



Australian Government

Department of Health and Ageing



Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Horizon Scanning Report

USCOM: Ultrasound cardiac output monitor for patients requiring haemodynamic monitoring

May 2007



© Commonwealth of Australia 2007

Online ISBN 1-74186-255-8

Publications Approval Number: P3 -1871

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at <http://www.ag.gov.au/cca>

Electronic copies can be obtained from <http://www.horizonscanning.gov.au>

Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

DISCLAIMER: This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements to health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

The Commonwealth does not guarantee the accuracy, currency or completeness of the information in this report. This report is not intended to be used as medical advice and it is not intended to be used to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. The Commonwealth does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information.

The production of this *Horizon scanning report* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This *Horizon scanning report* was prepared by Ms Linda Mundy, Ms Tracy Merlin, A/Prof Annette Braunack-Mayer and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, Mail Drop 511, University of Adelaide, Adelaide, South Australia, 5005.

Table of Contents

Executive Summary	1
HealthPACT Advisory	3
Introduction	4
Background	4
<i>Description of the technology</i>	4
<i>The procedure</i>	4
<i>Intended purpose</i>	6
<i>Clinical need and burden of disease</i>	6
<i>Stage of development</i>	8
Treatment Alternatives	9
Clinical Outcomes	13
<i>Safety</i>	13
<i>Effectiveness</i>	13
Potential Cost Impact	21
Ethical Considerations	22
Training and Accreditation	24
Limitations of the Assessment	25
<i>Search Strategy used for the Report</i>	25
<i>Availability and Level of Evidence</i>	27
Sources of Further Information	27
Conclusions	28
Appendix A: Levels of Evidence	30
Appendix B: Profiles of studies	32
Appendix C: HTA Internet Sites	36
Appendix D: Definitions	39
Appendix E: Normal haemodynamic ranges	41
References	42

Tables

Table 1	Cardiac output	15
Table 2	Time taken to perform examination with USCOM	19
Table 3	Inter-assessor agreement	20
Table 4	Literature sources utilised in assessment	26
Table 5	Search terms utilised	26

Figures

Figure 1	The USCOM monitor	5
Figure 2	Typical velocity time integral curve	5
Figure 3	Oesophageal Doppler probe	12

Executive Summary

The USCOM device is a non-invasive, ultrasound cardiac output monitor designed to measure and record changes in the haemodynamic status of critically ill patients transcutaneously. The USCOM utilises continuous-wave Doppler ultrasound and can measure both left and right cardiac output.

Cardiac output (CO) is the key variable in the assessment of haemodynamics especially in the management of critically ill, or peri-operative patients or patients undergoing anaesthesia. CO is important in terms of global tissue oxygen consumption, as changes in cardiac output will determine the amount of oxygen delivered to the tissues. The USCOM device may be used to confirm normal cardiac function, detect and quantify abnormal function, and to evaluate the effectiveness of cardiovascular therapies. The USCOM device is intended for use in a wide spectrum of patients including both adult and paediatric patients admitted to intensive care units, patients undergoing anaesthesia and those undergoing cardiac surgery.

In the intensive care and operating room setting, the “gold standard” method used to assess CO is bolus thermodilution using the standard pulmonary artery catheter (PAC). Although this technique is widely disseminated there is no evidence that it facilitates patient recovery or improves survival. Other methods for measuring CO include minimally invasive methods such as the Fick re-breathing method, which requires patients to be intubated with an endotracheal tube, dilution techniques using isotonic lithium chloride, the insertion of a transoesophageal Doppler transducer and pulse contour analysis of the aortic waveform. A truly non-invasive method for measuring CO is the thoracic electrical bioimpedance method, which correlates changes in the electrical impedance of the thoracic cavity that occur with the ejection of blood from the left ventricle into the ascending aorta.

There were no adverse events associated with the use of the USCOM device reported by any of the studies included for assessment.

Inter-assessor agreement between cardiac output as measured by medical staff undergoing training with the USCOM device, compared to values obtained by trained clinicians was good ($r=0.91$). Three studies found that trainees were able to rapidly acquire the skills necessary to produce reliable CO measurements in emergency department patients. In addition, two case series reported on the time required to use the USCOM device to obtain a cardiac output measurement at the scene of an emergency, prior to, or during patient transportation to hospital. Average time spent to gain a CO reading ranged from 15 to 25 seconds and did not contribute to extended times at the scene or transportation time.

Peer reviewed cross classification studies which compared CO levels obtained with USCOM to those obtained with the “gold standard” pulmonary artery catheterisation reported either a non-significant bias between the two techniques (-0.14 to 0.18) or a significant correlation ($r = 0.794$, $p < 0.01$). That is, there was no systematic difference between the two measures of cardiac output. Small limits of agreement, which included zero, indicated that

there was little difference in the two methods of measurement. These results were supported by two of the three abstracts which compared USCOM to measurements taken with PAC ($r = 0.80$, $r^2 = 0.714$), however one study reported a large bias (-1.04 ± 1.29 L/min) compared to the mean CO of 5.3 ± 0.57 L/min. Although the majority of studies indicated that USCOM measurements correlated highly with other methods of measuring CO, two studies reported that when CO values exceeded 5 L/min, the values obtained with the USCOM tended to underestimate cardiac output. This may suggest that the USCOM device may adequately measure CO values within the normal physiological range, however further validation studies for low and high CO states should be conducted. In addition, two studies found that clinicians were unable to obtain a successful Doppler signal at *both* the ascending aorta and the pulmonary artery, however a successful signal was able to be obtained from at *least* one of these locations.

There are currently no cost-effectiveness data available for the utilisation of the USCOM device for cardiac output monitoring. The USCOM unit is currently selling in Australia for \$35-42,000 and after the initial purchase of the unit (monitor and probe) there are no recurring costs, such as disposable consumables, apart from standard ultrasound conducting gel.

In conclusion, the USCOM device appears to be safe and effective for the measurement of cardiac output in critically ill patients. Further studies in patients in high and low cardiac output states may be recommended.

The USCOM device appears to be a clinically useful, although not unique, tool for the non-invasive assessment of cardiac output in critically ill patients. Although the USCOM device has been reported to underestimate cardiac output in patients with a high cardiac output, this is not considered to be a critical factor in the assessment of these patients. Although there are no data describing the effectiveness of the USCOM device to improve patient outcomes, the device produces comparable CO readings to the gold standard of pulmonary artery catheterisation. The USCOM device may complement existing cardiac output assessment tools and may find a role in conditions where it is more effective and practical to use this device than full echocardiography or pulmonary artery catheterisation.

Therefore HealthPACT recommends that this device be regarded as an appropriate means of assessing cardiac output in clinical circumstances in which other means of cardiac assessment are not practical.

Introduction

The National Horizon Scanning Unit, AHTA, Discipline of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of the ultrasound cardiac output monitor (USCOM) (Register ID number 000168).

USCOM Ltd provides the USCOM device to monitor cardiac output in patients who require haemodynamic monitoring. It is offered through cardiologists, anaesthetists and emergency care practitioners, and is currently in use in several centres in Australia.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of USCOM, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with the ultrasound cardiac output monitor, USCOM.

Background

Description of the technology

The procedure

The USCOM device is a non-invasive, ultrasound cardiac output monitor designed to measure and record changes in the haemodynamic status of critically ill patients transcutaneously. The USCOM utilises continuous-wave Doppler ultrasound and can measure both left and right cardiac output. A transducer is placed on the chest in either the left parasternal position to measure trans-pulmonary blood flow, or the suprasternal position to measure trans-aortic blood flow. The flow profile is displayed on the USCOM monitor (Figure 1) with the spectral display showing variations of blood flow velocity with time (Tan et al 2005). Novel algorithms are used to calculate and determine flow volumes from the raw Doppler data, independent of two-dimensional echocardiography measurement of flow diameters (Knobloch et al 2005b).

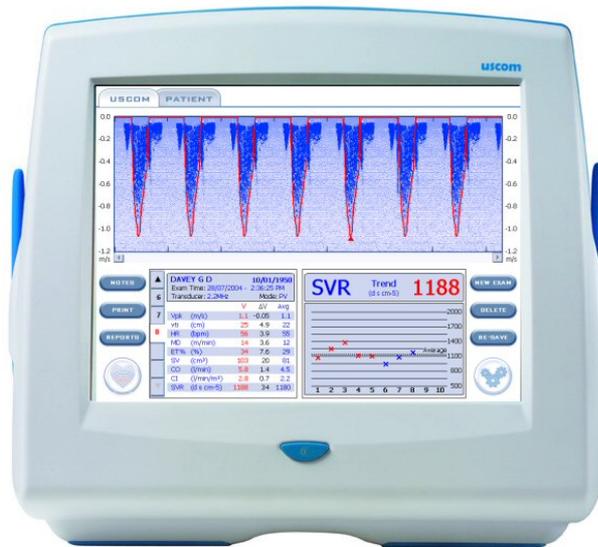


Figure 1 The USCOM monitor (printed with permission USCOM Pty Ltd)

The USCOM device allows for real time, beat-to-beat quantitative evaluation of 14 cardiac output parameters: cardiac index (CI), cardiac output (CO), peak velocity of flow (Vpk), velocity time integral (vti), heart rate (HR) ejection time per cent (ET%), stroke volume (SV), stroke volume index (SVI), stroke volume variability (SVV), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), minute distance (MD), mean pressure gradient (Pmn) and flow time (FT) (for definitions of these parameters see Appendix D) (Figure 2). For normal adult and paediatric values for these parameters see Appendix E. The device is highly portable, weighing less than seven kilograms and is powered by an internal battery (FDA 2005).

