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# Minimally Invasive Cardiac Output Monitoring in the Year 2012

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Lester Augustus Hall Critchley

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/54413>

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## 1. Introduction

“Cardiac output the “Holy Grail” of haemodynamic monitoring”

Physicians have been assessing the circulation long before the birth of Christ (BC). The Egyptian physicians used simple palpation of the pulse and the use of the pulse in Chinese medicine dates back over two thousand years. However, it was not until the 1940s that the clinical sphygmomanometer was invented, and blood pressure measurement became routinely available [1]. Today pulse rate and blood pressure measurement is performed in almost every patient.

Cardiac output is the volume of blood that is pumped by the heart around the systemic circulation in a given time period, usually one minute. It is equal to the volume pumped out by the heart in one contraction, known as stroke volume, multiplied by heart rate. The need to measure cardiac output in a clinical setting arose in the 1970s because of the development of intensive care units and the increasing need to manage unstable patients during high risk surgery. In parallel with these clinical developments the technology also became available to make more sophisticated cardiac output monitors and in particular monitors that can be used continuously at the bedside.

When evaluating the circulation, and thus haemodynamics, a very simply model can be drawn of the heart pumping blood through the arteries to peripheral capillaries and then returning to the heart via the veins. The haemodynamics of the model has flow, the cardiac output, leaving the heart, and passing through a resistance, the peripheral capillaries. Blood pressure is generated in the arteries by the heart pumping against this resistance. A very simple formula exists that describes the model of  $\text{Blood Pressure} = \text{Cardiac Output} \times \text{Peripheral Resistance}$ , which is often compared to Ohm's law for electricity (i.e.  $\text{Voltage} = \text{Current} \times \text{Resistance}$ ).

During clinical assessment pulse rate and blood pressure are very easy to measure. However, cardiac output and peripheral resistance are much less easy to obtain. Usually, the physician is only able to measure the pulse rate, and thus does not know how much blood the heart pumps each minute, nor the degree of the peripheral vasoconstriction. Knowing these variables becomes important when treating critically ill patients with low blood pressures who may be either hypovolaemic or septic, as it helps one to differentiate between the two conditions.

Cardiac output has proved very difficult to measure reliably in the clinical setting. The Fick method is considered the most accurate method and gold standard. It involves measuring oxygen uptake by the body and comparing oxygen content in arterial and venous blood samples. It is based on a very simple principle that blood flow through an organ is related to the uptake of a marker (oxygen) and the difference in concentration of that marker between blood entering (arterial) and blood leaving (venous) that organ, in the case of the Fick method, the heart and lungs. However, the method is cumbersome and time consuming, and usually performed in the laboratory. It is not suitable for bedside clinical use. The concept of using a marker is also used in other methods of cardiac output measurement, such as a dye and thermo (i.e. cold solution) dilution. Alternatively, a flow probe can be placed around the aorta, but this is highly invasive requiring surgery to access the heart or a beam aimed at the aorta that detects some property of flowing blood, such as the Doppler shift when using ultrasound. A secondary effect of blood flow or the action of the heart can also be used as a surrogate, such as bioelectrical changes in the thorax or the arterial blood pressure wave.

What makes cardiac output so difficult to measure accurately in the clinical setting, when compared to other haemodynamic variables, is its dispersion as blood travels away from the heart. Whereas the pulse rate and blood pressure can be measured from any location in the arterial tree, such as the arm, cardiac output should ideally be measured at its origin the ascending aorta, before it is split up into smaller regional blood flows.

Because of the clinical desire to know some patients' cardiac output and the inherent difficulties encountered when measuring cardiac output, developing a reliable bedside cardiac output monitoring has become the "Holy Grail" of haemodynamic monitoring.

In this chapter, I will review the main clinical methods available for measuring cardiac output and address the important issue of how they are evaluated.

## **2. Historical perspective**

### **2.1. Earliest theories and methods**

In the second century AD the Greek physician Galen taught his students that there were two distinct types of blood, nutritive venous blood arising from the liver and vital arterial blood arising from the heart. Galen believed that the heart acted not as pump, but sucked in blood from the veins which passed through tiny pores in the septum. Galen's explanation was believed until the beginning of the seventeenth century when an English physician William Harvey described the true nature of the circulation with the heart pumping blood around a system of arteries, capillaries and veins.

It was not until 1870 that cardiac output was first measured by the German physician and physiologist Adolf Fick using an oxygen uptake method. The Fick method was later modified in 1897 by Stewart to use a continuous saline infusion and then in 1928 by Hamilton to use a bolus injection of dye technique [2,3]

## **2.2. Dye dilution methods**

The Stewart-Hamilton dye dilution method to measure cardiac output was one of the earliest to be used clinically. In the 1950's indocyanine green dye became available clinically and was used to measure cardiac output, as well as blood volume and liver blood flow. However, sampling of arterial blood for dye levels was messy. A photocell detector placed on a finger was developed. Today, lithium dilution is the main indicator dilution technique in clinical use [4] and it is also a popular method in veterinarian practice.

## **2.3. The Swan-Ganz catheter**

The idea of using a cold temperature solution as an indicator, or thermodilution, dates back to the 1950's. At first fine catheter tubes were placed in the pulmonary artery, but this proved very difficult to perform clinically. The idea of using an inflated balloon to float the catheter tip into position was credited to Swan in 1970 and the triple lumen pulmonary artery catheter (PAC) with a thermistor at its tip to Ganz in 1971 [5,6]. Their PAC was produced by the Edwards Laboratory Company. The PAC became the principle method of measuring cardiac output and reached its peak usage by the end of the 1980's with sales worldwide of 1 to 2 million catheters per year. However, doubts about its clinical usefulness arose in the 1980's [7], which were later confirmed by several multicentre clinical trials [8,9]. Since the 1990's there has been a major decline in the use of the PAC catheter [10] as alternative technologies such as TOE have become available. Today, many anaesthetists and critical care doctors are unfamiliar with using PACs. Only a few companies worldwide still manufacture PACs notably Arrow International (Reading, PA, USA) and Edwards Lifesciences (Irvine, CA, USA). More sophisticated multifunction PACs are now being sold that measure continuous cardiac output using a heated wire and mixed venous oxygen saturation.

Minimally invasive cardiac out monitoring (MICOM) that measured cardiac output continuously at the bedside started to become available in the 1970's with the emergence of micro-processor and computer technology. Today they have become the main focus of clinical monitoring of cardiac output.

# **3. Background to main methods**

## **3.1. Bioimpedance**

In 1957 Nyboer made the observation that the cardiac cycle was associated with repetitive changes in thoracic impedance and that stroke volume could be estimated from the area under the curve of the resulting impedance waveform. In 1966 Kubicek applied this observation to

developing a method that could measure cardiac output in space by astronauts. Later he developed the first commercial impedance cardiograph, the Minnesota [11]. In the 1980's the BoMed NCCOM3 (BoMed Ltd., Irvine, CA, USA) (Figure 1) was developed by Bernstein and Sramek [12]. It used a modified Kubicek method to calculate cardiac output. It also automated the process calculating cardiac output, and provided continuous cardiac output readings in real-time. Thus, the first continuous MICOM had been developed.



**Figure 1.** The BoMed NCCOM3. It connects to the patients using eight skin surface electrodes applied to the mid-neck and lower chest at the level of the diaphragm. Two additional ECG electrodes can be added. The BoMed is calibrated by inputting the patient's height and weight. Cardiac output and related bioimpedance variables are displayed as numbers. Data is averaged over 16 heart-beats.

Unfortunately, the BoMed had problems with its reliability and was never accepted into clinical practice [13]. The presence of lung fluid corrupted impedance readings [14,15] and it was never determined with any certainty what the BoMed actually measured [16]. A digitalized version is still marketed and called the BioZ (CardioDynamics, San Diego, CA, USA). A number of companies have tried over the years to produce a more reliable version, but none have been very successful [17]. There is a haemodynamic monitoring system that incorporates bioimpedance cardiac output as one of its modalities called the Task-Force Monitor (CNSystems, Graz, Austria). It is used mainly to study autonomic responses such as syncope and head up tilting. There is also a device on the market called the NICOM (Cheetah Medical Ltd., Tel-Aviv, Israel) that uses a principle called bioresistance, which measures shifts in alternating current phase, rather than electrical resistance. Potentially, this device may be immune to the problems that afflicted the BoMed, but good validation data are still needed.



### 3.2. Doppler ultrasound

Ultrasound was first described in 1842. It was introduced into clinical practice in the 1950s by Ian Donald, a Scotsman. Echocardiography was developed in 1960's and used pulsed ultrasound for imaging. The measurement of blood flow using Doppler ultrasound was developed later to detect aortic and peripheral blood flow using continuous wave Doppler systems. In the 1980's Singer a London critical care physician was instrumental in the clinical development of oesophageal Doppler cardiac output monitoring [18]. In the early 1990's several prototype monitor and probe systems were developed such as the Hemosonic 1000, (Arrow International, Reading, PA, USA), and the Abbott ODM II, (Abbott Laboratories, Chicago, IL, USA). The only successful model has been the CardioQ, (Deltex Medical, Chichester, England) released in the early 1990's. In early 2000 an external continuous wave Doppler system was developed called the USCOM, (USCOM Ltd., Sydney, Australia). Previously one had to use echocardiography machines with limited Doppler capabilities for external monitoring. The USCOM measures cardiac output from both the ascending aorta and pulmonary artery using a hand held probe placed over the anterior neck (i.e. thoracic inlet) or left anterior chest wall (i.e. 3<sup>th</sup> to 5<sup>th</sup> intercostals spaces). Thus, the USCOM measures cardiac output intermittently.

