilution method (Stetz et al (1982)). It is surprising to find that this data is still currently used to set the precision of thermodilution method when used as a reference in all modern day validation studies of new cardiac output monitors. Considering that in-vitro, in-vivo and clinical studies will have different results and their findings should not simply be combined together. Therefore I have reviewed and divided cardiac output validation paper published since 1970s according to study type (Table 1.1-1.3).

a. In-vitro studies

In-vitro experiments evaluating the thermodilution PACs were usually conducted in a laboratory using a bench model and thermodilution catheters. The model mimicked the circulatory flow. The actual flow rate was usually measured using timed collection by a measuring cylinder. Several studies have conducted in-vitro comparisons using different model designs (Table 1.1).

Table 1.1. List of published studies that provided in-vitro evaluations of thermodilution catheters.

Authors	Number of determinations	Reference method (Flow medium)	Injectate (temperature, volume)
Forrester (1972)	54	Actual flow from the rotameter (steady glycine)	5% dextrose (iced, 10 ml)
Powner et al (1976)	Multiple	Actual flow from the pump system	10 ml of both room and iced water
Sauer et al (1977)	Multiple	Actual flow from the cylinder (steady water)	10 ml of iced water
Plachetka et al (1981)	Multiple	Actual flow from the cylinder (steady water)	10 ml of iced water
Runciman et al (1981)	Multiple	Actual flow from the cylinder (steady water)	10ml of both ambient and iced 5% dextrose
Bilfinger et al (1982)	420	Actual flow from the cylinder (steady human blood)	3, 5, 10ml of both room and iced saline
Jebson et al (1986)	Multiple	Actual flow from the cylinder (pulsatile flow, saline and blood)	10 ml of iced 5% dextrose
Norris et al (1986)	Multiple	Actual flow from the cylinder (steady water)	1, 2, 3, 5 ml of both room and iced 5% dextrose
Mackenzie et al (1986)	Multiple	Actual flow from the cylinder (steady and pulsatile mixer)	3, 5, 10 ml of both room and iced 5% dextrose
Mihaljevic et al (1995)	576	Actual flow from the electronic flowmeter (bovine blood and saline)	10 ml of ambient 0.9% sodium chloride solution
Rubini et al (1995)	Multiple	Actual flow from the cylinder (steady water)	10 ml of iced 5% glucose

b. In-vivo studies

In-vivo evaluation of thermodilution PAC requires placement of the catheter in the pulmonary artery by catheterization of the vena cava and right heart. Most live experiments that evaluate the thermodilution method use animal models such as the anaesthetized pig or dog. The Fick method or dye dilution have been commonly used as the reference method. Otherwise a flow probe has to be surgically placed on the aorta. I found 10 such animal experiments, using the pig or dog, except for one that used albino rats and and one that used female sheep, or ewes (Lin et al (1970), Renner et al (1993)) (Table 1.2).

Table 1.2. List of published studies that provided in-vivo evaluations of thermodilution catheters.

Authors	Animals	number	Reference method	Injectate (temperature, volume)
Fegler (1957)	Pigs (11-21kg)	25	Fick method	Ringer solution(12-25℃, 1-7 ml)
Lin (1970)	Albino rats	4	N/A	Injectate (4-23℃, 0.05-0.2 ml)
Arfors (1972)	Dogs (17-27kg)	19	Fick method	Saline (room, 10 ml)
Andreen (1974)	Dogs (16-49kg)	9	N/A	5% glucose (room, 10 ml)
Sibille (1975)	Dogs (15-22kg)	Multiple	Fick method	5% dextrose (iced, 3 ml)
Sorensen (1976)	Pigs (68-72kg)	8	Dye dilution (Tricarbocyanin)	5% dextrose (iced, 10 ml)
Pelletier (1979)	Dogs (14-40kg)	17	Electromagnetic flowmeter with cannulating probe and perivascular probe)	5% dextrose (iced or room, 10ml)
Runciman (1981)	Dogs (18-20kg)	7	Dye dilution (Indocyanine Green)	5% dextrose (iced, 10 ml)
Renner (1993)	ewes	6	Electromagnetic flow probe	5% dextrose (iced or room, 5 or 10 ml)
Bajorat (2006)	Pigs (30kg)	9	Ultrasonic peri-vascular transit-time flow meter	N/A

c. Clinical studies

Since the thermodilution method was ultimately developed for use in the clinical practice, clinical trials have been conducted to confirm the efficacy of its use. Before the thermodilution method was introduced into clinical practice, only Fick and dye dilution methods were available. Thus, these two methods were used as the reference methods against which thermodilution cardiac output was validated (Table 1.3).

Table 1.3. List of published studies that provided in clinical evaluations of thermodilution catheters.

Authors	Patients	Reference method	Injectate (temperature, volume)
Branthwaite (1968)	17	Fick method	5% dextrose or saline (room, 10ml)
Olsson (1970)	17 (292 readings)	Dye dilution	Saline (room, 7.5ml)
Ganz (1971)	20 (63 readings)	Dye dilution (Indocyanine green)	A known amount of cold indicator
Forrester (1972)	20 (150 readings)	N/A	5% dextrose (iced, 10 ml)
Enghoff (1973)	17 (235 readings)	Fick method and Dye dilution	Indicator (5, 10, 15 ml)
Andreen (1974)	5 (25 pairs of readings)	N/A	5% glucose (room, 10ml)
Weisel (1975)	65 (22 pairs of readings)	Dye dilution (Indocyanine)	5% dextrose (room, 10 ml)
Hodges (1975)	21 (77 pairs of readings)	Fick method	5% dextrose (iced, 10 ml)
Venkataraman (1976)	57	Dye dilution (indocyanine)	5% dextrose (iced, 10 ml)
Saadjian (1976)	23	Dye dilution	N/A
Kohanna (1977)	10 (125 readings)	Dye dilution (indocyanine)	5% Dextrose (room, 10ml)
Vandermoten (1977)	23	Fick method	N/A
Hoel (1978)	10 (573 readings)	Fick method	Saline (room, 3 or 5 ml)
Fischer (1978)	20 (200 pairs of readings)	Dye dilution (indocyanine)	Saline (room, 10ml)

Stawicki (1979)	10 (100 readings)	Fick method	5% dextrose (room and iced, 10 ml)
Elkayam (1983)	33	Dye dilution	5% dextrose (room and iced, 3, 5, 10 ml)
Daily (1987)	34	Fick method	Saline (room and iced, 10ml)
Nilsson (2004)	80 (638 readings)	N/A	Saline (iced, 10ml)

Data Analysis

The Bland and Altman statistical method involves plotting the bias against the mean cardiac output and determining limits of agreement when comparing two methods of cardiac measurements. It has been used since the 1980's and is now considered the most appropriate analytical method of evaluating the precision of cardiac output monitoring devices (Bland and Altman (1986)). Papers studying the accuracy and reproducibility of the thermodilution technique did not always use this standard statistical approach for comparing with the reference method. So I reviewed a series of paper and extracted the data points, using the software application called DataThief 3.0 (B.Tummers, Data Thief III. 2006). Data thief is able to determine X, Y coordinates of each point and output them as an excel spread sheet file by scanning graphs from cardiac output validation studies. Twelve figures from in-vitro studies, ten figures from in-vivo studies and thirteen figures from clinical studies were included in my analysis. Bland and Altman plots were drawn to show the agreement between thermodilution and the reference method, in these groups of studies (Table 1.1-1.3).

Result

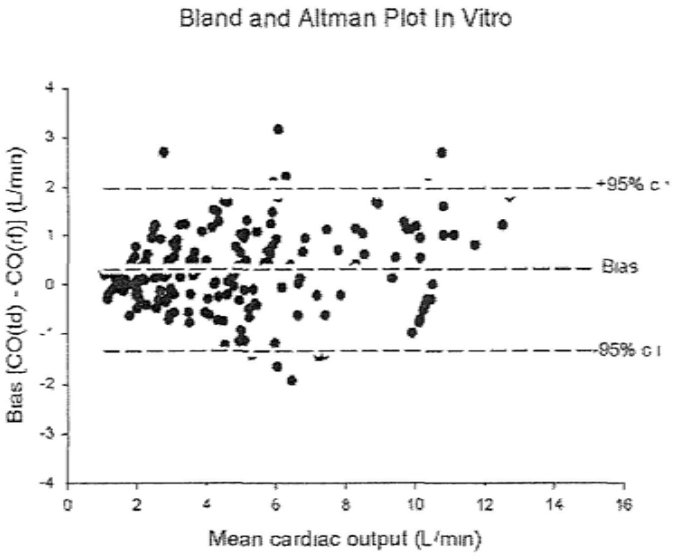


Figure 1.2. The Bland and Altman plot shows the limits of agreement of the thermodilution against reference method in the vitro studies. The percentage error was ±32.8%.

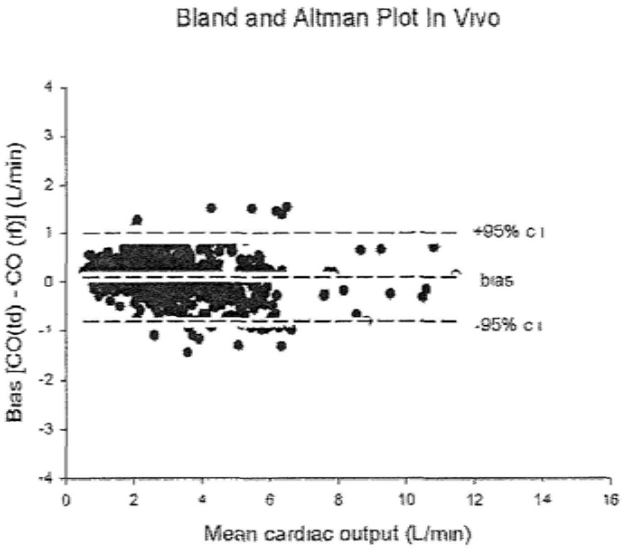


Figure 1.3. The Bland and Altman plot shows the limits of agreement of the thermodilution against reference method in the vitro studies. The percentage error was ±27.4%.

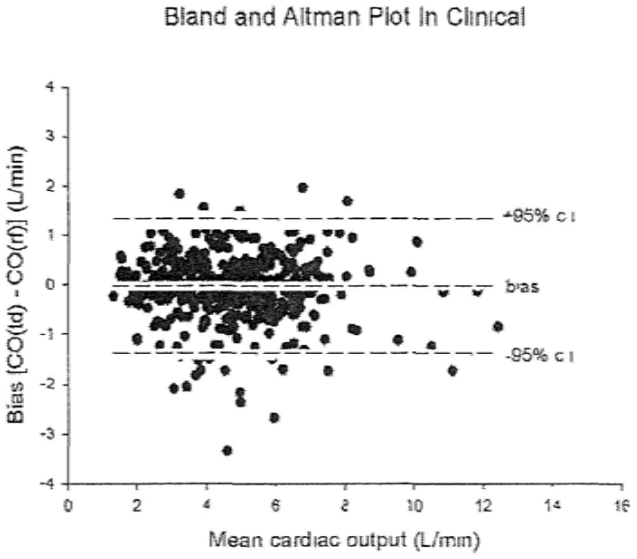


Figure 1.4. The Bland and Altman plot shows the limits of agreement of the thermodilution against reference method in the vitro studies. The percentage error was ±28.6%.

Conclusion

The studies from in-vitro, in-vivo, and clinical practice have respective characteristics. By dividing the studies into three groups and analyzing the data from three series of paper, I got the percentage errors of 32.8%, 27.4% and 28.6% for in-vitro, in-vivo, and clinical practice respectively.

There have been a series of studies looking at the characteristics of the thermodilution method since 1950s. From in-vitro, in-vivo to clinical studies, different conclusions were described. It is notable that in-vitro studies provided the worst percentage error (32.8%), despite using most accurate reference method (e.g. measured cylinder filling). Thus, in-vitro may not be as good as expected for reproducing in-vivo environments and testing thermodilution catheters. Historical data would suggest that live models are better (27.4% and 28.6%). However they do permit multiple readings test.

CHAPTER 2

ASSESSMENT OF THE PERFORMANCE OF THERMODILUTION CATHETERS IN-VITRO STUDIES

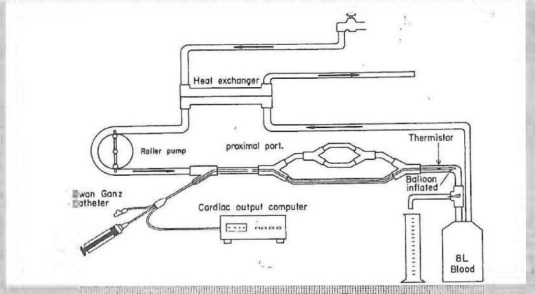
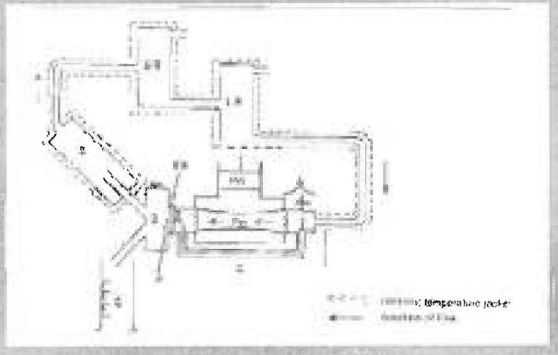
2.1 BACKGROUND

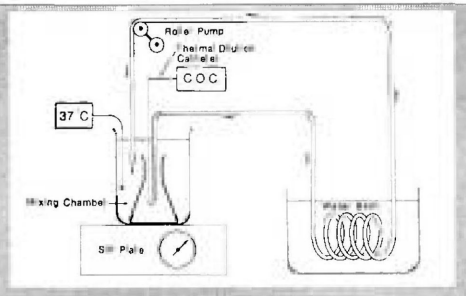
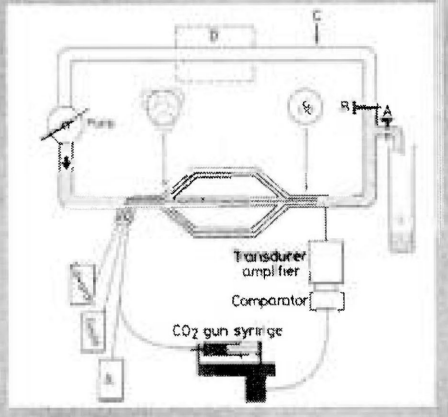
In-vitro evaluation of thermodilution PAC involves putting the catheter in some sort of laboratory bench top testing equipment that mimics circulatory flow. Flow measurement from thermodilution method is compared with the actual flow in the test rig usually measured by a flow meter or timed collection in a measuring cylinder. Several different design layouts have been described in the literature for building test rigs for thermodilution catheter testing. Designs are either constant or pulsitile flow in nature. Constant flow systems were based on either (a) a constant water pressure with flow regulator (Rubini et al (1995)), or (b) a variable speed roller pump (Bilfinger et al (1982), Norris et al (1986)). Some authors developed pulsatile systems based on (c) a piston pump system with unidirectional valves to mimic the pumping action of the heart. Such elaborate systems have been used mainly to investigate left ventricular ejection fraction catheters that use a very high response rate thermistor (Maruschak et al (1985), Santos et al (2002)). In regard to the circulating fluid, most studies were based on circulating water. Only one used human blood (Bilfinger et al (1982)) and one used glycine (Forrester et al (1972)). Flow rate was most commonly measured by timed

measuring cylinder filling. The temperature of the circulating fluid, was kept constant at 36 to 38℃ by a thermostated heater and water mixer. These different designs are summarized in the table below (Table 2.1).

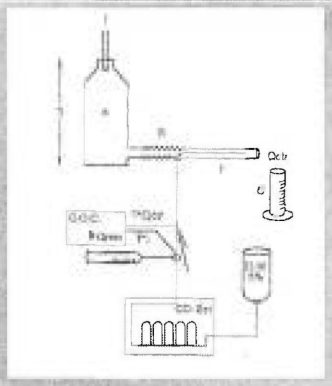
Based on the information gained from the above review of test rig designs, I will now describe the in-vitro model used for evaluating thermodilution catheter is this thesis. The main aim of this part of my thesis was to determine the true error when using currently available thermodilution PACs, with the purpose of applying this error to future clinical validation studies when setting limits of agreement, when thermodilution is used as the reference method.

Table 2.1. Summary of the different in-vitro models.

Authors and year of publication	Diagram showing schematic set-up	Brief description of each system
Bilfinger TV et al (1982)		Type of circulation: steady Power: a variable rate roller pump Fluid medium: human blood Measurement: timed cylinder filling and thermodilution
Jebson PJR et al (1986)		Type of circulation: pulsatile Power: a pulsatile pump using a piston Fluid medium: human blood diluted with normal saline Measurement: timed cylinder filling, magnetic flow meter and thermodilution

Norris SL et al (1986)		Type of circulation: steady Power: a roller-type blood pump Fluid medium: water Measurement: timed cylinder filling and thermodilution
Mackenzie JD et al (1986)		Type of circulation: steady and pulsatile Power: a sands 7400 pulsatile/constant flow pump Fluid medium: a mixture with packed red cells, polygeline, normal saline and silicone antifoam powder Measurement: timed cylinder filling and thermodilution

Rubini A et al (1995)



Type of circulation: steady

Power: a constant water pressure with flow regulator

Fluid medium: water

Measurement: timed cylinder filling and thermodilution

Santos I et al (2002)

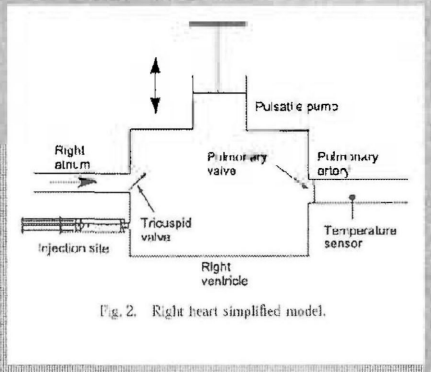


Fig. 2. Right heart simplified model.

Type of circulation: pulsatile

Power: a piston pump system with unidirectional valves

Fluid medium: water

Measurement: N/A

2.2 DEVELOPMENT OF THE TEST RIG

In this section of the thesis I described the development and design of the test rig I used to evaluate the in-vitro performance of thermodilution catheters.

My main requirements for the Test Rig were:

1. Generates stable flows from 0.5 to 10 L/min.
2. Maintains a constant water temperature equivalent to body temperature.
3. Has a flow chamber that mimics that found in human heart and pulmonary arteries that will accommodate a PAC.
4. Has a method of accurately measuring the flow rate within the rig.
5. Allows multiple catheter testing in the same test session.

2.2.1 LOCATION

Laboratory space, and in particular a bench with sink, was provide on the 6th floor, room 603 in the Li Ka Shing Institute of Health Sciences at the Prince of Wales Hospital, from January 2009 to December 2010 (Figure 2.1).

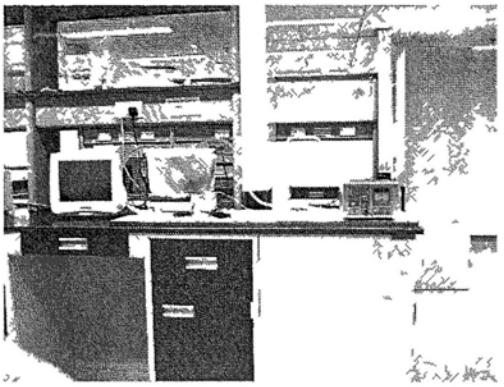


Figure 2.1. Setting for the bench study: Located in multipurpose laboratory on the 6th floor of the Li Ka Shing Institute of Health Sciences, Prince of Wales Hospital. Equipment and test rig set up on bench top.

2.2.2 DESIGN

The design of the test rig was kept relatively simple. It circulated tap water through a loop of soft plastic aquarium tubing that had an internal diameter of approximately 1.6cm. Flow rates of 0.5 to 10 L/min were generated by a constant rate electric aquarium water pump and variable orifice flow regulator. The flow remained constant and nonpulsatile at each regulator setting. The pump was placed in a 10 litre container, which acted as a reservoir to prime the pump. The temperature within the tank and test rig was kept constant at 36.5℃ by two heaters, thermostat, and water mixer (Figures 2.2a, 2.2b). An oscillating variable rate, or pulsatile pump, was also tried but easily broke down.

The flow rate through the test rig was measured continuously by an externally placed ultrasonic transit flow probe, size A16, and T106 small animal flow meter (Transonic System, Ithaca, New York, US) (Figure 2.9, 2.10, shown later). Ultrasound gel was applied to the inside of the probe housing to provide an acoustic contact with the outside of the tubing

(Figure 2.12, shown later). The probe was cleaned and gel was reapplied before each test session. However, the probe was not calibrated correctly for the thickness of the tubing wall, because it was calibrated in the factory for mammalian blood vessels which have a less thick vessel wall. Therefore, the test rig needed to be recalibrated before each test session by timed filling of a measuring cylinder (Figure 2.14, shown later).

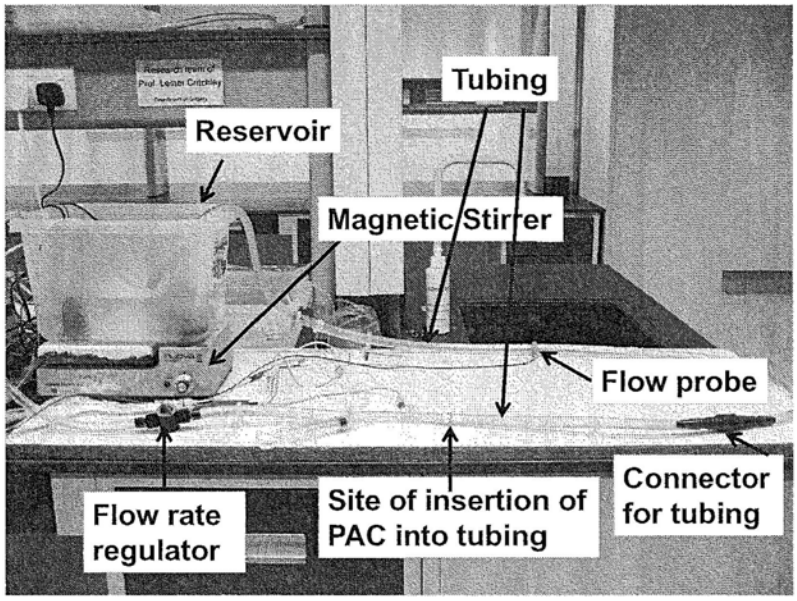


Figure 2.2a. The test rig assembled on a white wooden board and placed on the laboratory bench with sink in the background.

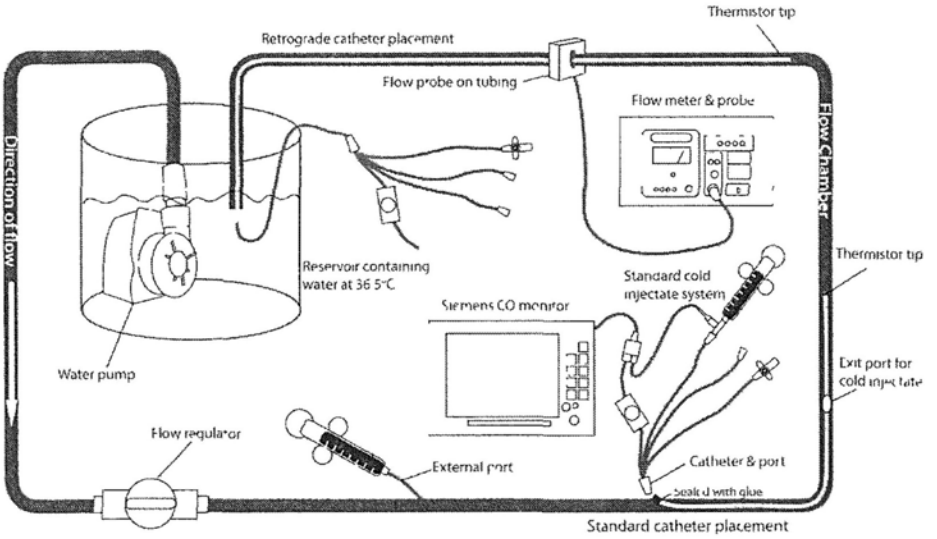


Figure 2.2b. Diagram outlining the design of the test rig. Water is circulated anti-clockwise around the rig. The water pump is placed in a 10 litre reservoir containing water heated to 36.5℃. Water is pumped at a constant flow rate through a flow constrictor, or regulator, and then into the length of tubing that forms the flow chamber. Flow in the rig is measured continuously by an externally placed flow probe. Thermodilution catheters are introduced into the tubing and flow chamber via a small puncture hole, which is sealed using glue. For retrograde (no dead-space) testing catheters are passed through the distal end of the tubing against the direction of flow, and the cold water indicator is injected into the tubing just distal to the flow regulator rather than via the catheter (drawn by Mr. Kafai Mak). The main components of the test rig are described in great detail below.

a. Water Reservoir

A simple plastic square container bought from a local shop was used. It acted as a reservoir to collect and provide an uninterrupted supply of water for the pump. Placed within the reservoir were: (i) a water pump and tubing; (ii) two electrical heaters; (iii) thermometer; (iv) stirrer a metal rotating bead placed at the bottom of the tank (Figure 2.2a, shown previously). The stirrer was used to assure an even water temperature.

b. Water Pump

A commercial aquarium water pump (SICCE, Padua, Italy) that had an open inlet turbine and connected to 1.6 cm diameter flexible outlet tubing was used (Figure 2.3). The pump was powered by the 230V AC mains supply.

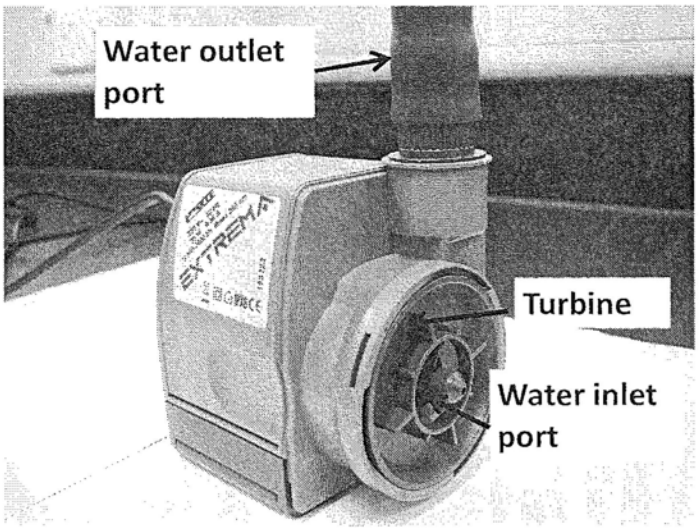


Figure 2.3. Heavy duty electrical water pump. The water in the reservoir is sucked into the inlet port and pumped out of the outlet port and circulated around the tubing system before being returned to the water tank.

When choosing a suitable pump for the test rig, pumps with different flow capacities were tested during the design stage. The SICCE pump provided a flow of 500 to 2500L/h, or approximately 40 L/min maximum flow. I found that the smaller capacity pumps (e.g. 5 L/min) were inadequate because they did not provide sufficient flow at the high end of the range. Although the pump has its own flow rate regulator, its range was limited, and it was inconvenient to use the regulator because the pump was under water. Thus I used a separate flow regulator to alter the flow rate within the test rig (Figure 2.4).

c. Flow Regulator

One difficulty with using the water pump was that its flow output was kept constant, as explained above, therefore, a flow regular, or restrictor, was included in the tubing downstream of the pump (Figures 2.4a and 2.4b). By turning the tap, which adjusted a variable orifice, the flow rate in the rig was easily controlled. At each regulator setting the flow rate in the test rig remained constant.

Figure 2.4a and 2.4b. Variable orifice flow regulator placed downstream to the pump. Flow rate was adjusted by turning the tap. The tap position was set against the reading from the flow meter.

d. Tubing and Flow Chamber

A length of clear plastic tubing, approximately 1.6 cm in diameter, was used to provide a loop that acted as a flow chamber and would mimic catheter placement in the pulmonary artery. Silicon tubing of a different diameter was used to accommodate the flow probe. This

tubing came from the cardiac by-pass roller pump used for heart operations. The reason for using this different section of tubing was that the diameter of the probe was 20 mm and to allow acoustic matching and transit of the transonic beam of the probe. All sections of tubing were linked by black plastic aquarium tubing connectors. The tubing was attached to a white hard-board base by plastic clips which prevented unwanted movement of the tubing.

The loop of tubing had several discrete sections (Figure 2.5a and 2.5b):

(i) Pump outlet hose and flow regulator,

(ii) Section that accommodated the insert of the thermodilution catheter,

(iii) Flow chamber with external flow meter including the silicon section of tubing, and

(iv) The return limb back to the water reservoir.

The flow chamber where the thermodilution detected changes in water temperature was made from a long piece of tubing that allowed uninterrupted, and laminar flow.

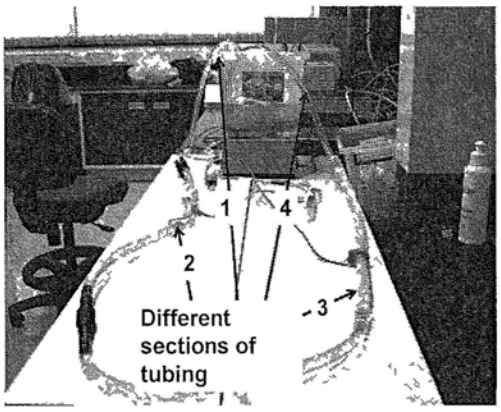


Figure 2.5a. Photograph showing the different sections of the tubing. Note the special piece of soft silicon tubing (section 3) which facilitate the external attachment of the transonic flow probe.