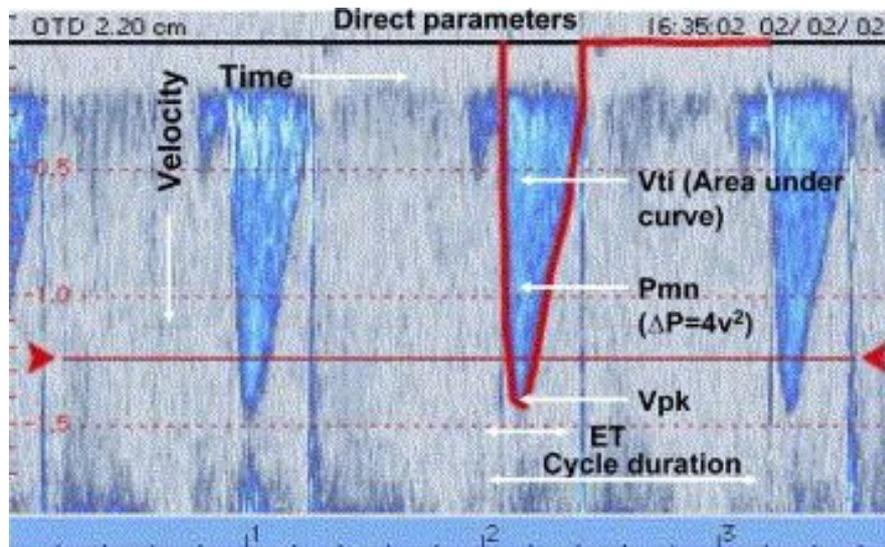


Figure 2 Typical velocity time integral curve (Chand et al 2006)

Intended purpose

Cardiac output (CO) is defined as the volume of blood ejected from the left ventricle per minute and is determined by heart rate, myocardial contractibility, pre-load and after-load (see Appendix D) (Allsager & Swanevelder 2003). CO is calculated as the product of the heart's stroke volume (the volume of blood pumped by the heart in one beat) and the heart rate (the number of beats per minute measured from systolic onset to systolic onset). CO is expressed as litres/minute with the normal range for adults and children 5.0-7.0 l/min and 3.5-7.0 l/min, respectively (USCOM 2006). However, it should be remembered that a simple summary of CO as "x" l/min should be considered in the context of time, ie CO is adequate or inadequate for a particular patient at one moment in time. CO information needs to be integrated into a global metabolic assessment including variables such as lactate levels and the level of oxygen saturation of haemoglobin (Tibby & Murdoch 2003).

CO is the key variable in the assessment of haemodynamics especially in the management of critically ill, or peri-operative patients or patients undergoing anaesthesia. CO is important in terms of global tissue oxygen consumption, as changes in cardiac output will determine the amount of oxygen delivered to the tissues. Low or inadequate cardiac output may result in oxygen deprivation at the tissue level, cellular hypoxia and may lead to irreversible multi-organ dysfunction. Low cardiac output may occur despite adequate haemoglobin concentrations and oxygen saturation (Allsager & Swanevelder 2003). Adequate perfusion is essential in critically ill patients, and implies that not only the perfusion *pressure* is high enough to maintain capillary patency within all organs, but that there is enough *flow* to deliver oxygen and substrates to the tissues and to remove metabolic by-products and carbon dioxide. In many instances only pressure is monitored in patients without consideration of the flow (Cholley & Payen 2005). A low CO may occur due to inadequate vascular volume, excessive after-load, poor contractibility, myocardial restriction, arrhythmia, diastolic dysfunction, vascular stenosis and/or insufficiency (Tibby & Murdoch 2003). An improved CO over time may indicate a positive response to medical therapy (De Maria & Raisinghani 2000).

The primary applications of the USCOM device are in the Emergency Department (heart failure, retrieval, resuscitation, haemorrhage, sepsis), Intensive Care Unit (post-surgical monitoring, heart failure, myocardial infarction) and in Paediatrics (sepsis, resuscitation, surgery) (USCOM 2006). The device may be used to confirm normal cardiac function, detect and quantify abnormal function, and to evaluate the effectiveness of cardiovascular therapies (FDA 2005).

Clinical need and burden of disease

The USCOM device is intended for use in a wide spectrum of patients including both adult and paediatric patients admitted to intensive care units, patients undergoing anaesthesia and those undergoing cardiac surgery (USCOM 2006). However, not all of these patients will require cardiac output assessment. The decision to measure CO should be a balance between the risks

involved with the measurement process (invasive versus non-invasive) and the potential benefit gained from the additional haemodynamic information (Tibby & Murdoch 2003).

In 1992 the Australian and New Zealand Intensive Care Adult Patient Database was established to collect data on the type, location and number of intensive care unit (ICU) admissions. In Australia and New Zealand there are 189 ICUs, including both public and private hospitals, containing 1,988 beds that are eligible to contribute to the database. Although only approximately 78 per cent of existing Australian ICUs and 37 per cent of New Zealand ICUs contribute to the database, it has been estimated that these units admitted 124,255 patients in 2003. No information was available as to the cause of these admissions (Stow et al 2006).

In Australia and New Zealand there are eight paediatric intensive care units which supply data to the paediatric intensive care database. In addition, there are eight general ICUs, based in metropolitan or regional areas, which predominantly admit adult patients but will also admit patients under the age of 16 years. In 2004, the paediatric database recorded that there were 7,329 paediatric admissions to ICUs in Australia and New Zealand, with a rate of admission of 1.4 per 1,000 children. Approximately 700 paediatric admissions were omitted from the database. The majority of admissions were for children under the age of five years (64.5%), with infants under the age of 12 months making up more than half of this group (37.4% of all paediatric ICU admissions). A third of this group were neonates less than 28 days old. Of these admissions, 22 per cent were admitted directly to the ICU from outside the hospital, 42 per cent were admitted from the operating theatre, 17 per cent from the emergency department and 18 per cent were admitted from wards. The most common diagnostic group admitted was those patients with a respiratory cause (23%), however post-operative cardiac surgery and injury accounted for 18 and 8.6 per cent of admissions, respectively. Although a cardiovascular diagnosis (other than cardiac surgery) accounted for only 5.9 per cent of all paediatric ICU admissions, it was associated with the highest level of mortality (13.4%, 95% CI [10.5, 16.9]). In addition, cardiovascular patients had the longest median length of stay (2.79 days) compared to other diagnostic groups (Norton & Slater 2005).

In the past it has been difficult to estimate the number of anaesthetics administered annually in Australia. However, during the period 2000-2002, the Australian and New Zealand College of Anaesthetists (ANZCA) introduced anaesthetic specific codes for general and regional anaesthesia, sedation and pain management procedures. For the 12 months from July 2001 to June 2002, there were 2.586 million anaesthetic procedures coded in Australia. During the triennium 2000-2002, there were 137 cases of anaesthesia-related mortality, a rate of one for every 56,000 anaesthetic procedures. The majority of these anaesthesia-related deaths occurred in medically compromised patients: either elderly or those undergoing urgent or emergency procedures (Gibbs & Borton 2006). There are no data available for the number of anaesthetic procedures performed in New Zealand.

There are numerous AR-DRG¹ numbers which refer to cardiac related surgery, which *may or may not* require cardiac output monitoring. In Australia during the year 2004-05, a total of 90,925 public hospital separations were recorded for cardiac related surgery other than amputation of limbs (AIHW 2006). In New Zealand during the period 2002-03, there were 69,925 discharges from publicly funded hospitals for patients with diseases of the circulatory system. Patients likely to require surgery are those with acute myocardial infarction (11,779), ischaemic heart disease (2,932), pulmonary disease (891), cardiomyopathy (493), cardiac arrest (123) and heart failure (7,122) (NZHIS 2006a). In addition, during the year 2002, a total of 4,751 patients underwent a coronary artery bypass procedure in publicly funded (4,007) or private hospitals (744) (NZHIS 2006b).

A number of Medicare Benefit Schedule (MBS) item numbers refer to left or right heart catheterisation for purposes including fluoroscopy, exercise stress test, shunt detection *and* cardiac output monitoring (MBS item numbers 22015, 38200, 38203 and 38206). In the period July 2005 to June 2006 there were 6,589 services associated with these item numbers provided in a *private* hospital setting. The MBS item number 13818 can *only* be used for CO measurement in an intensive care unit. In the same period there were 630 services associated with this item number in a *private* hospital setting (DHA 2006; Medicare Australia 2006). It would be envisaged that the majority of catheterisation procedures for CO monitoring in critically ill patients would take place in major public hospitals and that the number of procedures would be significantly higher.

Stage of development

The USCOM device is manufactured and distributed by USCOM Pty Ltd. The device was approved and registered by the Australian Therapeutic Goods Administration in November 2001 (ARTG number 81047). There are currently 28 USCOM units installed in Australian hospitals; however no units have been sold in New Zealand. Sites where the USCOM is in clinical use include St Vincent's Hospital (Sydney), Howard Florey Institute (Melbourne), Prince Charles Hospital (Brisbane), Royal Prince Alfred Hospital (Sydney) and the Royal Perth and Sir Charles Gairdner Hospitals (Perth). Department using the USCOM device include Emergency, Intensive Care Units and Anaesthetics (personal communication USCOM Pty Ltd, November 2006). In December 2003 the USCOM device gained CE Certification, enabling the device to be distributed and sold in the European market (USCOM 2004). The USCOM device gained approval from the US Food and Drug Administration in February 2005 (FDA 2005).

¹ AR-DRG = Australian Refined Diagnosis Related Groups

Existing comparators

Invasive techniques for monitoring CO

In the intensive care and operating room setting, the ‘gold standard’ method used to assess CO is bolus thermodilution using the standard pulmonary artery catheter (PAC). Although this technique was introduced over 30 years ago by Swan and Ganz and is widely disseminated with over 2-million catheters being inserted annually world-wide, there is no evidence that it facilitates patient recovery or improves survival (Harvey et al 2006; Smartt 2005).

A thermistor-tipped catheter (known as a Swan-Ganz catheter) is inserted into the pulmonary artery via a peripheral vein. Cold saline of a known temperature and volume is then injected into the right atrium from a proximal catheter port. As the saline mixes with the blood, it passes through the ventricle and into the pulmonary artery, cooling the blood. The blood temperature is measured at the catheter tip lying within the pulmonary artery. A computer is used to acquire the thermodilution profile and the flow is calculated (Klabunde 2006). When the thermodilution method was first introduced, CO was measured using injections of 10 ml of iced normal saline, with three or more injections required to gain a range of results within 10 per cent of each other to obtain an average CO. This technique allowed the measurement of right atrial and left ventricular filling pressures, pulmonary artery pressure and pulmonary wedged pressure. Current use of the PAC technique allows for multiple sized catheters to be inserted, allowing for the simultaneous continuous monitoring of multiple parameters including CO, stroke volume, systemic and pulmonary vascular resistance, right ejection fraction, stroke work index and right ventricular end-diastolic volume (Smartt 2005). The addition of fibre-optic technology allows the measurement of continuous mixed venous oxygen saturation (SVO₂) for assessment of oxygen delivery and consumption, with SVO₂ reflecting the overall oxygen reserve of the whole body. However, a normal SVO₂ value (70-75%) does not rule out impaired oxygen supply to a particular organ (Boldt 2002).