### 3.3. Pulse contour analysis

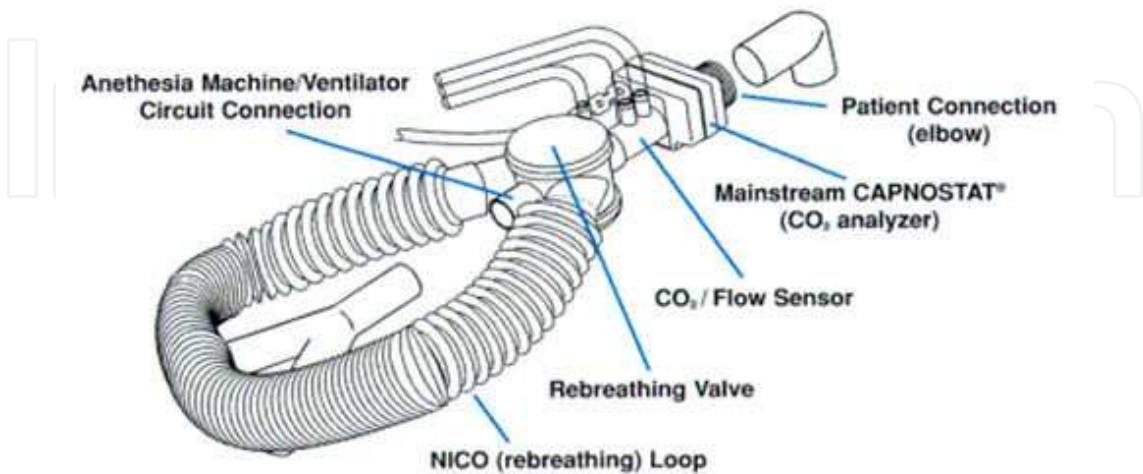
Noninvasive continuous blood pressure measurement using a pneumatic finger cuff (i.e. plethysmography) was developed over 30-year ago. In 1993 Wesseling et al described a method of using the finger cuff arterial pressure wave to derive cardiac output [19]. Their method known as "Model Flow" was incorporated into the Finapres series of noninvasive continuous blood pressure monitors. Currently, the manufacturers produce the Nexfin, (BMEYE, Amsterdam, Netherlands).

Systems that used the arterial blood pressure trace to measure cardiac output were later developed. In 1997 the first commercial system, the PiCCO (Pulsion, Munich, Germany) was released. The PiCCO was calibrated using transpulmonary thermodilution and monitored cardiac output from a femoral arterial line. Since, several other systems have been developed including in 2002 the LiDCO-plus (and later rapid), (LiDCO Ltd., Cambridge, England), and in 2004 the FloTrac-Vigileo, (Edwards Lifesciences, Irvine, CA, USA). Early versions of these monitors relied on external calibration, usually by thermodilution. However, more recent versions self-calibrate using patient demographic data. Pulse contour monitoring of cardiac output has not proved all that successful and current systems are unreliable when large fluctuations in peripheral resistance occur [20]. Recently there has been a change in the marketing policy. The focus is now towards "functional haemodynamic variables", such as pulse pressure and stroke volume variation in response to fluid and postural challenges.

### 3.4. Other methods

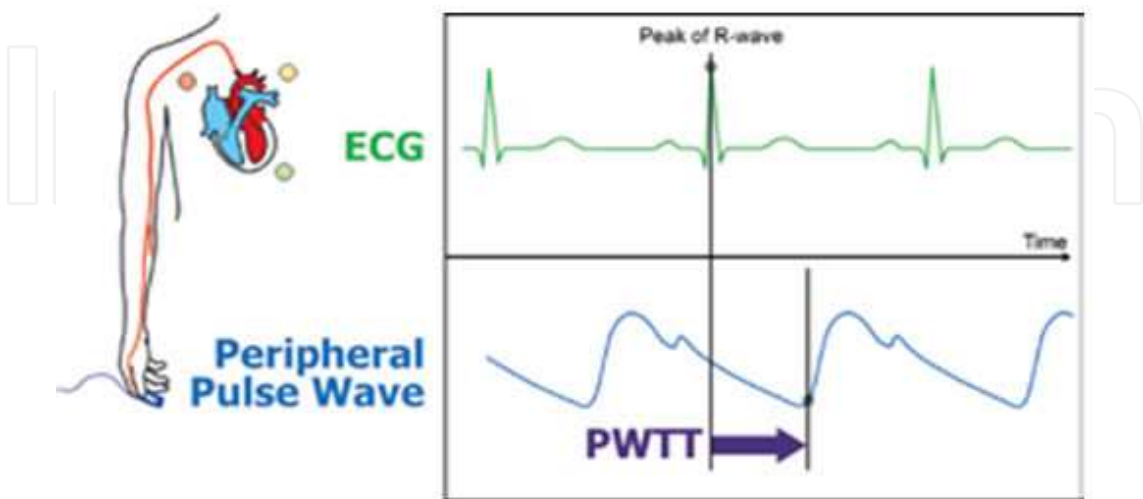
Several other novel techniques of measuring cardiac output have also been developed. In the 1970's researchers explored the possibility of using the mechanical impulse produced by heart as it contracted. In the 1990's a modified Fick method based on carbon dioxide rebreathing

that used a special breathing circuit extension loop was developed call the NICO (Respironics, Philips Healthcare, USA). The NICO is still produced but its use is restricted to intubated and ventilated patients (Figure 2).



**Figure 2.** Elaborate NICO rebreathing loop and circuit attachment that was added to the patient’s breathing circuit when performing the partial carbon dioxide rebreathing method.

In 2004 a device that used the time lags between the ECG and pulse oximetry signals was developed called the FloWave 1000, (Woolsthorpe Technologies, Brentwood, TN, USA). A Japanese group has recently developed a similar device called the esCCO monitor (Nihon Kohden, Tokyo, Japan) [21]. The esCCO also calculates pulse wave transit time from the ECG and pulse oximetry signal which it uses to calibrate the arterial pressure derived cardiac output (Figure 3).

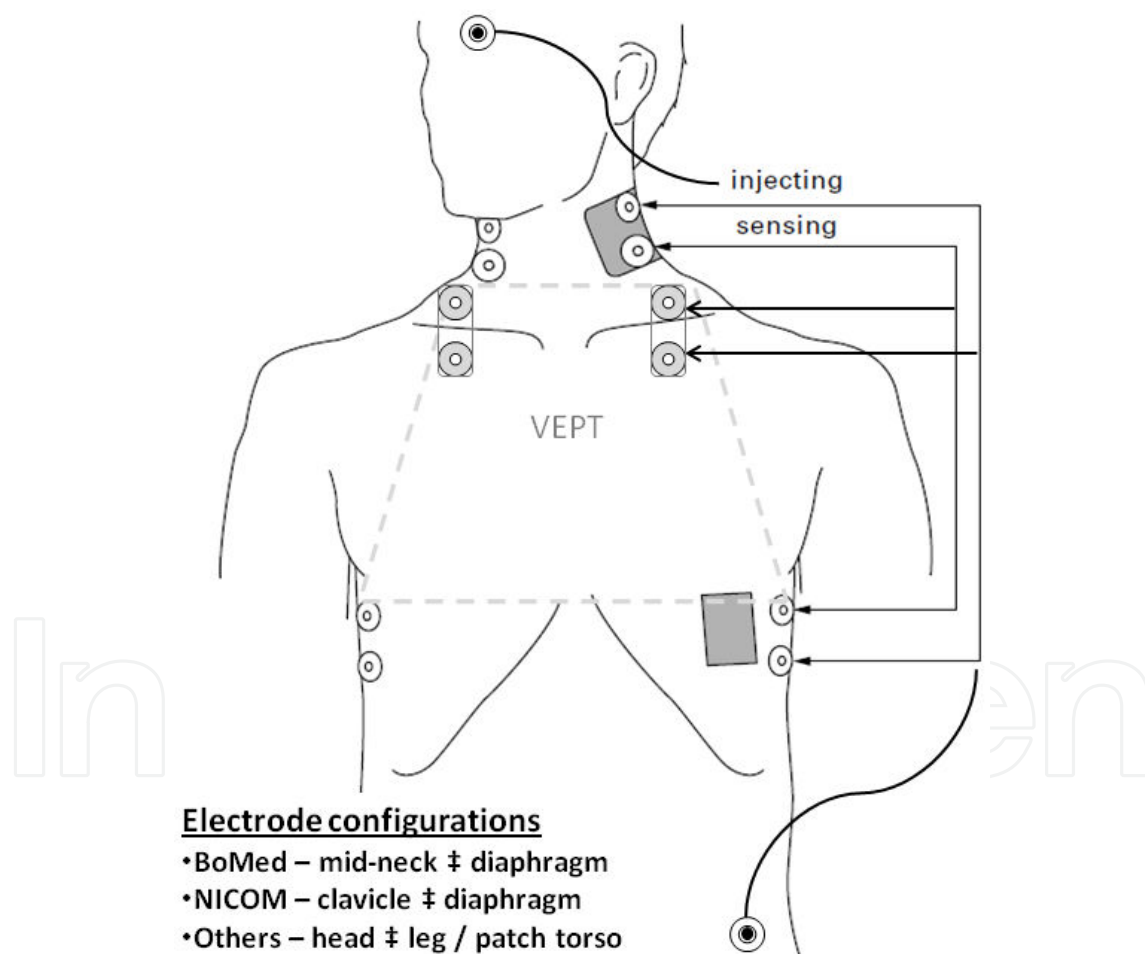


**Figure 3.** Illustration of the pulse wave transit time method used by the esCCO monitor. (Image from Nihon Kohden)

## 4. Description of the main methods

### 4.1. Bioreactance

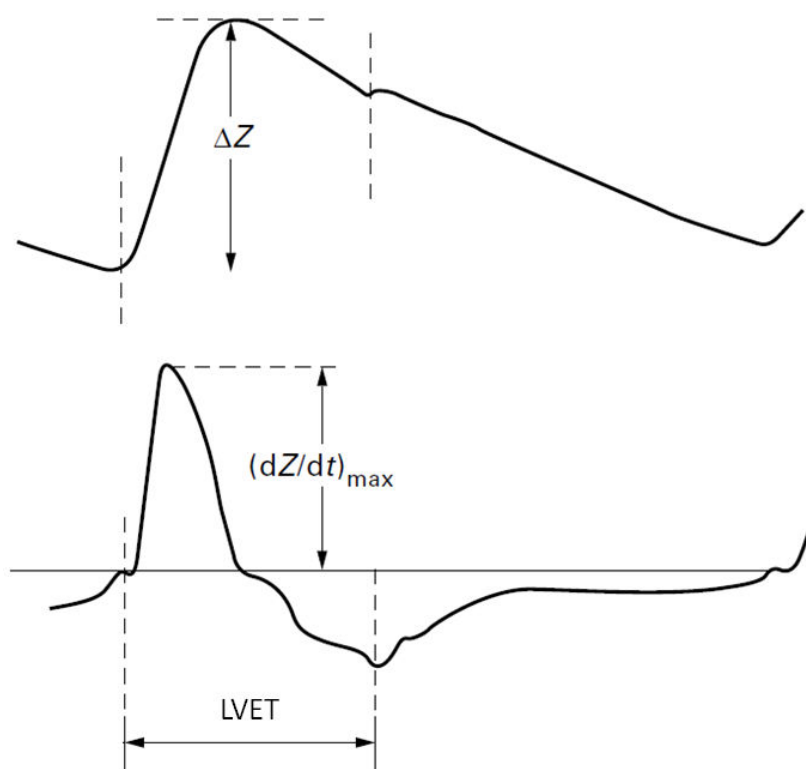
To understand how the bioreactance method (NICOM, Cheetah Medical) works one first must understand bioimpedance cardiac output. The older bioimpedance method involved detection of electrical resistance changes within the thorax. A high-frequency (50-100 kHz) low amplitude alternating current (<4mA), is passed between skin electrodes placed around the neck and upper abdomen. Inner current sensing skin electrodes detect voltage changes across the thorax and thus the impedance signal produced by the cardiac cycle (Figure 4). Originally, band electrodes were used, but in the BoMed this was changed to eight dot electrodes. Bioimpedance is safe electrically because of the high frequency and low amperage of the current. The only report of injury with its use has been a pacemaker malfunction [22].