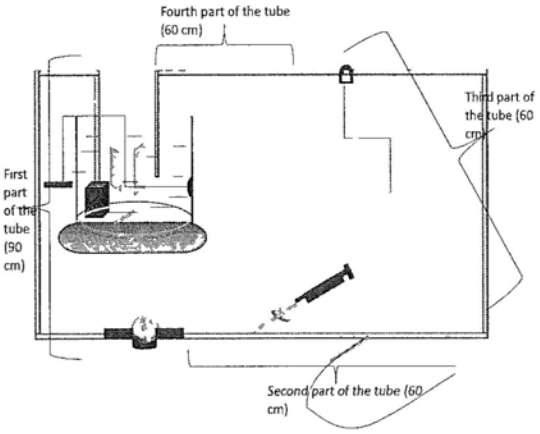


Figure 2.5b. Schematic diagram showing the different sections of the tubing.

e. Water Temperature

To mimic in-vivo temperature conditions the circulating fluid was kept at a temperature of 36-36.5℃, or body temperature. Two thermostatically controlled electrical heating elements (Easy Heater, Warsaw, Poland), designed for aquarium use, were attached to the walls of the water tank by suction cups (Figure 2.6). They were set to heat the water to 36℃ (e.g. maximum setting). An electronic thermometer was used to measure the temperature within the tank (Figure 2.7).

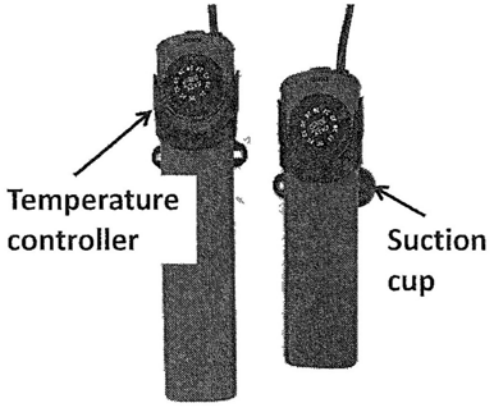


Figure 2 6 Pair of thermostatically controlled aquarium water heaters used to maintain the water temperature in the test rig

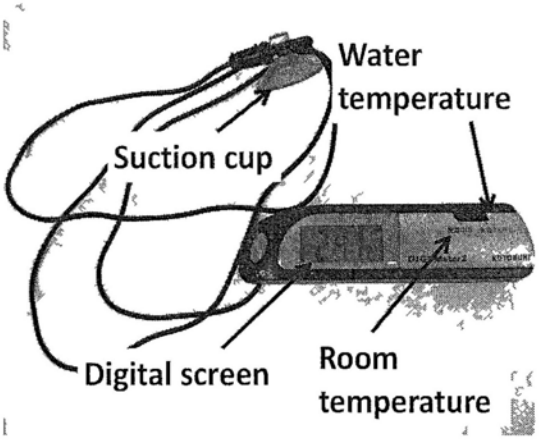


Figure 2 7 Electronic thermometer used to measure water temperature and room temperature

The water tank was placed on a magnetic water stirrer unit which facilitated mixing of the water and ensured a constant water temperature (Figures 2 8)

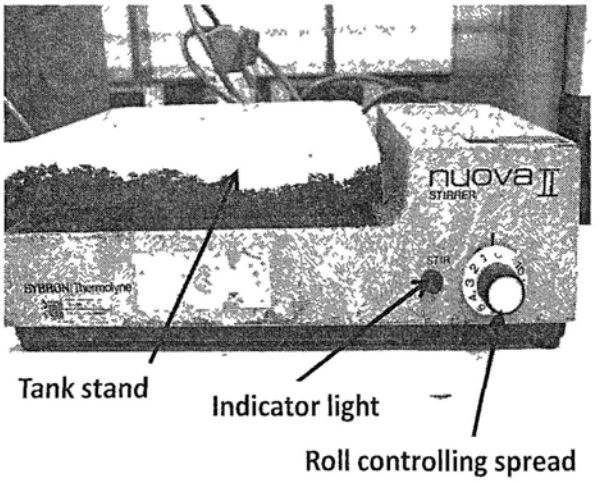


Figure 2.8. Magnet stirrer upon which the water reservoir was placed.

The stirrer rotated a metal bead that lay on the bottom of the reservoir.

f. Circulating Fluid

Tap water was used as the circulating fluid in the test rig, because it was easy to obtain and handle. Blood would have been difficult to obtain and would have been associated with many difficulties because it a biological fluid.

It was considered unnecessary in the initial stages of testing to use a biological fluid, because of the many associated difficulties. However, water does differ from blood, as blood is a non-Newtonian fluid and has a slightly lower heat capacity, 3.6 compared to 4.2 kJ/Kg/^{o}K. Such differences could affect the shape and size of the thermodilution curves.

2.2.3 FLOW MEASUREMENT SYSTEM

Flow rate of water through the test rig was determined using a Transonic flow probe placed around the soft section of silicon tubing (Figure 2.9 and 2.12). Ordinary aquarium tubing was found not to transmit ultrasound very well, so a silicon tube was used instead. The transonic method is based on the transit time of an ultrasound beam across the flow of liquid in the tubing, rather than measuring the Doppler shift frequency. The transit time increases with increasing flow rate as the beams path is deflected and takes a longer time to cross the tube. The transonic method can measure flow in aqueous, non-aerated fluids and does not require particulate content (n.b. Doppler requires red blood cells) or ionization of the circulating fluid (n.b. electromagnetic flow probes), thus my system ccould be used with tap water. The body of the A probe houses a combination of two emitting-receiving transducers and a fixed acoustic reflector. The probe was connected to a Transonic T106 small animal flow meter (Transonic System, Ithaca, NY, USA) (Figures 2.10 and 2.11). The Transonic system provided both continuous analog and digital flow readings, and had a rapid response time. The flow meter automatically identified the scaling and individual calibration factor of the flow probe to which it was connected. The Transonic system used in the study had been bought for previous animal studies involving anaesthetized dogs (Peng et al (2005 and 2008)).

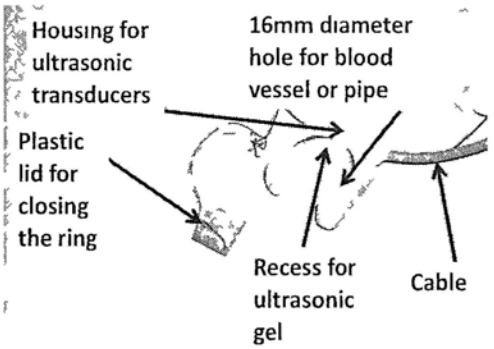


Figure 2 9 Transonic 16A flow probe

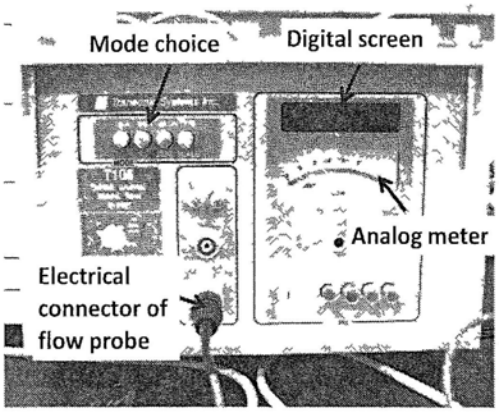


Figure 2.10. Transonic T106 single channel flow meter for use with the flow probe

The flow probe, used in my testing was 16A size with a 16mm internal diameter. It was placed around the softer piece of silicon tubing and the housing closed using a plastic lid that closed the ring (Figure 2.9). Ultrasonic gel (Figure 2.12) was applied liberally to the inner housing to ensure a good acoustic contact, once applied the gel remained in situ and the system continued to work without reapplication of gel for the duration of each day's experiment.

The probe was disconnected from test rig and cleaned at the end of each day.

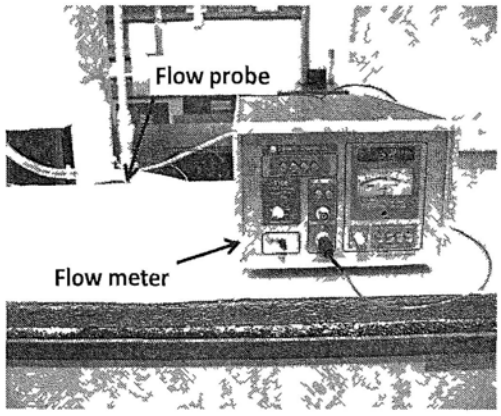


Figure 2 11 Arrangement for measuring flow in the test rig using the flow probe and meter

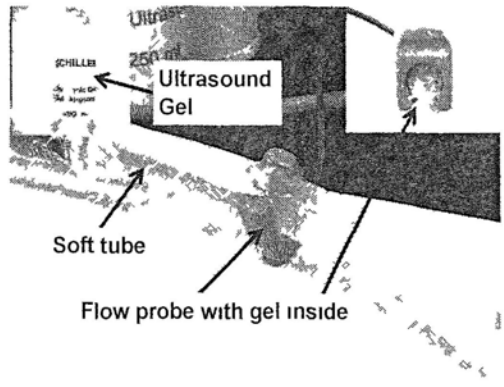


Figure 2 12 Close up of probe placement The ultrasound gel was applied to fully fill the probe housing, so that a good acoustic contact with silicon tube was achieved

2 2.4 CALIBRATION OF FLOW PROBE

The 16A flow probe was calibrated by the manufactures for use in animals, being applied major vessels like the aorta or pulmonary artery that have thin thickness vessel walls The silicon tubing used in the test rig had a significantly greater thickness which affected its calibration This is a well recognized problem when transonic probes are used in-vitro and resulted in my flow meter over reading by a factor of 1 5 times Therefore the flow meter in the test rig required calibration using timed filling of a glass flask of known capacity before each test session and after apply the probe to the tubing A 5 litre flask was used (Figure 2 13) When calibrating the test rig a steady flow rate, using the flow regulator (Figure 2 4), was

first set. The return end of loop of tubing was then redirected to fill the flask rather than return water to the reservoir (Figure 2.14). The time to fill the flask to a predetermined volume, usually 5 litre, was recorded. To calibrate the test rig a range of flow meter and flask readings were recorded and plotted to provide a calibration plot.

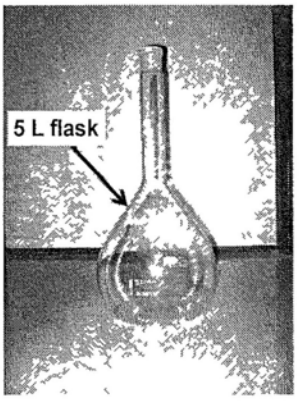


Figure 2.13. Glass flask (5 litre) used to calibrate the test rig. Makings showed the volume of liquid in the flask.

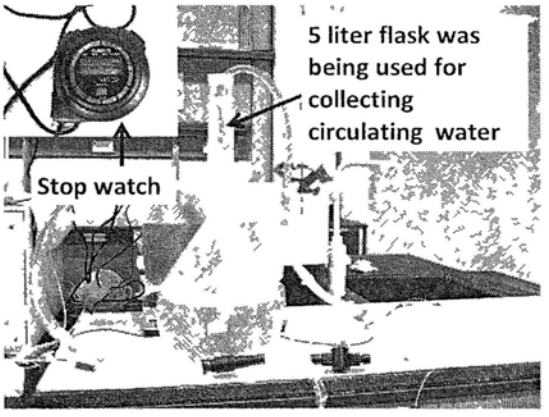


Figure 2.14. Calibration of flow probe using a 5 litre flask. Note water passing through test rig tubing is redirected into flask. The time for 5 litres to be collected is recorded using a stop watch. The flow rate shown by flow meter was also recorded.

The flask or cylinder method was considered the "gold standard" reference measurement for determining the flow rate through a test rig. However, this method was time consuming to

perform and when testing catheters, it would have been impractical to be repeatedly use cylinder measurements. Therefore, the flow meter which provided continuous flow rate readings was used but it needed to be calibrated over the working flow range of test rig (0.5 to 10.0 L/min) before each catheter testing session. A plot of the two readings, cylinder versus flow meter, was drawn to facilitate calibration (Figure 2.15).

Details of Calibration

Measurements were performed at 0.5 L/min incremental increases according to the transonic flow meter scale. One flask filling was performed for each reading. In later experiments, the incremental increase in flow was changed to 1L/min. Calibration was performed before each session of catheter testing.

Results

A range of flows from 1 to 10 L/min measured at 0.5 L/min intervals (shown by the flow meter) were plotted on a regression plot. In the example (Figure 2.15), despite good correlation ($r=0.99$; $P<0.0001$), there was poor agreement between the two methods. In this example the regression line was $Y = 1.540X - 0.237$, where Y = flow meter reading and X = timed cylinder reading, and the line deviated from the line of identity (i.e. $Y = X$). Thus, there was a significant gain in the flow meter readings of 1.54 fold. Therefore, the flow probe and

meter needed calibration before each use, and a correction factor derived from the slope of the regression line was used.

Precision of readings

Having determined the calibration constant for the flow meter, its accuracy and repeatability after calibration were evaluated.

The accuracy of individual flow meter readings (after correction for the offset in the calibration of the flow meter) was determined by using a modified Bland and Altman method (Bland et al (1986)) (Figure 2.16). The repeatability over time of the flow meter system readings was shown by comparing the plots of flow meter readings against cylinder collection time after 1h and 2h (Figure 2.17).

The bias between pairs of readings after correction was -0.0003 L/min and 95% confidence limits were -0.10 to +0.10 L/min (Figure 2.16). Based on a mean test rig flow rate of 4.0 L/min (i.e. cylinder range 1-7 L/min), the percentage error between the flow meter and the cylinder methods was ±2.5% (i.e. (0.10/(4.0)*100). Therefore, the errors in the cylinder and flow probe methods were less than ±2% (i.e. adding variances: 2.5% = $\sqrt{(\text{cylinder}^2 + \text{flow meter}^2)}$), which is keeping with previous estimates for the precision of the Transonic flow probe of ±1-2% (Bednarik et al (1995), Dean et al (1996)). There was no discernable difference between the two plots after 1h and 2h. Similar results were obtained after 3, 8 and

12h. Therefore, the calibration of the test rig was not expected to change significantly during each test session which could take many hours.

However, I did find between test sessions, when the flow probe was removed, cleaned and then reapplied, that the calibration of the test rig did alter (i.e. change in the slope of the calibration line). Thus, the correction factor needed to be re-determined every time before each new test session.

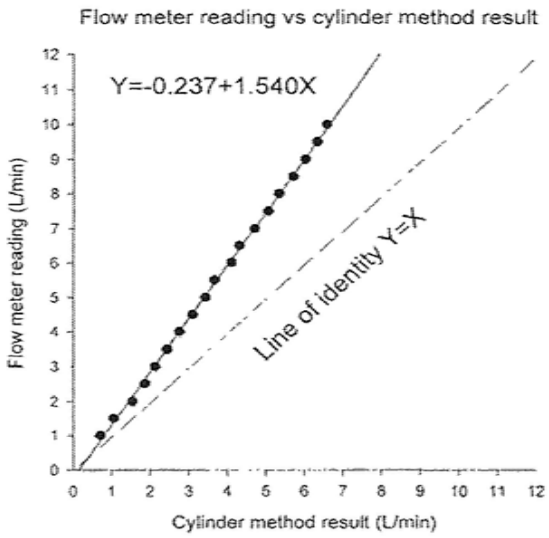


Figure 2.15. Regression line plot showing linear relation between the flow meter and cylinder. However, there is a significant deviation from the line of identity (Y = X) and the slope of the regression line on this day was 1.54, which was used to calibrate the test rig.

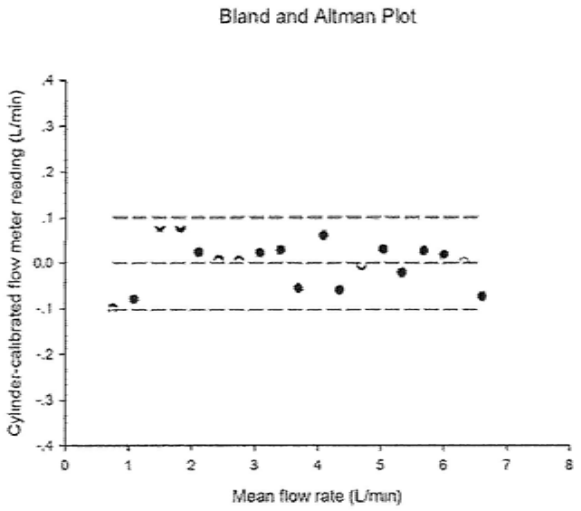


Figure 2.16. The modified Bland and Altman plot shows accuracy of the flow meter against cylinder after corrected using the 1.54 correction factor. The agreement between the two methods was ±2.5% (i.e. (limits of agreement (0.10/mean flow 4.0))%).

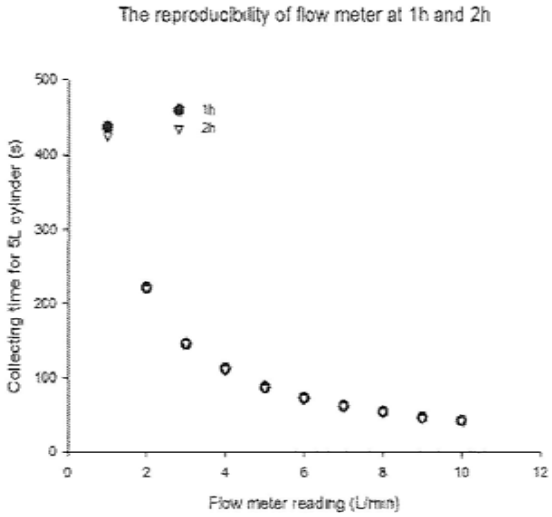


Figure 2.17. Plot showing the hyperbolic relationshi between the collection time and the flow meter (Reproducibility is shown by coincidence of data points at 1h and 2h. (Note that filled dots (1h) and open inverted triangles (2h) are superimposed)).

2.2.5 EQUIPMENT USED FOR THERMODILUTION MEASUREMENTS

Two well known brands of thermodilution PAC are currently used worldwide and were available in Hong Kong, the Arrow (Arrow Int., Teleflex Medical, Reading, PA, USA) (Figure 2.18) and, the Edwards Swan-Ganz (Edwards Life-sciences, Irvine, CA, USA) (Figure 2.19).

Standard triple-lumen 7Fr catheters were used. More sophisticated PACs are manufactured for measuring continuous cardiac output and mixed venous oxygen saturation. These catheters were not used due to their expense. A standard 7Fr thermodilution catheter costs around 500 HK dollars each, whereas these more advanced catheters cost from 1500 to 2000 HK dollars.

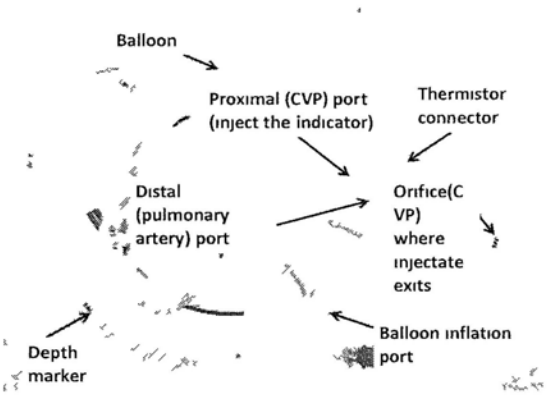


Figure 2.18. Arrow thermodilution PAC (7 Fr, 4 lumen).

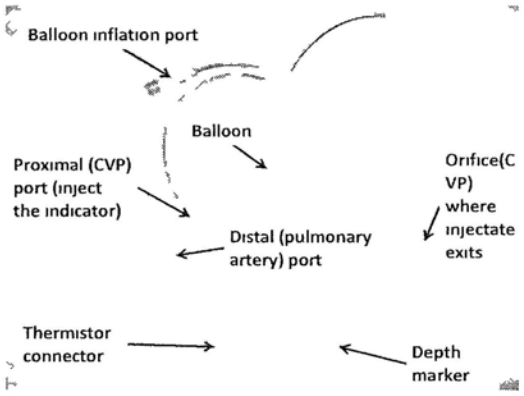


Figure 2.19. Swan-Ganz (Edwards) thermodilution PAC (7Fr, 4 lumen).

The performance of these thermodilution PACs were first assessed using a Siemens SC9000 monitor with attached cardiac output module (Siemens Medical Systems, Inc., Danvers, MA, USA). Thermodilution cardiac output measurements were made by injecting 5 ml of ice-cold saline using a standard PAC cooling coil and temperature measuring kit (Viggo-Spectramed Pte. Ltd., Singapore). The performance of two other cardiac output monitors was later assessed, the Sirecust 1261 (Siemens Medical Systems, Inc., Danvers, MA, USA) and the IntelliVue MP50 (Philips Medical Systems Inc., Andover, Massachusetts, USA) (Figure 2.20).

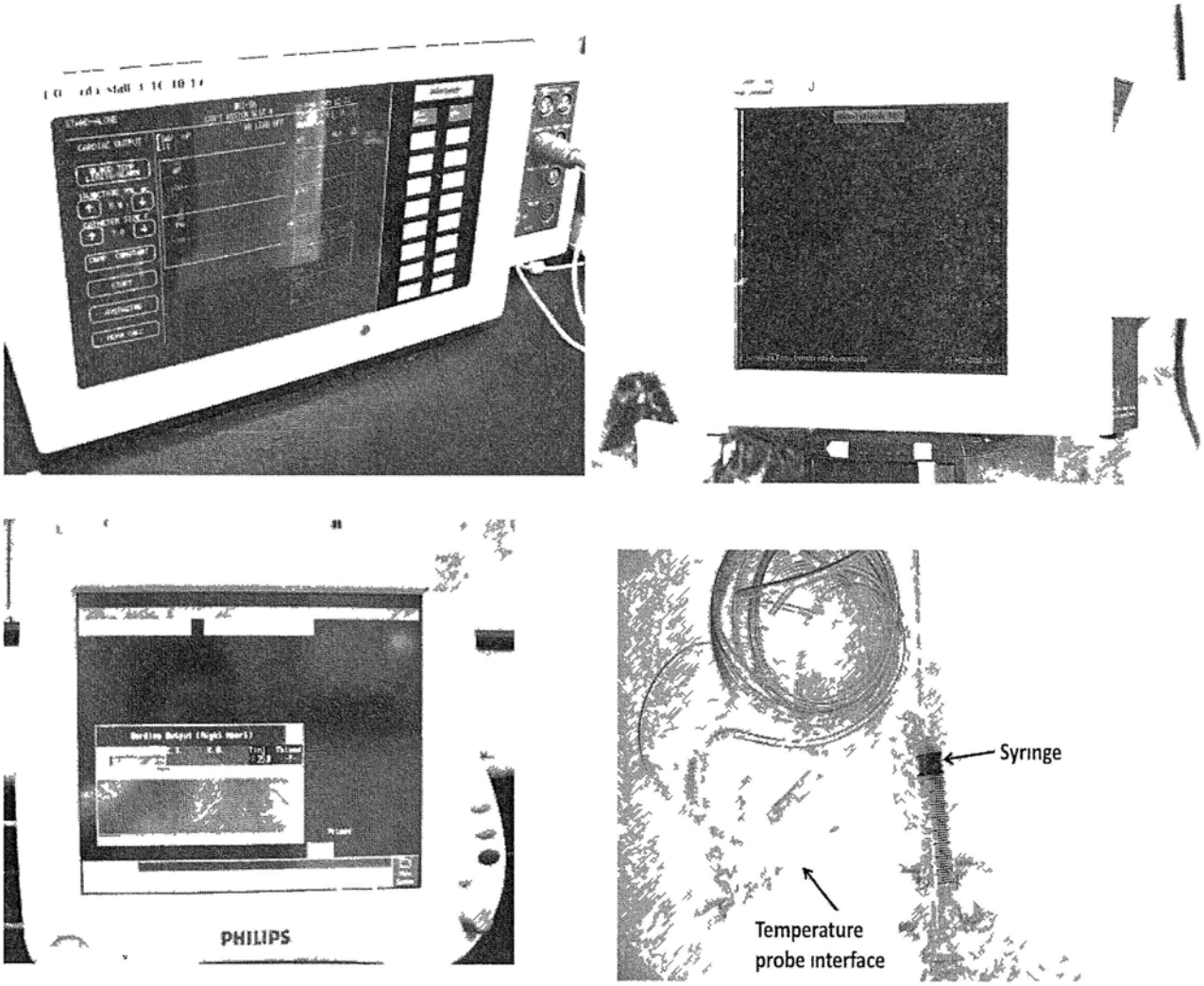


Figure 2 20 Photographs showing the three monitors and cooling coil used in the thesis Top left shows the front of the Siemens Sirecust 1261 monitor Top right is the Siemens SC9000 monitor and bottom left is the Philips IntelliVue MP50 Bottom right shows the standard cooling coil and disposable delivery system, injectate set with temperature probe interface

2.2.6 PERFORMING THERMODILUTION MEASUREMENT

When performing a thermodilution measurement, cold tap water (indicator) was injected into the flowing water of the test rig with the catheter tip thermistor downstream of the injection

site. The injection site varied depending on how the PAC was placed in the testing. Boluses of either 5 or 10 ml ice-cold (0℃ to 4℃) water (indicator) were injected. The PAC was connected by a cable to the monitor, which plotted and measured the area under the curve of temperature change detected by the thermistor at the catheter tip. Two methods were used to place the PAC within the test rig, and this affected the site where the cold indicator was injected either via the catheter central venous port (classical method) or directly into the flowing water (retrograde method).

Classical Method

Classical placement with the cold indicator being injected via the proximal central venous pressure (CVP) port of the PAC catheter and entering the flow chamber upstream to the catheter tip and thermistor. The catheter was introduced into the lumen of the test rig tubing via a small puncture hole made in the tubing wall (Figure 2.22).

To prevent water leakage, the puncture hole with catheter in situ was sealed with silicon glue prior to each testing session. The glue took 4 to 5 hours to dry. Thus, when using this classical catheter placement method only one catheter could be tested on any one day. Thus an alternative method of catheter placement was needed for multiple PAC testing.

Retrograde Method

Retrograde placement with the indicator being injected via a separate injection port glued into the tubing upstream of the catheter tip was used for multiple PAC testing (Figure 2 21) The PAC was now introduced into the test rig via the open distal end of the flow loop tubing as it returned water back into the 10 litre reservoir tank Thus, there was no need to puncture the tubing and wait for the silicon glue to dry, every time a different catheter was tested

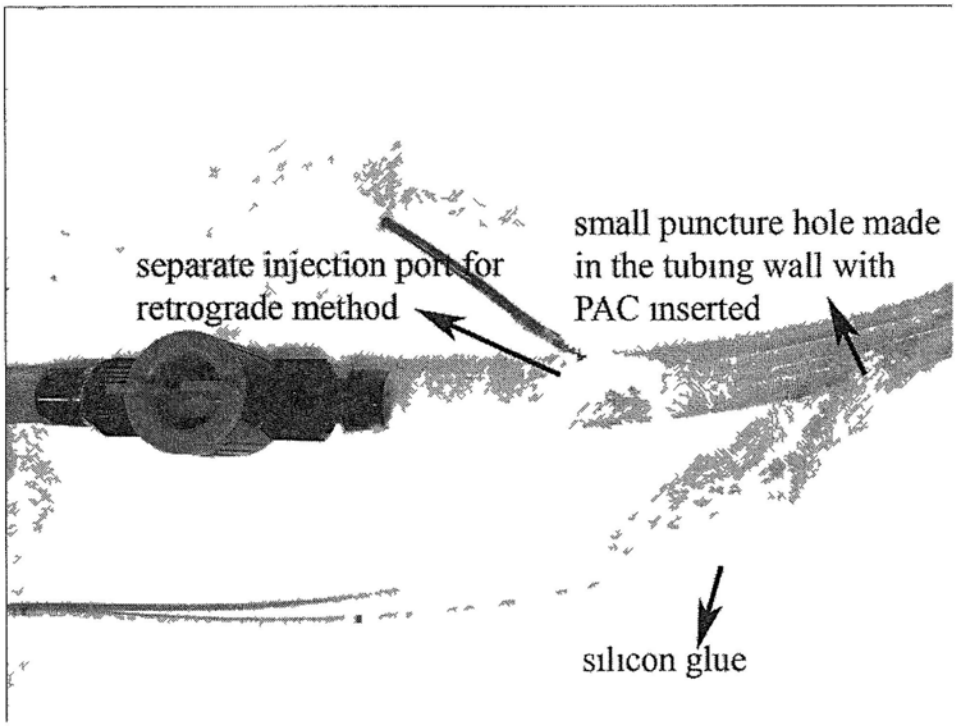


Figure 2 21 Section of the test rig that accommodates (a) the insertion of PAC via puncture hole which was sealed with silicon glue and (b) the retrograde method injection port, which was a proximal port taken from a PAC glued into the test rig

However, the use of the retrograde placement method created a very significant issue when testing catheters, as the dead space through which the injectate normally passed before

entering the flowing water was by-passed. The dead space of thermodilution PACs is part of the injection port that lies within the length of the catheter. Significant and unpredictable heat gain to the injectate volume occurs in this dead space. This issue has been discussed previously in my thesis (Chapter 1, review section). To minimize the dead space effect the catheter was flushed with cold water before injecting the main indicator. A number of experiments were performed in my thesis to specifically look at the effect on accuracy and repeatability of the presence of catheter dead space.

In clinical practice, the thermodilution PAC needs to be positioned in the pulmonary artery usually via a right internal jugular vein puncture approach (Figure 2.22). By inflating the balloon at the catheter tip (e.g. like a sail of a boat) it is taken by the blood flow through the chambers and values of the right heart into the pulmonary artery. Changes in vessel pressure measured from the tip of the catheter provide a guide to the position of the catheter tip, as it passes through the heart. The catheter can be used to measure pressures with the balloon deflated (PA pressure) or inflated (wedge pressure which reflects left atrial pressure). By injecting a bolus of cold saline into the right atrium via the proximal CVP port and measuring the temperature changes at the tip, cardiac output is also measured.