Despite the increased volume of information able to be gained from the insertion of a PAC, the use of this technique is in decline in favour of less invasive techniques due to high associated costs and the potential for inaccurate and therefore incorrect interpretation of measurements. In addition, the introduction of a central venous catheter places patients at risk of pulmonary artery rupture with balloon inflation, ventricular dysrhythmias, bacteraemia and endocardial lesions. Serious complications occur in 0.1-0.5 per cent of catheterisations with pulmonary artery rupture estimated to occur in 0.03-0.25 per cent of cases, with mortality at 41-70 per cent (Smartt 2005). A recent systematic review assessed 12 randomised controlled trials which compared patient outcomes (hospital mortality) with and without the use of a PAC in adult intensive care patients. Two groups of patients were identified: eight trials of patients undergoing routine major surgery (one large trial with 2,000 patients) and four trials of critically ill patients admitted to ICU for various reasons. All trials reported no difference in mortality between patients

who did and did not have a PAC inserted. The pooled odds ratio for the studies of intensive care patients was 1.05 (95% CI [0.87, 1.26]) and 0.99 (95% CI [0.73, 1.24]) for patients in the major surgery group. In addition, the insertion of a PAC did not affect the length of stay in either the ICU or hospital (Harvey et al 2006).

Although the Fick re-breathing method is considered to be the “gold standard” of non-invasive CO monitoring, it does require patients to be intubated with an endotracheal tube. Currently there is one commercially available device, the NICO sensor, able to measure CO using the partial re-breathing Fick technique, which requires patients to be under fully controlled mechanical ventilation (Chaney & Derdak 2002). The Fick principle is over a century old and relates CO to oxygen consumption and the arterio-venous oxygen content difference ($CI = VO_2 / (CaO_2 - CvO_2)$)² (Tibby & Murdoch 2003). This equation has been modified using CO₂ production and content to provide an estimation of CO ($CI = VCO_2 / (CaCO_2 - CvCO_2)$)³ for intubated patients receiving positive pressure ventilation. Expired gas from the lungs provides estimations of arterial CO₂. CvCO₂ values are more difficult to obtain but end-alveolar CO₂ values can be estimated by the use of the CO₂ dissociation curve, relating it to the blood concentration. To obtain more accurate CvCO₂ estimates, a partial re-breathing technique may be used for patients on a ventilator. An additional 150ml of dead space is introduced into the ventilator circuit. During baseline, air flow is directed through a valve. During the re-breathing phase, positive pressure activates the valve to direct the end-expired gas to the patient for inspiration. Re-breathing CO₂ reduces the blood-alveolar gradient and reduces the CO₂ flux. This has the effect of elevating arterial CO₂ content which stabilises during the next baseline phase. The ratio of the change in CO₂ elimination, and hence CO, is calculated by comparing measurements taken during the baseline and re-breathing periods (Allsager & Swanevelder 2003; Chaney & Derdak 2002). It is thought that this method is best suited to monitoring trends in CO of critically ill patients who have stable lung function rather than for diagnostic use (Chaney & Derdak 2002).

Dilution techniques to measure CO have been used for many years and are considered to be minimally invasive. An indicator, such as isotonic lithium chloride (150 mM), is injected as a bolus via a central or peripheral venous line. Blood flow is calculated by measuring the change in indicator concentration over time at a point downstream of the injection. Only small doses of lithium are required (0.3 mmol in an adult patient) as ion-selective electrodes, located in the arterial line, are able to detect minute changes in the arterial plasma concentration of lithium, which is not normally present in human plasma. CO is calculated from the area under the concentration-time curve, allowing for re-circulation (Allsager & Swanevelder 2003; Hett & Jonas 2004; Tibby & Murdoch 2003).

Another minimally invasive method of measuring beat-to-beat CO is the quantification of the change in stroke volume using pulse contour analysis of

² CI = cardiac index, VO₂ = oxygen consumption, CaO₂ = arterial oxygen content, CvO₂ = mixed venous oxygen content

³ CI = cardiac index, VCO₂ = CO₂ elimination, CaCO₂ = arterial CO₂ content, CvCO₂ = mixed venous CO₂ content

the aortic waveform. Pulse contour analysis requires the insertion of an arterial catheter, however many critically ill patients will have an existing arterial catheter inserted for routine blood sampling and monitoring. Although pulse contour analysis can be performed continuously, this method must be calibrated against another method of CO measurement, such as thermodilution. An individual calibration factor is determined and CO is then calculated using this factor combined with the measurement of the area under the systolic portion of the arterial pulse wave from the end of diastole to the end of the ejection phase. The performance of pulse contour analysis may vary in patients with abnormal waveforms or arrhythmias, however studies have demonstrated that this technique correlates well with thermodilution (Allsager & Swanevelder 2003; Chaney & Derdak 2002; Hett & Jonas 2004; Tibby & Murdoch 2003).

Non-invasive techniques for monitoring CO

The thoracic electrical bioimpedance method correlates changes in the electrical impedance of the thoracic cavity which occur with the ejection of blood from the left ventricle into the ascending aorta. Although blood and tissues impede electrical current, the volume and impedance of the tissues remain constant during cardiac ejection. The volume of blood in the chest changes with each stroke volume. This change in volume causes changes in impedance, which is detected by a number of electrical patches placed on the neck and thorax. Stroke volume and CO can be calculated, with the aid of an algorithm which interprets these changes in thoracic impedance (Allsager & Swanevelder 2003; Engoren & Barbee 2004). Studies in healthy volunteers have shown the bioimpedance method to be comparable to other methods, however trials of this technique in critically ill patients have produced poor results when compared to thermodilution. Advancing age and peri-operative fluid shifts in patients, pulmonary oedema, myocardial ischaemia and electrical interference may produce errors with CO measurement by bioimpedance (Allsager & Swanevelder 2003). The authors of a meta-analysis of 154 bioimpedance studies concluded that this method was more useful for studying trends in CO rather than as a diagnostic tool (Engoren & Barbee 2004).

CO may be calculated using either transthoracic or transoesophageal (most commonly used of the two techniques) Doppler techniques in conjunction with two-dimensional echocardiography. The oesophageal Doppler technique measures the blood flow in the descending aorta (Figure 3). Again, although the oesophageal Doppler technique is regarded as non-invasive, it requires that a Doppler transducer is introduced into the oesophagus of an anaesthetised, mechanically ventilated patient. Transoesophageal echocardiography may be used to calculate stroke volume⁴ which multiplied by the heart rate will give an estimate of CO (Berton & Cholley 2002; Chaney & Derdak 2002; Hett &

⁴ The flow velocity-time integral is known as stroke distance, which is the distance that a column of blood will travel along the aorta in one cardiac cycle. Stroke distance is converted to stroke volume and CO is calculated along with the morphological data from the 2D echocardiogram of the dimensions of the outflow ie the area in which the flow is pushed forward Tibby, S. M. & Murdoch, I. A. (2003). 'Monitoring cardiac function in intensive care', *Arch Dis Child*, 88 (1), 46-52

Jonas 2004). This technique requires a clinician trained in echocardiography but does supply functional and morphological information in addition to CO including regional wall abnormalities, valve regurgitation, diastolic dysfunction, chamber dilation and pericardial effusion (Tibby & Murdoch 2003).



Figure 3 Schematic representation of oesophageal Doppler probe demonstrating the close relationship between the oesophagus and the descending aorta (Berton & Cholley 2002)

Safety

No adverse events associated with the use of the USCOM device were reported by any of the studies included for assessment. The study by Haas et al (2006) reported 8/25 (32%) and 7/25 (28%) patients died whilst on the intensive care unit or a general ward, respectively. However these patients were seriously ill and their deaths could not be attributed to the use of the USCOM device (Haas et al 2006).

Effectiveness

Four of the five peer reviewed studies included for assessment in this report reported on the effectiveness of the USCOM device for monitoring cardiac output (Table 1). Of these, three were cross classification studies (level III-1 and III-2 diagnostic evidence) which compared CO levels obtained with USCOM to those obtained with the “gold standard” pulmonary artery catheterisation. Chand et al (2006) reported a non-significant bias between the two techniques of -0.14 and -0.03 for measurements taken at the ascending aorta and the pulmonary artery, respectively⁵. A similar small, non-significant bias (0.18) was reported by Tan et al (2005). Both studies reported small limits of agreement, which included zero indicating that there is little difference in the two methods of measurement. This finding was confirmed in the study by Knobloch et al (2005) who reported a significant correlation between CO measurements with the two techniques ($r = 0.794$, $p < 0.01$) (level III-2 diagnostic evidence).

Six of the abstracts included for assessment in this report were cross classification studies (level III-2 diagnostic evidence). Three of these studies compared CO levels obtained with USCOM to those obtained with PAC (Haas et al 2006; Kotake et al 2006; O'Driscoll et al 2005). As with the peer reviewed studies, high levels of correlation ($r = 0.80$, $r^2 = 0.714$) were reported in two of these studies. However, the study by Kotake et al (2006) reported a large bias (-1.04 ± 1.29 L/min) for measurements taken at the ascending aorta, compared to the mean CO of 5.3 ± 0.57 L/min. Although the bias was small for measurements taken at the pulmonary artery (-0.37 ± 1.21 L/min) the large standard deviation indicates variation in the measurements. One study reported in an abstract, compared CO measurements by the USCOM device to those obtained by the CardioWest implanted artificial heart (level III-2 diagnostic evidence) (Lichtenthal et al 2005). The difference in these measurements was small (0.03 ± 0.49 L/min) however there are few patients in this group and numbers are unlikely to increase in the near future. Cardiac output measurements by USCOM in patients attending a heart transplant clinic were compared to several methods of CO measurement including PAC, echocardiography, the implanted CardioWest device and the Fick principle (Phillips et al 2006b). Again, measurements with USCOM correlated

⁵ That is, there was no systematic difference between the two measures of cardiac output.

significantly ($r = 0.996$, $p = 0.005$). Similar results were reported when USCOM CO measurements were compared to those taken with 2-dimensional echocardiography in pre-term neonates ($r = 0.913$, $p < 0.005$) (Phillips et al 2006a).