**Figure 4.** Electrode configurations used by different bioimpedance devices. The BoMed used an eight electrode configuration with outer current injecting and inner current sensing skin dot electrodes. Some other devices were designed with fewer but larger patch electrodes on the head and lower torso (current injecting) and neck and lower thorax (current sensing). The bioreactance system (NICOM) also uses a four dual dot electrode configuration with the neck electrodes placed slightly lower at the level of the clavicles.

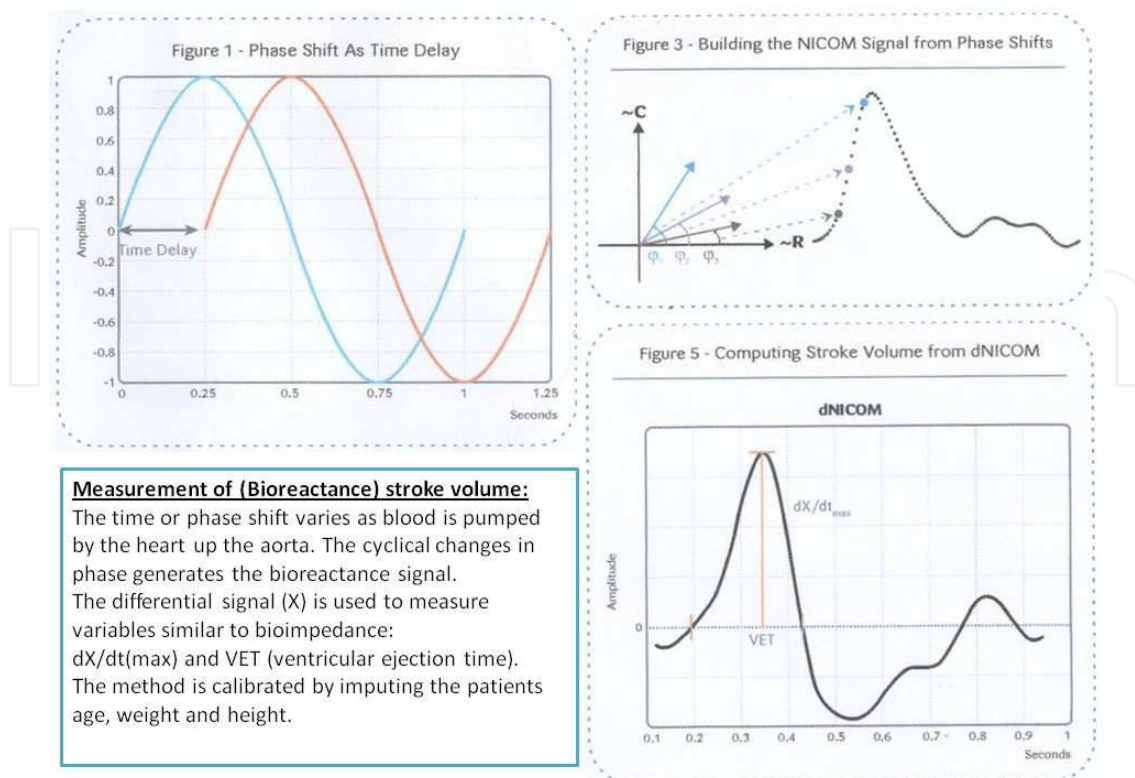


In the original description of the impedance method the area under the bioimpedance signal curve during systole was used to estimate cardiac output. To simplify the method Kubicek et al used the differential signal and its peak reading ( $dZ/dt(\max)$ ) as a surrogate for aortic blood flow [11]. The method also involves measuring the left ventricular ejection time (LVET) from the impedance signal (Figure 5).  $dZ/dt(\max)$  multiplied by LVET provides stroke volume, but the reading still needs to be calibrated. Cardiac output is calculated by multiplying by heart rate. Other bioimpedance variables measured from the waveforms include: (i) the thoracic impedance which can be used as an index of lung fluid, (ii) the systolic time intervals, pre ejection period (PEP) and LVET, which can be used to calculate ejection fraction and (iii) the second differential (i.e.  $d^2Z/dt^2(\max)$ ) which can be used as an index of contractility.



**Figure 5.** The bioimpedance method uses both the impedance signal ( $Z$  – upper waveform) and the differential signal ( $dZ/dt$  – lower waveform). From the differential signal the flow variable  $dZ/dt(\max)$  is measured. The time variable LVET is also measured. A number of other indices that reflect lung fluid and contractility are also measured.

Bioreactance uses a different electrical signal. It detects a property of alternating current called phase. An alternating current has a sinusoidal waveform. As the current flows through different body tissues its passage is delayed by capacitive and inductive tissue effects ( $X$ ) which cause a shift in its phase. As blood volume in the central thorax region varies with the cardiac cycle so does the phase shift of the current. Like resistance when measuring bioimpedance, a signal of the phase shift (bioreactance signal) can be plotted and from it variables that reflected blood flow ( $dX/dt(\max)$ ) and ventricular ejection time are measured (Figure 6). It is thought that the bioreactance signal is less affected by the factors that troubled the bioimpedance method, such as lung water [15].



**Figure 6.** The steps in deriving bioreactance cardiac output (Images from Cheetah Medical).

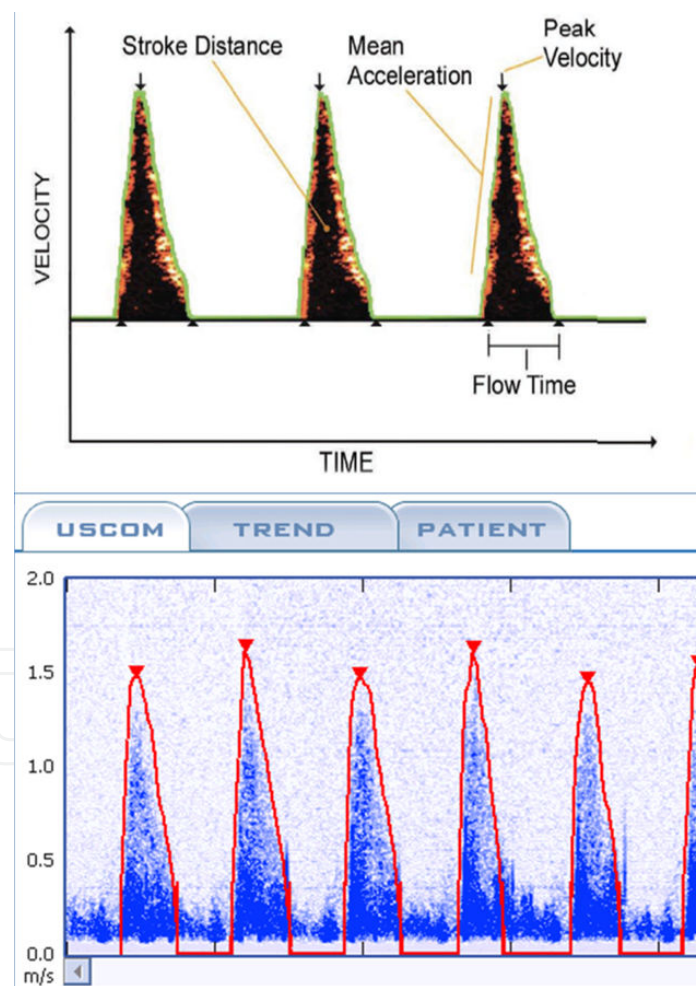
Like all surrogate cardiac output methods the bioreactance method needs to be calibrated. When using bioimpedance this requires estimation of the volume of electrically participating tissue (VEPT) lying between the current sensing electrodes. Kubicek et al modeled the thorax on a cylinder [11]. Bernstein later modified the equation to a truncated cone [12]. In the NICOM an undisclosed algorithm based on age, weight and height is used for calibration.

Just like bioimpedance, it is not known precisely what the bioreactance signal truly represents. Rather than the flow of blood, it probably reflects blood volume expansion in the aorta as the vessel distends with the rise in blood pressure generated during systole [16]. Thus readings may also be influenced by variations in peripheral resistance.

#### 4.2. Continuous wave Doppler

When pressure is applied to certain solid materials, notably crystals, they produce an electric charge. Equally, the same crystal will change shape when an electric charge is applied to it. This is known as the piezoelectric effect. If a high frequency current (i.e. 1-10 MHz) is applied the crystal will vibrate producing high frequency sound waves, or ultrasound. If the crystal is placed in contact with the skin the ultrasound will be propagated through the underlying tissues. When the ultrasound beam hits an interface between two tissue structures part of beam is reflected back. If a short burst of ultrasound is used and a second crystal is used as a receiver, then the time delays between transmission and return of this pulse can be used to create an image of the underlying tissue structure. This is the basis of ultrasound imaging.

When a beam of continuous ultrasound encounters moving blood cells flowing in a blood vessel the ultrasound is reflected back at a slightly altered frequency. This phenomenon is known as the Doppler effect. The change or shift in frequency is related to the velocity of the blood cells. The Doppler shift signal can be separated from the ultrasound signal and a profile of the Doppler signal displayed (Figure 7). The angle ( $\theta$ ) that the ultrasound beam makes with the direction of blood flow is also important as it affects the magnitude of the Doppler shift frequency. If the direction of the ultrasound beam is parallel to the blood flow the Doppler shift will be maximal, whilst a perpendicular angle of insonation produces no Doppler shift. The angle of insonation ( $\theta$ ) and Doppler shift frequency are related to the cosine of theta ( $\cos(\theta)$ ). The velocity of the blood flow is related to the Doppler frequency by the equation  $velocity = c \times f_D / 2 \times f_T \cos \theta$ , where  $f_D$  is the Doppler shift frequency,  $f_T$  is the ultrasound probe or transmitter frequency, and  $c$  is the speed of ultrasound in the tissues, 1540 m/s. The speed of sound in air is around 340 m/s.