In the test rig the catheters were tested under steady-state constant flow conditions, whereas circulating blood flow is pulsatile (i.e. pumping action of the heart). Furthermore, the

injectate is mixed with blood by filling and emptying of the chambers. In the first instance it was much easier to design a test rig that generates constant flows. The rig was later modified to generate pulsatile flow conditions, but with limited success. However, in order to simulate the human condition, the water temperature was kept constant at 36.5℃, and flow rates were chosen of 1 to 10 L/min which reflected the normal range for human cardiac output. However, thorough mixing of the injectate could not be simulated.

The shape of the temperature-time curve from the cardiac output monitor is of great importance and was inspected for acceptability after each measurement. The thermodilution curve should be smooth and characterized by a rapid rise to a peak and a slower return to baseline (Figure 1.1 in the review). As the temperature changes are small, less than 1℃, variations in blood temperature that synchronize with the pumping of the heart and normal respiration may contribute to some extent by causing irregularity of the curves but this does not generally alter the overall shape. However, irregular looking curves should be discarded since they are not reliable and are known to be caused by (i) inadequate mixing of the injectate, (ii) contact between the wall of the vessel and thermistor, (iii) rapid changes in heart rate or blood pressure, (iv) movement, and (v) abnormal respirations. In my experiments with the test rig, data was discarded if the thermodilution curve lacked on inspection a rapid upslope and a smooth downslope.

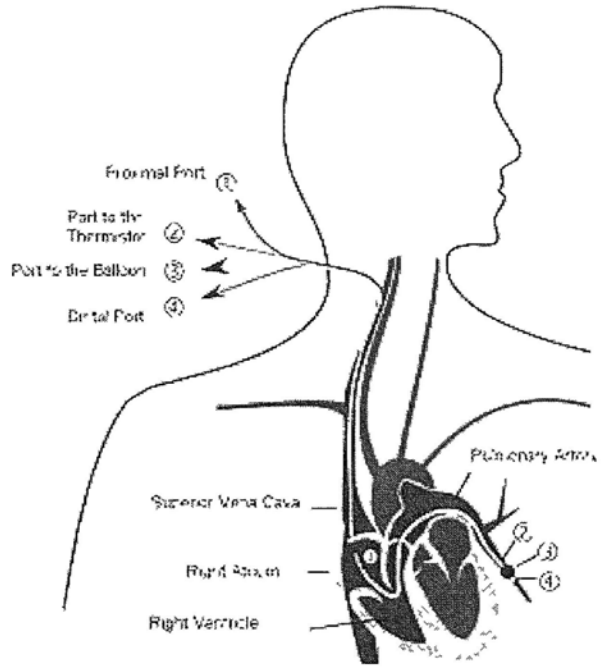


Figure 2.22. Schematic diagram showing the position of the PAC in the great vessels and chambers of the heart. The catheter is inserted usually via the internal jugular vein in the neck, then into the superior vena cava, right atrium, tricuspid valve and right ventricle. Finally, it is passed via the pulmonary valve into the pulmonary artery or branch of it. A floatation balloon is inflated to direct placement. The physician, then, injects a cold solution through the CVP port into the chambers of the right heart where mixing occurs and the temperature change of the blood is measured by the thermistor downstream from the flux of cooled blood passing through the pulmonary artery (http://en.wikipedia.org/wiki/File:Pulmonary_artery_catheter_english.JPG).

2.3 OUTLINE OF EXPERIMENTS AND RESULTS

2.3.1. EXTRINSIC FACTORS THAT AFFECT THERMODILUTION MEASUREMENTS

Many factors are known to affect the accuracy and reproducibility of the thermodilution method. Before measuring the error of the thermodilution method using PACs in my in-vitro model, a series of preliminary experiments were conducted that were intended to evaluate the influence of some of these factors. The main ones being investigated included: (1) The injectate properties: (a) Temperature (b) Volume (2) The catheter properties: (c) Ambient temperature; (d) Position of tip in lumen (thermistor) and (e) Dead space within catheter lumen.

2.3.1.1. INJECTATE PROPERTIES

a. Experiments investigating injectate temperature

Clinical thermodilution measurement is usually performed using one of two injectate temperatures, iced cold (0℃) and room temperature (23℃) . There are arguments in favor of using both of these temperatures (Chapter 1 review section). The cardiac output monitor can be set for both these temperatures, through usually the temperature of the injectate is also measured as part of injecting system. The effect of temperature on the accuracy and repeatability of consecutive thermodilution readings was studied using the test rig.

Data was collected at test rig flow meter readings ranging from 0.7 to 7 L/min (corrected for calibration). A single Arrow and a single Edwards catheter were used and measurements with and without dead space were performed (classical and retrograde methods). Five flow rates were used, with 5 readings being taken at each flow rate. For the highest level flow rate, I took 20 thermodilution readings so that I could calculate the coefficient of variation of the data. Taking the flow in test rig as the X axis, the thermodilution reading as the Y axis, I drew separate regression lines for each temperature of injectate. Statistical values such as coefficient of variation (CV = standard deviation/mean), slope and R-value of the regression lines were calculated. The CV value was from 20 readings taken at the highest flow rate (Figures 2.23a&b, 2.24a&b, Table 2.2).

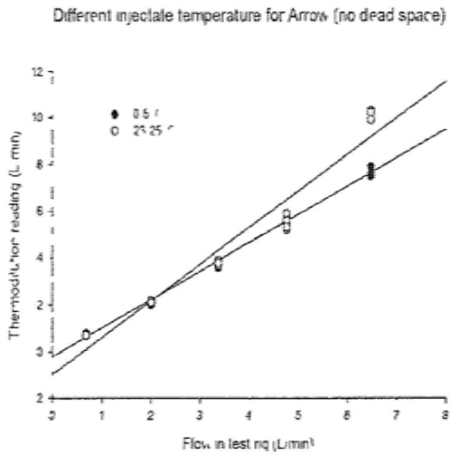


Figure 2.23a. Plot showing the influence of two different injectate temperatures using an Arrow catheter without dead space. The inter-reading variability (CV; n=20) was 3.1% for 0-5℃and 6.3% for 23-25℃.

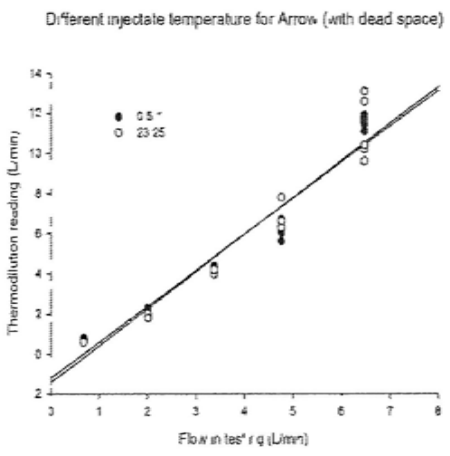


Figure 2.23b. Plot showing the influence of two different injectate temperatures using an Arrow catheter with dead space. The inter-reading variability (CV; n=20) was 9.7% for 0-5℃and 14.9% for 23-25℃.

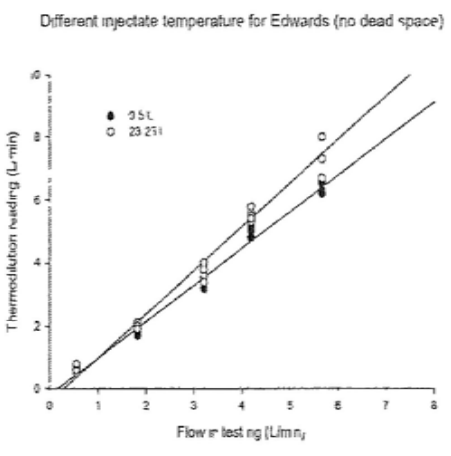


Figure 2.24a. Plot showing the influence of two different injectate temperatures using an Edwards catheter without dead space. The inter-reading variability (CV; n=20) was 3.1% for 0-5℃and 6.1% for 23-25℃.

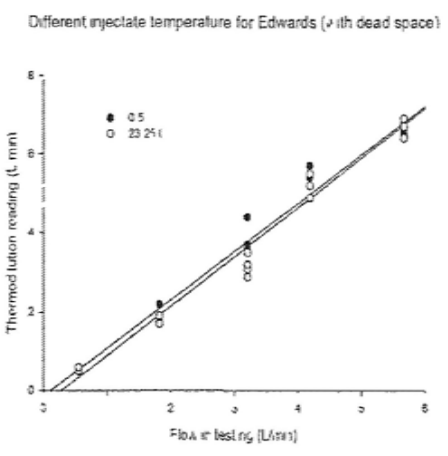


Figure 2.24b. Plot showing the influence of two different injectate temperatures using an Edwards catheter with dead space. The inter-reading variability (CV; n=20) was 5.1% for 0-5℃and 12.3% for 23-25℃.

Table 2.2. Data presented from one Arrow and one Edwards catheter, when using an ice cold and room temperature injectate. Data with and without (classical and retrograde methods) also shown. Statistical descriptions are coefficient of variation (CV), slope of regression line (m) and correlation coefficient (R-value). The ratio of the CVs comparing room to ice was also calculated.

Catheter Brand	Arrow				Edwards			
Dead space	*without*		*with*		*without*		*with*	
Temperature (℃)	0-4	23-25	0-4	23-25	0-4	23-25	0-4	23-25
CV	3.1%	6.3%	9.7%	14.9%	3.1%	6.1%	5.1%	12.3%
Slope	1.21	1.56	1.79	1.85	1.16	1.39	1.22	1.25
R-value	1.00	0.98	0.97	0.97	0.99	0.99	0.99	0.99

The data showed that all the regression lines had a good linear correlation (R-value>0.96) and thus trending ability. Comparing data from different groups, the groups without dead space had a lower coefficient variation than the group with dead space (i.e. dead space increased the CV readings by *2.3), whilst the groups using ice temperature injectate had a lower coefficient variation that the group using room temperature injectate (i.e. ratio of CV of room to ice equals to 1.9). Thus, eliminating the dead space and using the ice cold injectate helps to

reduce the error by a factor of 2.3*1.9 which equals a factor of 4.4. Furthermore, the improvements in error shown by the CV were proportional to the change in temperature drop. There was an approximate two fold improvement (i.e. *2.3 and *1.9). Similarly, the temperature drop (room 37-20=17℃; iced 37-0=37℃; ratio 37/17=2.2) showed an approximate two fold improvement. Slight differences between the two brands of catheters could also be seen, the Edwards gave a lower coefficient of variation than the Arrow catheters. But since only one catheter of each brand was used and the differences were small, I was unable to draw any true conclusions about the difference between catheter makes.

b. Experiments involving injectate volume

The thermodilution method is usually performed using one of two different volumes of injectate 5 or 10 ml. Occasionally 3 ml is also used. The cardiac output monitor software is designed to accept different injectate volumes. I studied the effect of these three injectate volumes on the accuracy and repeatability of consecutive thermodilution readings.

Data was collected at test rig flow meter readings ranging from 0.7 to 7 L/min (corrected). A single Arrow and single Edwards catheter were tested as previously and measurements with and without dead space were performed. Five flow rates were used, with 5 readings being taken at each flow rate. For the highest level rate, I took 20 readings in total for calculating the CV value. Taking the flow in test rig as the X axis, the thermodilution reading as the Y

axis, I drew separate regression lines to compare the effect of injecting three different volumes on the CV and regression line slope. Statistical values such as coefficient of variation, slope (m) and R-value of the regression lines were calculated (Figure 2.25, 2.26; Table 2.3).

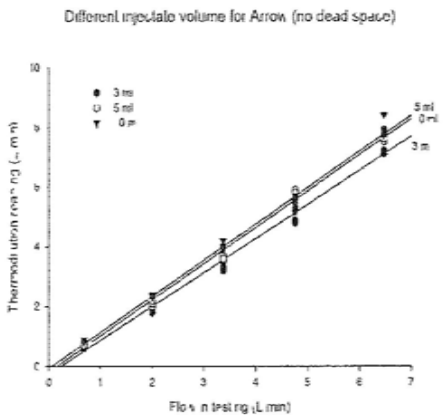


Figure 2.25a. Plot showing the effect of three different injectate volumes using an Arrow catheter without dead space. The inter-reading variability (CV; n=20) was 7.7% for 3ml, 3.1% for 5ml and 2.7% for 10ml.

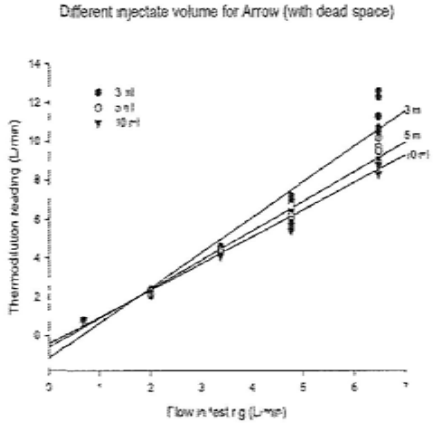


Figure 2.25b. Plot showing the effect of three different injectate volumes using an Arrow catheter with dead space. The inter-reading variability (CV; n=20) was 11.1% for 3ml, 9.7% for 5ml and 6.5% for 10ml.

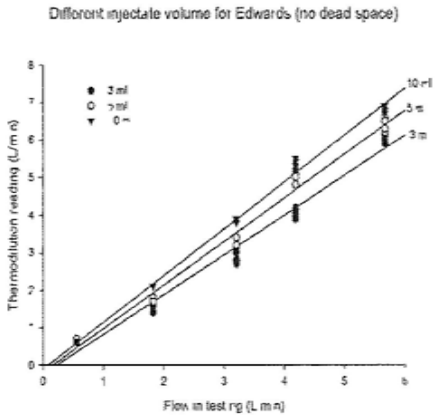


Figure 2.26a. Plot showing the effect of three different injectate volumes using an Edwards catheter without dead space. The inter-reading variability (CV; n=20) was 3.3% for 3ml, 3.1% for 5ml and 2.2% for 10ml.

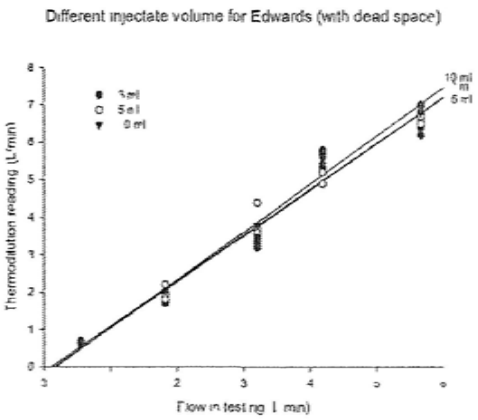


Figure 2.26b. Plot showing the effect of three different injectate volumes using ar Edwards catheter with dead space. The inter-reading variability (CV; n=20) was 3.6% for 3ml, 5.1% for 5ml and 2 3% foı 10ml.

Table 2.3. Summary of data analyzing the effects on performance of different volumes of injectate.

Catheter Brand	Arrow						Edwards					
Dead space	*without*			*with*			*without*			*with*		
Injectate volume (ml)	3	5	10	3	5	10	3	5	10	3	5	10
Coefficient of Variation	7.7%	3.1%	2.7%	11.1%	9.7%	6.5%	3.3%	3.1%	2.2%	3.6%	5.1%	2.3%
Slope	1.14	1.21	1.21	1.82	1.51	1.39	1.06	1.16	1.25	1.23	1.22	1.28
R value	1.00	1.00	1.00	0.98	0.99	0.98	0.99	0.99	1.00	0.98	0.99	0.99

The effect of using different injectate volumes was to alter the coefficient of variation predictably. The smallest volume of 3 ml gave a worst coefficient of variation while the largest 10 ml gave the best. But since the 5 ml and 10 ml injection had a similar CV, we chose 5 ml regarding the large volume's side effects in this in-vitro model. There was a linear relationship as flow increased for all the three volumes (R-value>0.97). Dead space affected calibration line slope, and the Arrow catheter performed differently to the Edwards catheter. The calibration lines for the Edwards catheter used with dead space were very similar, whereas the 3ml volume with Arrow catheter was significantly offset. This most likely reflects the correction factors used by the manufactures to compensate for the dead space effect in the Siemens9000 monitor.

2.3.1.2 CATHETER PROPERTIES

c. Experiment involvings different body temperatures

The temperature of the blood surrounding the PAC may also be a factor since in the clinical setting patients may present with different body temperature because of the fever, hypothermia etc. Thus, I compared the thermodilution readings using different ambient water temperatures.

As the upper limit of the water heaters was 37℃, I chose a temperature range from 30 to 36℃ which reflected temperatures that could be encountered in the clinical setting. Data was

collected for test rig flow meter readings ranging from 0.7 to 7 L/min (corrected) as previous, using water temperature setting at interval of 2℃ (e.g. 30, 32, 34, and 36℃). A single Arrow and single Edwards catheter were tested and only measurements with dead space (i.e. the classical method used in clinical practice) were performed. Taking the flow in test rig as the X axis, the thermodilution reading as the Y axis, I drew separate regression lines to compare the effect of different water temperature's.

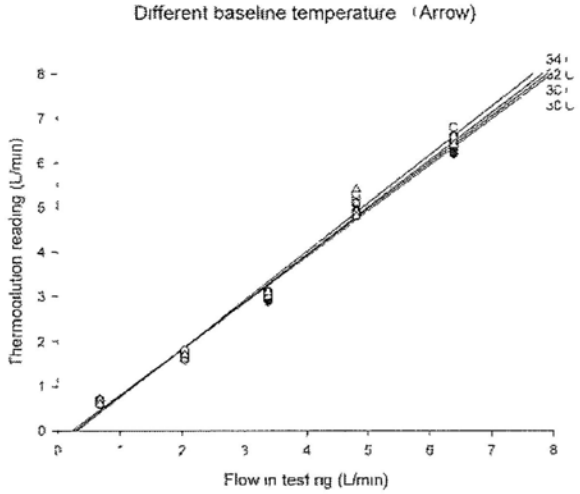


Figure 2.27a. Regression lines showing four different water temperatures using an Arrow catheter. Note that only slight differences in the slope occurred between the four lines. The gradient of the slope ranged from 1.03 to 1.09. When X=5L/min, Y ranged from 4.9 to 5.9L/min.

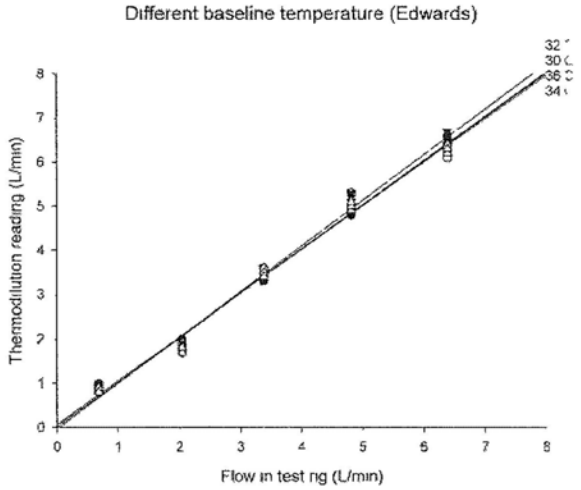


Figure 2.27b. Regression lines showing four different water temperatures using an Edwards catheter. Note that only slight differences in the slopes occurred between the four lines. The gradient of the slopes ranged from 0.99 to 1.03. When X=5L/min, Y ranged from 5.0 to 5.1L/min.

Water temperature changes did not affect the readings and performance of thermodilution significantly. There were only slight differences between the regression line for all four ambient temperature. At a flow rate of 5 L/min in the test rig, the thermodilution readings varied by 1L/min when using an Arrow catheter and by 0.1L/min when using an Edwards catheter, which suggested that Edwards catheter may be more stable in respect to water temperature. Overall, water and therefore body temperature has little effect on readings.

d. Experiment involving catheter tip position

Normally the distance from the injection port on the PAC to thermistor is fixed at 30 cm. But when I used retrograde method, the distance varied according to the position of the catheter tip. One of my concerns about using the test rig was if the position of the catheter tip and thermistor downstream from injection port could influence thermodilution readings. In particular, the distance that the injectate travelled and whether proper mixing of injectate occurred. Also, the position of the catheter tip within the test rig lumen and whether lying near the center or close to the vessel wall made a difference. I designed two experiments to investigate these issues: (i) Different lengths of the catheter using the retrograde method were inserted into the test rig, such that different injection port to catheter tip distances (range: 10-100cm) were tested. (ii) Different positions of the catheter tip in the catheter lumen (central and against tube wall).

(i) Ten placement lengths from 10 to 100 cm at intervals of 10 cm from injection port to catheter tip were selected. Taking the flow in test rig as the X axis, the thermodilution reading as the Y axis, I drew separate regression lines to show the effect of injection port to catheter tip or mixing distance on readings (Figure 2.28, Table 2.4).

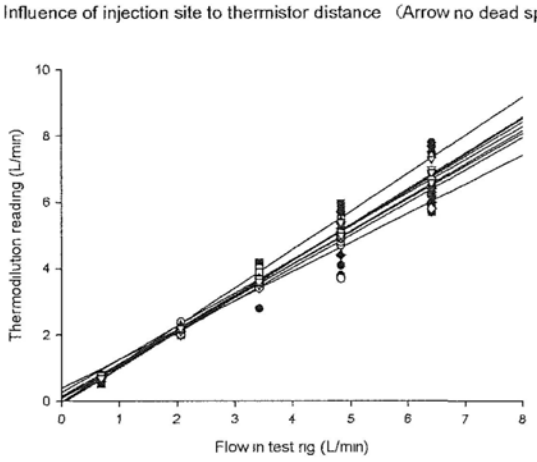


Figure 2.28a. Plot showing the influence of mixing distance when using an Arrow catheter. Slopes ranged from 0.880 to 1.151. When X=5L/min, Y ranged from 4.8 to 5.7L/min.

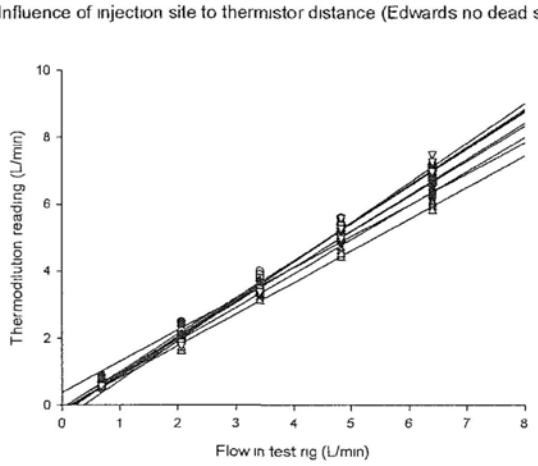


Figure 2.28b. Plot showing the influence of mixing distance when using an Edwards catheter. Slopes ranged from 0.931 to 1.180. When X=5L/min, Y ranged from 4.6 to 5.5L/min.

Table 2.4. Calibration slopes from the two catheters (Arrow and Edwards) at different depths of insertion into the test rig.

Distance (cm)	Arrow (slope)	Edwards (slope)
10	1.078	0.931
20	0.880	1.102
30	1.151	1.015
40	1.076	0.945
50	1.004	1.137
60	1.044	1.119
70	0.991	1.127
80	0.984	1.072
90	1.009	1.049
100	1.079	1.180

(ii) To investigate catheter tip position with the lumen of the test rig, I used a guide wire to position the thermistor tip and the thermistor (a) in the middle of the tube and (b) against the wall. Data was collected for test rig flow meter readings ranging from 0.7 to 7 L/min (corrected as preciously). A single Arrow and single Edwards catheter were used and measurements without dead space were only performed, because the catheter needed to be

frequently repositioned within the test rig. Taking the flow in test rig as the X axis, the thermodilution reading as the Y axis, I drew separate regression lines showing these two position's effect (Figure 2.29).

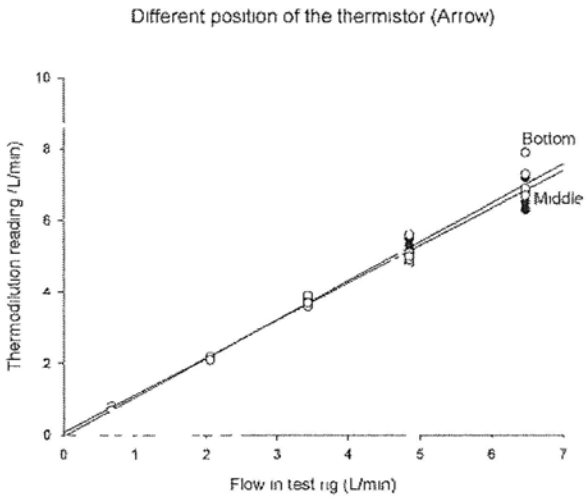


Figure 2.29a. Calibration lines showing different positions of the catheter tip within the lumen of the Arrow catheter. There is only a slight difference between the two lines. The slopes were 1.05 and 1.09. When X=5L/min, Y ranges from 5.3 to 5.4L/min.

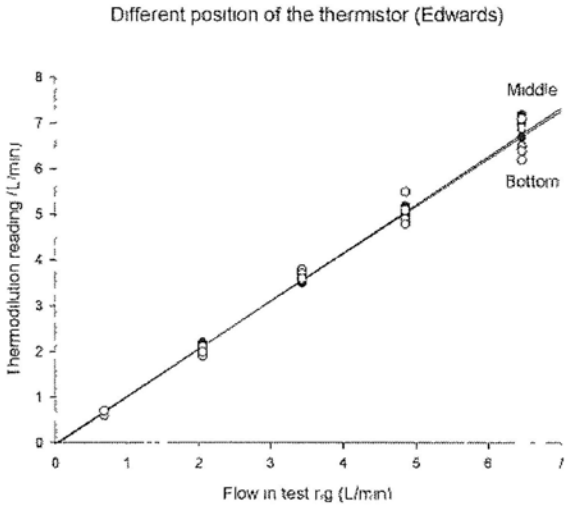


Figure 2.29b. Calibration lines showing different positions of the catheter tip within the lumen of the Edwards catheter. There is only a slight difference between the two lines. The slope ranges were 1.04 and 1.05. When X=5L/min, Y ranges from 5.1 to 5.2L/min.

By dividing the mixing distance into 10 cm intervals, I drew a series of regression lines. Although the calibration lines varied in slope between positions and the range of these variations were quite large, up to 0.9 L/min at 5 L/min. There was no systematic trend in the slopes over distance. However, changing the position of the catheter tip within the lumen did not affect the calibration slope.

It is puzzling why calibration value varied so much with mixing distance. Closer inspection (Table 2.4) reveals that at mixing distances of 50-70 cm, the catheters were more consistent, Arrow slope 1.00 (range 0.04) and Edwards slope 1.12 (range 0.01). Maybe the flow conditions and mixing was only sufficiently stable to provide consistent readings at this range of distance (50-70 cm) in the test rig.

For a classic thermodilution catheter the port is 30 cm from the thermistor, but mixing dynamics are different as in vivo the chamber of the heart are involved. Thus it would appear that positioning of the catheter within the test rig had an effect on study outcome.

Similar but more precisely, the different position of the tip was proved not to have the effects on thermodilution results. The predicted of Y values were limited within 0.1L/min which would definitely ignored in the process for evaluating the thermodilution catheters.

e. Experiments to show the influence of dead space

Two studies that further assess and show the effects of dead space on catheter performance.

(i) Ambient temperature around the dead space

Previously, in catheter properties section C (different body temperature; 30-36℃) I had shown that varying water temperature had little effect on catheter performance. However, a standard PAC is over 110 cm long and only part of this (approximately 50 cm or half) lies

within the body and circulation. The other half is exposed to ambient room temperature which may also affect performance. Therefore I wanted to investigate the effect of extremes of ambient temperature, zero degrees or body temperature on dead space. In this part, I placed the catheter and tubing outside the test rig into three different temperature environments (zero, room and body temperature: 0-5; 23-25; 36-37℃) and compared the effects on catheter performance.

Data was collected for test rig flow meter readings ranging from 0.7 to 7 L/min (corrected as previously). A single Arrow and single Edwards catheter were used and all measurements included dead space. Taking the flow in test rig as the X axis, the thermodilution reading as the Y axis, I drew separate regression lines to compare the different ambient temperature's effect. Statistical values such as coefficient of variation, slope and R-value of the regression lines were calculated (Figure 2.30, Table 2.5).

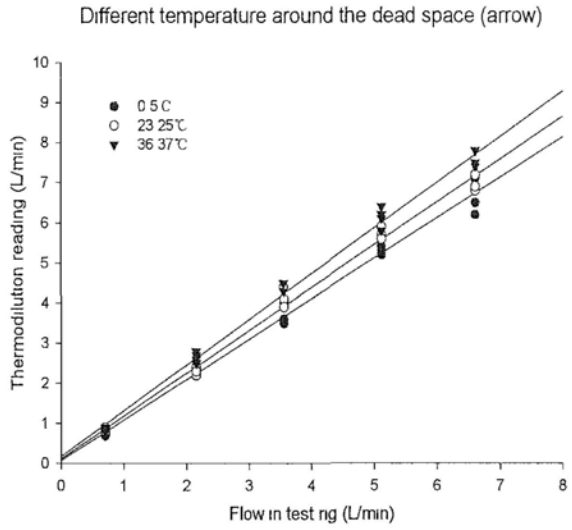


Figure 2.30a. Calibration plot showing the effect of 3 different ambient temperatures applied to the dead space of the Arrow catheter. The slopes ranged from 1.01 to 1.14. When X=5L/min, Y was 5.1, 5.4 and 5.9 L/min for 0-5, 23-25, 36-37℃ respectively.