The study by O'Driscoll et al (2005) reported good correlation of CO obtained with PAC with CO obtained with USCOM ($r^2 = 71.4\%$) for cardiac output values of <5 L/min. However, when CO values exceeded 5 L/min, then values obtained with the USCOM tended to underestimate those obtained with PAC (O'Driscoll et al 2005). Tan et al (2005) reported similar findings: when PAC returned CO values between 7.6 and 8.5 L/min, the USCOM device underestimated CO values by between 5.2 and 6.3 L/min (Tan et al 2005). This suggests that the USCOM device may adequately measure CO values within the normal physiological range, however further validation studies for low and high CO states are warranted.

One peer reviewed study (Chand et al 2006) and one abstract (Kotake et al 2006) (level III-1 and III-2 diagnostic evidence, respectively) reported being unable to obtain a Doppler signal using the USCOM device at either the ascending aorta (20 and 2.4% of occasions, respectively) or the pulmonary artery (10 and 16.5% of occasions, respectively). Although a successful signal was not always possible at *both* the ascending aorta or the pulmonary artery, both authors reported being able to obtain a successful signal from at *least* one of these locations in all patients. Chand et al (2006) gave the reasons for failure to obtain a signal in many cases as patient discomfort as the sternotomy incision in cardiac patients is adjacent to the suprasternal site for the ascending aorta. In addition, it was felt that learning curve for physicians may also be a factor.

The case series conducted on emergency patients being transported to hospital indicated that the USCOM device was feasible to use at the scene and during transportation to assess the CO of critically ill patients (level IV diagnostic evidence). Conventional methods of monitoring CO rely on good estimates of the patient's weight and height, which are difficult to ascertain in emergency situations. The USCOM device can be used to determine aortic minute distance independent of height and weight information and as such can be used as a rapid and early assessment of cardiac function. This may allow prompt and appropriate treatment of patients before their arrival at hospital, which may in turn lead to improved patient outcomes.

Many of the cross classification studies included in this assessment compared a single optimised USCOM measurement against a PAC measurement. The PAC method depends on signals being averaged over a time period, with results displayed after a processing delay. The USCOM device, however, measures instant beat-to-beat information. Therefore there may be some disagreement in the results obtained by these methods as measurements are not made simultaneously and are in fact assessing a different haemodynamic time sample. Most authors agreed that USCOM results may be more comparable with continuous CO obtained with PAC if a series of USCOM flow profiles were averaged (Knobloch et al 2005b).

Table 1 Cardiac output

Study	Level of Diagnostic Evidence	Study Design	Population	Outcomes
Chand et al (2006)	III-1	Cross classification of patients on USCOM compared to PAC	50 patients who had undergone elective off-pump coronary artery by-pass surgery	<p>Unable to obtain Doppler signals at ascending aorta in 10/50 (20%) of patients and at pulmonary artery in 5/50 (10%) of patients. Reasons for failure included learning curve and patient discomfort due to suprasternal site for ascending aorta signal is close to sternotomy incision.</p> <p>USCOM vs PAC</p> <p>CO-AO (n=40) Bias (L/min) ± SD [95%CI] 4.63 ± 0.90 L/min -0.14 ± 0.79 [-0.39, 0.11]</p> <p>CO-Pul (n=45) Bias (L/min) ± SD [95%CI] 4.67 ± 0.87 L/min -0.03 ± 0.55 [-0.19, 0.13]</p> <p>CI-AO (n=39) Bias (L/min/m²) ± SD [95%CI] 2.57 ± 0.46 L/min/m² -0.08 ± 0.5 [-0.24, 0.07]</p> <p>CI-Pul (n=44) Bias (L/min/m²) ± SD [95%CI] 2.58 ± 0.46 L/min/m² -0.02 ± 0.37 [-0.13, 0.08]</p> <p>SV-AO (n=40) Bias (ml) ± SD [95%CI] 48.7 ± 10.6 ml 1 ± 8 [-1.5, 3.5]</p> <p>SV-Pul (n=45) Bias (ml) ± SD [95%CI] 49.3 ± 9.4 1.6 ± 6 [-0.21, 3.4]</p>
Knobloch et al (2005)	III-2	Cross classification of patients on USCOM compared to PAC	36 consecutive cardiac intensive care patients undergoing surgical coronary re-vascularisation	<p>Post-operative 180 paired CO measurements</p> <p>CO (L/min) ± SD [95%CI]</p> <p>PAC 4.92 ± 2 [4.63, 5.22]</p> <p>USCOM 5.15 ± 1.98 [4.86, 5.44]</p> <p>Correlation of PAC and USCOM determined CO <i>r</i> = 0.794, <i>p</i> < 0.01</p> <p>Mean central venous saturation (CVS) 72 ± 9%, correlating with USCOM <i>r</i> = 0.474 and PAC <i>r</i> = 0.606, <i>p</i> < 0.01</p> <p>Stroke volume significantly correlated with USCOM <i>r</i> = 0.946, PAC <i>r</i> = 0.803 and CVS % <i>r</i> = 0.474, <i>p</i> < 0.01</p> <p>Mean difference between measures -0.23 ± 1.01 L/min</p> <p>Mean value of the means 5.04 ± 1.92 L/min</p> <p>Mean error -4.67 ± 19.9%</p> <p>Intra-operative CO measurement</p> <p>CO (L/min) ± SD</p> <p>PAC (n=6) 4.95 ± 1.02</p> <p>USCOM (n=6) 4.97 ± 0.98 NS</p>

USCOM = ultrasound cardiac output monitor, PAC = pulmonary artery catheter, CO-AO = cardiac output at ascending aorta, CO-Pul = right sided cardiac output, CI-AO = cardiac index at ascending aorta, CI-Pul = right sided cardiac index, SV = stroke volume at ascending aorta, SV-Pul = right sided stroke volume, SD = standard deviation, NS = no significant difference, CO = cardiac output

Knobloch et al (2006)	IV	Case series	44 consecutive emergency patients, 15 with thoracic pain, 29 without thoracic pain	<table border="1"> <thead> <tr> <th></th> <th>Thoracic pain (± SD) (n=15)</th> <th>No pain (±SD) (n=29)</th> </tr> </thead> <tbody> <tr> <td>CO (L/min)</td> <td>3.37 ± 1.1 <i>p</i> = 0.023</td> <td>5.06 ± 2.9</td> </tr> <tr> <td>CI (L/min/m²)</td> <td>1.67 ± 0.58 <i>p</i> = 0.001</td> <td>3.18 ± 1.34</td> </tr> <tr> <td>APV (m/s)</td> <td>0.75 ± 0.2 <i>p</i> = 0.236, NS</td> <td>0.90 ± 0.4</td> </tr> <tr> <td>VTI</td> <td>14.51 ± 5.39 <i>p</i> = 0.03</td> <td>19.45 ± 8.2</td> </tr> <tr> <td>HR (bpm)</td> <td>82 ± 23 <i>p</i> = 0.021</td> <td>101 ± 20</td> </tr> <tr> <td>MD</td> <td>11.2 ± 3.3 <i>p</i> = 0.001</td> <td>19.1 ± 8</td> </tr> <tr> <td>ET%</td> <td>50 ± 14 <i>p</i> = 0.007</td> <td>64 ± 18</td> </tr> <tr> <td>SV (ml)</td> <td>44 ± 17 <i>p</i> = 0.145, NS</td> <td>57 ± 28</td> </tr> <tr> <td>SVR (dyne*sec*cm⁻⁵)</td> <td>2,709 ± 891 <i>p</i> = 0.0001</td> <td>1,499 ± 661</td> </tr> <tr> <td>MAP (mmHg)</td> <td>106 ± 25 <i>p</i> = 0.010</td> <td>83 ± 17</td> </tr> <tr> <td colspan="3">Patients with seizure (n=6)</td> </tr> <tr> <td>CO</td> <td>7.5 ± 3.05</td> <td></td> </tr> <tr> <td>CI</td> <td>4.68 ± 1.12</td> <td></td> </tr> <tr> <td colspan="3">Patients with cardiopulmonary resuscitation (n=6)</td> </tr> <tr> <td>CO</td> <td>5.75 ± 3.3</td> <td></td> </tr> <tr> <td>CI</td> <td>3.12 ± 1.67</td> <td></td> </tr> <tr> <td colspan="3">Patients with thoracic pain (n=15) were not significantly different to patients without thoracic pain (n=29) in age (<i>p</i>=0.316), breathing frequency (<i>p</i>=0.747), oxygen saturation (<i>p</i>=0.887), blood glucose (<i>p</i>=0.70), time spent at scene (<i>p</i>=0.203) or transport time (<i>p</i>= 0.202). Glasgow Coma Score was significantly lower in the non-thoracic pain group (<i>p</i>=0.002)</td> </tr> </tbody> </table>		Thoracic pain (± SD) (n=15)	No pain (±SD) (n=29)	CO (L/min)	3.37 ± 1.1 <i>p</i> = 0.023	5.06 ± 2.9	CI (L/min/m ²)	1.67 ± 0.58 <i>p</i> = 0.001	3.18 ± 1.34	APV (m/s)	0.75 ± 0.2 <i>p</i> = 0.236, NS	0.90 ± 0.4	VTI	14.51 ± 5.39 <i>p</i> = 0.03	19.45 ± 8.2	HR (bpm)	82 ± 23 <i>p</i> = 0.021	101 ± 20	MD	11.2 ± 3.3 <i>p</i> = 0.001	19.1 ± 8	ET%	50 ± 14 <i>p</i> = 0.007	64 ± 18	SV (ml)	44 ± 17 <i>p</i> = 0.145, NS	57 ± 28	SVR (dyne*sec*cm ⁻⁵)	2,709 ± 891 <i>p</i> = 0.0001	1,499 ± 661	MAP (mmHg)	106 ± 25 <i>p</i> = 0.010	83 ± 17	Patients with seizure (n=6)			CO	7.5 ± 3.05		CI	4.68 ± 1.12		Patients with cardiopulmonary resuscitation (n=6)			CO	5.75 ± 3.3		CI	3.12 ± 1.67		Patients with thoracic pain (n=15) were not significantly different to patients without thoracic pain (n=29) in age (<i>p</i> =0.316), breathing frequency (<i>p</i> =0.747), oxygen saturation (<i>p</i> =0.887), blood glucose (<i>p</i> =0.70), time spent at scene (<i>p</i> =0.203) or transport time (<i>p</i> = 0.202). Glasgow Coma Score was significantly lower in the non-thoracic pain group (<i>p</i> =0.002)		
	Thoracic pain (± SD) (n=15)	No pain (±SD) (n=29)																																																								
CO (L/min)	3.37 ± 1.1 <i>p</i> = 0.023	5.06 ± 2.9																																																								
CI (L/min/m ²)	1.67 ± 0.58 <i>p</i> = 0.001	3.18 ± 1.34																																																								
APV (m/s)	0.75 ± 0.2 <i>p</i> = 0.236, NS	0.90 ± 0.4																																																								
VTI	14.51 ± 5.39 <i>p</i> = 0.03	19.45 ± 8.2																																																								
HR (bpm)	82 ± 23 <i>p</i> = 0.021	101 ± 20																																																								
MD	11.2 ± 3.3 <i>p</i> = 0.001	19.1 ± 8																																																								
ET%	50 ± 14 <i>p</i> = 0.007	64 ± 18																																																								
SV (ml)	44 ± 17 <i>p</i> = 0.145, NS	57 ± 28																																																								
SVR (dyne*sec*cm ⁻⁵)	2,709 ± 891 <i>p</i> = 0.0001	1,499 ± 661																																																								
MAP (mmHg)	106 ± 25 <i>p</i> = 0.010	83 ± 17																																																								
Patients with seizure (n=6)																																																										
CO	7.5 ± 3.05																																																									
CI	4.68 ± 1.12																																																									
Patients with cardiopulmonary resuscitation (n=6)																																																										
CO	5.75 ± 3.3																																																									
CI	3.12 ± 1.67																																																									
Patients with thoracic pain (n=15) were not significantly different to patients without thoracic pain (n=29) in age (<i>p</i> =0.316), breathing frequency (<i>p</i> =0.747), oxygen saturation (<i>p</i> =0.887), blood glucose (<i>p</i> =0.70), time spent at scene (<i>p</i> =0.203) or transport time (<i>p</i> = 0.202). Glasgow Coma Score was significantly lower in the non-thoracic pain group (<i>p</i> =0.002)																																																										
Tan et al (2005)	III-2	Cross classification of patients on USCOM compared to PAC	24 mechanically ventilated patients who had undergone cardiac surgery	<p>Forty sets of paired measurements were obtained from 22/24 (92%) of patients. Unable to obtain acceptable signal in 2/24 (8%) of patients. Satisfactory flow profiles were obtained in 30/40 (75%) of examinations in the supine position. A 15°-30° left lateral tilt was required for the remaining 10/40 (25%) examinations.</p> <p>Mean of difference (estimate of bias) PAC CO vs USCOM CO 0.18 ± 0.82 95%CI [-0.09, 0.44], SE= 0.13</p> <p>The limits of agreement for 2 techniques -1.43 (-1.88 to -0.98) and 1.78 (1.33 to 2.23)</p>																																																						