**Figure 7.** Doppler flow profiles from the oesophagus (upper - CardioQ) and the supra-sternal window (lower - US-COM). Velocity is shown on the y-axis (m/s) and time along x-axis. The outline of each Doppler signal is automatically detected and drawn. The area of each envelope (stroke distance) is related to stroke volume. A series of cardiac cycles are shown. (Upper image from Deltex Medical)

Blood flow in the aorta pulsates rather than being continuous, thus a continuous Doppler ultrasound signal needs to be recorded with sufficient sampling rate to show the details of the flow profile (Figure 7). Most ultrasound machines are imaging systems and use pulses of ultrasound to measure distance from the probe or depth like radar or sonar. Doppler is different because it detects change in velocity rather than position and requires a continuous ultrasound beam from a transmitting crystal and a separate receiving crystal. From the Doppler profile of blood flow in the aorta the peak velocity of the blood and the duration of flow can be determined. By drawing an envelope around the Doppler flow profile one can calculate the total flow during systole, which is called the stroke (or minute) distance (Figure 7).

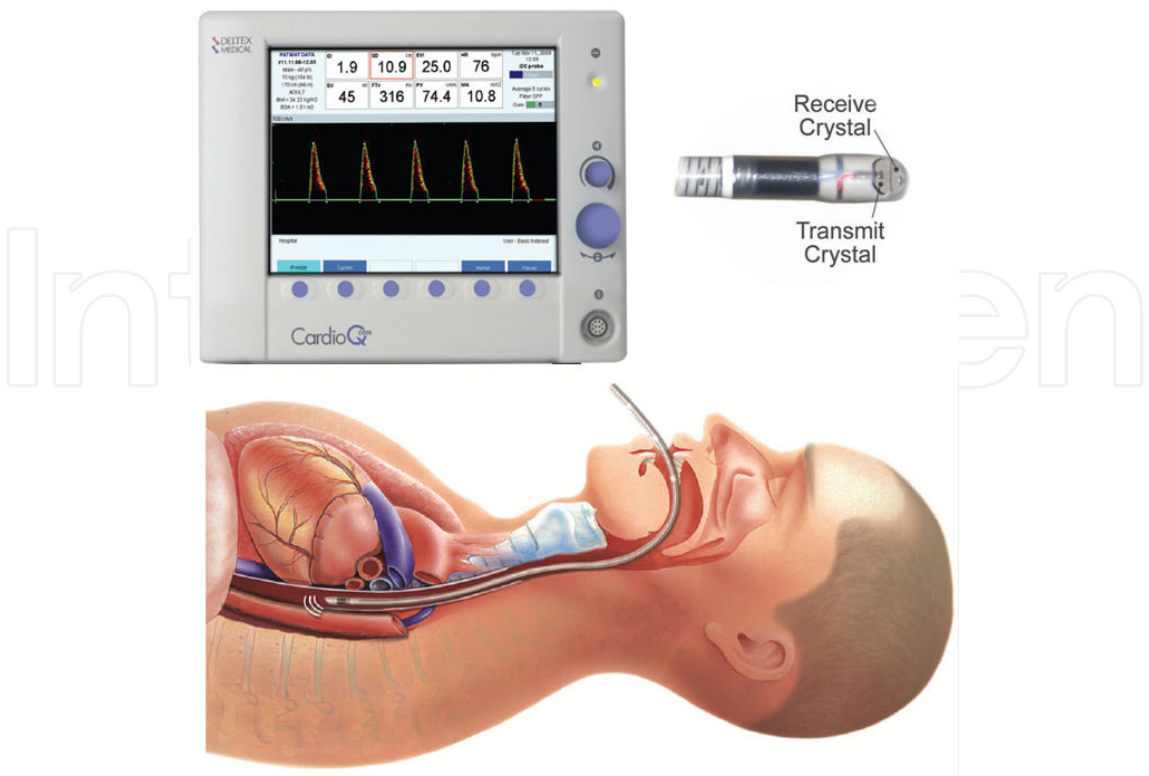
To convert stroke distance to a volume (i.e. stroke volume) the cross-sectional area of the blood vessel is needed. In conventional echocardiography machines this is measured by ultrasound imaging using the relationship  $CSA = \pi \times d^2 / 4$ , where CSA = cross sectional area and d = diameter of blood vessel.

Two Doppler cardiac output systems are currently on the market, the CardioQ (Deltex Medical) (Figure 8) and the USCOM (USCOM Ltd.) (Figure 9). Neither measures the CSA of the aorta directly and both estimate it but in different ways. The CardioQ uses an empirical algorithm based on population data, where the calibration constant is based on the patient's age, gender, height and weight. As the CardioQ measures blood flow from descending aorta where about 30% of the blood flow has left the aorta for the head and arms, its algorithm corrects for this reduction in total flow. The USCOM measures blood flow across the aortic or pulmonary valve. It uses an empirical formula to calculate valve CSA [23] which also requires the patient's age, gender, weight and height.

The angle of insonation with blood flow of the probe needs to be considered. When the CardioQ is used its probe is in the oesophagus and lies parallel to the descending aorta. The ultrasound crystals at the tip are set to 45-degrees (Figure 8). Therefore, its angle of insonation is 45-degrees. The USCOM probe has a wide beam angle. It is directed at the aortic or pulmonary valves and its beam axis usually lies almost parallel to the direction of flow because of the anatomy. Thus, the angle of insonation ( $\theta$ ) is close to 90-degrees and the cosine of the angle approximates to 1.0. Neither device is corrected for deviations in beam angle to blood flow.

Focusing of the probe to obtain the optimal and maximum Doppler signal plays an extremely critical role in using these two Doppler devices effectively. Focusing can be performed both visually by observing the shape of Doppler profiles on the monitor screen or by listening to the quality of the audible Doppler signal. Various numbers of patient examinations are quoted to acquire competence in the focusing technique, 12 for the CardioQ and 20 for the USCOM [24,25]. However, it takes a much longer time to become sufficiently familiar with the different signal sounds and patterns to recognize when a truly reliable signal has been obtained. Significant experience and psychomotor skill is needed to be able to acquire clinically reliable data, with the CardioQ being easier to learn. Both companies provide training and support.





**Figure 8.** The CardioQ oesophageal Doppler monitor. Monitor and probe tip shown with transmitter and receiver crystals set at a 45-degree angle. Anatomical diagram shows insertion of the probe into the oesophagus via the mouth and insonation of the aorta which lies posterior. (Images from Deltex Medical)



**Figure 9.** USCOM monitor showing Doppler signal data on its screen. The flow profiles are automatically outlined to measure stroke volumes. Below numerical readings are displayed. Lower right is a trend plot of saved cardiac output readings. The hand held USCOM probe is shown in front of the monitor. Ultrasound gel is applied to the probe to improve its acoustic contact.



In addition to measuring stroke volume and cardiac output, both Doppler devices provide internal software to (a) calculate other haemodynamic parameters, (b) display data trends and (c) store data for future reference. One particularly useful parameter measured by these Doppler systems is the flow time corrected (FTc), an index of preload or ventricular filling. It measures the duration of systole corrected for heart rate. More advanced models are sold that calculate inotropy and oxygen delivery from the blood pressure and oxygen saturation readings.

#### 4.3. Pulse contour analysis

The arterial pulse contour method in essence is very simple. An arterial catheter is inserted into a peripheral artery, usually the radial or femoral. The catheter is connected to a pressure transducer which is zeroed and checked for under or over damping. The analog arterial pressure signal is fed into a device that calculates cardiac output from the trace. However, there are at least ten different algorithms that can be used to derive cardiac output from arterial pressure. The theoretical basis to these different algorithms is extremely complicated and involves different mathematical models that describe the circulation and adjust for changes in its impedance and compliance of the peripheral circulation. A brief outline of how these algorithms is given.

- a. The simplest model that describes the circulation is the pressure = flow  $\times$  resistance relationship. The area under the arterial pressure curve is directly proportional to cardiac output providing peripheral resistance remains constant. Unfortunately, peripheral resistance does not remain constant. It is constantly changing under the influence of the sympathetic nervous system which helps to maintain blood pressure and the circulation as body position changes or the person exercises.
- b. Changes in peripheral resistance are reflected in diastolic pressure, so the simplest adjustment to the model is the use of pulse pressure (i.e. systolic-diastolic) rather than the arterial pressure to calculate cardiac output. This method is used in several pulse contour systems.
- c. The dynamics of the circulation is not as simple as pressure = flow  $\times$  resistance. The circulation is a pulsatile system and when the heart pumps the arterial system has to expand to accommodate the additional blood. Windkessel compared the arterial system to a capacitor and proposed a two element model of the circulation with both resistive and capacitive components.
- d. The two element model still did not describe the circulation in its entirety. Wesseling et al added a third inductive element to compensate for time lags as blood flowed through the arterial system [19]. Their three-element model was called "Model Flow" and was first used in the Finapres, a finger blood pressure cuff technology.
- e. Although, blood flow in the ascending aorta occurs during systole, as the blood travels more distally a significant proportion of blood flow also occurs in diastole and this component forms part of the peripheral arterial pressure wave. Thus, algorithms that measure cardiac output from a peripheral site such as the radial artery also should compensate for the diastolic component. One method is to identify the dichotic notch in the pulse wave and thus differentiate between the systolic and diastolic components.

- f. Finally, just as arterial pressure and blood flow changes over the course of one cardiac cycle, so does the impedance and compliance of the circulation. In most Windkessel based models the impedance and compliance remains static. The Liljestrand-Zander model compensates for this non-linearity. Sun in his thesis on cardiac output estimation using arterial blood pressure waveforms found the Liljestrand-Zander algorithm to be the most robust one he tested [26].

The main pulse contour systems currently available use several of these models. The FloTrac-Vigileo (Edwards Lifesciences) uses an empirical model based of pulse pressure and vascular tone. The PiCCO (Pulsion) uses a Windkessel model measuring area under the pressure curve. The LiDCO uses a similar approach but calculates the power, or root mean square (RMS), under the pressure curve. The PRAM-MostCare (Vytech) calculates the pulsatile area under both the systolic and diastolic curves [26,27].

Pulse contour systems need to be calibrated. The early models used a reading from a second cardiac output measurement system, such as thermodilution. However, this proved inconvenient and not conducive to clinical sales. Thus, later models were designed that self calibrated using patient demographic data. The PiCCO uses transpulmonary thermodilution and the LiDCO-plus lithium dilution. Self calibration is performed by the FloTrac, LiDCO-rapid and PRAM-MostCare methods (Figure 10). Normograms have been developed based on population data and require input of the patient's age, gender, weight and height.



**Figure 10.** Four main pulse contour monitors being used. FloTrac-Vigileo (top left), PiCCO with femoral artery catheter that provides transpulmonary thermodilution (top right), LiDCO with user card (bottom left) and PRAM-MostCare (bottom right). LiDCO system also provides lithium dilution cardiac output. (Images downloaded from manufacturers websites)

#### 4.4. Noninvasive pulse contour

Very few pulse contour systems are available that measure arterial blood pressure using a finger cuff. The most well known system is the Nexfin (BMEYE) (Figure 11). It is able to track blood pressure from the digital artery in real time. Cardiac output is calculated from a three element Windkessel model [19].