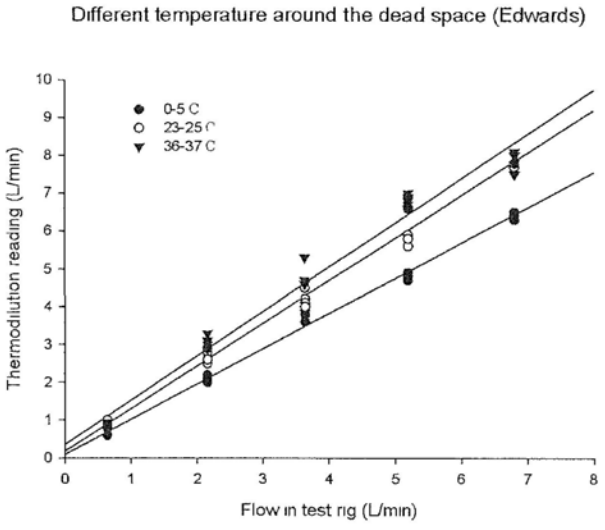


Figure 2.30b. Calibration plot showing the effect of 3 different ambient temperatures applied to the dead space of the Edwards catheter. The slopes ranged from 0.93 to 1.17. When X=5L/min, Y was 4.8, 5.8, and 6.2 for 0-5, 23-25, and 36-37℃ respectively.

Table 2.5. Table showing the different ambient temperature effects, statistical values such as coefficient of variation, slope and R-value of the regression lines were calculated.

Catheter Brand	Arrow			Edwards		
Ambient Temperature	*0-5℃*	*23-25℃*	*36-37℃*	*0-5℃*	*23-25℃*	*36-37℃*
CV	3.95%	3.90%	3.81%	2.17%	6.44%	9.61%
5 L/min value	5.1	5.4	5.9	4.8	5.8	6.2
Slope	1.01	1.07	1.14	0.93	1.13	1.17
R-value	1.00	1.00	1.00	1.00	0.99	0.99

According to the data, the ambient temperature at 0-5℃ gave the best coefficient of variation for Edwards and the most accurate predicted Y values at the level of 5 L/min. It provided evidence of existence of the dead space effect. Since I used the ice injectate, the ambient temperature which was equivalent to the injectate temperature should have the least effects on the result, which exactly what my results showed. There was also a difference between two brands of catheters. Although the Arrow catheter performed with the same variability over a range of ambient temperatures, the Edwards catheter system was more unstable, having less random variation at 0-5℃ but significant more at body temperature. Therefore the algorithm to the Edwards system is clearly sensible to ambient temperature, unlike to

Arrow system. It is notable worthy that different makes of catheters perform differently with respect to how they are set up to compensate for catheter dead space.

(ii) Different injectate volumes

Inconsistencies in the volume of injectate give when using a set volume bolus may also affect the reading. But to what extent does this affect the readings? To investigate this factor further, I chose different volumes of cold water injectate from 3 to 7 ml, when the pre-set volume on the monitor was 5 ml and then determined the effect on thermodilution readings.

Data was collected for test rig flow meter readings ranging from 0.7 to 7 L/min (corrected as previously). A single Arrow and single Edwards catheter were used and measurements with and without dead space were performed. Taking the flow in test rig as the X axis, the thermodilution reading as the Y axis, I drew separate regression lines to compare the effects of injecting different volume's with the monitor set to 5 ml. Statistical values such as slope and R-value of the regression lines were calculated (Figure 2.31-2.34 Table 2.6).

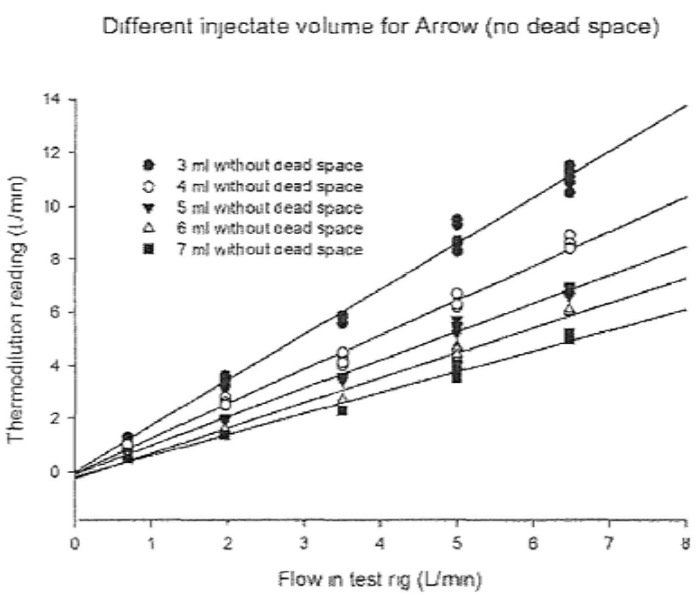


Figure 2.31a. Calibration plot showing the result of injecting different volume when monitor set to 5 ml (Arrow catheter without dead space).

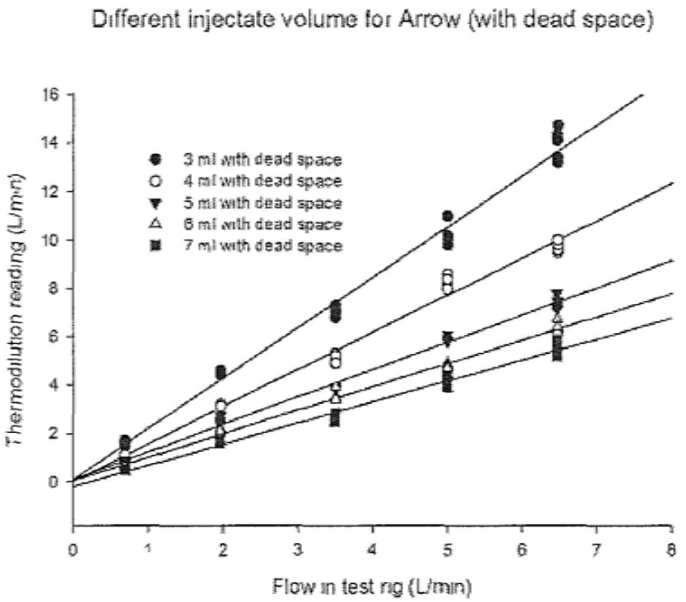


Figure 2.31b. Calibration plot showing the result of injecting different volume when monitor set to 5 ml (Arrow catheter with dead space).

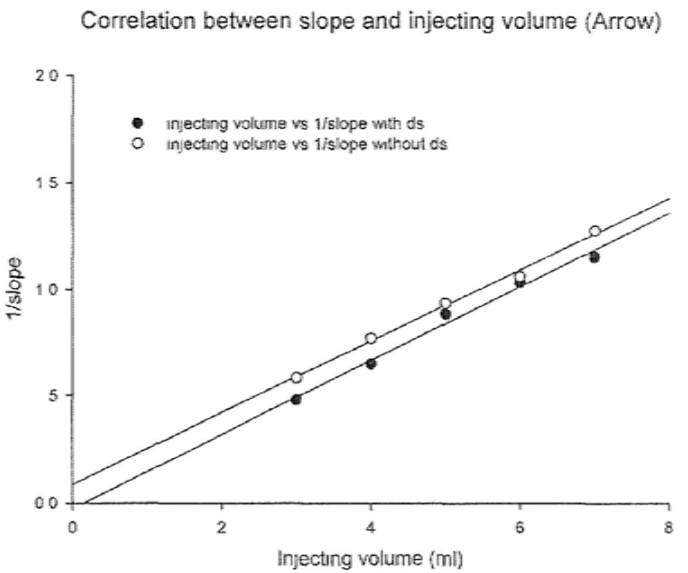


Figure 2.32. Regression line showing the relationship between slope and injected volume for the Arrow catheter using both the with and without dead space methods.

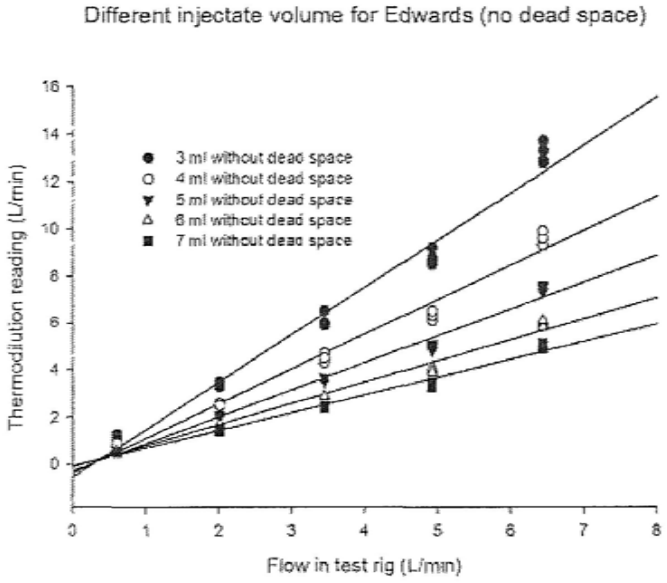


Figure 2.33a. Calibration plot showing the result of injecting different volume when monitor set to 5 ml (Edwards catheter without dead space).

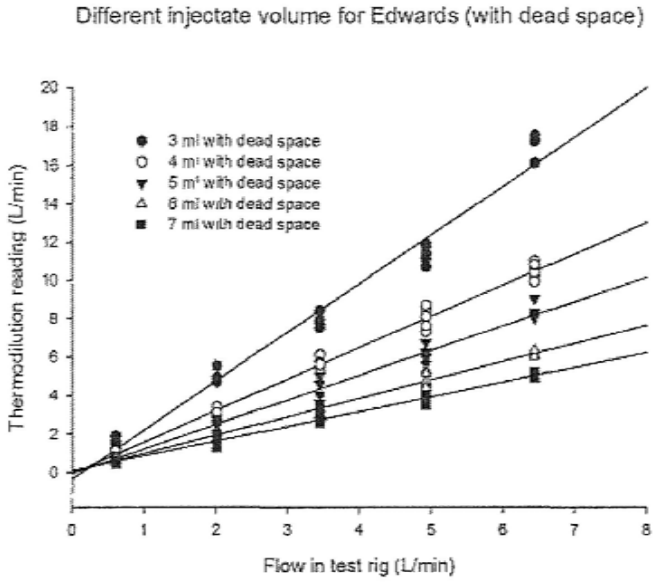


Figure 2.33b. Calibration plot showing the result of injecting different volume when monitor set to 5 ml (Edwards catheter with dead space).

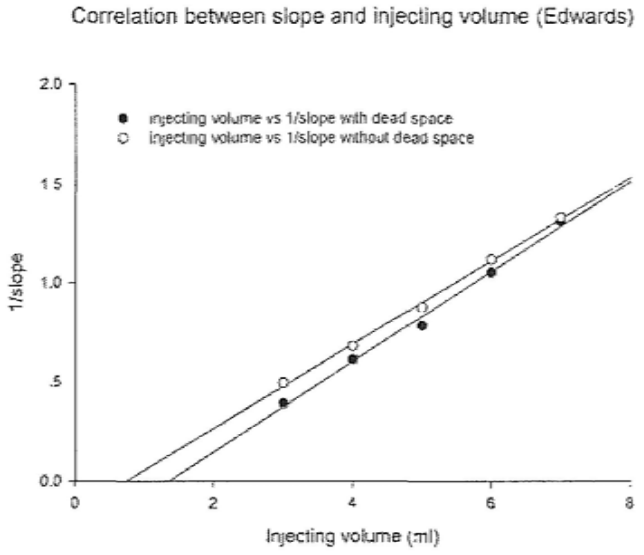


Figure 2.34. Regression line showing the relationship between slope and injected volume for Edwards catheter using both the with and without dead space methods.

Table 2.6. Slopes and R-values of the regression lines for different injectate volumes.

	Arrow									
	Without dead space					With dead space				
volume(ml)	3	4	5	6	7	3	4	5	6	7
Slope	1.72	1.30	1.07	0.94	0.78	2.10	1.54	1.13	0.97	0.87
R value	1.00	1.00	1.00	0.99	0.99	1.00	0.99	1.00	1.00	0.99
Y when X=5 (L/min)	8.6	6.5	5.3	4.6	3.8	10.6	7.7	5.8	5.0	4.2
	Edwards									
	Without dead space					With dead space				
volume(ml)	3	4	5	6	7	3	4	5	6	7
Slope	2.01	1.47	1.14	0.89	0.75	2.54	1.63	1.28	0.95	0.76
R value	0.99	0.99	0.99	0.99	1.00	0.99	0.99	0.99	0.99	0.99
Y when X=5 (L/min)	9.5	7.0	5.4	4.3	3.8	12.4	8.2	6.4	4.8	4.0

Injecting volume had a very reproducible effect on calibration as shown by calibration plots.

According to the Y value when X=5 L/min, we could see that the most accurate Y value

occurred at the volume of 5 ml when using the method without dead space, but at the volume of 6 ml when using the method with dead space.

When coming to the 1 ml percentage error (i.e. Y(4ml)-Y(5ml)/Y(5ml), or Y(5ml)-Y(6ml)/Y(5ml)), we could see the differences between the 1 ml more and 1 ml less.

For the method without dead space, the 1 ml percentage error was 13.2% for 6 ml, and 22.6% for 4 ml in Arrow; and 20.4% for 6 ml, and 29.6% for 4 ml in Edwards catheter. For the method with dead space, the 1 ml percentage error was 13.8% for 6 ml, and 32.8% for 4 ml in Arrow; and 25% for 6 ml, and 28.1% for 4 ml in Edwards catheter.

2.3.2. INTRINSIC FACTORS THAT AFFECT THERMODILUTION MEASUREMENTS

In this section on the catheter testing, my objective was to determine the performance characteristics of thermodilution catheters using the test rig. The errors in thermodilution measurements were treated as having two distinct components: (a) that due to random variations arising from the act of making a reading (the inter-reading random error or precision) and (b) that due to systematic variations in the measurement equipment (the between-catheters and monitoring system errors). Protocols were developed that treated the the two sources of error separately.

2.3.2.1. THE RANDOM COMPONENT

The random component of the error was investigated by taking sets of repeated readings at a series of flow rates (1-10L/min). A single catheter of each brand, Arrow and Edwards, was tested. To determine the influence of catheter dead-space on the size of this error, both the classical (with dead-space) and retrograde (without dead-space) PAC placement methods were evaluated. A set of 10 readings were taken at a single constant flow rate. Further, sets of 10 readings were then taken at 1 L/min incremental increases over a range of flow rates from 1 to 10 L/min (n.b. based on the uncorrected flow meter reading, therefore, the true range was approximately 0.7-7 L/min, as the correction factor was 1.5). The Siemens SC9000 monitor was used to measure cardiac output in the first instance.

Data was collected for test rig flow meter readings ranging from 0.7 to 7 L/min (corrected). Both Arrow and Edwards catheters were tested and measurements with and without dead-space were performed (Figure 2.35).

The random component of the error was determined by calculating its coefficient of variation (CV). First, the mean and SD for the set of 10 readings was determined. The CV was calculated using the SD divided by the mean, which was expressed as a percentage (CV = (SD/mean) %). This was repeated for each flow rate, and then the average CV for all the CV measurements was determined.

To standardize my error measurement that was based on the CV that used 1 SD I converted it to the more commonly accepted presentation of 95% confidence intervals, and multiplied the average CV by ±1.96. Error measurement in the thesis will refer to 95% confidence intervals unless the CV value is specifically stated.

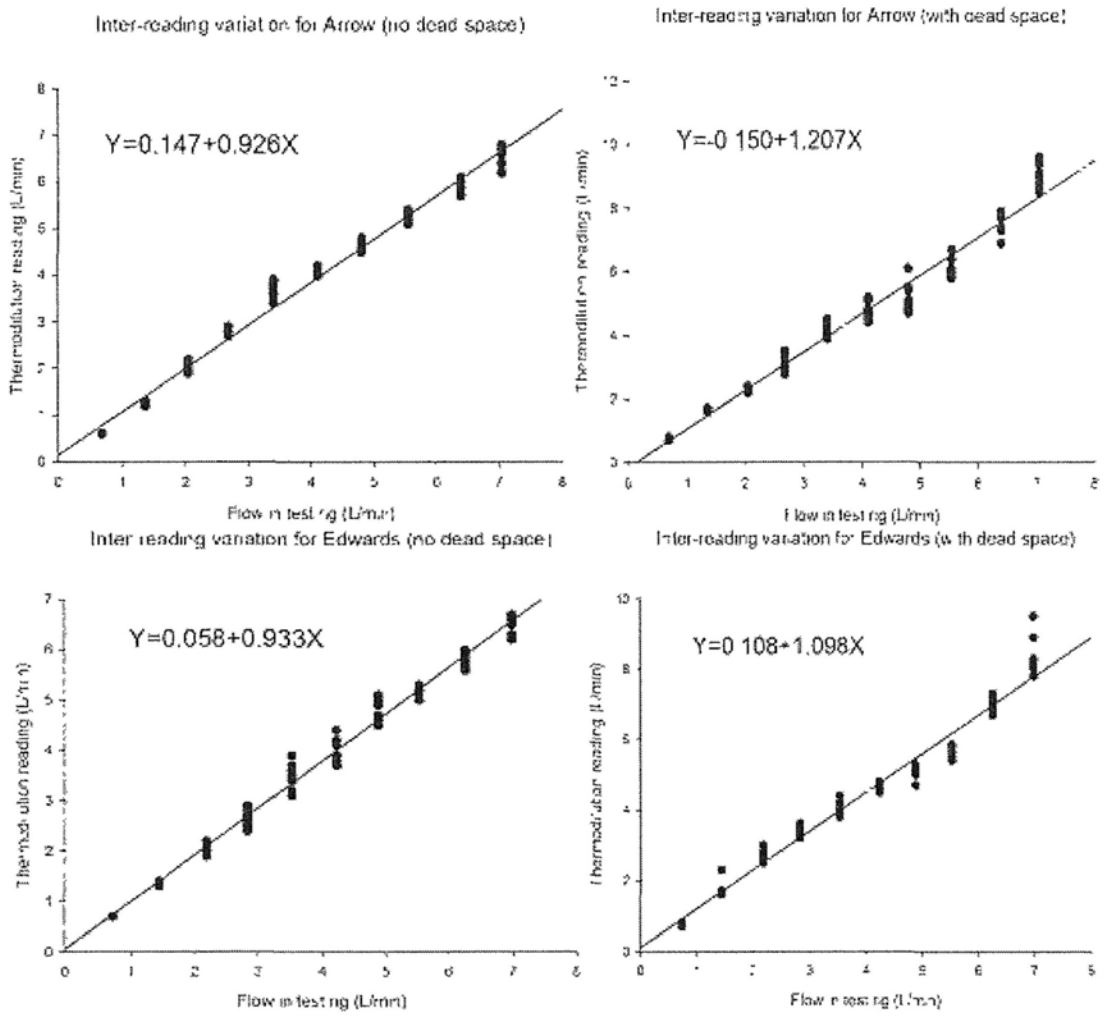


Figure 2.35. Plots showing the inter-reading variability when performing single-bolus thermodilution measurements with the Siemens SC9000 cardiac output monitor. Data for Arrow (upper) and Edwards (lower) catheters, without (left) and with (right) catheter dead space. Sets of 10 readings were collected at each flow rate. Note the slightly nonlinear relationship of data to the regression line.

The CV for classical or standard readings (with dead space) were 5.4% and 4.8% for Arrow and Edwards, respectively. Thus, the component of error arising from random measurement error was 10.6% and 9.4%, respectively.

The presence of dead space increased the mean inter-reading CV from 2.7% to 5.4% for Arrow and 3.8% to 4.8% for Edwards catheters ($P<0.001$; t-test). The presence of dead-space also affected the slopes of the calibration lines with the thermodilution readings being higher and gradient steeper when dead-space was present (Table 2.7).

Table 2.7. Summary of coefficient of variation (CV) data from the two brands of PAC tested over a range of flow rates.

Placement	Standard		Retrograde	
Dead-space	*(with)*		*(without)*	
Catheter Brand	Arrow 7Fr	Edwards 7Fr	Arrow 7Fr	Edwards 7Fr
Slope of line	1.21	1.10	0.93	0.93
CV data (mean(ci))	5.4(4.2-6.7)%	4.8(2.7-6.8)%	2.7(1.6-3.7)%	3.8(2.1-5.4)%
Error	10.6%	9.4%	5.3%	7.4%

However, it was also notable that in the four plots (Figure 2.35) that the average readings did not increase in an absolutely linear fashion and with dead space in particular a biphasic relationship existed where at 3 L/min readings were above and at 6 L/min readings were below the calibration line.

2.3.2.2. THE SYSTEMATIC COMPONENT

The systematic component of the error was investigated by plotting a regression, or calibration, line for a single PAC, measuring parameters that describe the line and repeating the process for several PACs. Such data were collected from 5 Arrow and 5 Edwards PACs. Only the retrograde method of PAC placement was used because the protocol required frequent changes of PAC in the test rig. Five paired readings were collected at each of 5 flow rates between 0 to 10 L/min (the uncorrected flow meter reading), and used to plot a calibration line for each PAC. By plotting the regression line for data over a range of flow rates, the random component of the error arising from the between-readings variation was eliminated, leaving only the systematic component.

From each regression line plot of catheter performance a number of statistical variables that quantified its calibration line were determined:

(1) the slope or gradient (m);

(2) the correlation coefficient (r);

(3) the predicted value for a thermodilution reading (without any random component) when the flow in the rig was set at 5 L/min, which was calculated from each calibration line equation ($Y = mX + c$);

(4) the deviation of the slope of the calibration line ($m - 1$) from the line of identity ($Y = X$). The gradient of the calibration line can be used to quantify the systematic component of the measurement error. Because the gradient is independent of flow rate, it provides a normalized estimate of systematic error that is unaffected by flow rate. The slope of each calibration line is formed by the hypotenuse of a right-angled triangle a, b, and c, for which a is the horizontal side and b is the vertical side. The slope or gradient (m) is simply b/a. When analyzing calibration lines, the important statistic is their deviation from the line of perfect agreement or identity $Y = X$, which has a gradient of unity ($m = 1$). The deviation (Δm) of the calibration line from this line (Δm) is $(b/a) - 1$. When deviation angles are small (e.g. <10 degrees), a very simple relationship can be applied to the systematic error component and Δm in which the systematic error approximates to the value of Δm. Therefore, if $\Delta m = 0.05$, the systematic error is 5%, etc. The proof is based on the geometric relationship that $\Delta m = \tan \Delta \theta = \Delta b/a$ for the small triangle and angle formed between the line of identity and the calibration line. To calculate the average divergence of the calibration lines, I used only absolute or positive values of Δm. Using the slope (m) and delta slope (m-1) of the calibration line was a very simple approach to quantifying systematic errors. However, I did

experiment with other variable such as angle of the line, but considered it over complicated matters. Another issue was the Y-axis crossing of the calibration line or the constant in the calibration line equation (Y=mx+C) as after the line did not pass though zero. In general with the test rig the calibration lines crossed the Y-axis fairly close to the zero point, so it was ignored in my analysis. The average divergence (mean (Δm)) for all catheters tested provided an estimate of the CV for the systematic error, which was expressed as a percentage. This was multiplied by 1.96 to provide the systematic error component.

Calibration lines were drawn using data taken at 5 data points. Data from 5 Arrow and 5 Edwards PACs was shown. The slope of the calibration lines from individual catheters varied (Figure 2.36, Table 2.8).

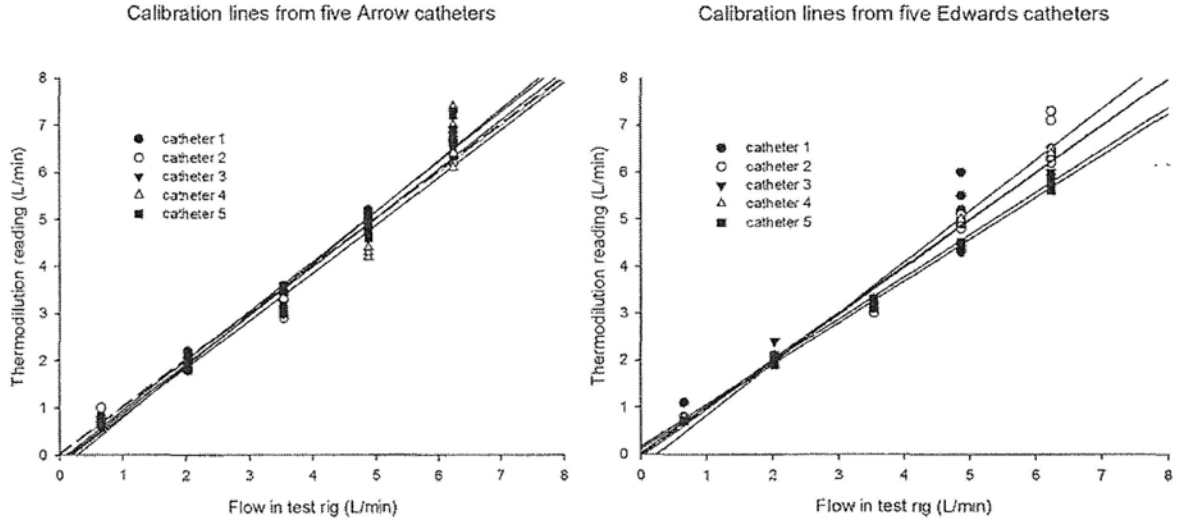


Figure 2.36. Plots comparing the calibration lines for 5 different Arrow catheters (left), and 5 different Edwards catheters (right). Lines constructed from sets of 5 readings taken at

different flow rates between 0 and 7 L/min (corrected). Line of identity (Y=X) shown by dotted lines.

Table 2.8. Data from five (1-5) Arrow and five Edwards catheters showing the variations in slope, deviation and correlation coefficients

Arrow	1	2	3	4	5
Slope	1.06	1.04	1.09	1.01	1.09
Deviation	6%	4%	9%	1%	9%
R-value	0.99	0.99	0.99	0.98	0.98
Edwards	1	2	3	4	5
Slope	0.99	1.08	0.90	1.00	0.89
Deviation	1%	8%	10%	0%	11%
R-value	0.98	0.99	1.00	0.99	1.00

The mean (range) predicted readings at a 5 L/min flow for Arrow PACs was 5.1 (4.9 to 5.2) L/min and for the Edwards PACs was 4.9 (4.6 to 5.2) L/min. The deviation (e.g. average CV [systematic]) of the slopes from the line of identity for Arrow PAC was $\pm$5.8% and for Edwards PAC $\pm$6.0%, and overall was $\pm$5.9%. Although the calibration lines from the Arrow catheters were more uniform than were those from the Edwards catheters, they were not as close to the line of identiy, lying slightly above it.

On the basis of my CV data, the component of error arising from the random errors for Arrow and Edwards PACs were $\pm$10.6% and $\pm$9.4%, respectively, and overall was $\pm$10.0% (e.g.

95% confidence intervals). On the basis of my calibration line data, the systematic components of the error were ±11.4% and ±11.8%, respectively, and overall was ± 11.6%. Therefore, the total estimated error for a single thermodilution reading, derived from CV (random) and CV (systematic) was ±15.3%, and this was reduced to 13.0% for triplicate readings ($CV = \sqrt{(CVorCE(rand)^2 + CV(syst)^2}$).

2.3.2.3. DIFFERENCE IN THE PERFORMANCE OF THREE CARDIAC OUTPUT MONITORS

Three different models of cardiac output monitors were compared, (a) Simens SC9000, (b) Sirecust 1261, and (c) IntelliVue MP50. The experimental set-up and statistical analysis were the same as those described previously. These monitors were chosen because they were the three available monitors in my institution.

The same protocols used to assess random and systematic errors were used to compare the performance of two other cardiac output monitors (Figure 2.37, Table 2.9).