SD = standard deviation, CO = cardiac output, CI = cardiac index, APV = aortic peak velocity, VTI = velocity time integral, HR = heart rate, MD = minute distance, ET% = ejection time per cent, SV = stroke volume, SVR = systemic vascular resistance, MAP = mean arterial pressure, USCOM = ultrasound cardiac output monitor, PAC = pulmonary artery catheter, SE = standard error

Abstract				
Haas et al (2006)	III-2	Cross classification of patients on USCOM compared to PAC	25 sedated and mechanically ventilated ICU patients	1315 USCOM measurements obtained and based on means, 263 paired measurements of PAC and USCOM were analysed. Correlation PAC vs USCOM r = 0.8024 r ² = 0.6438
Knobloch et al (2005) In German, abstract in English	IV	Case series	32 emergency patients (cardiac, non-cardiac, sepsis, anaphylactic reaction, haemodynamically unstable) 19 of these patients were unconscious	CO 4.8 ± 0.71 L/min CI 2.4 ± 0.3 L/min/m ²
Kotake et al (2006)	III-2	Cross classification of patients on USCOM compared to PAC	40 ICU patients	CO 5.3 ± 0.57 L/min CO-AO (126 measurements) Bias ± precision -1.04 ± 1.29 Relative error (%) -18 ± 22 CO-Pul (103 measurements) Bias ± precision -0.37 ± 1.21 Relative error (%) -3 ± 21 Doppler signal could not be obtained 3/126 (2.4%) occasions at AO and 17/103 (16.5%) occasions at Pul
Lichtenthal et al (2005)	III-2	Cross classification of patients on USCOM compared to CardioWest device	4 patients implanted with the CardioWest artificial heart device	460 serial measurements on 4 patients Mean (± SD) USCOM CardioWest CO (L/min) 7.26 ± 0.66 7.23 ± 0.57 Mean difference 0.03 ± 0.49 L/min Mean error 0.34% SV (ml) 55.0 ± 4.6 54.6 ± 3.7 Mean difference 0.42 ± 3.66 ml Mean error 0.64% HR (bpm) 132 ± 5 132 ± 4 Mean difference -0.38 ± 3.7 bpm Mean error -0.38%

USCOM = ultrasound cardiac output monitor, PAC = pulmonary artery catheter, CO = cardiac output, CI = cardiac index, CO-AO = cardiac output at ascending aorta, CO-Pul = right sided cardiac output, SD = standard deviation, HR = heart rate, bpm = beats per minute

O'Driscoll et al (2005)	III-2	Cross classification of patients on USCOM compared to PAC	15 patients undergoing right heart catheterisation as part of their clinical management	83 paired data sets Correlation PAC vs USCOM $r^2 = 0.714$ Bias and limits of agreement 0.12, -1.21 to +1.45 L/min
Phillips et al (2006)	III-2	Cross classification of patients on USCOM compared to CardioWest (n=7), Fick (n=3), Echocardiography (n=2), PAC (n=11) and the USCOM device	24 patients attending heart failure transplant clinic	Mean (\pm SD) USCOM All other methods CO L/min 4.69 \pm 2.35 4.68 \pm 2.39 Mean difference 0.002 \pm 0.204 L/min Mean error -1.0% Correlation All methods vs USCOM $r = 0.996$
Phillips et al (2006)	III-2	Cross classification of patients on USCOM compared to 2D echocardiography	37 preterm neonates	Mean (\pm SD) USCOM Echocardiography CO (L/min) 0.37 \pm 0.14 0.36 \pm 0.19 $r = 0.9134$ $p < 0.005$ Mean difference 0.00 \pm 0.081 L/min Mean error -3.7%

USCOM = ultrasound cardiac output monitor, PAC = pulmonary artery catheter, CO = cardiac output, SD = standard deviation

Only two low quality studies (level IV diagnostic evidence) reported on the time required to use the USCOM device to obtain a cardiac output measurement (Table 2) (Knobloch et al 2006; Knobloch et al 2005a). Both studies reported on the use of the device in the assessment of patients undergoing emergency transportation. In a clinic setting, at least 45 minutes is required before a CO measurement can be made after right heart catheterisation. Therefore, it is highly unlikely that comparative data on the use of the USCOM device versus conventional pulmonary artery catheterisation would be obtained in an emergency setting (Knobloch et al 2006). Average time spent to gain a CO reading ranged from 15 to 25 seconds and did not contribute to extended times at the scene or transportation time. The authors concluded that the USCOM was a valuable tool in the rapid assessment of seriously ill patients who require emergency transportation, and that the pre-clinical haemodynamic information gained may assist with appropriate treatment once the patient reaches hospital. In addition, both studies reported that the USCOM device was easy to use in the cramped confines of the emergency helicopter and that no interference by the rotor of the helicopter was experienced during examinations.

Table 2 Time taken to perform examination with USCOM

Study	Level of Diagnostic Evidence	Study Design	Population	Outcomes
Knobloch et al (2006)	IV	Case series	44 consecutive emergency patients, 15 with thoracic pain, 29 without thoracic pain	<p>Average USCOM examination took 15 ± 8 seconds with a maximum of 30 seconds spent to improve signal quality</p> <p>Time at scene and transport time were not affected by the use of USCOM</p> <p>Average time at scene with USCOM = 21.2 ± 15 mins</p> <p>Average time at scene without USCOM = 20 ± 17 mins</p> <p>NS</p> <p>Average transport time with USCOM = 12 ± 6 mins</p> <p>Average transport time without USCOM = 14 ± 5 mins</p> <p>NS</p>
Knobloch et al (2005) In German, abstract in English	IV	Case series	32 emergency patients (cardiac, non-cardiac, sepsis, anaphylactic reaction, haemodynamically unstable) 19 of these patients were unconscious	Average USCOM examination took 25 seconds

USCOM = Ultrasound cardiac output monitor, NS = no significant difference

One full text study and two abstracts reported the inter-assessor agreement in cardiac output assessed by medical staff undergoing training with the USCOM device, compared to values obtained by trained clinicians (Table 3) (Dey & Sprivulis 2005; Losey et al 2005; Tam et al 2006). All studies found that trainees were able to rapidly acquire the skills necessary to produce reliable CO measurements in emergency department patients. *Intra*-assessor reliability correlated with the ability to obtain a clear image and during training the intra-assessor CO difference improved with the number of patients assessed (Dey & Sprivulis 2005). Dey and Sprivulis (2005) reported a significant *inter*-assessor correlation of CO measurements ($p = 0.02$), whilst Losey et al (2005) reported significant *inter*-assessor correlations of cardiac and stroke volume index ($p < 0.001$).

Table 3 Inter-assessor agreement

Study	Level of Diagnostic Evidence	Study Design	Population	Outcomes
Dey and Sprivilis (2005)	IV	Case series	21 conscious emergency department patients	<p>Trainee image scores Improved from 5th patient 4.6/6 95%CI [4.0, 5.3] to 20th patient 5.5/6 95%CI [5.0, 6.0]</p> <p>Assessment of CO positively correlated with image quality score $r = 0.21$ 95%CI [0.05, 0.36]</p> <p>Intra-assessor CO difference Improved from 5th patient 17% 95%CI [4, 25] to 20th patient 5% 95%CI [0, 11] $p = 0.02$</p> <p>Inter-assessor CO difference 0.2 L/min 4%, 95%CI [3, 6]</p> <p>Inter-assessor CO correlation $r = 0.91$ 95%CI [0.85, 0.95], $p = 0.001$</p> <p>Inter-assessor CI difference 0.1 L/min/m² 4%, 95%CI [2, 6]</p>
Abstract				
Losey et al (2005)	IV	Case series	49 conscious emergency department patients	<p>52 paired measurements of CI and SVI were performed in 44/49 (90%) patients by trainees compared to results obtained by 2 blinded trained operators</p> <p>Inter-assessor CI correlation $r^2 = 0.87$ 95%CI [0.83, 1.04], $p < 0.001$ kappa = 0.84</p> <p>Inter-assessor SVI correlation $r^2 = 0.84$ 95%CI [0.80, 1.03], $p < 0.001$ kappa = 0.80</p>
Tam et al (2006)	IV	Case series	119 conscious emergency department patients	<p>Intra-assessor CO correlation $r^2 = 0.86$ 95%CI [0.81, 0.90]</p> <p>Mean CO difference between each pair of operators (3 total) -0.23 L/min 95%CI [-0.38, -0.06] and 0.09 L/min 95%CI [-0.10, 0.28] and 0.31 L/min 95%CI [0.15, 0.47]</p>

CO = cardiac output, CI = cardiac index, SVI = stroke volume index

In summary CO measurements taken with the USCOM device correlate highly with CO measurements obtained with the “gold standard”, pulmonary artery catheterisation, and other methods of measuring CO. However, the USCOM device may tend to underestimate when CO levels are higher than 5.0 L/min. There are no data describing the effectiveness of the USCOM device to improve patient outcomes. In addition no safety data were reported on the use of USCOM or pulmonary artery catheterisation to monitor cardiac output.