**Figure 11.** Finger cuff system used by the Nexfin. (Image from BMEYE)

#### 4.5. Partial carbon dioxide rebreathing

In patients connected to a ventilator and breathing circuit it is possible to measure cardiac output using a modified Fick method based on carbon dioxide. A loop of dead-space tubing is intermittently added to the patient circuit which facilitates the rebreathing of carbon dioxide (Figure 2). Based on certain assumptions and measuring carbon dioxide levels in the circuit cardiac output is derived. The NICO (Respironics) was the only system to be produced. The system was not very successful because it too sensitive to interruption of the regular breathing patterns.

### 5. Clinical areas & indications

#### 5.1. Overview

MICOM has a number of desirable features: (i) It can provide continuous patient monitoring, (ii) it is relatively safe to use clinically, and (iii) it can be simple to use. The main modalities currently being used clinically are Doppler, pulse contour and bioactance. These modalities have different attributes and thus each modality works better in different clinical areas. Bioimpedance devices are no longer in regular clinical use.

## 5.2. Anaesthesia

In the operating room setting a skilled operator who can interpret haemodynamic data is nearly always in attendance. Therefore, safety and reliability rather than ease of use are the main issues when selecting a MICOM for anaesthesia.

Until recently cardiac output monitoring was seldom used in anaesthesia unless the patient was having ultra-major surgery or had a significant circulatory problem. In the past a pulmonary artery catheter would have been used to monitor heart function. In more recent times the vogue has been to use transoesophageal echocardiography (TOE), though TOE does not measure cardiac output continuously. Thus, MICOM had not until very recently been widely implemented in anaesthesia.

However, anaesthetic interest in MICOM has grown in recent years and this interest has been largely driven by changes in our understanding of intra-operative fluid management [28]. Goal directed therapies have become popular with new MICOM systems being developed to drive protocols. The most successful of these protocols has been goal directed fluid therapy guided by oesophageal Doppler in high risk surgical patients. A number of low powered clinical trials attest to improved patient outcomes with its use have been published [29]. It is now being recommended in Britain and Europe as part of enhanced surgical recovery programs [30,31].

MICOM can be used to monitor haemodynamics during major high risk surgery. It has become popular in specialized areas of anaesthesia such as managing the circulation and intravenous fluids of patients undergoing oesophageal surgery and there are other examples.

I will now describe the pros and cons of the main MICOM modalities with reference to anaesthesia and operating room use.

Successful use of Doppler is very operator dependant as the probe has to be refocused regularly to assure reliability and this can prove very time consuming and distracting for the solo anaesthetist.

Oesophageal Doppler (CardioQ) provides continuous monitoring, but its placement in the oesophageal limits its use to unconscious (anaesthetized) and sedated patients. Furthermore, operations involving the head and neck or upper gastrointestinal tract may prohibit its use because of interference with the surgical field.

External precordial Doppler (USCOM) requires use of a hand held probe that is focused via the thoracic inlet and sternal notch on the aortic valve. The flow signal from the pulmonary artery via the left 3<sup>rd</sup> to 5<sup>th</sup> intercostals space can also be used but is less popular in anaesthesia because access to the anterior wall is often restricted, lung ventilation may obscure the probe beam and repositioning of the patient to improve the signal is prohibited. During anaesthesia the probe can be used more effectively to locate the Doppler signal from the aortic valve because discomfort from pressure applied to the thoracic inlet is no longer felt. Readouts are in real-time and the monitor benefits from data trending. Serial changes from up to four flow parameters can be displayed. The type of surgery may restrict use of the probe, such as head and neck operations and the prone position. The quality of the external Doppler signal and thus its reliability are very patient dependant. Age appears to have major effect with reliability

declining over the age of 50-years. A 12-point scoring system that determines the quality of the Doppler flow profile has been described by Cattermole and this score helps to determine whether readings are reliable [32].

Use of pulse contour cardiac output necessitates the placement of an arterial line which limits use to more major hospital centres and high risk surgical cases. It provides continuous monitoring and thus during anaesthesia it can be used to monitor haemodynamics and drive goal directed protocols. Also, once set up it requires very little adjustment unlike Doppler systems. There are at least four pulse contour systems on the market. However, the reliability of these systems in anaesthesia and intensive care has been questioned because current algorithms do not compensate for changes in peripheral resistance, particularly when vasopressor drugs are used [33].

We do not know much about the clinical performance of bioimpedance devices (NICOM, Cheetah Medical) and whether they are more reliable when compared to bioimpedance. However, bioimpedance does have several features that make it theoretically the perfect monitor. It is noninvasive and safe, it provides continuous cardiac output monitoring, it does not require a great deal of skill to set up and it is inexpensive to run. It is being promoted in the anaesthesia field as a cardiac output monitor and to drive goal directed protocols.

### 5.3. Intensive care

MICOM is used in intensive care to manage critically ill patients with circulatory shock and to optimize ventilator settings such as when positive end expiratory pressure (PEEP) and lung recruitment strategies are used. Monitoring systems that measure cardiac output accurately are needed for bedside diagnosis, whilst reliable trending ability is needed to guide fluid and cardiovascular drug therapies. In addition to cardiac output, oxygen delivery ( $DO_2$ ) and indices of contractility are also monitored. In more stable patients such as head injuries MICOM can be used for continuous surveillance to pick up sudden alterations in the patient's condition.

The use of Doppler systems is limited because the patient has to be sedated to tolerate an oesophageal probe and external Doppler does not provide continuous patient monitoring. Oesophageal Doppler was originally developed for the intensive care setting [18] and still has a role in haemodynamic optimization, lung ventilation and driving goal directed therapies. Signal quality can be an issue when using external Doppler (USCOM), particularly in elderly patients with low cardiac outputs. As Doppler MICOM requires time and skill to operate and obtain reliable signals, and an intensive care doctor trained in its use may not always be available, some intensive care units have moved towards training nursing staff in its use.

The use of pulse contour methods in intensive care is attractive as most critically ill patients have an arterial line in-situ and continuous monitoring of their haemodynamic status is required. Furthermore, once it is set up pulse contour methods require very little adjustment. The main issue has been the reliability of current systems. It is a worrying fact that in response to a potent vasoconstrictor such as phenylephrine pulse contour cardiac output increases, whereas other cardiac output modalities like thermodilution and Doppler decrease [33]. The



algorithms currently being used to convert pressure to blood flow are still in need of improvement. The most successful pulse contour system in use in the intensive care setting is the PiCCO plus (Pulsion) that integrates transpulmonary thermodilution readings with femoral artery pulse contour readings. The PiCCO system can be upgraded to measure blood volume, liver blood flow and mixed venous saturation. The FloTrac-Vigileo system (Edwards Lifesciences) also been upgraded from just monitoring cardiac output to a more global approach in their new EV1000 clinical platform monitor.

Functional haemodynamic monitoring has also become popular using arterial trace based parameters such as stroke volume (SVV) and pulse pressure (PPV) variation to guide therapy [34].

#### **5.4. High dependency units**

When MICOM is used in high dependency areas for patient monitoring continuous noninvasive systems are required. Pulse contour systems can be used providing the patient has an arterial line. The noninvasive nature of bioreactance (NICOM) makes it a potentially useful monitor in this setting.

#### **5.5. Accident and emergency**

MICOM has two potential roles in accident and emergency (i) to facilitate resuscitate and (ii) rapid bedside haemodynamic assessment of patients. Thus, systems that can be rapidly set up and used at the bedside are ideal.

For resuscitation both Doppler and pulse contour methods can be used, though for pulse contour monitoring an arterial line would need to be set up. Furthermore, a self calibrating system would be necessary. The development of noninvasive external, supra-sternal and precordial, Doppler (USCOM) has resulted in some novel application in the emergency medicine setting. Assessment of cardiac output in elderly patients admitted with general malaise can help identify early septic shock and may potentially reduce the number that need intensive care admission. Bedside cardiac output measurement in patients with hypertension helps one to differentiate between high peripheral resistance and high cardiac output as a cause and helps in determining the most appropriate drug therapy.

#### **5.6. Medicine and cardiology**

NICOM in medicine contribute to the haemodynamic assessment of patients by providing cardiac output and related measurements. They form part of multiple modality haemodynamic investigation systems, such as the Task Force Monitor (CNSystems), where they are used to assess autonomic dysfunction in diabetes and postural reflexes in patients with syncope by head up tilting and similar tests. In cardiology they have been used to optimize pacemaker settings. MICOM devices that are noninvasive such as bioimpedance and finger plethysmography tend to be used.

## 5.7. Paediatrics

Most MICOM modalities have been adapted for use children. Noninvasive modalities like external Doppler (USCOM) has become increasingly popular in children because there is no need to insert lines. It works extremely well in small children and neonates as signal acquisition is good [35]. There is a growing interest in developing its use in paediatric intensive care for clinical situations such as rapid identification and treatment of shock [36].

## 5.8. Cost and availability

When using MICOM running costs need consideration. In addition to the monitor most systems require disposable items to operate. Oesophageal Doppler requires disposable oesophageal probes which are made for single use (Figure 8). The FloTrac-Vigileo uses a disposable pressure transducer (Figure 10). The PiCCO uses a femoral artery catheter that also acts as a thermodilution catheter. The LiDCO and PRAM systems work on a credit card system to buy user time (Figure 10). The NICOM uses purpose made skin electrodes (Figure 4). The NICO had a disposable breathing attachment to facilitate carbon dioxide rebreathing (Figure 2). Most of these disposables are priced around the same cost as thermodilution catheter. The only system that does not require disposable items other than ultrasound gel is the USCOM. The ultrasound probe is cleaned between patient uses. Financing ones supply of these disposable items can be a problem when first introducing what is a relatively new and unproven technology into ones clinical practice and may limit use. Manufacturers will calm that it is a necessary evil to sustain the company financially and replay their investment in research and development.

# 6. Overview of clinical validation

## 6.1. Main objectives

The aim of clinical validation is to determine whether a new monitor measures cardiac output reliably, which is done by comparing its performance with that of an accepted clinical standard such as single bolus thermodilution cardiac output. If the new monitor performs as well or better than the reference method, it can be accepted into clinical practice.

However, there are two important aspects to reliable cardiac output measurement:

- i. The accuracy of individual readings, and
- ii. The ability to detect changes, or trends, between readings.

The type of clinical data and statistic analysis needed to evaluate these two aspects are different.