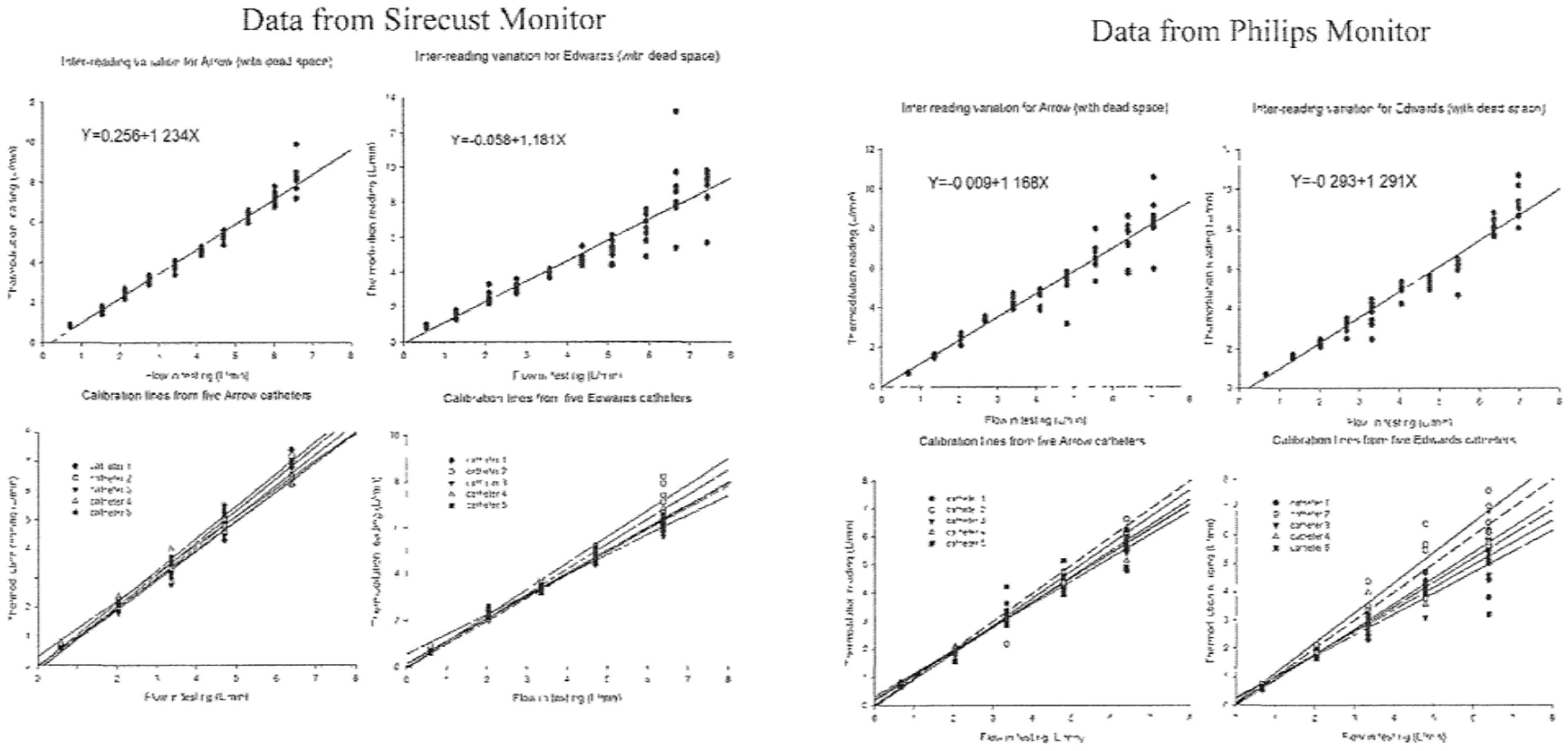


Figure 2.37. Plots showing the random error and calibration lines for both Arrow and Edwards catheters when using both the older Simens Sirecust 1261 monitor and the Philips IntelliVue MP50 monitor. Line of identity (Y = X) shown by dotted lines in calibration plots.

Table 2.9. Comparison of performance of three different models of cardiac output monitor. The mean (range) inter-reading variability is shown by CV(readings). The between catheters variability is shown by (i) the predicted values at a 5 L/min flow rate and (ii) by CV(catheter). The error for each monitor is derived from the combined CV components readings (e.g. PE = √(PE(reading)2 + PE(catheter)2), averaged for the two brands of catheter, and multiplied by1.96 to give confidence intervals. Both single and triplicate PE data shown.

Monitor	Siemens SC9000		Siecust 1261		Philips MP50	
Catheter	Arrow (n=5)	Edwards (n=5)	Arrow (n=5)	Edwards (n=5)	Arrow (n=5)	Edwards (n=5)
CV(readings) (%)	5.4(4.2-6.7)	4.8(2.7-6.8)	6.1(4.5-7.7)	10.9(7.1-14.7)	8.3(4.9-11.6)	7.0(3.9-10.0)
Slope (mean(SD))	1.06(0.03)	0.97(0.07)	1.05(0.06)	1.00(0.10)	0.89(0.06)	0.90(0.10)
Predicted (L/min)	5.0(4.9- 5.2)	4.9(4.6- 5.2)	5.3(4.9-5.5)	5.2(4.8-5.6)	4.6(4.4-4.8)	4.6(3.9-5.4)
CV(catheter) (%)	5.8%	6.0%	6.2%	8.0%	11.4%	15.8%
Readings:	***Single***	***Triplicate***	***Single***	***Triplicate***	***Single***	***Triplicate***
PE(readings) (%)	10.0%	5.8%	17.3%	10.0%	15.0%	8.7%
PE(catheter) (%)	11.6%	NA	13.9%	NA	26.7%	NA
PE(overall) (%)	15.3%	13.0%	22.2%	17.1%	30.6%	28.1%

There were significant differences between the performances of the three cardiac output monitors. The Siemens SC9000 monitor readings were more precise than the other two monitors in respect to the inter-reading and between catheter variability (Table 2.9). The errors for the Sirecust 1261 and the Philips MP50 monitors were 45% and 100% greater than those from the Siemens SC9000 monitor. The 5 Arrow catheters provided more consistent readings than the 5 Edwards catheters. The calibration lines and their slopes were more consistent with the Siemens SC9000 monitor, but the Philips MP50 significantly under-read (Figure 2.37, Table 2.9).

2.3.3. PULSATILE MODEL FOR THE EVALUATION

In view of the pulsatile nature of the human circulation, I also experimented with a simple pulsatile adaptation of the test rig. I added an electronic controlled board which generated an oscillating amplitude current to drive the water pump, resulting in a pulsatile flow rate at an adjustable rate of 60 to 100 cycles per minute. A series of evaluations including random error and systematic error were performed using previous test rig protocols.

2.3.3.1 CALIBRATION

First I validated the pulsatile model using timed cylinder filling. A linear relationship between flow meter and cylinder readings was shown, with a calibration factor of 1.42 for the example shown (Figure 2.38).

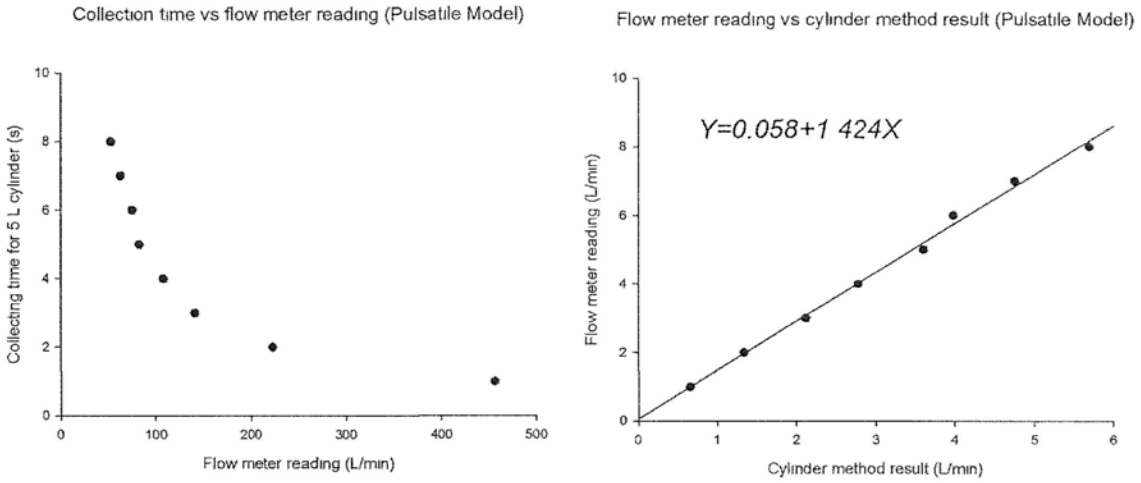


Figure 2.38. Regression plot showing the linear relation between the flow meter and cylinder methods with readings taken over the range of test rig flow rates under pulsatile flow conditions.

2.3.3.2. THE RANDOM VARIATION BETWEEN INDIVIDUAL THERMODILUTION MEASUREMENTS

Because the pulsatile model limited the range flow rates of the pump, data was only collected for test rig flow meter readings ranging from 0.7 to 5 L/min (corrected). Both Arrow and Edwards catheters were used and measurements with and without dead-space were performed. Only the Siemens SC9000 monitor was used for this part of my investigations (Figure 2.39).

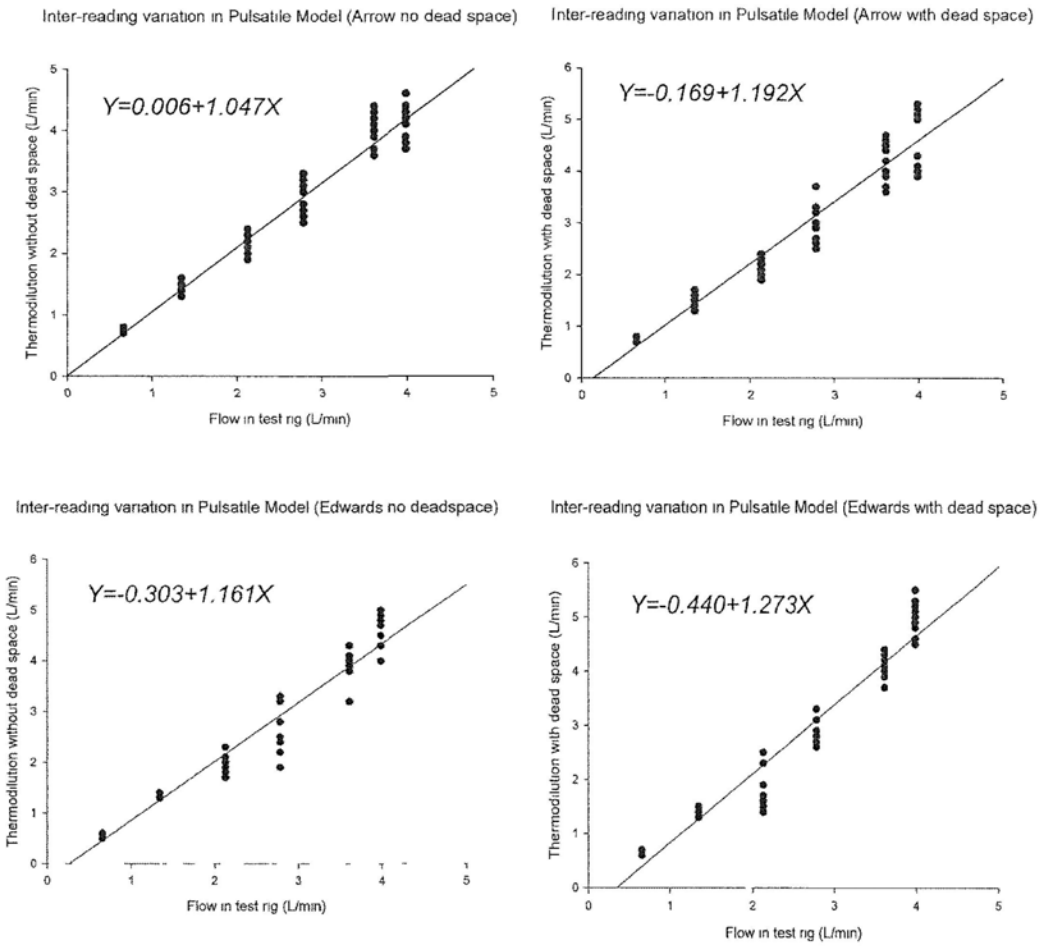


Figure 2.39. Plots showing the inter-reading variability for pulsatile flow when performing single-bolus thermodilution measurements using the Siemens SC9000 cardiac output monitor. Data for Arrow (upper) and Edwards (lower) catheters, without (left) and with (right) catheter dead space. Sets of 10 readings were collected at each flow rate. Note the slightly nonlinear relationship of data to the regression line, most noticeable when using the Edwards catheters.

The CVs for standard readings (with dead space) were 8.9% and 8.1% for Arrow and Edwards, respectively. Thus, the component of error arising from random measurement error was 17.4% and 15.9%, respectively.

The presence of dead space had a minor effect on the mean inter-reading CV from 7.2% to 8.9% for Arrow and 8.4% to 8.1% for Edwards catheters (Table 2.10).

Table 2.10. Summary of data showing the random variation between thermodilution measurements over a range of flow rates for the two brands of catheter using pulsatile flow conditions.

Placement	Standard		Retrograde	
Dead-space	*(with)*		*(without)*	
Catheter Brand	Arrow 7Fr	Edwards 7Fr	Arrow 7Fr	Edwards 7Fr
	(n=5)	(n=5)	(n=5)	(n=5)
Gradient of line	0.97	0.973	0.983	0.973
CV(mean(95ci))(%)	8.93(6.01-11.85)	8.07(3.22-12.92)	7.2(5.79-8.61)	8.37(4.54-12.20)
Error(%)	17.50	15.82	14.11	16.41

Combining the data between with and without dead space, I found that the pulsatile readings were less sensitive to the effect of dead space, and also had almost twice the variation compared to continuous flow.

2.3.3.3 COMPARISON OF CALIBRATION LINES FROM INDIVIDUAL CATHETERS

Data were collected from 5 Arrow and 5 Edwards PACs. Only the retrograde method of PAC placement was used because the protocol required frequent changes of PAC in the test rig. Five paired readings were collected at each of 5 flow rates between 0 to 5 L/min (corrected), and used to plot a calibration line for each PAC. The slope of the calibration lines from individual catheters varied (Figure 2.40, Table 2.11).

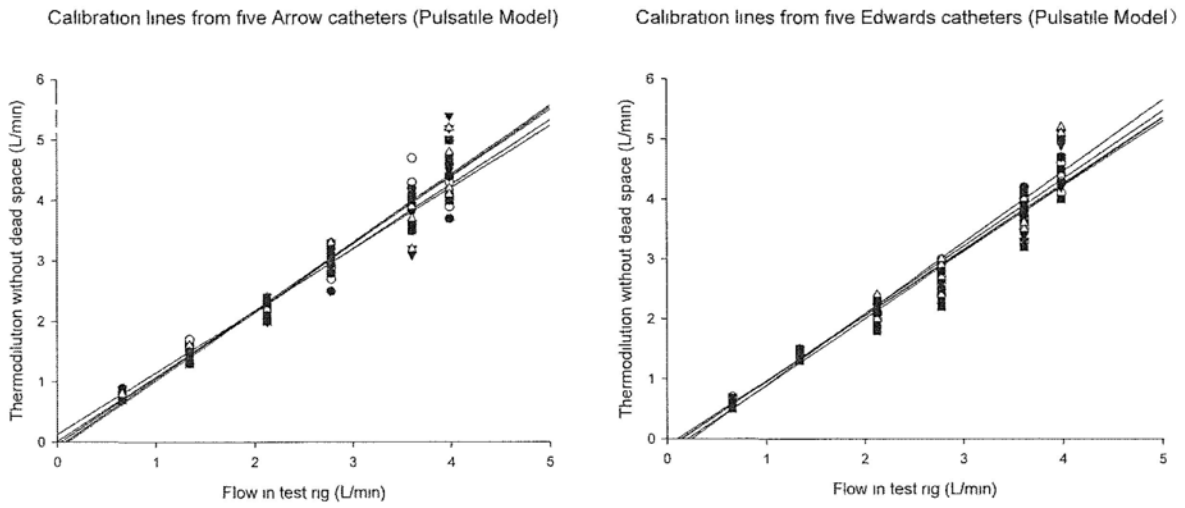


Figure 2.40. Plots comparing the calibration lines for 5 different Arrow catheters (left), and 5 different Edwards catheters (right) using pulsatile flow conditions. Lines constructed from sets of 5 readings taken at different flow rates between 0 and 5 L/min (corrected).

Table 2.11. Data from five (1-5) Arrow and Edwards catheters showing the variations in slope, deviation and correlation coefficients from a pulsatile model.

Arrow	1	2	3	4	5
Slope	1.022	1.107	1.131	1.063	1.13
Deviation	2.2%	10.7%	13.1%	6.3%	13.0%
R-value	0.981	0.973	0.968	0.977	0.987
Edwards	1	2	3	4	5
Slope	1.103	1.083	1.127	1.188	1.117
Deviation	10.3%	8.3%	12.7%	18.8%	11.7%
R-value	0.983	0.985	0.973	0.973	0.969

The deviation (average CV [systematic]) of the slopes from the line of identity for Arrow PAC was $\pm$9.1% and for Edwards PAC was $\pm$12.4%, and overall was $\pm$10.7%. Compared to the result from the steady state model, the deviations were also increased two fold.

However, these data are based on assuming that the line of identity is the baseline. When the mean deviation is used as the baseline the CV [systematic] become $\pm$4.7% and $\pm$4.0% and $\pm$4.4% overall, which may be a more realistic value for the catheter, as whether steady state or pulsatile flow is used should not make any difference to catheter calibration.

2.4 DISCUSSION

2.4.1 TEST RIG DESIGN

In buiding the test rig I was able to satisfy my main design goals, though flow rates were restricted to 0 to 7 L/min. The precision with which flow rates could be measured in the rig was within ±1-2%, which was in keeping with most gold standard measurements of cardiac output (Critchley et al (2010)).

However, data from an in-vitro laboratory investigation should be treated with caution when applied to a clinical setting. In-vitro testing of thermodilution catheters may not mimic clinical use, but it does have a number of important advantages. Flow through the rig can be precisely determined to ±1-2% (calibration data from my study). There is no limitation on the number of readings, and thus a full range of flow rates can be tested which in my investigation facilitated the plotting of calibration lines and estimating the systematic component. In later experiments using a pig model, the quality and quantity was less good. However, the model also had a number of significant limitations. (i) Tap water rather than blood was used as the circulating fluid. The obvious problems of working with a biological fluid such as blood make water the most convenient fluid with which to work. However, blood differs from water by being (a) a non-Newtonion fluid and (b) having a lower heat capacity, 3.6 compared to 4.2 kJ/Kg/^{o}K, respectively, a factor of 0.9. Differences in heat exchange between the cold injectate and circulating fluid can affect the size of the

thermodilution curve and therefore the size of cardiac output readings. Some authors have used a correction factor into their calculation of cardiac output to compensate for under reading when water is used (Andreen et al (1974)). To mimic the non-Newton effect of blood, some investigations have used blood substitutes, such as polygeline (Mackenzie et al (1986)), which would a possible direction for further work using the test rig. (ii) The tip of the PAC in-vivo is normally placed in the pulmonary artery or one of its branches. In the test rig it was placed in a straight piece of 1.6cm diameter tubing which may have affected my results. Although path to catheter, or mixing distance varied in its effect, there was a suggestion that mixing and repeatability of reading was best at 50-70 cm (Table 2.4). Therefore, the absence of any mixing chamber and reliance on laminar flow to mix the cold injectate may have worsened my in-vitro results.

(iii) Another important cause of measurement error with thermodilution not addressed by my investigation was lung ventilation, which causes cyclical variations in cardiac output. Timing of the cold injection is therefore important when performing thermodilution. Whether readings should be performed at random times or synchronized with the ventilator cycle and its effect on precision would need consideration in any clinical trial (Reuter et al (2010)).

Three different design layout styles were described in the literature for building a test rig for thermodilution catheter testing. Designs involved either constant or pulsitile flow systems.

Constant flow systems were based on either (a) a constant water pressure with flow regulator (Rubini et al (1995)), or (b) a variable rate roller pump (Bilfinger et al (1982), Norris et al (1986)). Some authors developed (c) a piston pump system with unidirectional valves to mimic the pumping action of the heart, which they used to investigated left ventricular ejection fraction catheters with a high response rate thermistor (Santos et al (2002),Maruschak et al (1985)). Most designs were based on circulating water. Only one used human blood (Bilfinger et al (1982) and one used glycine (Forrester et al (1972)). Flow rate was most commonly measured by timed measuring cylinder filling. The temperature of the water, or blood, was kept constant at 36 to 38℃ by a thermostated heater and water mixer. In my design, I used a constant flow of water, rather than pulsitile, for ease of construction. A heavy duty aquarium pump was used in preference to a roller pump.

2.4.2. EXTRINSIC FACTORS - INJECTATE

The main outcomes from this part of my investigation were that:

(i) The ice cold injectate was more reliable and provided data with less random variability, shown by the lower CV value. Hence, the choice of iced water as an indicator for my in-vitro model was made.

(ii) The choice of injectate volume was more controversial. In my test rig injectate volumes of 5 and 10 ml had a similar CV, (3.1 and 2.7%) (P=0.37), whereas a 3 ml injectate had a

larger CV 7.7% (P=0.02). Thus, 5 ml was used as the injectate volume in my in-vitro model. I was also concerned that injecting a large volume 10 ml compared to 5 ml, would lead to a more uneven injection and thus flow profile which would affect the measurement of the area under the curve by the monitor. Therefore I chose an injectate of 5ml of ice cold water at 0 to 4℃. Ice cold water theoretically provides a greater thermal challenge (2 to 37℃) than room temperature water (22 to 37℃), and thus the amplitude of the thermodilution curve is larger and readings should be more precise. Injectate volumes above 5ml are reported to have little influence on CV and the precision of readings (Reuter et al (2010)). However, larger volumes can reduce precision because of the recirculation of the indicator (Ruciman et al (1981)).

(iii) The dead space effect of the PAC was perhaps the most important factor that affects the precision of cardiac output measurements. By developing a retrograde method of testing, I was able to eliminate dead space from the catheter and thus investigate it more thoroughly. When using the retrograde method, I found the CV and random error component was smaller than when using the classical method which included significant dead space. When exposing the dead space into different ambient temperatures (zero to body temperature), the temperature which was the most close to that of the injectate (zero temperature) gave the greatest precision and smallest CV. These results confirmed that the dead space of the catheter was a major contributor to error when performing thermodilution measurements of cardiac output.

Strictly speaking, the results from this part of my study pertain only to an in-vitro system. It is quite possible that the precision of in-vivo measurements could be substantially different. Traditionally, investigators have used 1-6 injections of 5-10 ml of iced or tepid indicators. However, the feature that most previous investigations have in common is the lack of any evidence that the accuracy of their thermodilution technique was known. So data from my in-vitro studies is useful in understanding what sort of error will be encountered (Nilsson LB et al (2004)).

In the part of my work that evaluated the influence of the injectate temperature, calibration lines were parallel, and close together when the dead space method was used, but these lines diverged when the retrograde without dead space method was used. Also the linearity of calibration line was less when the dead space was eliminated particular with the Edwards catheters (see correlation coefficients). This demonstrates the key role of dead space as a factor in the cardiac output monitor algorithm which is set up to compensating for the dead space. Furthermore the CV for both Arrow and Edwards catheter were larger when dead space was used, which was to be expected. However, a more in depth analysis of the algorithm modification used by different monitor systems was beyond the score of this thesis.

Also, important was the effect on injectate temperature on the CV for both no dead space and dead space methods. Results were comparable between the Arrow and Edwards catheter with

the Edwards catheter performing slightly better than the Arrow catheter using the classical dead space method, 5.1-12.3% versus 9.7-14.9%, respectively. The use of ice, compared to room temperature, also had a near two fold improvement in CV, presumably reflecting that fact that the thermal energy (heat reductant) was twice using ice, 31-36℃ versus 11-13℃ respectively.

Therefore, based on these experiment results, the use of iced water provides more reliable single bolus readings with a CV of 10% for Arrow and 5% for Edwards, and the monitor is not properly set up or calibrated for non dead space use. In regard to this last statement the Siemens SC9000 cardiac output monitor software would appear to perform better with Edwards rather than Arrow catheter and there appears to be some non-linearity over the range of flows with Edwars catheter, but not apparent with Arrow catheter.

Increasing the volume of injectate improved the CV and thus the precision of single shot thermodilution readings to below 3%. The Edwards catheter performed better than the Arrow catheter (2.3% versus 6.5%) with 10ml injectate again suggesting a compatibility problem with the software of the Siemens SC9000 monitor.

Theoretically, in terms of injectate volume and temperature, larger volumes of colder solutions should cause larger temperature changes in clinical use and thus minimize some of the impact of pulmonary artery temperature variations. However, larger volumes of colder

solutions may increase the possibility of measurement errors and loss of indicator (cold) before mixing. In fact, varied conclusions existed about these factors: Some researchers found the room temperature acceptable when comparing with the common iced injectate in clinical practice (Shellock FG et al (1983), Faybik P et al (2004)). Others believed there should be some extra condition such as a dual thermistor catheter if we used the room temperature injectate instead of the iced injectate (Berthelsen PG et al (2002). There were also some publications describing the factors combining the injectate temperature and the indicator amount. And the common view is the 10-ml inced injectates should be the most accurate choice, but the 5-ml iced injectates and 10-ml room injectates are also accecptable for the clinical practice (Elkayam et al (1983); Renner et al (1993); Pearl RG et al (1986)). But their vitro model is different from the clinical practice, so I established a standard method by doing pre-testing the evaluations.

I also evaluated the influence of the injection site to the thermistor distance when I used a modified method of retrograde catheter placement without dead space. In particular I was concerned that using small lengths 10-40 cm may affect calibration due to insufficient mixing and long length 50-100 cm due loss definition of the dilution curve. There were no statistical differences or trend in the slopes between different distances. However, in order to deduce any effect from this factor, I maintained the distance consistent on 30 cm. When using a standard thermodilution catheter the through catheter injection port for the cold saline

injectate is situated 30 cm downstream of the thermistor. Therefore I was able to eliminate any potential port to thermistor distance effect in my test rig.

Catheter dead-space also plays an important role in PAC thermodilution measurement error. A typical PAC is just over 1-meter in length and has three lumens. One of these lumens, the CVP port, is used to inject the cold indicator and has a volume of approximately 1 ml, which is referred to as dead-space. This dead-space contributes significantly (e.g. 10-20%) to the volume of the injectate (e.g. 5-10ml). Indeed if the temperature of the fluid in the dead-space is different from that of the indicator, then the thermal effect and thus the measurement of cardiac output is altered. As the temperature of the dead-space fluid is difficult to control, it becomes a major source of variability in cardiac output readings. Heat gain by the injectate as it passes through the dead space may also be a factor and can be influenced by (i) injection time which should be less than 4s, (ii) length of catheter place intravenously, (iii) the temperature of the blood and (iv) the haemoglobin level (Forrester et al (1972)). Minimizing the effect of dead-space therefore becomes an important consideration in PAC manufacture. The impact of dead-space on precision was shown in the first part of my investigation, where I compared the CV of measurements with and without it. The presence of dead-space added up to 5% to the total error for a single reading (Table 2.9).

2.4.3. INTRINSIC FACTORS – STEADY STATE AND PULSATILE TESTING

The main outcomes from this part of my work were that:

(i) Individual single bolus thermodilution readings have a CV of at best of ±5%, or component of the error of ±10%, and this value could be improved to ±6% by using the average of three readings.

(ii) Errors in thermodilution reading could also arise from the differences between catheter systems, which can not be quantified by simply taking serial readings and calculating the CV. By plotting calibration lines for each catheter and measuring the slope (m) I was able to estimate the systematic component of the error which was ±12% at best.

(iii) The overall error for thermodilution measurements based on my CV data for the random and systematic errors combined was ±15% for a single reading and ±13% for triplicate readings, albeit from in-vitro steady flow testing using the Siements SC9000 monitor.

(iv) The choice of monitor also had a significant effect on the precision of readings, as some monitors were more reliable than others. I found that compared to the Siemens SC9000, the Sirecust 1261 monitor increased the error by 45% and Philips MP50 monitor by 100%. This increased the error for single and triplicate reading to ± 22-31% and ± 17-28%, respectively, which are larger than the errors quoted by Stetz et al of 22% and 13% some 30-years ago (Stetz et al (1982)).

(v) For the pulsatile model, based on my CV data, the component of error arising from the random errors for Arrow and Edwards PACs were ±17.5% and ±15.8%, respectively, and overall was ±16.7% (e.g. 95% confidence intervals). Based on my calibration line data, the systematic components of the error were ±17.8% and ± 24.3%, respectively, and overall was ±21.1%. Therefore, the total estimated error for a single thermodilution reading, derived from CV (random) and CV (systematic) was ± 26.9%, and this would be reduced to 23.2% for triplicate readings (e.g. CV = $\sqrt{(CVorCE(rand)^2 + CV(syst)^2}$). Compared to steady state model, the average CV was increased about 3.4% (5.1-8.5%), and the overall error was increased about 11.6% (15.3-26.9%).

The repeatability of serial thermodilution readings has been investigated previously in both in-vitro models (Bilfinger et al (1982), Forrester et al (1972), Hoel et al(1978)) and clinical settings (Andreen et al (1974), Fischer et al (1978), Kohanna et al (1977), Olsson et al (1970), Vandermoten (1977)) Repeatability in most of the studies was measured from serial thermodilution reading and quoted as the CV based on standard deviation, rather than 95% confidence intervals as used today. For in-vitro studies the CVs were about 5% (range: 2.5 to 8.5%), which was in keeping with my Siemens 9000 result of 5.1%. For in-vivo or clinical testing the CVs were higher and ranged from 4.8 to 8.6%. However, only Fischer et al have specifically measured both random and systematic errors arising from the catheter system (Fischer et al (1978)). Using a statistical analysis based on repeatability data from paired

thermodilution and dye dilution readings they were algebraically able to derive the random and systematic error components using the adding of variances approach. These authors found a systematic component of the error for thermodilution of 5% (CV), which was in keeping with my result of 5.9%. For dye dilution the systematic error was 15%.

More up-to-date information on the precision of the current makes of thermodilution PAC is not readily available in the literature and there have been calls to reappraise the current accepted error of thermodilution readings of ±20% (Berthelsen et al (2002), Nilsson et al (2004)). Work dating back before 1982 published by Stetz et al (Stetz et al (1982)) is still used today to set the precision of the reference method thermodilution in most validation studies. Stetz et al performed a statistical review of nine papers published between 1968 and 1979 that provided CV reproducibility data on the performance of thermodilution and from this data determined the minimum acceptable percentage change in cardiac output between a single or triplicate set of readings. Ambient room temperature and volume of 10ml was used for the injectate in most of these studies. From their meta-analysis Stetz et al recommended precision for thermodilution readings of 13% (triplicate readings) and 22% (single reading) and these are still in use today (Stetz et al (1982)). Data from my in-vitro study of 15.3 and 13.0% would suggest that these limits are still close to the truth and therefore the precision of the thermodilution method has not been improved over the last twenty to thirty years.

My data also showed that the choice of cardiac output monitor can also have a significant effect on the size of the precision, which increased by over 45% for the Sirecust and 100% for the Philips monitors. Thus, the precision can vary greatly when using different monitoring systems and this brings into question the choice of a standard precision of ±20% for thermodilution measurement and the subsequent use of percentage error of less ±30% to test new cardiac output device performance (Critchley et al (1999)). In many published studies at present, the choice of monitor and catheter is not stated, or even worse, the reader does not know whether a variety of different monitors and catheters have been used.