The skills required to operate the USCOM device and to obtain reproducible results may be acquired in a relatively short training period by clinical staff.

Potential Cost Impact

Cost Analysis

There are currently no cost-effectiveness data available for the utilisation of the USCOM device for cardiac output monitoring.

Simple costings

The USCOM unit is currently selling in Australia for \$35-42,000 (personal communication USCOM Ltd). After the initial purchase of the unit (monitor and probe) there are no recurring costs, such as disposable consumables, with the exception of standard ultrasound conducting gel (Chand et al 2006). At the time of writing, it is unclear what the lifetime of the USCOM device is, however USCOM Ltd estimate that if used over a three-year period, the cost of the unit plus seven per cent interest would total \$50,820, which would equate to \$1,412 per month of operation (personal communication USCOM Ltd). This does not, however, include training costs for medical staff or costs associated with time spent for medical staff performing cardiac output measurements. The comparator, pulmonary artery catheterisation, is covered by the MBS item number 13818. Although there are several item numbers (22015, 38200, 38203, and 38206) which cover either left or right heart catheterisation, *only* item number 13818 is specifically for the measurement of cardiac output in an intensive care unit. The total fee for this item number is \$100.50, which covers the cost of the *insertion* of the Swan-Ganz catheter. Other costs associated with this procedure include anaesthetising the patient and the purchase of the Swan-Ganz single use catheter. MBS item number 21943 (fee \$87.50) can be used *only* for the initiation of management of anaesthesia for the insertion of the Swan-Ganz catheter under MBS item number 13818. The current price for the single use Swan-Ganz catheter is approximately \$100 and this should be combined with a CO set for optimal CO monitoring (syringe, plunger and contamination shield) at a cost of \$30 (personal communication, Edwards LifeSciences Pty Ltd). Although other

costs would be associated with PAC, such as nursing care and time spent on ICU, these costs would also apply to patients diagnosed with the USCOM device. Therefore an estimate of the total cost of PAC without these additional costs would be approximately \$318. The basic cost of the USCOM for one year, based on a 3-year lifespan, would be \$16,940, which would be equivalent to 53 pulmonary artery catheterisations.

In addition, the USCOM device may be used to monitor CO in a wide range of patient groups (anaesthesia, cardiology, intensive care and paediatrics) in whom arterial catheterisation may be considered too invasive or unnecessary.

With the increasing use of the USCOM monitor in Australian hospitals a cost-effectiveness study comparing its use to conventional pulmonary artery catheterisation would be feasible and informative.

Ethical Considerations

Informed Consent

Both professional guidelines and scholarship in medical ethics acknowledge that seeking and gaining consent for anaesthesia and the procedures associated with it is ideally undertaken by the anaesthetist who will be providing the treatment, rather than delegating this task to another treating clinician (ANZCA 2005, White 2004). Whether the actual information provided to patients about anaesthetic treatments need extend to a detailed discussion of the type of CO monitoring to be undertaken is less clear. The basic requirement is that “the patient should be provided with the information that a reasonable patient in the position of that patient might wish to know, and to which she/he might attach significance” (ANZCA 2005). This requirement would be the same for all methods of CO monitoring.

Seeking consent for use of the USCOM device is likely to be complicated by the fact that most patients diagnosed using the USCOM device are seriously or critically ill, and are not in a position to give consent as to which method of cardiac output monitoring they would prefer. In these situations, discussion with the patient, or other persons able to make decisions on the patient’s behalf, needs to take place as soon as possible.

Patients’ best interests

The USCOM device offers patients a non-invasive means of cardiac monitoring and as such may be an attractive diagnostic option. By obtaining rapid cardiac output readings, more appropriate therapeutic options may be available to patients, which may in turn decrease time spent in ICU or total time spent in hospital (Knobloch et al 2006). Although evidence presented in this report supports the effectiveness of the USCOM device in measuring CO compared to PAC, there are no data supporting improved patient outcomes for either intervention.

The USCOM device is small and light, easily transportable and relatively inexpensive compared to other major items of medical equipment. In addition, the USCOM device has been shown to be a useful tool in the rapid assessment of emergency patients before or during transportation to major medical centres.

Access Issues

After initial training, which may be provided by the company via a training module, clinicians would be capable of producing reliable results using the USCOM to monitor cardiac output in a short period of time. This would make the USCOM device an ideal candidate for use in rural and remote medical facilities, where cardiac specialists capable of performing right heart catheterisation may not be resident. In addition, nursing staff may be trained in the use of the USCOM and would be able to communicate results to the appropriate clinician.

Training

USCOM Pty Ltd has developed a training program for all medical staff use in the USCOM device. The training program is supported by education materials in printed and digital form. USCOM has developed training and education materials in the form of two books ("Quick Guide" and "The Basics") and a CD-Rom for a step-by-step explanation of how USCOM works and how to learn to use it in daily clinical practice (USCOM 2006). In addition, a training system called the "Fremantle Protocol" has been devised by clinicians working in the Emergency Department of the Fremantle Hospital in Western Australia. The objectives of this protocol were to develop a training package for the USCOM device and to determine the number of proctored studies required for the necessary skill acquisition to perform cardiac assessment without supervision. This protocol also developed guidelines for acceptable values of cardiac output obtained with the USCOM. An audiovisual training package was developed by the authors of this protocol, which includes a basic review of ultrasound, the validity of the continuous wave Doppler technique and the actual use of the USCOM device. During the development of the protocol, four emergency physicians and one geriatrician, all with no previous ultrasound experience, underwent hands-on training with healthy adult volunteers as "patients". Skill acquisition was assessed after the fifth, 10th, 15th and 20th examination. The authors concluded that physicians with no prior experience were able to be trained in the use of the USCOM device and could produce reliable cardiac output estimations over the course of 20 patient assessments (Dey & Sprivulis 2005).

USCOM Pty Ltd has also established links with the Australian Institute of Ultrasound to provide external education for USCOM users, providing independent recognition of operational competence (USCOM 2006).

Clinical Guidelines

There are currently no Australian guidelines for the use of the USCOM device for the purposes of monitoring cardiac output. However the Cardiac Society of Australia and New Zealand have published guidelines for competency in diagnostic catheterisation and coronary angiography (CSANZ 2005).

In 2001 the Australasian College of Emergency Medicine published the document "Guidelines for the minimum criteria for ultrasound workshop". It is recommended that these guidelines be read in conjunction with the document "Credentialling for ED Ultrasonography". To obtain credentials in ultrasonography the candidate is required to attend an instructional workshop, perform and record a requisite number of accurate proctored Emergency Department Ultrasounds, and pass an exit examination. Emergency Department Sonologists must meet ongoing maintenance requirements in order to maintain their credentials. The objectives of the ultrasound workshop are to understand: the theory of ultrasound, the practical applications and

limitations of focussed emergency ultrasound and to demonstrate a proficiency in performing and interpreting emergency ultrasound scans (ACEM 2000; ACEM 2001).

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of the ultrasound cardiac monitor, USCOM, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The medical literature (Table 4) was searched utilising the search terms outlined in Table 5 to identify relevant studies and reviews, until November 2006. In addition, major international health assessment databases were searched.

Table 4 Literature sources utilised in assessment

Source	Location
<i>Electronic databases</i>	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
<i>Internet</i>	
Australian Clinical Trials Registry	http://www.actr.org.au/default.aspx
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US FDA, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html

Table 5 Search terms utilised

Search terms
MeSH Monitoring, physiological/ instrumentation, Hemodynamic Processes, Ultrasonography, Doppler, Stroke volume, Cardiac output
Text words USCOM, ultrasound cardiac output monitor, Noninvasive hemodynamic monitor*, continuous wave Doppler device, Doppler ultrasonography,
Limits English, Human

Availability and Level of Evidence

Five peer reviewed studies and nine abstracts from conference proceedings were included for assessment in this Horizon Scanning Report. The five peer reviewed studies included three cross classification studies, which compared the USCOM device to other methods of CO measurement (usually pulmonary artery catheter) (1 level III-1 and 2 level III-2 diagnostic evidence) and two case series (level IV diagnostic evidence) (Chand et al 2006; Dey & Sprivulis 2005; Knobloch et al 2006; Knobloch et al 2005b; Tan et al 2005). Four of these studies were concerned with the assessment of the USCOM device in clinical settings, whereas one study reported on the inter- and intra-assessor variability when training new clinicians in the use of USCOM. Of the nine abstracts included, six were cross classification studies (level III-2 diagnostic evidence), which compared the safety and effectiveness of the USCOM device to pulmonary artery catheterisation or 2D-echocardiography (Haas et al 2006; Kotake et al 2006; Lichtenthal et al 2005; O'Driscoll et al 2005; Phillips et al 2006a; Phillips et al 2006b). The remaining three abstracts were case series (level IV diagnostic evidence), two of which reported on inter-assessor variability in the training of new medical staff with the USCOM device (Knobloch et al 2005a; Losey et al 2005; Tam et al 2006). See Appendix B for profiles of these studies.

Sources of Further Information

Two trials are currently underway in the United Kingdom. One trial is assessing the ability of emergency nurses to reliably assess patient CO with the USCOM device whilst the other trial is being conducted to determine a reference range for left and right ventricular output in healthy neonates. Both trials are expected to be finalised early in 2007 (NHS 2006).