If ones objective is to diagnose a low or high cardiac output, then the accuracy of individual readings in relation to the true value is of greatest importance. However, if ones objective is to follow the change in haemodynamic response to a therapeutic intervention, then serial cardiac output readings are needed and their absolute accuracy becomes less important,

providing the readings reliably show the changes. This division into two roles may at first seem a little pedantic, but a monitor that does not measure cardiac output accurately may still be useful clinically if it detects trends reliably. As most bedside cardiac output monitors used today are now able to measure cardiac output continuously, although many are not particularly accurate, the issue of being a reliable trend monitor becomes very relevant. Unfortunately, the majority of published validation studies have only addressed accuracy [37].

## 6.2. Understanding errors

The error that arises when measuring cardiac output has two basic components:

- i. Random error that arises from act of measuring and
- ii. Systematic error that arises from the measurement system.

If I use a measuring tape to measure the heights of patients attending a clinic, my readings may vary by few millimeters from the true height of each patient. This is random error. But if the measuring tape is stretched by 2 to 3 centimeters, then every reading I take will consistently under read the height of each patient by a few centimeters. This is a systematic error. The division of measurement error into random and systematic components plays an important role in the choice of statistical techniques used for validation.

One of main sources of systematic error is imprecise calibration. Calibration is performed by (a) measuring cardiac output using a second method such as thermodilution, or (b) using population data to derive cardiac output from the patient's demographics, (i.e. age, height and weight)). Unfortunately, cardiac output, and related parameters vary between individuals. In the Nidorf normogram used to predict aortic valve size when using suprasternal Doppler cardiac output the range of possible values about the mean for valve size at each height is  $\pm 16\%$  [23]. This gives rise to a significant systematic error between patients and this error impacts upon accuracy when Bland-Altman comparisons are made against a reference method [38]. However, reliability during trending may still be preserved because trending involves a series of readings from one single patient. Providing the systematic error remains constant, and the random measurement errors between the series of readings are acceptably low, the monitor can still detect changes in cardiac output reliably.

The accepted method of presenting errors in validation statistics is to use (a) percentages of mean cardiac output and (b) 95% confidence intervals, which approximates to two standard deviations. The term precision error is used, and should not be confused with the percentage error which is one of the outcomes of Bland-Altman analysis.

## 7. Addressing statistical issues

### 7.1. Simple comparisons against a reference method

Validation in the clinical setting is usually performed by comparing readings from the method being tested against a reference method. Traditionally single bolus thermodilution cardiac

output performed using a PAC has been used. The average of three thermodilution readings is used, and aberrant readings that differ by more than 10% are rejected, in order to improve the precision. However, thermodilution is not a gold standard method and significant measurement errors, both random and systematic, arise when it is used. It is generally accepted that thermodilution has a precision error of  $\pm 20\%$ . True gold standard methods such as aortic flow probes have precision errors of less than  $\pm 5\%$ . Thus, thermodilution is an imprecise reference method and its use greatly influences the statistical analysis. Most of the benchmarks against which the outcomes of validation studies are judged are based on this precision of  $\pm 20\%$ .

Other more precise and gold standard reference methods could be used, such as the Fick method or a flow probe surgically placed on the aorta. However, in the clinical setting their use is inappropriate and thus the current clinical standard for cardiac output measurement thermodilution via a PAC is used. The current decline in the clinical use of PACs has left a void. Thus, some recently published validation studies have used transpulmonary thermodilution using the PiCCO system or oesophageal Doppler monitoring using the CardioQ as alternative reference methods.

## 7.2. The precision error of thermodilution

Recently, the precision of  $\pm 20\%$  for thermodilution has come under scrutiny. The reason that thermodilution is said to have a precision error of  $\pm 20\%$  can be attributed to our 1999 publication on bias and precision statistics which first proposed percentage error [39]. In the 1990's consensus of opinion was that for a monitor to be accepted into clinical use it should be able to detect at least a change in cardiac output of 1 L/min when the mean cardiac output was 5 L/min, which was a 20% change [40,41]. Furthermore, Stetz and colleagues meta-analysis of studies from the 1970's validating the thermodilution method suggested that it had a precision of 13-22% [42]. The 30% benchmark percentage error that everyone today quotes was based on a precision error of  $\pm 20\%$  for thermodilution. However, it is now seems that the precision of thermodilution can be very variable and depends on type of patient and measurement system used [43]. Recently Peyton and Chong have suggested that the precision of thermodilution may be as large as  $\pm 30\%$  [44].

## 7.3. Study design

Study design becomes significant when ability to detection trends, in addition to accuracy, is investigated. To determine accuracy one needs only a single pair of cardiac output readings, test and reference, from each patient. Test refers to the new method being validated and reference to the clinical standard thermodilution, though ideally a gold standard method should be used. Readings, test and reference, should ideally be performed simultaneously, because cardiac output is not a static parameter and fluctuates between cardiac cycles. The size of the study usually includes twenty or more pairs of readings.

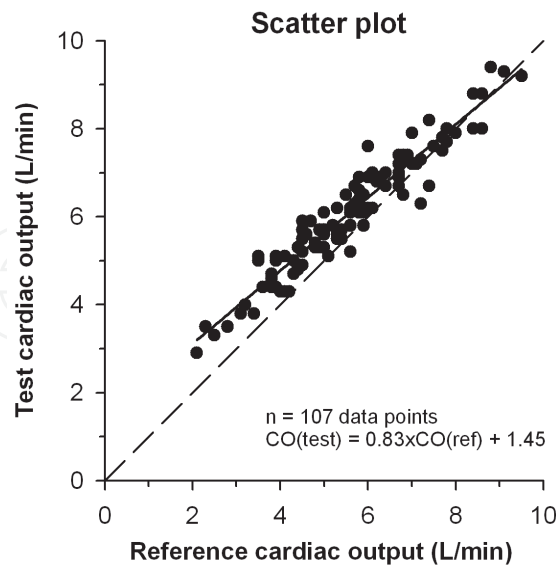
Study design becomes more complicated if the ability to detect trends is being investigated. A series of paired readings from the same patient are now needed that show changes in cardiac

output. A wide range of values of cardiac output readings is also needed. A new parameter called delta cardiac output ( $\Delta\text{CO}$ ) is calculated for both test and reference data which uses the difference between consecutive readings. Trend analysis is performed on the  $\Delta\text{CO}$ s. The data can be collected (a) at random or (b) at predetermined time points. Readings collected at random can lead to uneven data distribution. Thus, a more rigid protocol with data being collected at predetermined time points tends to be used. Commonly 6 to 10 time points are used. A typical protocol for a patient having cardiac surgery might be: (T1) - before anaesthesia, (T2) – after induction, (T3) - after sternotomy, (T4) – after by-pass, (T5) – after closure of the chest and (T6-8) - at set times on the intensive care.

## 8. Graphical presentation and analysis

### 8.1. Scatter plots

Validation data first should be plotted on a graph that shows the relationship between the test and reference cardiac output readings. The simplest approach is to plot the data on a scatter plot where the x-axis represents the reference readings and the y-axis represents the test readings (Figure 12). The data points should lie within close proximity to the line of identity  $x=y$  for there to be good agreement. A regression line can be added. However, correlation is not performed if the aim of the analysis is to assess the agreement between two methods rather than assessing trending ability. This point was highlighted by Bland and Altman when they published their well known method of showing agreement [45].

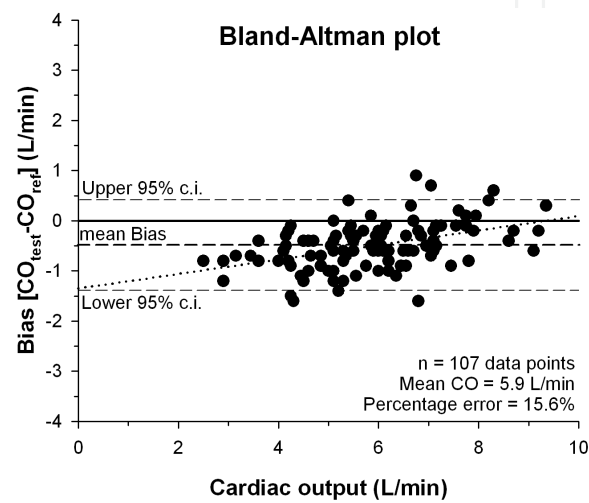


**Figure 12.** Scatter plot showing test and reference cardiac output (CO) data points. The regression line (solid) crosses y-axis at 1.45 L/min, indicating an offset in calibration between the two methods. A line of identity (dashed)  $y=x$  is added. There is good agreement between the test and reference methods because data points lie close to the regression line. The correlation coefficient ( $r$ ) is not provided.



## 8.2. The Bland-Altman plot

The agreement between two measurement techniques, test and reference, is evaluated by calculating the bias, which is the difference between the each pair of readings, test minus reference. In the Bland-Altman plot the bias of each pair of readings (y-axis) is plotted against the average of the two readings (x-axis) (Figure 13). Then, three horizontal lines are added to the plot: (a) The mean bias for all the data points and (b) The two 95% confidence interval lines for the bias ( $1.96 \times$  standard deviation of the bias) known as the “Limits of Agreement”. Sufficient data should also be provided to allow the calculation of percentage error.



**Figure 13.** Bland and Altman plot showing test and reference cardiac output (CO) data points. The mean bias and limits of agreement lines (dashed) have been added to plot. 95% of the data points falls between these limits. The percentage error has been calculated from the mean CO and limits of agreement. Note the slightly skewed distribution of the data shown by the sloping regression line (dotted).

## 8.3. Modifications to the B-A plot

- i. Some investigators argue that the best estimate of cardiac output (x-axis), or the reference value, should be used instead of the average.
- ii. When the study protocol collects more than one set of data from each patient the limits of agreement should be adjusted for repeated measures. The effect of having multiple readings from the same subject is to reduce the influence of systematic errors, thus decreasing the standard deviation of the bias and narrowing the limits of agreement. As a consequence the limits become falsely small. Two recent articles describe how to perform a correction for repeated measures [46,47]. The models used in the two corrective methods are slightly different.
- iii. The Bland-Altman plot assumes that both the test and reference methods have the same calibrated scales for measuring cardiac output. Otherwise, the distribution of data will be sloping and the limits of agreement falsely wide. Bland and Altman described a logarithmic transformation to deal with this scenario [45].

#### 8.4. Which parameters should be present?

In the past many authors have not known how to present their cardiac output data from validations studies in a meaningful and useful manner. When presenting data on a scatter plot one should include the number of data points in the plot. Attention also needs to be given the scale used on the axes so that false impressions of the spread of the data are avoided. Ideally the axes should be of equal scale and range from zero to the maximum value of cardiac output. If a regression line is added, the equation of line should be shown. Correlation analysis is not required unless serial data that shows trending is being used.