The most likely reason for the systematic component of the error is slight manufacturing differences between individual catheters. Pilot data comparing calibration lines when the tip of the PAC was placed in different positions within the flow chamber did not show such wide variations. Manufacturers do not provide this sort of quality control information about the performance of their PACs. Therefore my estimates of systematic errors provide an alternative source of such information. Data from the Sirecust and Philips monitors showed an even wider variation in calibration lines, which suggests that an important issue exists regarding precision and the interface between different PAC and monitor systems. Further investigation of this issue is needed.

When the precision of the reference method is undetermined, which is a criticism of most published studies, acceptance criteria of less than ±30% cannot be applied with any great certainty. In a recent paper Cecconi et al proved that without knowing the precision of the reference method it is difficult to interpret the meaning of the percentage error, or limits of agreement, from Bland and Altman analysis (Cecconi et al (2009)). My results confirm that the precision of the reference method can vary quite considerably between studies and thus stresses their message. However, their advice to measure the precision of the reference method at the bedside using serial readings and calculate the reproducibility using the CV is not totally correct because only the random component, and not the systematic component, of the error are measured. Unfortunately, it is the only possible measurement of precision that can easily be made at the bedside. Therefore, I suggest adding the best available estimate of the systematic component. Based on data from my investigation this would be ±11.6%.

There were several limitations and problems I encountered during the construction and use of the pulsatile model: (i) Because the flow rate was not continuous, the flow meter showed a pulsatile range reading instead of the steady reading in the constant flow model. Thus I had to take an average reading for each of flow. (ii) As the pump I bought was designed for constant rather than pulsatile flow. It resulted in 3 pumps breaking down and needing replacement.

CHAPTER 3

ASSESSMENT OF THE PERFORMANCE OF THERMODILUTION CATHETERS IN A PORCINE MODEL

3.1 INTRODUCTION

Having completed an in-vitro evaluation of the reliability and accuracy of standard single bolus thermodilution catheters or PACs, the next step was to determine their reliability and accuracy in-vivo. In Hong Kong the most accessible animal model was the domestic pig, which was frequently used at the Chinese University and Prince of Wales Hospital, for surgical workshops. However, I did need to convert experimental techniques developed in the department's previous canine (dog) model to the pig (Peng et al (2005) and (2006)).

3.2 SETTING AND EQUIPMENT

3.2.1. LOCATION

All animal experiments were conducted in Research Unit Surgical Operating Room of the Laboratory Animal Services Centre (LASEC), which is located on the ground floor of the Basic Clinical Science Building at the Prince of Wales Hospital.

3.2.2. APPROVALS

(i) License to perform Animal experiments in Hong Kong for department of Health

Ref No.: (08-311) in DH/HA&P/8/2/1 Pt.5, valid from 11 March 2009 to 10 March 2011, holder: Yang Xiaoxing

(ii) Animal Experimentation Ethics Committee (AEEC) Approval, Ref No. 07/014/ERG and 464007.

3.2.3. ANIMALS

Domestic pigs, supplied by the LASEC, Chinese University of Hong Kong.

Age was approximately 3 months and, weight 30 kg.

Housing of pigs prior to anaesthesia and experimentation was at LASEC faculty at the Prince of Wales Hospital using: Rooms equipped with locks. Room temperature and humidity were regulated (e.g. 24±2℃; 55±10%).

Feeding and drinking water were provided: Untreated pig food and tap water.

All experiments were terminal, and lasted 9 (7-11) hours.

3.2.4. MATERIALS

3.2.4.1 DRUGS

Anaesthetic agents

(i) Induction (given intramuscularly)

Xylazine (20mg/ml) (Alfasan, Woerden, Holland)

Ketamine (100mg/ml) (Alfasan, Woerden, Holland)

Atropine (0.6mg/ml) (Atlantic Laboratories Corp. Ltd, Bangkok, Thailand)

Pentobarbital ***given intravenously*** (200mg/ml) (Alfasan, Woerden, Holland)

(ii) Maintenance of Anasethesia (given by intravenous infusion)

Ketamine (100mg/ml) (Alfasan, Woerden, Holland)

Propofol (10mg/ml) (Braun, Melsungen AG, Germany)

Muscle paralysis *(given intramuscularly)*

Vecuronium (4mg/ml) (N.V. Organon, OSS, Holland)

Analgesic *(given intramuscularly)*

Temgesic (0.3mg/ml) (Reckitt Benckiser Healthcare Ltd, Hull, England)

Cardiac drugs *(given by intravenous infusion)*

(i) Inotrope and Vasopressor (to increase cardiac output and peripheral resistance)

Dopamine (40mg/ml) (Hospira Inc, Lake Forest, USA)

Epinephrine [Adrenaline] (1mg/ml) (Hospira Inc, Lake Forest, USA)

Norepinephrine [Noradrenaline] (1mg/ml) (Hospira Inc, Lake Forest, USA)

(ii) Vasodilator and Beta blocker (to reduce cardiac output and peripheral resistance)

Glyceryl trinitrate (1mg/ml) (Hameln Pharmaceuticals Gmbh, Hameln, Germany)

Betaloc (1mg/ml) (Astrazeneca AB, Sodertajie, Sweden)

Anticoagulant

Heparin (1000IU/ml) (Hospira Inc, Lake Forest, USA)

Intravenous Fluid

Normal Saline 0.9% (Baxter Healthcare Ltd, Shanghai, China)

Gelofusine (B.Braun Medical AG, Crissier, Switzeland)

3.2.4.2 EQUIPMENT

(i) Administration of Anaesthesia

LP10 Ventilator (Nellcor and Puritan Bennett, Boulder, USA)

Endo-tracheal tube (Teleflex Medical Gmbh, Kermen, Germany)

Intravenous cannula and administration sets (Edwards Life-sciences, Irvine, California, USA)

Terufusion Syringe Pump Model STC-520 (Terumo Corporation, Tokyo, Japan)

(ii) Surgical

Surgical diathermy (Valleylab, Boulder, Colorado, USA)

Surgical instruments (e.g. bone cutter, forceps, scissors, scalpel, suture, etc. Obtained locally)

(iii) Monitoring

Arterial pressure monitoring set (Edwards Life-sciences, Irvine, California, USA)

Pressure Transducer (Edwards Life-sciences, Irvine, California, USA)

8.5 Fr gauge Swan-Ganz catheter sheath (Edwards Life-sciences, Irvine, California, USA)

Urine catheter with metered collection bag (URO Technology SDN.BHD, Johor, Malaysia)

(iv)Flow Measurement Equipment

16A and 20A large vessel Flow probes (Transonic System, Ithaca, New York, USA)

Flow meter T106 (Transonic System, Ithaca, New York, USA)

Pulmonary Artery Thermodilution Catheters

(i) Arrow (Arrow Int., Teleflex Medical, Reading, Pennsylvania, USA)

(ii) Edwards Swan-Ganz (Edwards Life-sciences, Irvine, California, USA)

Siemens SC9000 cardiac output monitor (Siemens Medical Systems, Inc., Danvers, Massachusetts, USA)

(v) Warming Equipment

Warming blanket (TUV Rheinland of North America Inc, Newtown, USA)

3.3 METHODOLOGY

3.3.1. ANAESTHESIA

First, the pig was sedated with an intramuscular injection of (2ml of xylazine(20mg/ml), 6ml of ketamine(100mg/ml) and 2ml of atropine(0.6mg/ml), 10ml in total) (Figure 3.1). This made the pig easier to manage. A 20- gauge hypodermic needle, length of 3 - 4 cm, was used to ensure that the injection was delivered into the muscle. An extension tube was used to prevent dislodgement as the pig struggled while the drug mixture was being injected.

Once sedated, a central or lateral ear vein was cannulated using a 22- gauge butterfly needle which was taped to the ear lobe. Both ears were cannulated.

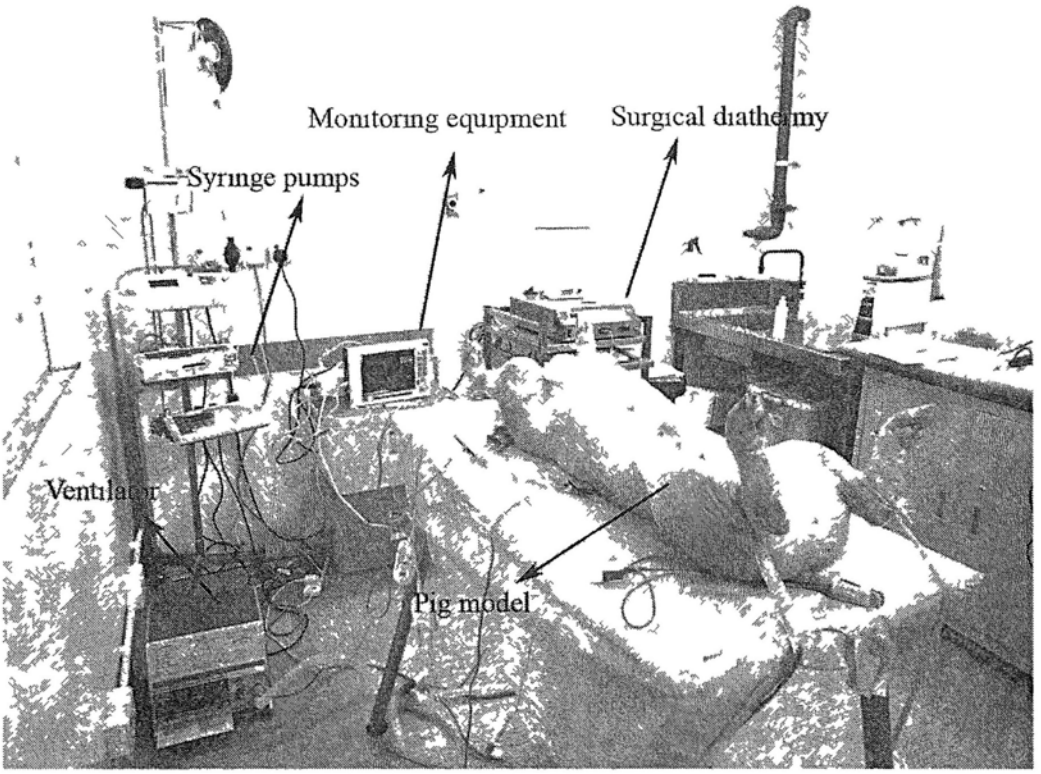


Figure 3 1 Operating room of Research Unit of LASEC with anaesthetized pig prepared and tied to operating table In background ventilator and syringe pumps (left) and monitoring equipment (back)

Full anaesthesia was induced with an intravenous bolus of 10 ml of 2% pentobarbital The pig was allowed to breath spontaneously until the airway was secured by tracheotomy or tracheal intubation During the period of surgical preparation and experimentation (10am-7pm), anasethesia was maintained with a continuous infusion of ketamine (2ml/h) and propofol (15-20ml/h) given by separate infusion pumps

Mechanical ventilation of the lungs was provided by using volume control mode set to a tidal volume 400 ml, Respiration frequency 14 breaths/min, Inspiration time 1 5s Ventilation could also be triggered by inspiratory efforts, level -2 5 cm H_2O

Muscle relaxation was provided with vecuronium. Homeostasis and in particular body temperature was maintained by on table warming blanket kept at 45℃.

3.3.2. SURGICAL PREPARATION

3.3.2.1 SECURING THE AIRWAY

Intubation in pigs can be technically difficult because of the overlying epiglottis. Tracheotomy was used instead. A longitudinal incision was made in the skin just above the sternal notch. Just below the thyroid, the neck muscles were separated, the membrane covering the trachea was divided, the rings of cartilage that make up the trachea was identified. The trachea was mobilized and a transverse incision of 1 cm between two tracheal cartilage rings was made by a scalpel blade (Figure 3.2). A 6.5 mm inner diameter tracheal tube was inserted into the trachea.

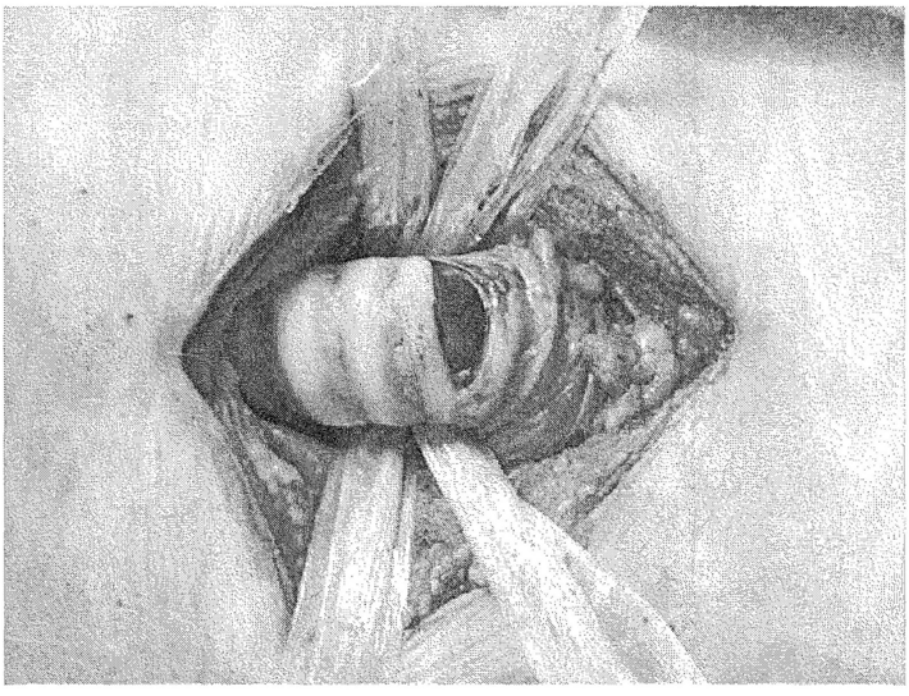


Figure 3.2. Longitudinal incision in the anterior neck of the pig following dissection through the skin and muscle, the trachea was identified and isolated. Then a transverse cut was made by a scalpel into the trachea and a trachea tube inserted into the lumen, facilitating ventilation.

3.3.2.2 PLACEMENT OF THE PULMONARY ARTERY CATHETER

Preparation of Equipment

a. The lumens of the catheter were flushed with saline to check patency and to remove any blood clot (from previous use) and air bubbles.

b. The integrity of the balloon at the tip was checked for major asymmetry and for leaks by inflating and submerging in water.

c. The pressure monitoring system used to guide advancement of the catheter tip into pulmonary artery via the chambers of the heart was checked.

d. The electrical continuity and operation of the catheter tip thermistor was checked by the cardiac output monitor.

Site of insertion

The pig's right internal jugular vein was used. Its anatomical position was determined as it arises from the base of the skull, in the posterior compartment via the jugular foramen, as a continuation of the jugular bulb of the sigmoid sinus. At the level of the thyroid cartilage which was palpated the internal jugular vein lies lateral and immediately deep to the body of the sternomastoid muscle, somewhat posterior and lateral to the carotid artery, which was used as a landmark. With the pig in a supine position and the head turned slightly to the left, the carotid artery was identified by gentle palpation using the index and middle fingers of the left hand and a longitudinal skin incision made.

Surgical part

A standard venous cut-down technique using surgical diathermy was used to locate the vein. As the pig has very tough skin, a percutaneous needle approach would have been difficult. A 5 cm long incision was made approximately 3 cm to the right of the midline. The skin, subcutaneous tissues, and muscle were separated and the internal jugular vein identified. A 3 cm section of vein was exposed and mobilized by blunt dissection. Care was taken not to over manipulate the vein because it went into spasm easily, which made cannulation more difficult. Two lengths of suture were placed

around the vein proximally and distally to control movement and bleeding from the vein during cannulation.

The proximal suture was lifted slighted to empty the vein, and a 8.5Fr thermodilution catheter sheath was introduced into the vein. The sheath acted as an insertion port and guide for the catheter. The sheath was left in the vein so that I could easily change catheters during the experiment.

Placement of the catheter

The pulmonary artery catheter was connected to the pressure transducer set and Siemens monitor, which displayed a pressure waveform which indicated the position of the catheter as it passed through the chambers of the right heart: The right atrium, right ventricle and into the pulmonary artery (Figure 3.3).

a. The catheter was inserted via the sheath and, advanced until pressure tracing indicates that tip of catheter is in the right atrium (e.g. venous pressure waves of 0-5 mmHg amplitude).

b. The balloon was then inflated to facilitate passage through the tricuspid valve, right ventricle (e.g. 25/0 mmHg), pulmonary valve (e.g. 25/15 mmHg), and into the pulmonary artery (e.g. occlusive wave 10-15 mmHg). The waveforms and pressure readings were shown on the monitor screen (Siemens SC9000) while the catheter was being advanced and provided definitive evidence of the position of the catheter tip as it was advanced into the pulmonary artery (Figure 3.3).

c. Once positioned in the pulmonary artery the balloon was deflated and, the catheter was in correct position for thermodilution measurements. The proximal central venous injection port of the catheter should have been in the right atrium, and the thermistor in the pulmonary artery.

d. The cardiac output computer of Siemens monitor was used to measure cardiac outputs.

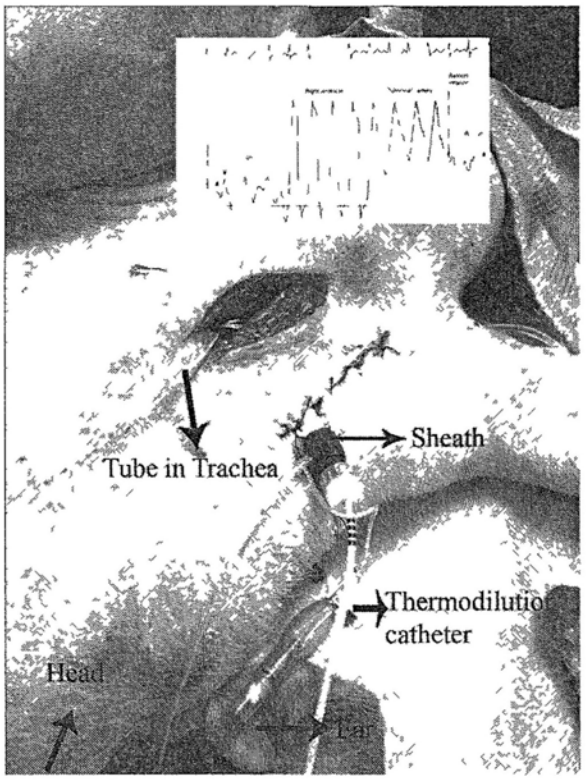


Figure 3.3. Thermodilution catheter inserted via sheath set and stitched into pig's right interior jugular vein. Endotracheal tube inserted via tracheotomy incision also shown. The pressure waveforms (upper insert) were used to guide advancement of the pulmonary artery catheter tip into the pulmonary artery.

Thermodilution Measurement

A bolus of 10 ml normal saline solution kept at room temperature was injected at a constant rate via the proximal central venous port of the catheter within a four seconds period. The temperature change curve was recorded by the monitor and cardiac output calculated. Curves were discarded if the thermodilution curve lacked a rapid upslope

or a smooth down slope. The method of calculation is described elsewhere in my thesis (Chapter 1).

3.3.2.3. INSERTION OF THE ARTERIAL CATHETER

Preparation of Equipment

a. The lumens of the catheter were flushed with saline to clear patency and to remove any air bubbles.

b. The same pressure monitoring system as used for placement of the thermodilution catheter was set up and connected to the Siemens monitor.

c. A 500 ml bag of normal saline with heparin 100 IU added was connected to the transducer set. The set was flushed from time to time, to keep the catheter patent.

Site of insertion

The femoral artery was located in the femoral triangle below the inguinal ligament. The superficial branch was chosen for the arterial pressure monitoring. It was located by palpating the arterial pulse.

Surgical technique

A 4 cm longitudinal incision was made over the femoral artery using surgical cutting diathermy. The skin, and subcutaneous tissue were cut and the femoral artery was located by blunt dissection. A 3 cm section of artery was exposed. Two lengths of suture was placed around the artery both proximally and distally to control movement and bleeding from the artery during cannulation (Figure 3.4).

The proximal suture was lifted slighted to empty the vessel and to control bleeding. The arterial pressure monitoring catheter was introduced into the artery using a standard guide wire. The catheter was then fixed in position by tightening the two lengths of suture placed around the artery.

Measurement system

The arterial catheter was then connected to the Siemens monitor. The continuous arterial pressure waveform and numerical readings were displayed (Figure 3.4).

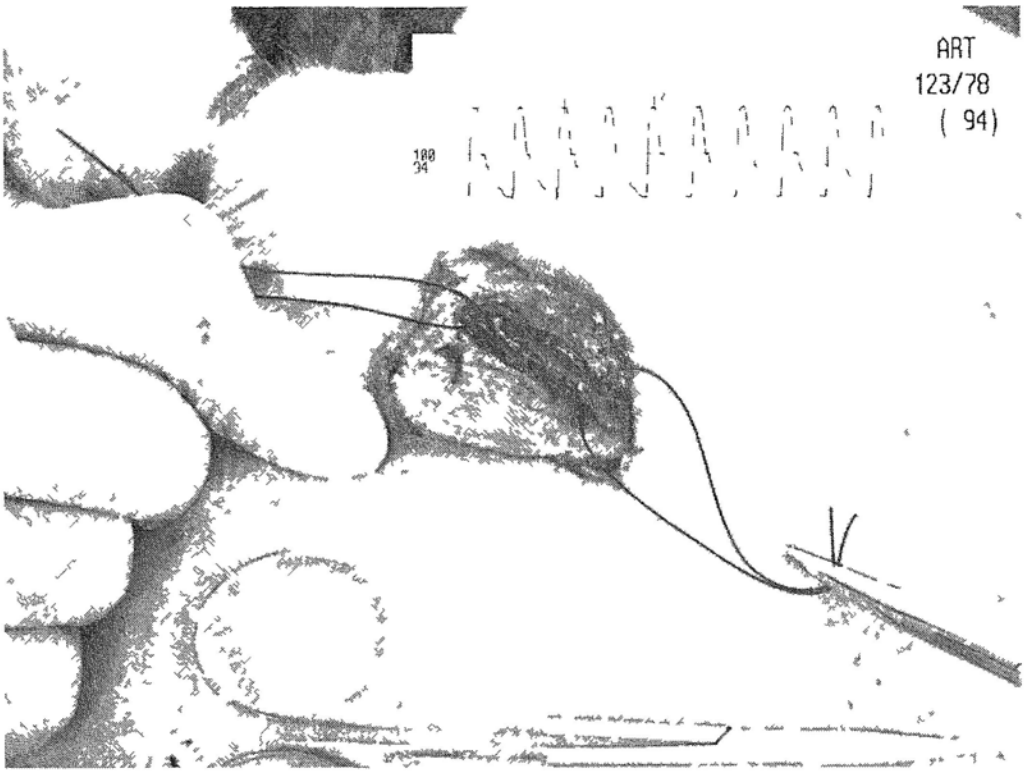


Figure 3.4. Exposed right femoral artery with placement of two controlling sutures. The arterial catheter was inserted into the lumen of the artery and was connected to the monitor. Mean arterial pressure was recorded.

3 3 2 4. CATHETERIZATION OF THE BLADDER

To prevent urine leakage the bladder was catheterized Cystotomy rather than urethral catheterization was used because catheterization of the male urethra in pigs can be difficult to perform and maintain

A cyctotomy was performed through a 5cm vertical incision using cutting surgical diathermy over the lower abdomen below the umbilicus and, in the midline and two finger widths above the pubic symphisis The skin, superficial fascia, linea alba were all cut, the transversus abdominus muscle spit, and the peritoneum displaced by blunt dissection. The bladder lumen was located by needle aspiration of urine or by

visualizing its vesicular plexus A small incision in the bladder wall was made and the catheter was inserted A purse-string suture was used to secure the catheter The skin incision was closed by interrupted suture A urine collection bag and meter was connected to the catheter (Figure 3 5)

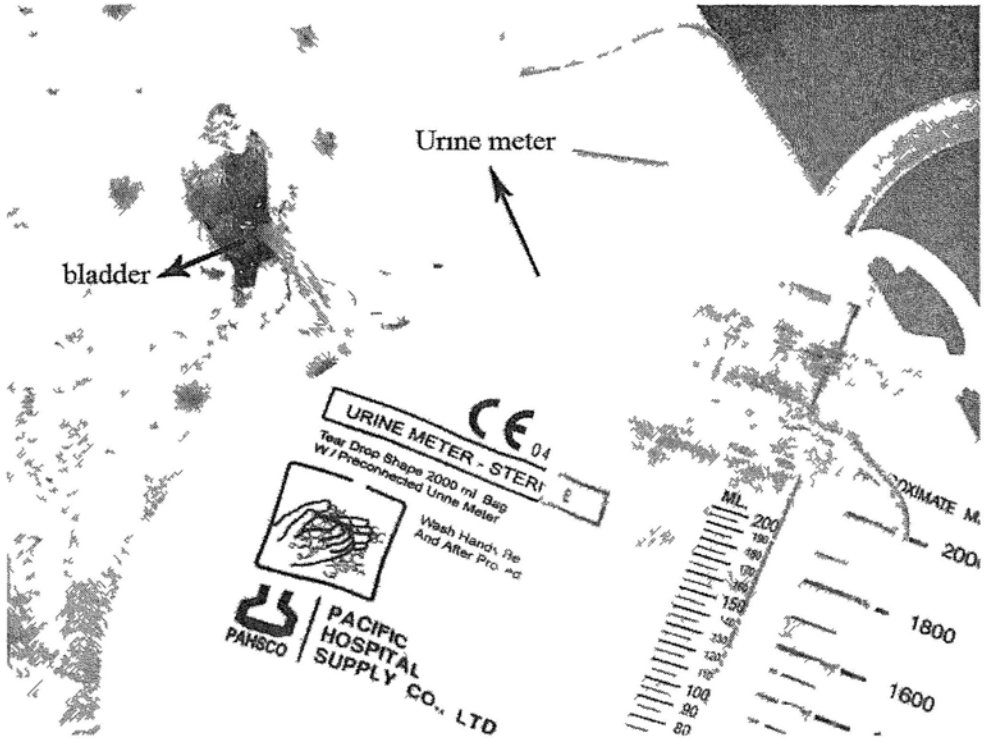


Figure 3 5 Cystotomy incision, catheter inserted into bladder and connection bag

3 3 2 5 PLACEMENT OF THE AORTIC FLOW PROBE

I first practiced on dead pig carcasses to familiarize myself with the anatomy and technique These were pigs that had been used in workshops and their carcasses had been discarded I experimented with two methods to open the chest, (a) midline sternotomy and (b) left thoractomy After considering the factors involved such as difficulty, bleeding, extent of incision, and exposure of the aorta, I chose a left lateral thoracotomy However, unlike the departments previous surgical approach of

separating the ribs in dogs, because of the more muscular rib cage, I excised the overlying ribs using a bone cutter. This method of removing the rib (e.g. 4th rib) had been previously described in sheep by (Bednarik and May, (1995)).

Probe placement technique

The pig was anaesthetized and tied to the operating table in a supine position. The skin was cleaned and, a curved incision of about 8 cm long over the 3rd or 4th anterior intercostal space was made using cutting surgical diathermy. The edges of the skin incision were retracted, and the fat, muscle, fascia were dissected down until the ribs became visible. Care was taken not to damage any vessels or nerves, thus avoiding bleeding or muscle twitching.

The thoracic cavity was opened and left lung allowed to collapse. The anterior part of the third and fourth, (or fourth and fifth ribs depending on the location of the heart of the pig), were removed using bone cutters thus exposing the beating heart within the pericardium. The pericardium was grabbed just above (proximal) the auricular appendage by forceps and a small 0.5 cm long incision was made using scissors. Then the pericardium over the left atrial appendage was opened longitudinally. The pericardial incision was extended cephalad to the superior vena caval pericardial reflection, avoiding the nerves, to expose the pulmonary artery and underlying the aorta (Figure 3.6). Both the pulmonary artery and the aorta were grasped by the fingers and pulled caudally. The adventitia between the pulmonary artery and the aorta was separated by carefully blunt finger dissection until the space was large

enough to accommodate the A series transonic flow probe. Unlike our previous dog work, these young pigs and fat did not have to be dissected off the aorta (Peng et al (2006)) Next the flow probe was slipped around the ascending aorta with the probe rotated until its opening was pointing out of the wound. The cable of the probe exited the wound cephalad so that it did not impinge on the pulmonary artery which lay just beside the aorta (Figure 3.7). The housing of the flow probe was filled with gel to assure a good acoustic contact with the vessel.

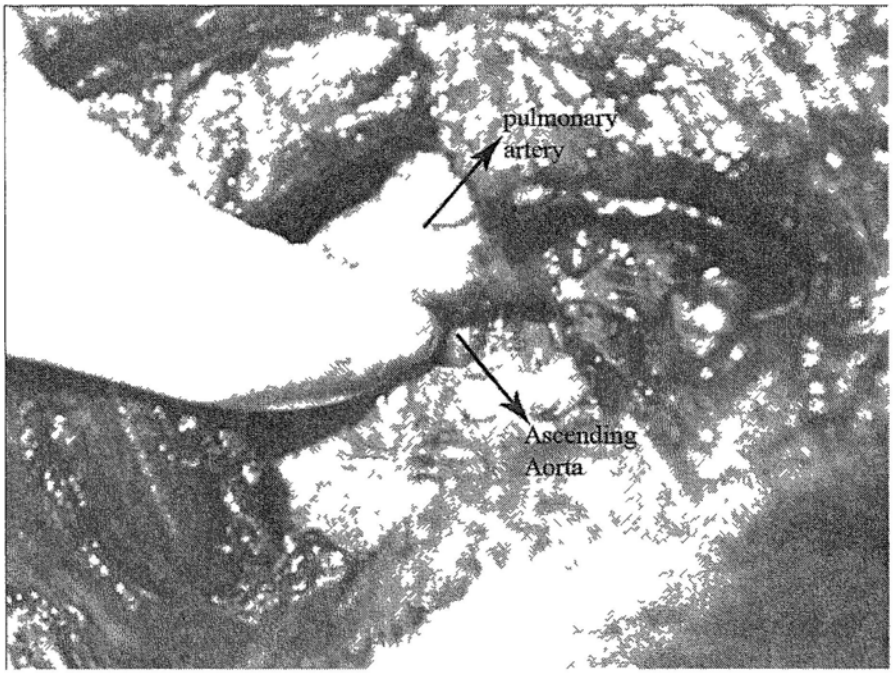


Figure 3.6. The pulmonary artery and the ascending aorta both exposed. The ascending aorta seen lying under the pulmonary artery.