A randomised controlled trial is currently recruiting 350 school aged children (aged 12-16 years) to evaluate the effect of plasma volume on cardiac performance during short-term high intensity exercise among high school adolescents. The main outcomes of the study are cardiac function measurements using the change of stroke volume as the primary indicator. All cardiac function measurements will be made using the USCOM device (ACTR 2006).

A director of USCOM Ltd, R. Phillips is cited as an author on two of the five peer reviewed papers and on five of the nine conference papers.

Conclusions

The USCOM device is a non-invasive, ultrasound cardiac output monitor designed to transcutaneously measure and record changes in the cardiac output of critically ill patients. The USCOM device employs continuous-wave Doppler ultrasound and is capable of measuring both left and right cardiac output. The USCOM device is intended for use in a wide spectrum of patients including both adult and paediatric patients admitted to intensive care units, patients undergoing anaesthesia and those undergoing cardiac surgery. The USCOM device may be used to confirm normal cardiac function, detect and quantify abnormal function, and to evaluate the effectiveness of cardiovascular therapies.

The ‘gold standard’ method used to assess CO is thermodilution using a standard pulmonary artery catheter (PAC). This technique is widely disseminated, however there is limited evidence that it improves patient recovery or survival. Other methods for measuring CO include the Fick re-breathing method, dilution techniques using isotonic lithium chloride, the insertion of a trans-oesophageal Doppler transducer, pulse contour analysis of the aortic waveform and thoracic electrical bioimpedance.

None of the studies included for assessment in this report described any adverse events associated with the use of the USCOM device.

Three good quality, peer reviewed studies compared CO levels obtained with USCOM to those obtained with the “gold standard” pulmonary artery catheterisation. (level III-1 and III-2 diagnostic evidence). One study reported a significant correlation between CO measured by the two techniques ($r = 0.794$, $p < 0.01$), whilst the other two studies reported a non-significant bias between the two techniques (-0.14 to 0.18). The limits of agreement were small and included zero, indicating that there was little difference between the two methods. High correlations ($r = 0.80$ and $r^2 = 0.714$) were also reported by two of the three abstract studies which compared USCOM to PAC (level III-2 diagnostic evidence). However, the third study reported a large bias (-1.04 ± 1.29 L/min) for measurements taken at the ascending aorta, compared to the mean CO of 5.3 ± 0.57 L/min. Although the majority of cross classification studies demonstrated a high correlation between CO measurements obtained with USCOM compared to other methods, two studies reported that when CO values exceeded 5.0 L/min, then the USCOM device tended to underestimate cardiac output. This suggests that the USCOM device may adequately measure CO values within the normal physiological range, however further validation studies for low and high CO states are warranted. Two studies found that they were unable to obtain a successful Doppler signal at *both* the ascending aorta and the pulmonary artery, however a successful signal was able to be obtained from at *least* one of these locations (level III-1 and III-2 diagnostic evidence).

In addition, case series evidence suggests that the USCOM device was feasible to use at the scene of trauma and during transportation of emergency patients, to assess the CO of critically ill patients (level IV diagnostic evidence).

Average time spent to gain a CO reading in these situations ranged from 15 to 25 seconds and did not contribute to extended times at the scene or

transportation time. This may allow prompt and appropriate treatment of patients before their arrival at hospital, which may in turn lead to improved patient outcomes.

Inter-assessor agreement of cardiac output measured by medical staff undergoing training with the USCOM device, compared to values obtained by trained clinicians was good. Three studies found that trainees were able to rapidly acquire the skills necessary to produce reliable CO measurements in emergency department patients (level IV diagnostic evidence).

There are currently no cost-effectiveness data available for the utilisation of the USCOM device for CO monitoring. In Australia, the USCOM unit currently sells for approximately \$35-42,000. There are no recurring costs associated with use of the USCOM device after the initial purchase of the unit, which includes a monitor and probe. The comparator, pulmonary artery catheterisation, is covered by the Medicare Benefits Schedule (MBS) item number 13818, which specifically covers the measurement of CO in an intensive care unit. The total fee for this item number is \$100.50, which covers the cost of the *insertion* of the Swan-Ganz catheter. Other costs associated with this procedure include anaesthetising the patient (MBS item number 21943, fee \$87.50) and the purchase of the single use catheter (a total approximate cost of \$130). With the increasing use of the USCOM monitor in Australian hospitals a cost-effectiveness study comparing its use to conventional pulmonary artery catheterisation would be feasible and informative.

In conclusion, the USCOM device is capable of measuring cardiac output in a non-invasive manner and appears to be accurate, rapid, well tolerated and relatively inexpensive when compared to the “gold standard” of pulmonary artery catheterisation. The main advantage of utilising the USCOM device to monitor CO is that, unlike PAC, patients do not need to be anaesthetised, which should increase the utility of the device and enable assessment of a wider patient population. No safety issues associated with the use of the device were reported. In addition, the device is highly portable and the learning curve for skills acquisition by clinicians is short. However, ideally the USCOM device should be further validated for patients with high and low cardiac output states

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis ^{**}	Prognosis	Aetiology ^{††}	Screening
I *	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ^{§§} among consecutive patients with a defined clinical presentation ^{††}	A prospective cohort study ^{***}	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ^{§§} among non-consecutive patients with a defined clinical presentation ^{††}	All or none ^{§§§}	All or none ^{§§§}	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study [‡] Interrupted time series without a parallel control group	Diagnostic case-control study ^{††}	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ^{††}	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

[§] Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

[†] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

[‡] Comparing single arm studies ie. case series from two studies.

^{††} The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au.

^{§§} The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

^{†††} Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

^{††††} Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

^{†††††} At study inception the cohort is either non-diseased or all at the same stage of the disease.

^{§§§} All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

^{††††††} If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: (Bandalier editorial 1999; Lijmer et al 1999; Phillips et al 2001)

Appendix B: Profiles of studies

Study	Location	Study design	Study population	Study details	Outcomes assessed
Chand, R. Mehta, Y. Trehan, N. (2006)	New Delhi, India	Diagnostic evidence level III-1	50 patients who had undergone elective off-pump coronary artery by-pass surgery Mean age 59.2 ± 10.14 years (range 37-78 years) Mean height 166.58 ± 9.23 cm (range 148-187 cm) Mean weight 72.06 ± 15.57 kg (range 34-105 kg)	CO was simultaneously obtained using PAC and the USCOM device post surgery. Invasive and non-invasive measurements made simultaneously with blinded observers.	Cardiac output
Dey, I. Sprivulis, P. (2005)	Perth, Australia	Diagnostic evidence level IV	21 conscious emergency department patients	Five physicians underwent training with USCOM device to evaluate the reliability of USCOM in the emergency department setting. Compared to results obtained from 2 trained physicians blinded to results from trainees.	Intra-assessor cardiac output difference Inter-assessor cardiac output difference
Knobloch, K. Lichtenberg, A. Winterhalter, M. Rossner, D. Pichlmaier, M. Phillips, R. (2005)	Brisbane, Australia	Diagnostic evidence level III-2	36 consecutive cardiac intensive care patients undergoing surgical re-vascularisation Mean age 67.2 ± 10 years Mean height 170 ± 8 cm Mean weight 79 ± 14 kg NYHA functional heart assessment class 3.1 ± 0.3	CO was simultaneously obtained using PAC and the USCOM device during re-vascularisation procedure (18 measurements) and post-surgically	Cardiac output

Knobloch, K. Hubrich, V. Rohmann, P. Lupkemann, M. Gerich, T. Krettek, C. Phillips, R. (2006)	Hanover, Germany	Diagnostic evidence level IV	44 consecutive emergency patients, 15 with thoracic pain, 29 without thoracic pain Mean age 62.8 ± 22 years (range 2-91 years) Blood pressure 127 ± 34 over 74 ± 19 mmHg Mean arterial pressure 92 ± 23 mmHg Heart rate 93 ± 24 beats/min Oxygen saturation 94 ± 8% Blood glucose 114 ± 71 mg/dL Glasgow Coma Scale 10.9 ± 5 (range 3-15)	CO was obtained in emergency patients being transported by helicopter	Cardiac output
Tan, H.L. Pinder, M. Parsons, R. Roberts, B. van Heerden, P.V. (2005)	Perth, Australia	Diagnostic evidence level III-2	24 mechanically ventilated patients who had undergone cardiac surgery Mean age 63.5 years (range 43-78 years) Mean BMI 28.9 ± 5.2	CO was simultaneously obtained using PAC and the USCOM device post surgery	Cardiac output
Abstract					
Haas, L.E.M. Tjan, D.H.T. van Wees, J. van Zanten, A.R.H. (2006)	Netherlands	Diagnostic evidence level III-2	25 sedated and mechanically ventilated ICU patients	CO was simultaneously obtained using PAC and USCOM device	Cardiac output
Knobloch, K.K. Hubrich, V. Rohmann, P. Lupkemann, M. Phillips, R. Gerich, T. Krettek, C. (2005) In German, abstract in English	Hanover, Germany	Diagnostic evidence level IV	32 emergency patients (cardiac, non- cardiac, sepsis, anaphylactic reaction, haemo- dynamically unstable) 19 of these patients were unconscious. Age range 17 months to 92 years	CO was obtained in emergency patients being transported by helicopter	Cardiac output

Kotake, Y. Suzuki, T. Katori, N. Serita, R. Takeda, J. (2006)	Tokyo, Japan	Diagnostic evidence level III-2	40 ICU patients	CO was simultaneously obtained PAC and the USCOM device	Cardiac output
Lichtenthal, P. Phillips, R. Sloniger, J. Copeland, J. (2005)	Arizona, USA	Diagnostic evidence level III-2	4 patients implanted with the CardioWest artificial heart device	CO was simultaneously obtained using the CardioWest and USCOM devices	Cardiac output
Losey, T. Nguyen, H.B. Corbett, S.W. Wittlake, W.A. (2005)	California, USA	Diagnostic evidence level IV	49 conscious emergency department patients	Medical staff underwent training with USCOM device to evaluate the reliability of USCOM in the emergency department setting. Compared to results obtained from 2 trained physicians blinded to results from trainees.	Intra-assessor cardiac output difference Inter-assessor cardiac output difference
O'Driscoll, G. Wright, J.J. Wright, I.W. Green, D.J. Phillips, R.A. (2005)	Brisbane, Australia	Diagnostic evidence level III-2	15 patients undergoing right heart catheterisation as part of their clinical management	CO was simultaneously obtained PAC and the USCOM device	Cardiac output
Phillips, R.A. Lichtenthal, P.J. Sloniger, J. West, M.J. Burstow, D.J. Copeland, J.G. (2006)	Arizona, USA	Diagnostic evidence level III-2	24 patients attending heart failure transplantation clinic Mean age 46.5 years (range 3 months to 82 years)	CO was simultaneously obtained using the CardioWest (n=7), Fick (n=3), Echo- cardiography (n=2), PAC (n=11) and the USCOM device	Cardiac output
Phillips, R. Paradisis, M. Evans, N. Southwell, D. Burstow, D. West, M.J. (2006)	Brisbane, Australia	Diagnostic evidence level III-2	37 preterm neonates Mean weight 1.13 ± 0.47 kg	Comparison of CO obtained with 2D echo- cardiography and the USCOM device	Cardiac output