Similar issues apply to the Bland-Altman plot. In particular, the range of cardiac output on the x-axis and the range of values for bias need to be appropriate. If several plots comparing data from several devices or patient groups are shown the scales on each plot should be equivalent.

The important data measured using the Bland-Altman analysis are:

- i. The mean bias,
- ii. The standard deviation of the bias which is presented as the 95% confidence intervals or Limits of Agreement,
- iii. The mean cardiac output and
- iv. A calculated parameter called the percentage error.

The study size and percentage error at least should be presented with the Bland-Altman plot.

#### 8.5. Percentage error and the 30%

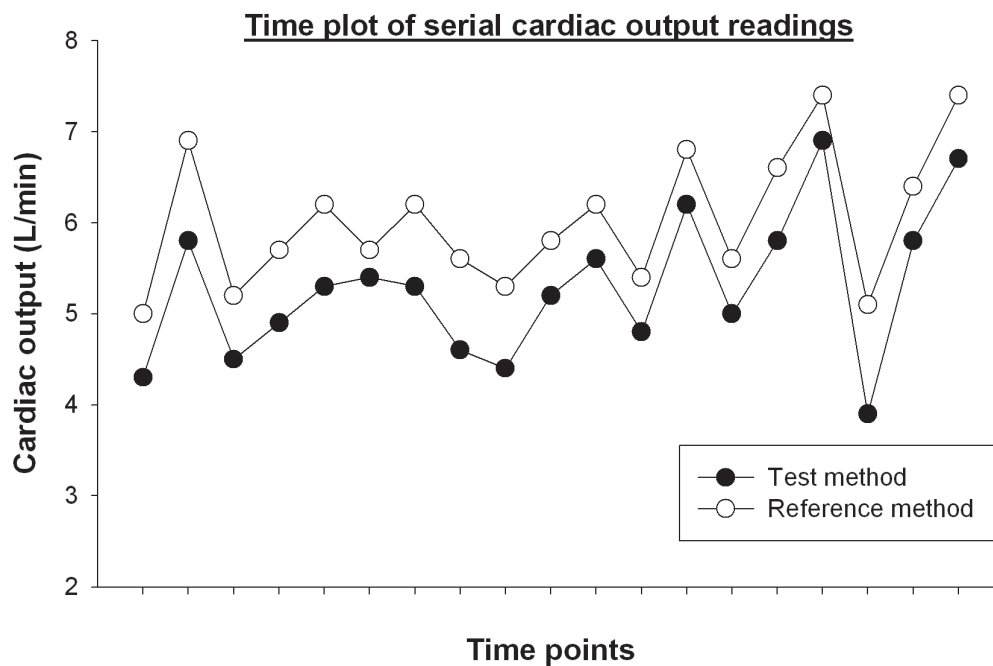
The percentage error is calculated using the formula “ $1.96 \times \text{standard deviation of the bias} / \text{mean cardiac output}$ ” and is expressed as a percentage. It represents a normalized version of the limits of agreement. The percentage error enables one to compare data from different studies when the ranges of cardiac outputs are different. Even today many authors still fail to present percentage error.

Following a meta-analysis of data from cardiac output studies published pre-1997 that used Bland-Altman analysis we proposed that when the percentage error was less than 28.4%, it was reasonable to accept the new test method. However, the reference method had to be thermodilution with an estimated precision was  $\pm 20\%$  [39]. Our work lead to the 30% benchmark for percentage error quoted in many publications over the last a decade. An error-gram was published in our 1999 paper to allow for adjustment to this threshold when reference methods of different precision errors were used.

#### 8.6. Showing reliable trending ability

To assess the trending ability of a new monitor against a reference method one uses serial cardiac output readings. The simplest way to show trending is to plotting the test and reference methods together against time (Figure 14). However, time plots only show data from a single subject, but to confirm reliable trending data from several subjects needs to

be shown. Also, time plots provide only graphical evidence and an objective measure of trending is also needed.



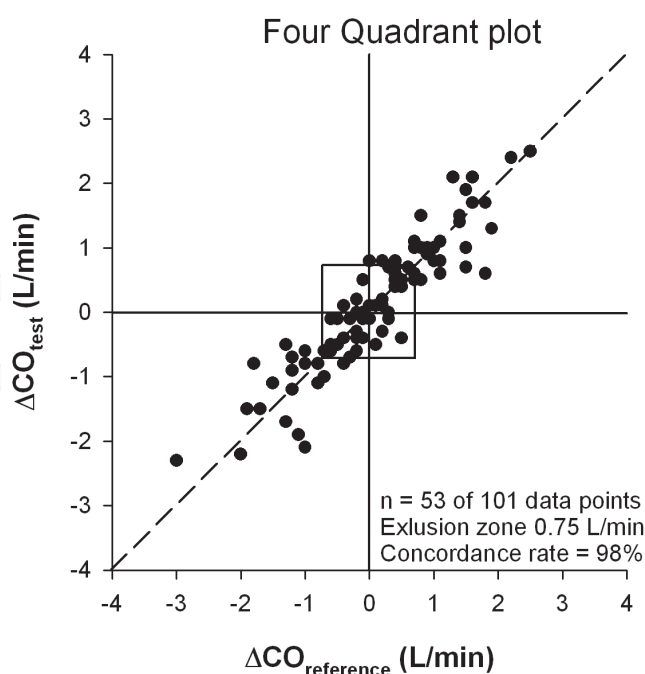
**Figure 14.** Time plot showing the relationship between test and reference cardiac output readings over time. Data pairs come from a single patient collected at intervals during surgery. The test method follows changes in reference cardiac output despite the test method under-reading by approximately 0.75 L/min. Thus, reliable trending ability is demonstrated in the patient.

### 8.7. The four-quadrant plot

The variable commonly used to assess trending in statistical analysis is delta cardiac output ( $\Delta\text{CO}$ ), the difference between successive readings, or the change in cardiac output ( $\text{CO}_b - \text{CO}_a$ ).

Bland-Altman analysis does not show trending, so other analytical methods are used. There is limited consensus on which analytical method should be used [37]. In clinical trials concordance using a four-quadrant plot has become the standard method.

The four quadrant plot is simply a scatter plot showing delta cardiac output ( $\Delta\text{CO}$ ) for the test method against the reference method. Because the changes in cardiac output are used, the x and y axes pass through zero (0,0) at the centre of the plot. The delta data points should lie along the line of identity ( $y=x$ ) if good trending is present (Figure 15). The earliest reference to this method appeared in the mid 1990's [48,49].



**Figure 15.** Four quadrant scatter plot comparing changes in test and reference cardiac output ( $\Delta\text{CO}$ ) readings. The plot is divided into four quadrants about the x and y axis that cross at the centre (0,0). Data points lie along the line (dashed) of identity  $y = x$ . A square exclusion zone is drawn at the centre to remove statistical noise. Concordance analysis is performed by counting the number of data points remaining after central zone exclusion that lie within the two quadrants of agreement (upper right and lower left). In the plot 98% of the data concurs, thus trending ability is very good. Supra-sternal and oesophageal Doppler were being compared.

The concordance is measured as the proportion of data points in which either both methods change in a positive direction (i.e. increase and lie within the right upper quadrant) or change in a negative direction (i.e. decrease and lie within the left lower quadrant). Data points that do not concord (i.e. change in different direction) lie within the upper left or lower right quadrants. The concordance rate is the percentage of data points that are in concordance or agree regarding the direction of change of cardiac output.

### 8.8. The central exclusion zone

One of the main problems encountered when using the four quadrant plot is that data points close to its centre, which represent relatively small cardiac output changes, often do not concord because random error effects are of similar magnitude to the cardiac output changes. This phenomenon results in statistical noise that adversely affects the concordance rate. Perrino and colleagues introduced a central exclusion zone to reduce the level of these random error effects [49].

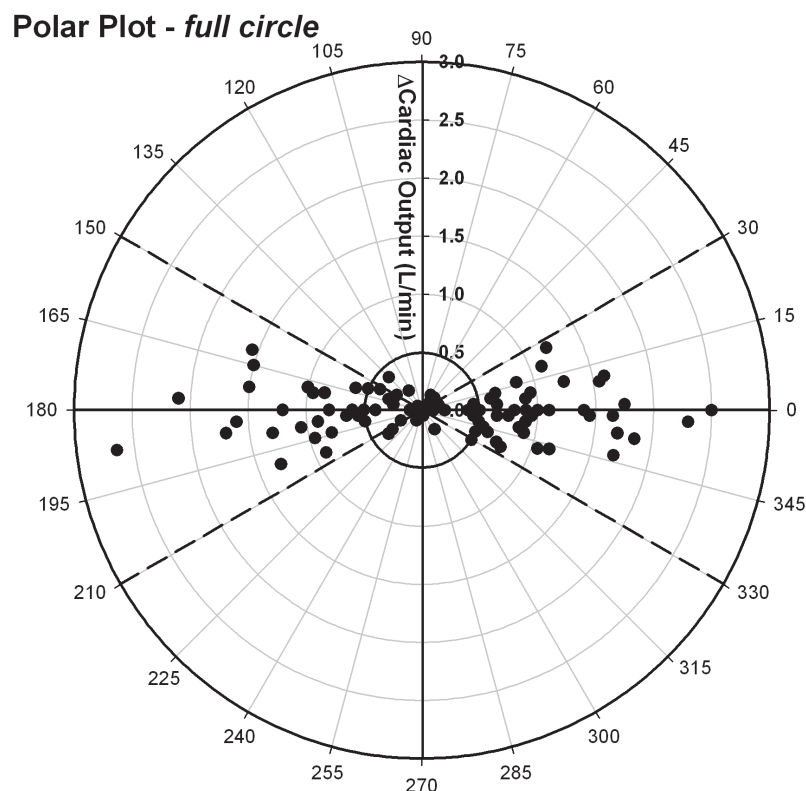
Receiver operator characteristic (ROC) curve analysis of Perrino and colleagues data was performed to predict the most desirable exclusion zone [48]. For a mean cardiac output of 5.0 L/min these author recommended an exclusion zone of 0.75 L/min or 15%. In the above example it can be seen that after central zone exclusion of data, most of the remaining data lie

with the upper right (i.e. positive changes) and lower left (i.e. negative changes) quadrants of concordance. The concordance rate is 98% as one data point lie outside these quadrants.

When performing concordance analysis one needs to know what is an acceptable rate? In a recent publication on trend analysis, we analyzed data from nine studies that used concordance analysis. From this data we concluded that for good trending ability to be shown against thermodilution as a reference method the concordance rate should be 92% or above [37].