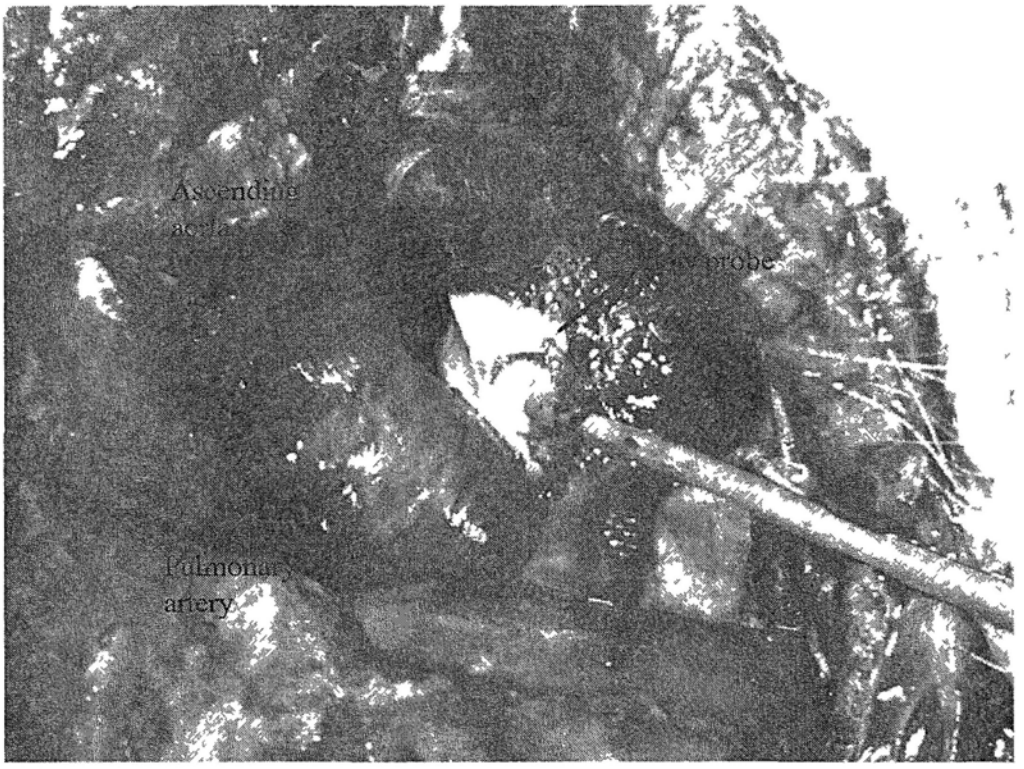


Figure 3.7. Flow probe shown placed around the ascending aorta, and behind the pulmonary artery.

3.3.2.6. MANIPULATION OF CARDIAC OUTPUT

Catecholamine class drugs dopamine, epinephrine (or adrenaline) and norepinephrine (or noradrenaline) were used to increase the cardiac output. They were administered by intravenous infusion. Positive inotropic and chronotropic effects were induced via increased β_1 receptor activation which resulted in an increased cardiac output. A short acting β-blocker and glyceryl trinitrate were used to decrease cardiac output. In later experiments I increased the rate of the maintenance propofol infusion to reduce cardiac output. Rates of drugs were kept constant for several minutes to facilitate steady-state circulatory conditions. The plan was to induce flow conditions ranging from low to high cardiac outputs.

3.4 OUTLINE OF EXPERIMENTAL PROTOCOL

3.4.1 OBJECTIVE

In performing in-vivo pig experiments, I wished to determine the random and systematic errors defined in my previous in vitro bench work for both Arrow and Edwards PACs.

A range of cardiac outputs were produced using cardiovascular drugs, both stimulatory and inhibitory.

(a) To determine the random component I measured the coefficient of variation of a series of readings during steady state conditions, for several PACs.

(b) To determine the systematic component I compared (i) the mean bias for several catheter within the same experimental animal (ii) I found it too difficult to collect sufficient data to draw calibration lines for more than two catheters in the same pig, but (iii) I did compare gradient from catheter used in different pigs.

(c) I also investigated the effect of treatments and extremes in cardiac output, high and low levels of cardiac output on the error.

My use of pigs and what I investigated is outlined in Table 3.1.

3.4.2 LIMITATIONS TO THIS SECTION OF WORK

I found that the pig model was not as stable and easy to work with and collect data from as the in-vitro bench model. Pigs are well known as being poor experimental animal models and often die prematurely. However, they were readily available and cheap to obtain in Hong Kong.

My experiments were limited to 10 pigs due to time and funding constraints.

Table 3.1. Outline of how each pig was used.

Pig	Weight (kg)	Complications	Procedure	Catheters used	Objective	Data analysis
1	32	N/A	(1) Anaesthesia (2) Securing the airway (3) Ventilation (4) Placement of PACs (5) Insertion of arterial pressure monitoring catheter (6) Bladder catheterization (7) Placement of the aortic flow probe	Compared 2-Arrow and 2-Edwards	Compare variation and bias between different catheters and determine the random and systematic components of the error.	Coefficient of variation and Modified Bland and Altman
2	30	N/A		Compared 5-Arrow and 5-Edwards		
3	31	N/A		Compared 1-Arrow and 1-Edwards	Determine the systematic error by constructing calibration lines for two or more catheter	Regression analysis and Bland and Altman
4	31	Atrial and ventricular fibrilation		One Edwards study terminated early		
5	27	N/A		Compared 1-Arrow and 1-Edwards		
6	30	N/A		One Arrow	Performance of thermodilution catheters under control and extreme circulatory conditions	Scatter plot and Bland and Altman
7	30	N/A		One Arrow		
8	27	N/A		One Arrow		
9	30	N/A		One Arrow		
10	31	N/A		One Arrow		

3.4.3 RESULTS

3.4.3.1 DEMOGRAPHIC DATA

Data was collected from ten anaesthetized pigs between October 2010 and February 2011. One additional pig was used but died before data could be collected due to pulmonary artery rupture while placing the flow probe. Young male pigs were ordered about 3 months in age with a mean weight of 30kg (range: 27-32kg). The average duration of each experiment from the time of inducing anaesthesia to death of the pig was 9 hours (range: 7-11 hours).

3.4.3.2 HAEMODYNAMIC DATA

Haemodynamic data was analyzed as two groups: (i) baseline, and (ii) treatment in which cardiovascular drugs were used to vary cardiac output.

Data from ten pigs are presented. One hundred and two sets (e.g. mean values from 480 pairs) of data were collected (42-baseline and 60-following treatment).

Baseline cardiac output (mean (s.d.)) was 2.1(0.5) and 2.2(0.6) L/min for flow meter and thermodilution readings, respectively. Baseline mean arterial pressure (MAP) was 85 (range: 69-122) mmHg, heart rate (HR) was 87 (range: 58-109) beat/min and systemic vascular resistance (SVR) was 2909 (range: 1881-4152) dyn·s/cm^5 (SVR was calculated using the formula SVR= (MAP – CVP)*80/CO dyn·s/cm^5 where CVP was assumed to be 5 mmHg). The range of cardiac output following treatments were 0.5 to 4.4 and 0.7 to 5.5 L/min for flow meter and thermodilution, respectively. MAP

ranged from 44 to 131 mmHg and systemic vascular resistance from 1081 to 6651 dyn·s/cm^5.

3.4.3.3. MEASUREMENT ERRORS

Previously, in-vitro experiments (e.g. test rig) involved varying flow rates and changing catheters to facilitate the evaluation of both random and systematic errors. In the in-vivo model (e.g. living model) two pigs were allocated to evaluating the random and systematic error components.

a. Random Error

In pig 1, two Arrow and two Edwards catheters were tested. Data for both baseline and treatment were evaluated. Nine pairs of readings were collected at each cardiac output level.

In pig 2, five Arrow and five Edwards catheters were used with three sets of readings being collected for each of the ten catheters. As three sets of readings at each flow rate and for each catheter were collected, CV could not be reliably assessed as the degree of freedom of the data was too small (df=2).

Data analysis

Errors were only analyzed using data from the baseline group. The random error was described by the coefficient of variation (CV=SD/Mean) for each catheter and flow rate (Table 3.2).

Table 3.2. Coefficient of variation data from pig 1. All cardiac output measurements were taken at baseline.

Catheter	CO (L/min)									CV (±%)
1	2.4	2.3	2.4	2.4	2.4	2.4	2.4	2.3	2.4	1.9
2	2.8	2.6	2.7	2.7	2.5	2.5	2.4	2.4	2.4	5.9
3	2.0	1.9	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.7
4	2.6	2.7	2.6	2.7	2.6	2.6	2.6	2.6	2.7	1.9
Overall	2.5	2.4	2.4	2.5	2.4	2.4	2.4	2.3	2.4	2.8

The mean random error at baseline was ±2.8% and the estimated precision was ± 5.5%.

However, the validity of CV depends on stable cardiac output throughout the collection period. Catheter 2 appeared to have cardiac output change from 2.8 L/min to 2.4 L/min during the collection period which was more than a 10% change, thus, it may not have provided valid random error data. Thus, under ideal stable conditions the random error of thermodilution measurement in-vivo could be below 5%.

b. Systematic Error

From pig 1, I used mean baseline cardiac output from each of the four catheter tested to provide a measurement of the bias between flow probe and the thermodilution measurement. From pig 2 I used similar mean baseline cardiac output data from each of the ten catheters tested.

Data analysis

Bland and Altman plots were drawn to analyze the systematic errors between different catheters using mean cardiac output data from pig 1 and 2. Only baseline data was used. In pig 1 treatment data was added to the plot to test if systematic difference (bias) between catheters remained constant when cardiac output was increased (Figure 3.8).

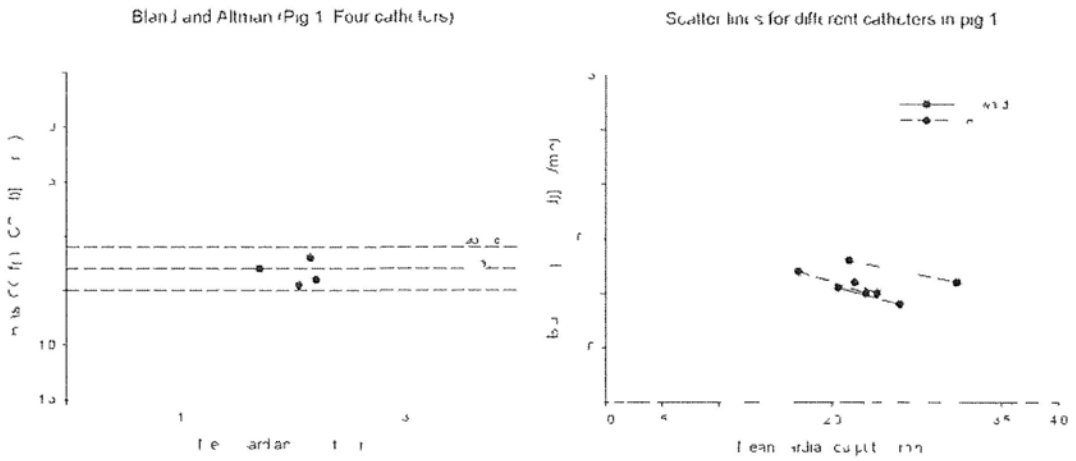


Figure 3 8a Bland and Altman plot (left) showing the mean baseline cardiac output data from pig 1 data of four catheters The 95% confidence intervals gave indicator of systematic error between catheters Second plot (right) showed that systematic error (bias) decreased slightly as cardiac output increased

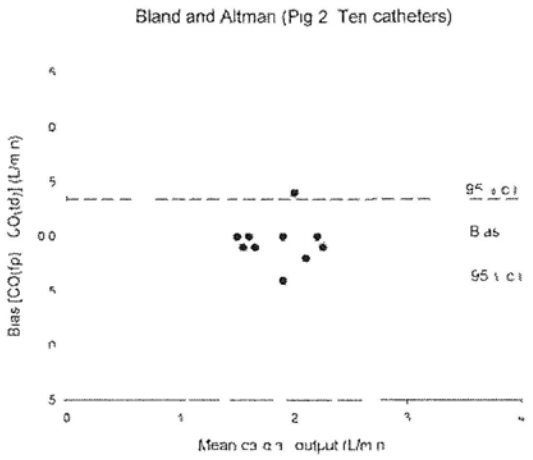


Figure 3 8b Bland and Altman plot showing mean baseline cardiac output data for pig 2 from ten catheters The 95% confidence interval gave an indicator of systematic error (or bias) between catheters

In pig 1 the mean bias was -0.3 L/min and in pig 2, it was -0.05 L/min. In pig 1 the 95% confidence intervals of the analysis was -0.104 to -0.496 L/min and in pig 2, it was -0.442 to 0.342 L/min. This translated to percentage error ((1.96*SD(bias))/mean CO) in pig 1 of ±9.7%, and in pig 2 of ±21.0%. When drug treatment was used to increase cardiac output, the bias in pig 1 increased slightly and these changes were parallel, suggesting that the systematic component of the error remained constant when cardiac output increased.

The percentage errors in Pig 1 (±9.7%) and pig 2 (±21.0%) were determined by multiplying the standard deviation of the bias by 1.96 to give 95% confidence intervals (Critchley and Critchley (1999)).

However, these standard deviations were based on low number of mean cardiac output, n=4 and n=10 respectively. If the numerator 1.96 is corrected for degrees of freeom df=3 and df=9 respectively, 1.96 becomes 3.18 and 2.26 respectively and revised percentage for pig 1 is 15.7% and pig 2 is 24.2%. Therefore the systematic error in our study for PACs, assuming the flow probe calibration error remained constant was around 20%, whereas the random error was 5%.

3.4.3.4. AGREEMENT AND TRENDING BETWEEN THE FLOW METER AND THERMODILUTION

The agreement and trending ability of the thermodilution method was further evaluated using two catheters and a range of circulation conditions. Data was collected from two pigs, pig 3 and pig 5. One Arrow and one Edwards catheter were used in each pig. The flow probe readings were assumed to reflect linear changes in

cardiac output and were considered as a gold standard. Cardiac output ranged under the influence of cardiovascular drugs from 0.5 to 6.0 L/min. Flow rates were stratified into low, medium and high cardiac output states based on the nature of intervention (e.g. cardiovascular depression, baseline and stimulation). Data from pig 4 should have been used for this experiment but the pig was unstable and died at an early stage.

Data analysis Paired cardiac output readings were compared using regression analysis and a modified Bland and Altman analysis that eliminated systematic bias due to calibration of each catheter. The modified plot had a near zero bias and showed only the random component of the error over a range of readings. This was done by correcting data for slope bias in the regression plot. A similar approach had been used when validating flow probe in the test rig against the cylinder filling method.

(1) Data pairs from each catheter were first plotted on a regression line plot (Figure 3.9, Table 3.3), with flow meter reading as the X-axis, and thermodilution reading as the Y-axis. Data from each catheter was treated separately. Statistical variables that described each regression line, which included the slope and correlation coefficient (R-value), were derived.

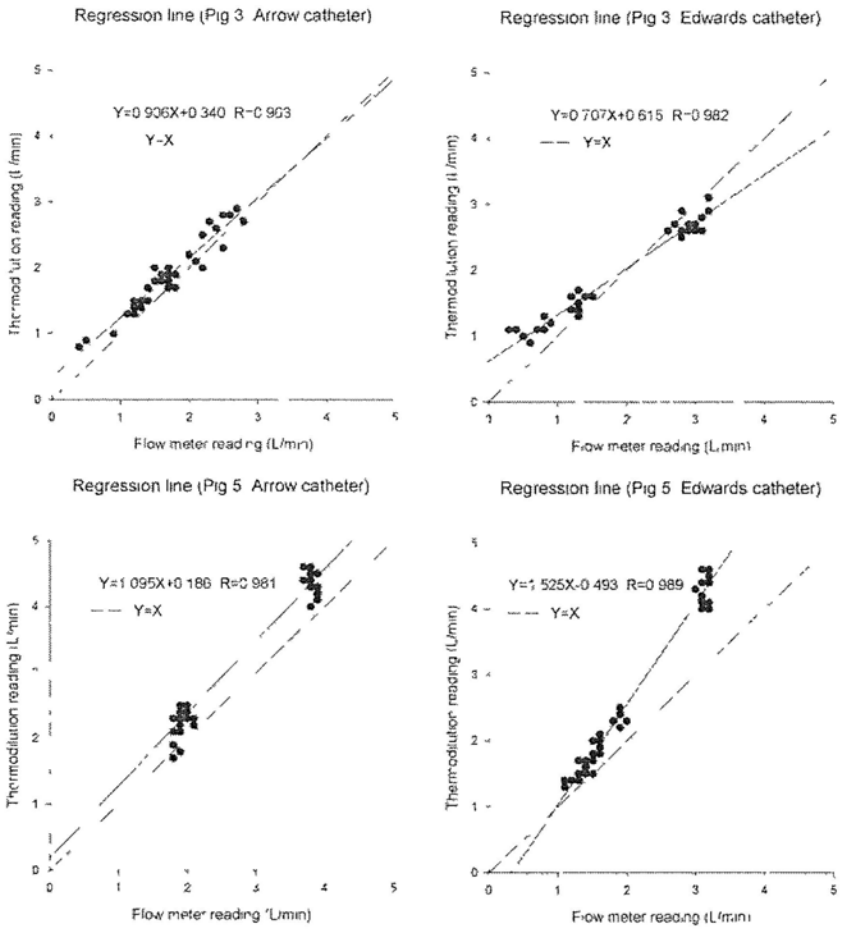


Figure 3.9. Regression plots for each of four catheters. Data is from 2 pigs. Baseline and treatment data are included. Regression line shown by solid line and line of identity (Y=X) shown by dashed line. Plots show linear trending over a range of cardiac output values, though the spread of data was not always complete. Note the variations in slope of regression line, indicating calibration differences between each catheter.

Table 3.3. Table showing the slope (m) and R-value for each regression line in the two pigs. Correlation is good , R-value > 0.96, but the slope of each regression line varies, m=0.9 to 1.5.

Pig	Catheter	Slope (m)	R-value
3	Arrow	0.906	0.963
3	Edwards	0.707	0.982
5	Arrow	1.095	0.981
5	Edwards	1.525	0.989

(2) A modified Bland and Altman plot was drawn that eliminated systematic or calibration error. Data from the four catheters and two pigs was combined. The systematic errors were eliminated by correcting the thermodilution readings for calibration errors using the regression line slope data. From each regression plot the slope (m) was determined. By dividing the individual thermodilution readings by the slope (m) they were corrected or normalized for any offset due catheter calibration.

The modified Bland and Altman plot could be used to determine the random error component of the measurement error over a range of cardiac output values (Figure 3.10).

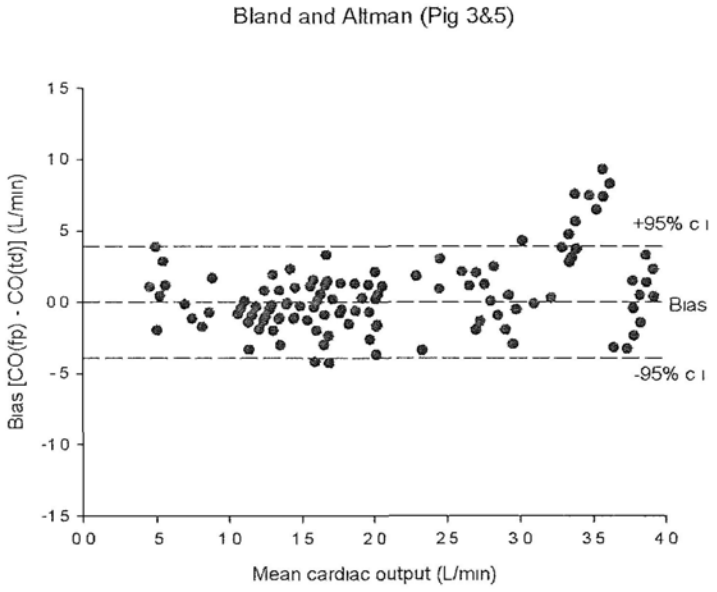


Figure 3.10. Modified Bland and Altman plot showing the agreement between flow probe and thermodilution data pairs, with the systematic component of the error due to calibration eliminated.

For the modified Bland and Altman plot, the bias was 0 L/min, mean cardiac output was 2.0 L/min and limits of agreement were -0.392-0.392 L/min, giving an overall percentage error for the random component of $\pm$19.3%.

3.4.3.5. COMPARISONS BETWEEN BASELINE AND TREATMENT CARDIAC OUTPUTS

Besides the accuracy of thermodilution measurements, an increasingly important issue when using cardiac output monitoring, is the ability to detect acute haemodynamic changes or trending. I used a number of pigs (6-10) to investigate trending over a range of cardiac output value using a single catheter. Different cardiovascular drugs were used to regulate blood pressure, cardiac contractility and heart rate, resulting in

changes in cardiac output. Pairs of readings taken at different flow rates were then compared to baseline data.

Data analysis

(1) Data from 6-pig experiments was analyzed (Pig4, 6-10). Sets of cardiac output readings were taken over 5 minute periods of stable haemodynamics that followed each treatment intervention. Data from each period was averaged. Cardiac output was increased (e.g. Dopamine and Adrenaline) and decreased (e.g. Glyceryl Trinitrate and Betaloc) using drug infusions. Baseline (e.g. no drug intervention) and drug treatment groups were analyzed separately.

Regression plots for each pig experiment and modified Bland and Altman plots of data from all 6 pigs are shown (Figure 3.11). Some data points from pigs 4 and 6 were not include because: (i) Pig 4 had very low cardiac output readings as it was unstable and died. (ii) Pig 6 had very high cardiac outputs due to mixing and overdose of the drugs (Figure 3.12, Table 3.4). These two pigs were on the learning curve to control cardiac output with drug therapy.

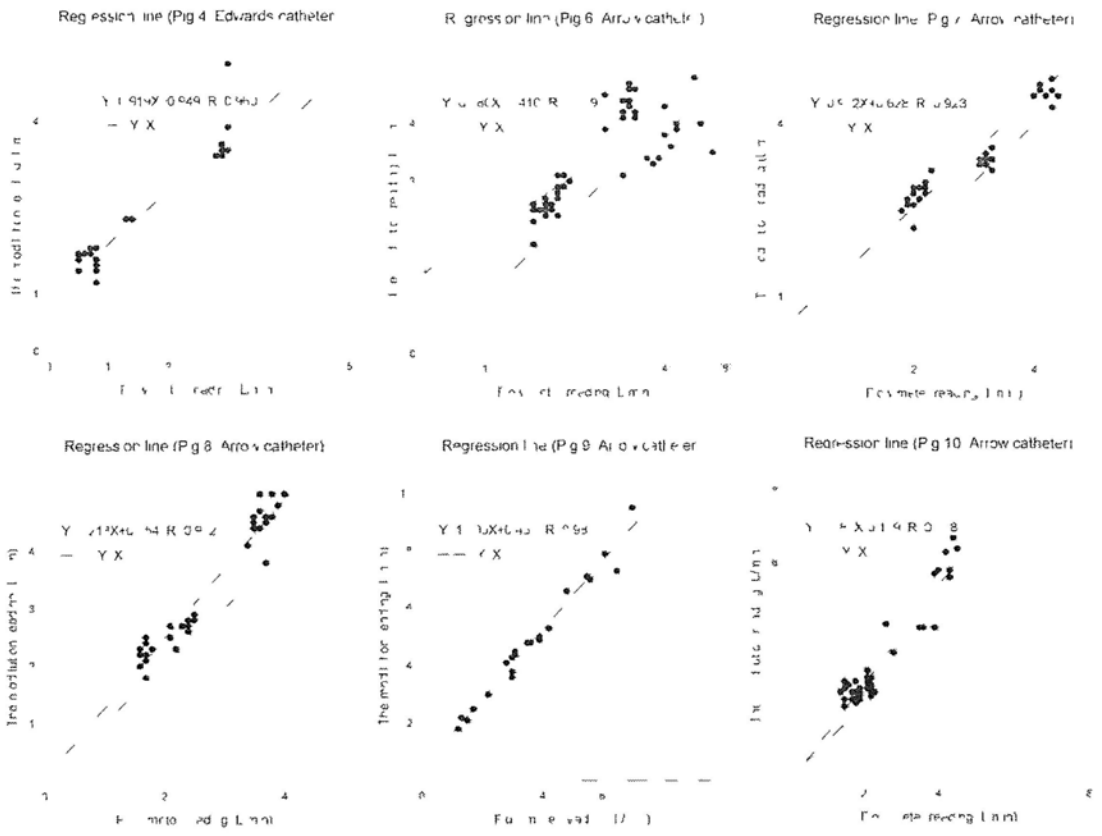


Figure 3.11. Regression plots showing data from the 6 pigs. A single catheter was used in each pig. In pigs 8 to 10 the same PAC was used.

Table 3.4. Table showing the slope (m) and correlation coefficient (R-value) for each pig.

Pig	Catheter	Slope (m)	R-value
4	Edwards	0.919	0.960
6	Arrow	0.680	0.779
7	Arrow	0.962	0.923
8	Arrow	1.213	0.972
9	Arrow	1.195	0.987
10	Arrow	1.385	0.948

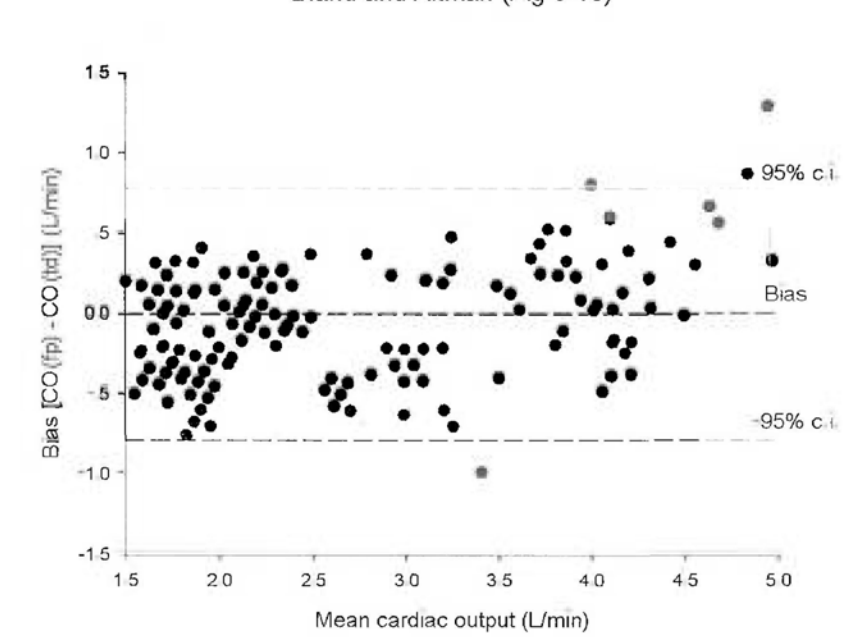


Figure 3.12. Modified Bland and Altman showing the bias due to random error between pairs of cardiac output readings. Data from 6 pigs table at baseline and during treatment.

The bias was 0 L/min, the mean cardiac output was 2.7 L/min and limits of agreement were -0.784-0.784 L/min, giving an overall percentage error of ±28.9%.

(2) The effect of treatment intervention on the measurement error was further evaluated by separating the two sets of data (e.g. baseline and treatment intervention) on a regression and Bland and Altman plot (Figure 3.13, 3.14).

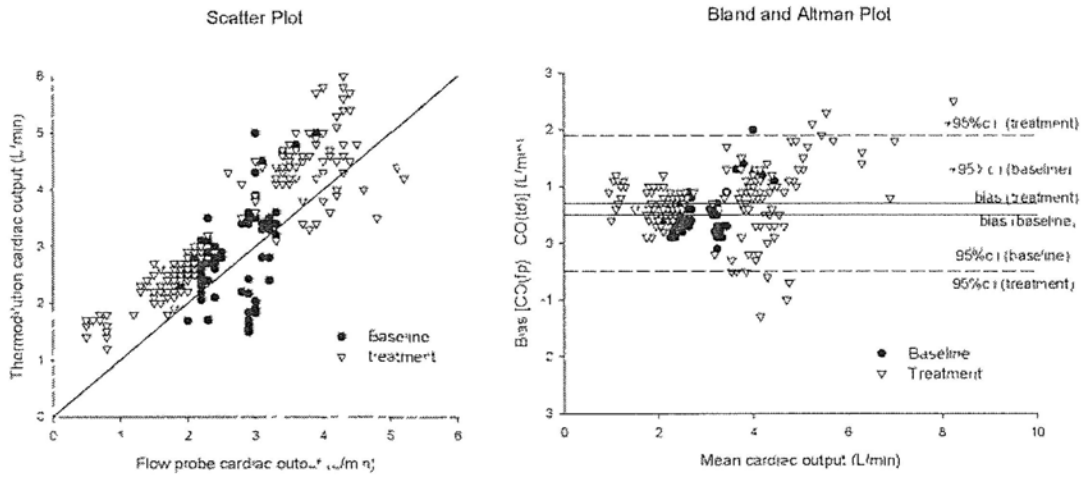


Figure 3.13. Regression and Bland and Altman plots showing the distribution of data from the line of identity (scatter plot) and bias (Bland and Altman) when readings were taken at low and high cardiac outputs. The influence of treatment intervention was to increase the scatter of data.