### 8.9. Polar plots

Concordance analysis and the four quadrant plot have limitations. The changes in cardiac output between the test and reference methods can be very different yet concord if both have the same direction of change and the magnitude of the change in cardiac output plays no part in the analysis other than determining what data is excluded. To address these issues we developed a method of concordance analysis based on converting the data to polar coordinates. The polar angle represented agreement whilst the radius represented the magnitude of change in cardiac output [50]. The polar data is generated from the  $\Delta\text{CO}(\text{test})$  and  $\Delta\text{CO}(\text{reference})$ . Descriptions on how to draw polar plots are found in our paper.



**Figure 16.** The polar plot displays  $\Delta\text{CO}$  data. The axis of the plot lies at 0-degree (and 180-degrees). It is equivalent to the line of identity  $y=x$  on the scatter plot (figure 12), except that the plot has been rotated clockwise by 45-degrees. Concordance limits are drawn at  $\pm 30$ -degrees. A circular exclusion zone of 0.5 L/min is drawn at the centre. Data points that lie within



these limits concord. Positive changes in cardiac output ( $\Delta\text{CO}$ ) (right half) and negative  $\Delta\text{CO}$  (left half) are presented on opposite halves of the plot. The mean polar angle and radial limits of agreement for data have been omitted.

Our earliest description of polar plots used a full 360-degree circle to show both positive and negative directional changes (Figure 16). The data points are seen to lie within narrow  $\pm 30$ -degree sectors about the polar axes signifying good trending ability. When 30-degree limits are used the allowable differences in size of  $\Delta\text{CO}$  are limited to a ratio of 1 to 2, rather than just direction of change.

The half moon plot was later developed to show positive and negative  $\Delta\text{CO}$  changes together (Figure 17).

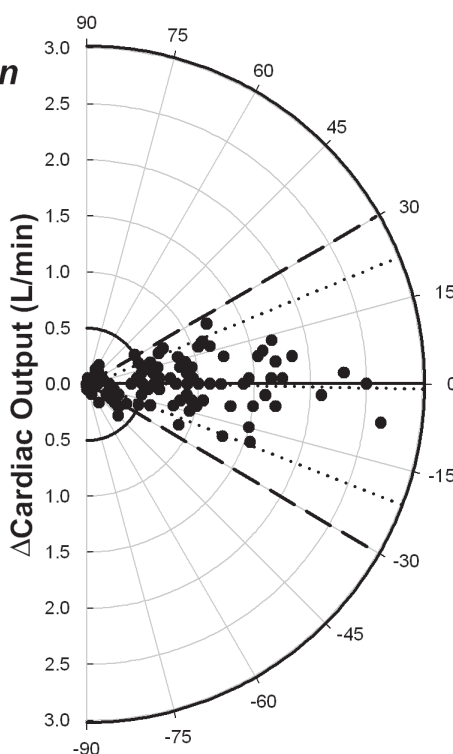
The plot provides several parameters that describe trending:

- i. The mean polar angle which shows the deviation in agreement from the polar axis zero-degrees. It is a measure of difference in scale between the test and reference methods.
- ii. The radial limits of agreement which are 95% confidence intervals of the polar angles. If the angles lie within the 30-degree boundaries the original x-y  $\Delta\text{CO}$  values will differ by less than 1 to 2 (i.e. half to double) in 95% of paired readings.
- iii. The polar concordance rate which for comparisons against thermodilution are set at 30-degrees, but there is currently limited data to support these limits.

### Polar Plot - *half moon*

**Polar plot set up:**  
Exclusion zone 0.5 L/min  
n = 69 of 114 data pairs

**Polar analysis:**  
Angular bias = -0.4 degrees  
Radial limits (95% c.i.)  
= -22 to 21 degrees  
Polar concordance  
(at <30 degrees) = 100%



**Figure 17.** Half-moon polar plot showing the same data as the full-circle plot, but all within the same semi-circle. The mean polar angle and radial limits of agreement are now shown. A central exclusion zone circle removes data points where the changes in cardiac output are small. Trending of cardiac output is good because most of the data points lie within the 30-degrees of the polar axis (0-degrees). Concordance is performed by counting the percentage of data points that lie within this zone. Outcomes of the polar analysis are provided with the plots. (Graphs drawn using Sigma Plot version 7.0).

The exclusion zone is used for similar reasons as in the four quadrant plot. However, as the radial distance is mean cardiac output rather than the hypotenuse of a triangle bounded by two cardiac output readings reference and test, its 'size needs to be smaller by a ratio of 1 to 1.4. Thus, rather than using 0.75 L/min or 15% as in the four quadrant plot, we used 0.5 L/min.

### 8.10. Making sense of the outcomes

If evidence based approaches are to be adopted when using MICOM devices in ones clinical practice then data from clinical validation studies will need to be critically reviewed. Marketing information from most manufactures of MICOM devices provide lists of publications that they claim support their product. In reviewing such data one needs to ask the following questions:

- i. Is the study design and data appropriate?
- ii. Have the correct statistics been used?
- iii. Have the correct criteria been applied to results?
- iv. And are the conclusions correct?

Study design is critical. (a) A sufficient number of patients should have been studied, though calculating the power of validation studies is not easy. Comparison of study size with other similar validation studies may help. (b) Type of patients and clinical setting effects results. Situations where a wide range of cardiac outputs and conditions (i.e. peripheral resistance) are encountered provide a rigorous test of performance. (c) Some of the early and more favourable validation studies using pulse contour devices were performed in cardiac surgery patients in whom haemodynamics were kept relatively stable. It was only when the same devices were tested in more labile liver transplant patients with cirrhosis that the problem with these devices and peripheral resistance became apparent [51].

The different statistical methods used in validation have been systematically covered previously. (a) If a simple test versus reference method comparison has been performed then only Bland-Altman analysis is needed, but make sure the outcomes of the analysis are properly presented, including the percentage error. (b) If a sophisticated study design that allows trending to be assessed has been used, then concordance analysis using the four quadrant plot, and possibly a polar analysis should have been used to show trending. Check that central exclusions zones have been applied to the  $\Delta\text{CO}$  data. (c) Animal studies are slightly different because of extent and quality of data that can be collected, and it is reasonable to use regression analysis.

When interpreting the results of Bland-Altman analysis: (a) Make sure the precision error of the reference method is correct. Normally for thermodilution it is  $\pm 20\%$ , but other modalities

may have different precisions and criteria may need correcting, like the 30% for percentage error. (b) Make sure all the outcomes of the Bland-Altman analysis have been presented. The key to interpreting Bland-Altman is the percentage error which needs the mean cardiac output and limits of agreement to be calculated. (c) Make sure that the limits of agreement have been correct for repeated measures [46,47].

When interpreting the results of concordance analysis: (a) Make sure central exclusion zones have been used. These should be shown on the four quadrant plot. (b) Make sure the exclusion criteria used in the plot are appropriate, usually set at 15% or 0.75 L/min when mean cardiac output is 5 L/min. (c) Make sure the precision error of the reference method is known as this will affect the threshold criteria for good trending. (d) When thermodilution is the reference method a concordance rate of above 90-95% signifies good trending ability of the test method.

Polar plots are relatively new to trend analysis so their usefulness and threshold criteria for good trending still need to be set. However, they are an excellent method of showing trend data from multiple patients and for good trending data should lie within the 30-degree radial limits [50].

When reading authors conclusions regarding their validation study data, be skeptical about what is written, as the statistical analyses is often incomplete and authors tend to exaggerate their findings. In general the percentage error should be less than 30% for good agreement and the concordance rate above 90-95% for good trending ability.

## 9. Laboratory data

### 9.1. Advantages of animal models

Testing in animal models has two big advantages:

- i. More invasive and precise gold standard methods of monitoring cardiac output can be used, such as flow probes surgically place on the ascending aorta. Thus, the limitations of comparing against thermodilution can be avoided. The original flow probes were electromagnetic, but today ultrasonic transit time flow probes are used.
- ii. The ranges of circulatory conditions and cardiac outputs that can be studied are much greater than in humans for ethical reasons.

### 9.2. Showing accuracy and trending

Bland-Altman and concordance analysis can still be used to assess accuracy and trending. However, the ability to perform multiple readings over a range of cardiac output and conditions against a gold standard method allow the test method to be fully assessed. Regression analysis and correlation now are the appropriate methods for analyzing the data. Regression plots from each animal experiment are used to show how the test method behaves over a range of cardiac output. The regression line defines the relationship between test and flow probe methods. Correlation reflects the repeatability and trending ability of the test method, rather

than the agreement between methods. Either  $r$  or  $R^2$  are quoted.  $R^2$  is used when a relationship exists between the two methods. The correlation coefficient ( $R^2$ ) ranges from 0 to 1, where a value  $> 0.9$  signifies good correlation. Ideally, if the test and reference (i.e. flow probe) methods are correctly calibrated, their data should lie along the line of identity  $y=x$  and correlation can also be performed along this line, which is known as Lin's concordance. Alternatively, the interclass correlation coefficient (ICC) is used. These methods were used in our 2005 paper to validate the supra-sternal Doppler method in anaesthetized dogs [52].

### 9.3. Current status of technology in 2012

Bioimpedance is no longer used clinically. Bioreactance (NICOM, Cheetah Medical) has only recently been released and still needs further clinical evaluation. It is being promoted in a wide range of clinical areas.

Pulse contour methods have not proved universally successful because of issues with the current algorithms failing to cope with swings in peripheral resistance. The PiCCO has a role in intensive care for continuous cardiac output monitoring in combination with transpulmonary thermodilution. The other modalities seem more useful when used to measure "functional haemodynamic variables" such as stroke volume variation in response to the straight leg raise test and fluid challenge. They are now being promoted to drive fluid optimization protocols.

Oesophageal Doppler (CardioQ, Deltex Medical) appears to be a useful intra-operative and intensive care monitor of haemodynamic status. It has been used successfully to drive goal directed fluid therapy protocols in high risk surgical patients. It has recently become popular in Britain as part of enhanced surgical recovery programs. External Doppler (USCOM) is less commonly used but appears useful in a number of clinical settings including paediatrics.

Other MICOM technology does exist but none currently have a major role to play in developing patient monitoring.

## Nomenclature

MICOM – Minimally invasive cardiac output monitoring

TOE – Transoesophageal Echocardiography

PAC – Pulmonary Artery Catheter

CSA – Cross sectional area

LVET – Left ventricular ejection time

PEP – Pre ejection period

VEPT – Volume of electrically participating tissue

ECG – Electrocardiogram

$\Delta$ CO – delta cardiac output

## Author details

Lester Augustus Hall Critchley

Address all correspondence to: [hcritchley@cuhk.edu.hk](mailto:hcritchley@cuhk.edu.hk)

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, S.A.R.

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