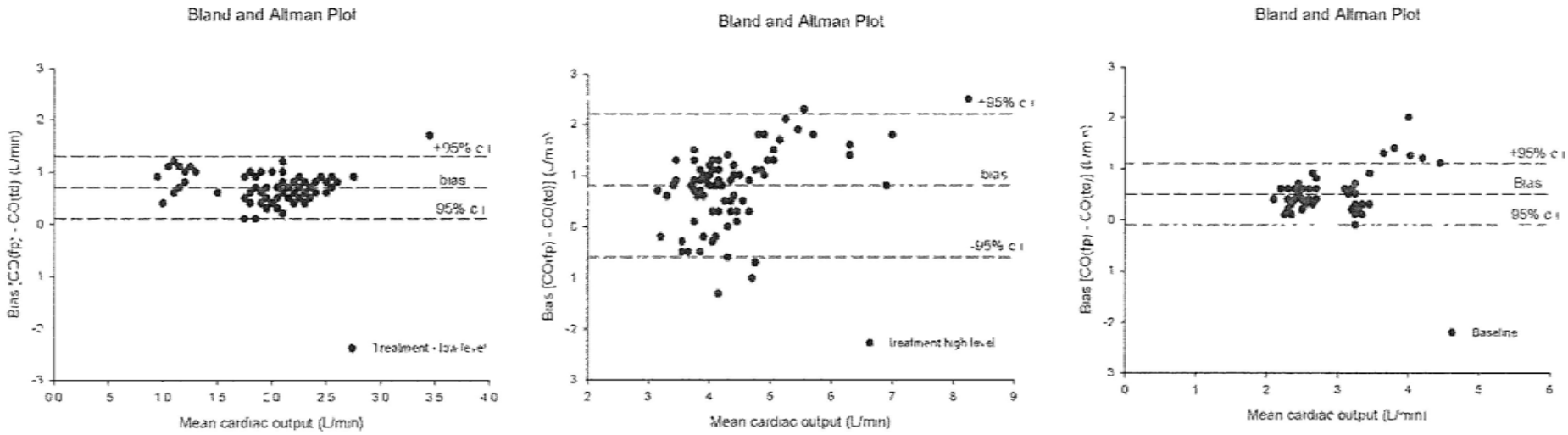


Figure 3.14. Bland and Altman plots showing the spread of bias data points for different groups (low cardiac output, baseline and high cardiac output). Note the spread of data in the high level cardiac output group.

For baseline data the bias was 0.5 L/min, mean CO was 2.9L/min and limits of agreement -0.1-1.1 L/min with percentage error of ±20.7%. Following treatment the bias was 0.7 L/min, mean CO was 3.2 L/min and the limits of agreement widened to -0.5-1.9 L/min with a widened percentage error of ±37.5% (Table 3.5).

Table 3.5. Table showing statistical analysis results for both baseline and treatment groups.

Index	Baseline	Treatment
Regression Equation	Y(td)=1.132X(fp)+0.150	Y(td)=1.028(fp)+0.654
R-value	0.851	0.927
Bias (L/min)	0.5	0.7
Mean CO (L/min)	2.9	3.2
Limits of agreement (L/min)	-0.1-1.1	-0.5-1.9
Percentage error (%)	20.7	37.5

Table 3.6. Individual percentage errors for all the 6 pigs. Comparison between baseline and treatment data is made.

Pig	Percentage error (%)	
	Baseline	Treatment
4	20.97	35.05
6	18.09	37.02
7	7.04	13.86
8	9.47	20.13
9	4.9	22.8
10	17.0	37.9
Average	12.9 (SD=6.6)	27.8 (SD=10.2)

The average percentage error for baseline group was ±12.9%, which was increased to ±27.8% when treatment to vary CO was used (Table 3.6).

3.5 DISCUSSION

The main findings from this part of my work were:

(i) The random error (PE(random)) in resting conditions, or at baseline, was ±5.5% (data from 1-pig). However, following drug infusions to vary cardiac output the random error increased to ±19.3% (data from 2-pigs).

(ii) The systematic error (PE(systematic)) in resting conditions was approximately ±20% (data from 2-pigs). Data from further pig experiment suggested a wide variation in calibration (i.e. greatly varying regression line slopes) supporting this finding.

(iii) Therefore, the overall percentage error (PE(random & systematic) from in vivo studies when cardiac output is varied over a wide range of values and data from many subjects are combined would be close to ±30%.

(iv) Although thermodilution was seen to trend changes in cardiac output (data from 10-catheters in 8-pigs), Bland and Altman analysis returned an overall percentage error of ±28.9%. As my reference method was the Transonic flow probe and considered to be a gold standard method with a low measurement error of 1-2%, this percentage supports my previous finding that the thermodilution catheter when used in vivo has an error of up to ±30%.

(v) Further Bland and Altman analysis showed that at rest (baseline) the percentage error was ±20.7% and when circulatory conditions and cardiac output were varying

this percentage increases to ±37.5%. Therefore, data from cardiac output validation studies where thermodilution is the reference method can be very variable in its precision depending on the type of circulatory conditions that exist during the investigation.

By using an anaesthetized pig model, I succeeded in setting up an in-vitro model for evaluating thermodilution catheter performance. Cardiac output in the model was measured using a transonic flow probe which was surgically placed on the ascending aorta via a left thoracotomy approach, which was developed first in dead pigs using the methods developed in previous departmental work. However, instead of separating the ribs with a retractor, or rib spreader, it was easier, because of the more muscular build of the pig, to resect the anterior part of the 3rd and 4th ribs to gain access to the pericardium and aorta. A lateral approach was preferred to a more direct midline sternotomy approach because less bleeding occurred. A similar conclusion was made in the department's previous dog work (Peng et al (2006)).

My main objective were to determine in-vivo, (a) the random error component, (b) the systematic or calibration component and (c) the effects of changing cardiac output on precision and trending ability.

Determining the random error was relatively simple and was performed in one pig experiment using 4 catheters. A random error of $\pm 5.5\%$ was found, but this was only for baseline conditions. I did not manage to determine the random error over a range of cardiac output, as maintaining static cardiac output rate for sufficient long periods

of time with infusions of cardiovascular drugs proved too difficult. Therefore ±5.5% may be an underestimate for extreme flow conditions measured by thermodilution.

To try and further define the random component of the error, I used a modified version of the Bland and Altman plot, which corrected for calibration error using the slope of the regression line (m) and a correction factor, and theoretically should have eliminated the systematic component to leave the random error component. This analysis comprised data both at baseline and during treatment. My derived value for the random error was ±19.3%, significantly larger than ±5.5% for baseline only data (Pigs 3 and 5, Figure 3.10). Similar data from my single catheter experiments was ±28.9% (Pigs 6-10, Figure 3.12), but this percentage may have been excessively high because of widely spread data at the high level of cardiac output.

Determining systematic error was more problematic as again it was too difficult to construct good quality calibration lines and use several catheters in my pig model. Therefore, I based the measurement of calibration error on the variation in mean bias between catheters under baseline flow conditions. The number of catheter changes available was maximized to ten in one pig. My estimates of the systematic error were quite large compared to my in-vitro work and ranged from ±15.7% to ±24.2% (Pigs 1 and 2). Further experiments comparing calibration line data from several pigs suggested that slopes could vary quite significantly (m=0.7 to 1.4, Pigs4, 6-10)

Correlation coefficients for data of most of the catheters tested over a range of cardiac output value (i.e. 1-5 L/min) where about R>0.95, supporting reliable trending ability

by thermodilution catheter. Not that readings were generally the average of several readings (n=3).

Bland and Altman analysis data comparing baseline and treatment (high and low cardiac output) data repeatedly showed deterioration in percentage error from ±20.7% for baseline to ±37.5% for treatment (Table 3.5) and ±12.9% to ±27.8% (Table 3.6), when the systematic component removed. This data support the general clinical impression the thermodilution readings become more unreliable when haemodynamic become extreme or unstable.

I did not find the pig model as easy to work with in terms of collecting good evaluation data as the in-vitro test rig. The time available to perform sufficient thermodilution measurements was limited, varying cardiac output by drug infusion was not that predictable and changing catheters took time. I also found that several of the catheters failed to function properly in my later experiments. Thus, the data that I was able to collect was limited compared to my previous experience with the test rig.

CHAPTER 4

SUMMARY

In clinical medicine, using the principle of thermodilution to measure cardiac output with a pulmonary artery catheter remains the reference standard against which new methods of cardiac output monitoring are measured. Cardiac output measured by thermodilution is however prone to error. When comparing new techniques, precision is usually considered to be ± 20%. This estimate is based on work completed nearly 30 years ago. (Stetz et al (1982)) It may be argued that better materials, manufacturing processes and sophisticated computer software should have improved the precision of modern thermodilution measurements.

In this thesis I was able to complete my goals of reappraising thermodilution catheter measurement errors in both in-vitro and in-vivo settings, using modern equipment. A simple in-vitro test rig was developed to evaluate the precision of thermodilution cardiac output measurements under non-pulsatile and then pulsatile conditions. Subsequently an in-vivo pig model was developed. In both models the thermodilution cardiac output measurements were compared with an accurate and appropriately calibrated flowmeter.

I found that that the precision of the thermodilution catheter in the continuous (non-pulsatile) flow test rig was quite predictable. Of the factors tested, catheter dead-space had a significant effect on precision. To allow the measurement error to be

more systematically investigated, statistical analytical methods were developed to define random and systematic (calibration) components of the measurement error. As a result of this statistical approach, the in-vitro the random component of the error was determined to be ±10% and the in-vitro systematic component ±11.6%, providing an overall error of ±15.3% for single bolus. In clinical practice and for comparison purposes an average of three readings is usually employed and under these conditions the overall error decreased slightly to ±13%. Overall error was, however, strongly influenced by the type of monitor used to process signals and this affected the percentage of overall error by up to 100%.

When pulsatile flow was generated in the test rig, the overall percentage error increased to ±27% for single readings and ±23% for the average of triplicate readings, with random and systematic components being ±17% and ±21% respectively (triplicate readings).

The pig in-vivo model was found to be unstable when haemodynamic alterations were pharmacologically induced. Therefore the in-vivo data collected was less complete and therefore more difficult to interpret with confidence. One notable observation was that there was a substantial difference in overall error between measurements obtained from the animal during resting/control cardiac output conditions and measurements collected after the cardiac output was pharmacologically increased or decreased. The random error component varied from ±5% to ±20% determined by varying haemodynamic conditions.

Unfortunately, because of the instability of the model under induced conditions, the systematic component of overall error could only be determined under resting/control conditions. There was clear evidence that each placement of the thermodilution catheter within the pig resulted in a significant variation in calibration against the flow probe reading and thus systematic error that was quantified as ±20%. These data suggested that true percentage error for thermodilution catheters, random and systematic combined was approximately ±30%. Further visual verification was observed using the classic Bland and Altman analysis. The observed a range of error within the 95% CIs was from ±20 to 40% with narrower clustering around the bias observed during resting/control conditions and wider dispersion during high and low cardiac output conditions.

On the basis of my studies, I can conclude that the error of thermodilution cardiac output measurements made with modern techniques is not substantially divergent form that provided by previously published data. There were, however, substantial errors introduced by certain types of monitor, the in-vivo setting, and in particular the circulatory conditions being studied. Investigators should be aware of these factors when thermodilution cardiac output measurement is used as a gold standard in future investigations.

REFERENCES

Andreen M. (1974). Computerized measurement of cardiac output by thermodilution: methodological aspects. Acta Anaesthesiol Scand, 18(4), 297-305.

Arfors KE, Malmberg P. (1972). Thermodilution measurement of cardiac output. A study in dogs comparing direct FICK with an automated thermodilution method (Fisher Cardiac Output Computer). Acta Chir Scand 138(8), 761-4.

Bachofen H, Bloom DA, Farhi LE. (1971). Determination of cardiac output by ether dilution. J Appl Physiol, 30(1), 131-5.

Bajorat J, Hofmockel R, Vagts DA, Janda M, Pohl B, Beck C, Noeldge-Schomburg G. (2006). Comparison of invasive and less-invasive techniques of cardiac output measurement under different haemodynamic conditions in a pig model. Eur J Anaesthesiol, 23(1), 23-30.

Baxley WA, Cavender JB, Knoblock J. (1993). Continuous cardiac output monitoring by the Fick method. Cathet Cardiovasc Diaqn, 28(1), 89-92.

Baylor P. (2006). Lack of agreement between thermodilution and fick methods in the measurement of cardiac output. J Intensive Care Med, 21(2), 93-8.

Bednarik JA, May CN. (1995). Evaluation of a transit-time system for the chronic measurement of blood flow in conscious sheep. J Appl Physiol, 78(2), 524-30.

Bein B, Renner J, Scholz J, Tonner PH. (2006). Comparing different methods of cardiac output determination: a call for consensus. Eur J Anaesthesiol, 23(8), 710.

Berthelsen PG, Eldrup N, Nilsson LB, Rasmussen JP. (2002). Thermodilution cardiac ouput. Cold vs room temperature injectate and the importance of measuring the injectate temperature in the right atrium. Acta Anaesthesiol Scand, 46(9), 1103-10.

Biais M, Nouette-Gaulain K, Cottenceau V, Vallet A, Cochard JF, Revel P, Sztark F. (2008). Cardiac output measurement in patients undergoing liver transplantation: pulmonary artery catheter versus uncalibrated arterial pressure waveform analysis. Anesth Analg, 106, 1480-6.

Biancofiore G, Critchley LA, Lee A, Bindi L, Bisa M, Esposito M, Meacci L, Mozzo R, DeSimone P, Urbani L, Filipponi F. (2009). Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. Br J Anaesth, 102, 47-54.

Bilfinger TV, Lin CY, Anagnostopoulos CE. (1982). In vitro determination of accuracy of cardiac output measurements by thermal dilution. J Surg Res, 33(5), 409-14.

Bland JM, Altman DG. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1(8476), 307-10.

Branthwaite MA, Bradley RD. (1968). Measurement of cardiac outputby thermal dilution in man. J Appl Physiol, 24(3), 434-8.

Cecconi M, Grounds M, Rhodes A. (2007). Methodologies for assessing agreement between two methods of clinical measurement: are we as good as we think we are? Curr Opin Crit Care, 13(3), 294-6.

Connors AF, Speroff T, Dawson NV, Thomas C, Harrell FE, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. (1996). The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA, 276(11), 889-97.

Cornell WP, Braunwald E, Brochenbrough EC. (1961). Use of krypton85 for the measurement of cardiac output by the single-injection indicator-dilution technique. Circ Res, 9, 984-8.

Critchely LA, Critchley JA. (1999). A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. J Clin Monit Comput, 15(2), 85-91.

Critchley LA, Calcroft RM, Tan PY, Kew J, Critchley JA. (2000). The effect of lung injury and excessive lung fluid, on impedance cardiac output measurements, in the critically ill. Intensive Care Med, 26, 679-85.

Critchley LA, Lee A, Ho AM. (2010). A critical review of the ability of continuous cardiac output cardiac output monitors to measure trends in cardiac output. Anesth Analg, 111(5), 1180-92.

Critchley LA, Peng ZY, Fok BS, James AE. (2005). The effect of peripheral resistance on impedance cardiography measurements in the anaesthetized dog. Anesth Analg, 100, 1708-12.

Daily EK, Mersch J. (1987). Thermodilution cardiac outputs using room and ice temperature injectate: comparison with the Fick method. Heart Lung, 16(3), 294-300.

Dale J, Jespersen L. (1987). Determination of cardiac output with a modified Fick method using estimated instead of measured oxygen consumption. Scand J Clin Lab Invest, 47(8), 759-763.

Davies GG, Jebson PGR, Glascow BM, Hess DR. (1986). Continuous Fick cardiac output compared to thermodilution cardiac output. Crit Care Med, 14, 881-5.

Dhingra VK, Fenwich JC, Walley KR, Chittock DR, Ronco JJ. (2002). Lack of agreement between thermodilution and fick cardiac output in critically ill patients. Chest, 122(3), 990-7.

Doering L, Dracup K. (1988). Comparisons of cardiac output in supine and lateral positions. Nurs Res, 37(2), 114-8.

Elkayam U, Berkley A, Azen S, Weber L, Geva B, Henry WL. (1983). Cardiac output by thermodilution technique. Effect of injectate's volume and temperature on accuracy and reproducibility in the critically ill patient. Chest, 84, 418-22.

Enghoff E, Staffan S. (1973). Thermal dilution for measurement of cardiac output in the pulmonary artery in man in relation to choice of indicator volume and injection time. Upsala J Med Sci, 78, 33-7.

Faybik P, Hetz H, Baker A, Yankovskaya E, Krenn CG, Steltzer H. (2004). Iced versus room temperature injectate for assessment of cardiac output, intrathoracic blood volume, and extravascular lung water by single transpulmonary thermodilution. J Crit Care, 19, 103-7.

Fegler G. (1954). Measurement of cardiac output in anesthetized animals by thermo-dilution method. J Exp Physiol, 39, 153-64.

Fegler G. (1957). The reliability of the thermodilution method for determination of the cardiac output and the blood flow in central veins. Q J Exp Physiol Cogn Med Sci, 42(3), 254-66.

Fick A. (1870). Uber die messing des blutquantums in deu herzventrikeln. Sitz der Physik-Med ges Wurlzberg, 16.

Fischer AP, Benis AM, Jurado RA, Seely E, Teinstein P, Litwak RS. (1978). Analysis of errors in measurement of cardiac output by simultaneous dye and thermal dilution in cardiothoracic surgical patients. Cardiovasc Res, 1978, 12, 190-9.

Forrester JS, Ganz W, Diamond G, McHugh T, Chonette DW, Swan HJ. (1972). Thermodilution cardiac output determination with a single flow-direted catheter. Am Heart J, 83, 306-11.

Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJ. (1971). A new technique for measurement of cardiac output by thermodilution in man. Am J Cardiol, 27(4), 392-6.

Gonzalez J, Delafosse C, Fartoukh M, Capderou A, Straus C, Zelter M, Derenne JP, Similowski T. (2003). Comparison of bedside measurement of cardiac output with the thermodilution method and the Fick method in mechanically ventilated patients. Crit Care, 7(2), 171-8.

Grose BL, Woods SL, Laurent DJ. (1981). Effect of backrest position on cardiac output measured by the thermodilution method in acutely ill patients. Heart Lung, 10(4), 661-5.

Hamilton WF, Moore JW, Kinsman JM, Spurling RG. (1928). Simultaneous determination of the pulmonary and systematic circulation times in man and of a figure related to the cardiac output. Amer J Physiol, 84, 338-344.

Hillis LD, Firth BG, Winniford MD. (1985). Analysis of factors affecting the variability of Fick versus indicator dilution measurements of cardiac output. Am J Cadiol, 56(12), 764-8.

Hobbs JT, Edwards EA. (1966). Reproducibility of the indicator-dilution method using I-125 in haemodynamic studies. J Cardiovas Surg (Torino), 7(1), 34-9.

Hodges M, Downs JB, Mitchell LA. (1975). Thermodilution and Fick cardiac index determinations following cardiac surgery. Crit Care Med, 3(5), 182-4.

Hoel BL. (1978). Some aspects of the clinical use of thermodilution in measuring cardiac output. With particular reference to the Swan-Ganz thermodilution catheters. Scand J Clin Lab Invest, 38(4), 383-8.

Hugenholtz PG, Wagner HR, Gamble WJ, Polanyi ML. (1969). Direct read-out of cardiac output by means of the fiberoptic indicator dilution method. Am Heart J, 77(2), 178-86.

Jebson PJ, Karkow WS. (1986). Pulsatile flow simulator for comparison of cardiac output measurements by electromagnetic flow meter and thermodiution. J Clin Monit. 2(1), 6-14.

Kim ME, Lin YC. (1980). Determination of catheter wall heat transfer in cardiac output measurement by thermodilution. Clin Exp Pharmacol Physiol, 7, 383-9.

Klocke FJ, Greene DG, Koberstein RC. (1968). Indicator-dilution measurement of cardiac output with dissolved hydrogen. Circ Res, 22(6), 841-53.

Kohanna FH, Cunningham JN Jr. (1977). Monitoring of cardiac output by thermodilution after open-heart surgery. J Thorac Cardiovasc Surg. J Thorac Cardiovasc Surg, 73(3), 451-7.

Levett JM, Replogle RL. (1979). Thermodilution cardiac output: a critical analysis and review of the literature. J Surg Res, 27(6), 392-404.

Lin YC, Dawson CA, Nadel ER, Horvath SM. (1970). Reliability of cardiac output measured by thermodilution method in small animals. Comp Biochem Physiol, 34(1), 245-50.

Linton NW, Linton RA. (2002). Is comparison of changes in cardiac output, assessed by different methods, better than only comparing cardiac output to the reference method? Br J Anaesth, 89(2), 336-7.

Mackenzie JD, Haites NE, Rawles JM. (1986). Method of assessing the reproducibility of blood flow measurement: factors influencing the performance of thermodilution cardiac output computers. Br Heart J, 55(1), 14-24.

Mahutte CK, Jaffe MB. (1995). Effect of measurement errors on cardiac output calculated with O_2 and modified CO_2 Fick methods. J Clin Monit, 11(2), 99-108.

Maruschak GF, Schauble JF. (1985). Limitations of thermodilution ejection fraction: degradation of frequency response by catheter mounting of fast-response thermistors. Crit Care Med, 13, 679-82.

Mayer J, Boldt J, Poland R, Peterson A, Manecke GR Jr. (2009). Continuous arterial pressure waveform-based cardiac output using the Flow Trac/Vigileo: a review and meta-analysis. J Cardiothorac Vasc Anesth, 23, 401-6.

Mellette HC, Booth RW, Ryan JM, Rieser GF. (1958). The use of bromsulphalein (B.S.P.) as an indicator for the determination of cardiac output by the dye dilution technique. J Lab Clin Med, 51(3), 441-7.

Mihaljevic T, Von Segesser LK, Tonz M, Leskosek B, Seifert B, Jenni R, Turina M. (1995). Continuous versus bolus thermodilution cardiac output measurements – a comparative study. Crit Care Med, 23(5), 944-9.

Nanas JN, Anastasiou-Nana MI, Sutton RB, Menlove RL, Tsagaris TJ. (1986). Comparison of Fick and dye cardiac outputs during rest and exercise in 1022 patients. Can J Cardiol, 2(4), 195-9.

Nelson LD, Houtchens BA. (1982). Automatic vs manual injections for thermodilution cardiac output determinations. Crit Care Med, 10(3), 190-2.

Nilsson LB, Nilsson JC, Skovgaard LT, Berthelsen PG (2004). Thermodilution cardiac output—are three injections enough? Acta Anaesthesiol Scand, 48, 1322-7.

Normann RA, Johnson RW, Messinger JE, Sohrab B. (1989). A Continuous Cardiac Output Computer Based on Thermodilution Principles. Ann Biomed Eng, 17(1), 61-73.

Norris SL, King EG, Grace M, Weir B. (1986). Thermodilution cardiac output – an in vitro model of low flow states. Crit Care Med, 14(1), 57-9.

Olsson B, Pool J, Vandermoten P, Varnauskas E, Wassen R. (1970). Validity and reproducibility of determination of cardiac output by thermodilution in man. Cardiology, 55(3), 136-48.

Pearl RG, Rosenthal MH, Nielson L, Ashton JP, Brown BW Jr. (1986). Effect of injectate volume and temperature on thermodilution cardiac output determination. Anesthesiology, 64, 798-801.

Pelletier C. (1979). Cardiac output measurement by thermodilution. Can J Surg, 22(4), 347-50.

Peng ZY, Critchley LA, Fok BS (2005). An investigation to show the effect of lung fluid on impedance cardiac output in the anaesthetized dog. Br J Anaesth, 95, 458-64.

Peng ZY, Critchley LA, James AE (2006). Comparison of Blunt Versus Surgical Dissection for Aortic Flow Probe Placement in the Dog. Scand J Lab Anim Sci, 33(4), 227-35.

Peng ZY, Critchley LA, Joynt GM, Gruber PC, Jenkins CR, Ho AM (2008). Effects of norepinephrine during intra-abdominal hypertension on renal blood flow in bacteremic dogs. Crit Care Med, 36(3), 834-41.

Pesola HR, Pesola GR. (1993). Room-temperature thermodilution cardiac output. Central venous vs side port. Chest, 103(2), 339-41.

Plachetka JR, Larson DF, Salomon NW, Copeland JG. (1981). Comparison of two closed systems for thermodilution cardiac outputs. Crit Care Med, 9(6), 487-9.

Powner DJ, Snyder JV. (1978). In vitro comparison of six commercially available thermodilution cardiac output systems. Med Instrum, 12(2), 122-7

Reddy PS, Curtiss EI, Bell B, OToole JD, Salerni R, Leon DF, Shaver JA. (1976). Determinants of variation between Fick and indicator dilution estimates of cardiac output during diagnostic catheterization. Fick vs. dye cardiac outputs. J Lab Clin Med, 87(4), 568-76.

Renner LE, Morton MJ, Sakuma GY. (1993). Indicator amount, temperature, and intrinsic cardiac output affect thermodilution cardiac output accuracy and reproducibility. Crit Care Med, 21, 586-97.

Reuter DA, Huang C, Edrich T, Shernan SK, Eltzsching HK. (2010). Cardiac output monitoring using indicator-dilution techniques: basics, limits, and perspectives. Anesth Analg, 110(3), 799-811.

Rubini A, Del Monte D, Catena V, Attar I, Cesaro M, Soranzo D, Rattazzi G, Alati GL. (1995). Cardiac output measurement by the thermodilution method: an in vitro test of accuracy of three commercially available automatic cardiac output computers. Intensive Care Med, 21, 154-8.

Runciman WB, Ilsley AH, Roberts JG. (1981). An evaluation of thermodilution cardiac output measurement using the Swan-Ganz catheter. Anaesth Intensive Care, 9(3), 208-20.

Saadjian A, Quercy JE, Torresani J. (1976). Cardiac output measurement by thermodilution: methodologic problems. Med Prog Technol, 3(4), 161-7.

Sanders RJ, Sullivan RG. (1968). Cardiac output determination with radioactive 85-krypton. J Surg Res, 8(11), 522-7.

Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, Jacka M. (2003). A Randomized, Controlled Trial of the Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients. N Engl J Med, 348(1), 5-14.

Santos I, Ferreira da, Rocha A, Assis de O, Nascimento F, Souza Neto J, Valvano JW. (2002). Measurement of ejection fraction with standard thermodilution catheters. Med Eng Phys, 24, 325-35.

Sauer MT, Scoggins WG, O'Donohue WJ Jr. (1977). Comparison of three thermodilution cardiac output computers. Respir Care, 22(9), 940-4.

Shellock FG, Riedinger MS, Bateman TM, Gray RG. (1983). Thermodilution cardiac output determination in hypothermic postcardiac surgery patients: room vs ice temperature injectate. Crit Care Med, 11, 668-70.

Sibille L, Prasquier R, Vallois JM, Gaudebout C, Pocidalo JJ. (1975). Cardiac output measurement with a simplified thermodilution technique. Comparison with the Fick method. Biomedicine, 23(2), 64-7.

Snyder JV, Powner DJ. (1982). Effects of mechanical ventilation on the measurement of cardiac output by thermodilution. Crit Care Med, 10(10), 677-82.

Sorensen MB, Bille-Brahe NE, Engell HC. (1976). Cardiac output measurement by thermal dilution: reproducibility and comparison with the dye-dilution technique. Ann Surg. 183(1), 67-72.

Stawicki JJ, Holford FD, Michelson EL, Josephson ME. (1979). Multiple cardiac output measurements in man. Evaluation of a new closed-system thermodilution method. Chest, 76, 193-7.

Stetz CW, Miller RG, Kelly GE, Raffin TA. (1982). Reliability of the thermodilution method in the determination of cardiac output in clinical practice. Am Rev Respir Dis, 126(6), 1001-4.

Stevens JH, Raffin TA, Mihm FG, Rosenthal MH, Stetz CW. (1985). Thermodilution cardiac output measurement. Effects of the respiratory cycle on its reliability. JAMA. 254(15), 2240-2.

Stewart GN. (1897). Researches on the circulation time and on the influences which offset it. IV. The output of the heart. J Physilo, 22, 159-183.

Synder JV, Powner DJ. (1982). Effects of mechanical ventilation on the measurement of cardiac output by thermodilution. Crit Care Med, 10(10), 677-82.

Thrush D, Downs JB, Smith RA. (1995). Continuous thermodilution cardiac output: agreement with Fick and bolus thermodilution methods. J Cardiothorac Vasc Anesth, 9(4), 399-404.

Vandermoten P, Bernard R, De Hemptinne J, Gillet JM, Lenaers A. (1977). Cardiac output monitoring during the acute phase of myocardial infarction: accuracy and precision of the thermodilution method. Cardiology, 62, 291-5

Venkataraman K, De Guzman MF, Hafeez Khan A, Haywood LJ. (1976). Cardiac output measurement: a comparison of direct Fick, dye dilution and thermodilution methods in stable and acutely III patients. J Natl Med Assoc, 68(4), 281-4.

Weisel RD, Vito L, Dennis RC, Berger RL, Hechtman HB. (1975). Clinical applications of thermodilution cardiac output determinations. Am J Surg, 129(4), 449-54.