Tam, M.K. Tang, C.O. Lai, K.H.W. Yeung, V.T.Y. Man, E.L.K. Lam, A.H.L. Rainer, T.H. (2006)	Hong Kong	Diagnostic evidence level IV	119 conscious emergency department patients	Medical staff underwent training with USCOM device to evaluate the reliability of USCOM in the emergency department setting.	Inter-assessor cardiac output difference
---	-----------	------------------------------------	--	---	--

USCOM = ultrasound cardiac output monitor, CO = cardiac output, PAC = pulmonary artery catheter, ICU = intensive care unit, NYHA = New York Heart Association

Appendix C: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
<http://www.med.monash.edu.au/healthservices/cce/evidence/>
- Health Economics Unit, Monash University
<http://chpe.buseco.monash.edu.au>

AUSTRIA

- Institute of Technology Assessment / HTA unit
<http://www.oecaw.ac.at/ita/welcome.htm>

CANADA

- Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) <http://www.aetmis.gouv.qc.ca/en/>
- Alberta Heritage Foundation for Medical Research (AHFMR)
<http://www.ahfmr.ab.ca/publications.html>
- Canadian Coordinating Office for Health Technology Assessment (CCHOTA) <http://www.cadth.ca/index.php/en/>
- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database <http://www.mycabot.ca>
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University <http://www.chepa.org>
- Centre for Health Services and Policy Research (CHSPR), University of British Columbia <http://www.chspr.ubc.ca>
- Health Utilities Index (HUI)
<http://www.fhs.mcmaster.ca/hug/index.htm>
- Institute for Clinical and Evaluative Studies (ICES)
<http://www.ices.on.ca>

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
http://www.dihta.dk/publikationer/index_uk.asp
- Danish Institute for Health Services Research (DSI)
<http://www.dsi.dk/engelsk.html>

FINLAND

- FINOHTA <http://www.stakes.fi/finohta/e/>

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)
<http://www.anaes.fr/>

GERMANY

- German Institute for Medical Documentation and Information (DIMDI)
/ HTA <http://www.dimdi.de/dynamic/en/>

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
<http://www.gr.nl/adviezen.php>

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
<http://nzhta.chmeds.ac.nz/>

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
<http://www.kunnskapssenteret.no/>

SPAIN

- Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud
"Carlos III"/Health Technology Assessment Agency (AETS)
<http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp>
- Catalan Agency for Health Technology Assessment (CAHTA)
<http://www.aatrm.net/html/en/dir394/index.html>

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
<http://www.sbu.se/www/index.asp>
- Center for Medical Health Technology Assessment
<http://www.cmt.liu.se/>

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
<http://www.snhta.ch/>

UNITED KINGDOM

- NHS Quality Improvement Scotland
http://www.nhshealthquality.org/nhsqis/qis_display_home.jsp?pContentID=43&p_applic=CCC&pElementID=140&pMenuID=140&p_service=Content.show&
- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)
<http://www.hta.nhsweb.nhs.uk/>
- University of York NHS Centre for Reviews and Dissemination (NHS CRD) <http://www.york.ac.uk/inst/crd/>
- National Institute for Clinical Excellence (NICE)
<http://www.nice.org.uk/>

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
<http://www.ahrq.gov/clinic/techix.htm>
- Harvard School of Public Health – Cost-Utility Analysis Registry
<http://www.tufts-nemc.org/cearegistry/index.html>
- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC) <http://www.bcbs.com/tec/index.html>

Appendix D: Definitions

Cardiac output (CO) is the volume of blood pumped by the heart in one minute

$$CO = SV \times HR$$

Cardiac index (CI) is the cardiac output indexed with body surface area

$$CI = CO/BSA$$

Stroke volume (SV) is the volume of blood pumped by the heart in one beat

$$SV = vti \times CSA$$

Stroke volume index (SVI) is the stroke volume indexed with body surface area

$$SVI = SV/BSA$$

Stroke volume variation (SVV) is the variation in stroke volume

$$SVV = (SV_{max} - SV_{min} \times 100) / ((SV_{max} + SV_{min})/2)$$

Systemic vascular resistance (SVR) is the pressure against which the heart pumps

$$SVR = 80 \times (MAP - CVP) / CO$$

Systemic vascular resistance index (SVRI) is SVR indexed with body surface area

$$SVRI = SVR \times BSA$$

Peak velocity (Vpk) is the highest velocity of blood flow through the valve

Heart rate (HR) is the number of beats per minute measured from systolic onset to systolic onset

Flow time (FT) is the systolic flow time (systolic ejection)

$$FT = t_{ET}$$

Ejection time per cent (ET%) is the per cent of cycle duration occupied by systolic ejection

$$ET\% = (ET / \text{cycle duration}) \times 100$$

Velocity time integral (vti) is the integral of the flow profile ie the distance the blood travels in one beat

$$vti = \int_0^{FT} v(t) dt$$

Minute distance (MD) is the distance the blood travels in one minute independent of valve area

$$MD = vti \times HR$$

BSA = body surface area

CSA = cross-sectional area

MAP = mean arterial pressure : $MAP \sim BP_{dia} + ((BP_{sys} - BP_{dia})/3)$

BP_{dia} = blood pressure, diastolic

BP_{sys} = blood pressure, systolic

CVP = central venous pressure

Source: (USCOM 2006)

After-load is the load that the heart must eject blood against and is closely related to the aortic pressure, or more precisely, is related to ventricular wall stress. The pressure that the ventricle generates during systolic ejection is close to aortic pressure, unless aortic stenosis is present. At a given pressure, wall stress and therefore after-load is increased by an increase in radius (ventricular dilation). A hypertrophied ventricle (thickened wall) reduces wall stress and after-load. After-load is increased when aortic pressure and systemic vascular resistance are increased, by aortic valve stenosis, and by ventricular dilation. When after-load increases, there is an increase in end-systolic volume and a decrease in stroke volume. Pre-load is defined as the initial stretching of the cardiac myocytes prior to contraction. Pre-load cannot be determined in the intact heart, therefore other indices of preload are used such as ventricular end-diastolic volume or pressure. Changes in ventricular pre-load affect ventricular stroke volume: increased pre-load increases stroke volume, whereas decreased pre-load decreases stroke volume by altering the force of contraction of the cardiac muscle (Klabunde 2006).

Appendix E: Normal haemodynamic ranges

Parameter	Adult normal range	Paediatric normal range (aged 2.5 to 16 years)
Cardiac output (CO)	5.0 – 7.0 l/min	3.5 – 7.0 l/min
Cardiac index (CI)	2.4 – 3.6 l/min/m ²	3.4 – 5.0 l/min/m ²
Stroke volume (SV)	64 – 100 ml	40 – 95 ml
Stroke volume index (SVI)	35 – 50 ml/m ²	40 – 60 ml/m ²
Systemic vascular resistance (SVR)	1000 – 1600 dynes x sec/cm ⁵	900 – 1700 dynes x sec/cm ⁵
Systemic vascular resistance index (SVRI)	2000 – 3100 dynes x sec/cm ⁵ /m ²	1200 – 2000 dynes x sec/cm ⁵ /m ²
Aortic peak velocity	1.0 – 1.4 m/s	1.2 – 1.6 m/s
Pulmonary peak velocity	0.6 – 0.9 m/s	0.7 – 1.1 m/s
Heart rate (HR)	Infants – 10 years = 70-110 bpm 10 years – adult = 60 – 100 bpm	Infants – 10 years = 100-160 bpm 10 years – adult = 70 – 110 bpm
Flow time (FT)	0.31 – 0.37 ms	0.29 – 0.35 ms
Ejection time per cent (ET%)	PV 36% AV 35 – 47%	37 – 51%
Velocity time integral (vti)	21 – 31 cm	23 – 33 cm
Minute distance (MD)	PV = 17 m/min AV = 15 – 22 m/min	8 – 12 years PV = 15 m/min AV = 18 – 27 m/min

bpm = beats per minute, AV = aortic valve, PV = pulmonary valve

The dyne is a unit of force. One dyne is equal to exactly 10⁻⁵ newtons and can be defined "the force required to accelerate a mass of one gram at a rate of one cm per second squared" (Wikipedia 2006)

Source: (USCOM 2006)

References

- ACEM (2000). *Credentiailling for ED Ultrasonography* [Internet]. Australasian College for Emergency Medicine. Available from: <http://www.medeserv.com.au/acem/open/documents/ultrasonography.htm> [Accessed 28th November 2006].
- ACEM (2001). *Guidelines for minimum criteria for ultrasound workshop* [Internet]. Australasian College for Emergency Medicine. Available from: <http://www.medeserv.com.au/acem/open/documents/ultrasoundworkshop.htm> [Accessed 28th November 2006].
- ACTR (2006). *Paediatric Exercise and Cardiac Performance Study* [Internet]. Australian Clinical Trials Registry. Available from: https://actr.org.au/registry/trial_review.aspx?ID=81677 [Accessed 12th December 2006].
- AIHW (2006). *AIHW National Hospital Morbidity Database* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/drgv5_9899-0405 [Accessed 4th December 2006].
- Allsager, C. M. & Swanevelder, J. (2003). 'Measuring cardiac output', *British Journal of Anaesthesia*, 3 (1), 15-19
- ANZCA (2005). Guidelines on consent for anaesthesia or sedation [Internet]. Australian and New Zealand College of Anaesthetists. Available from: http://www.medeserv.com.au/anzca/pdfdocs/PS26_2005.PDF [Accessed 29th January 2007].
- Bandolier editorial (1999). *Diagnostic testing emerging from the gloom?* [Internet]. Bandolier. Available from: <http://www.jr2.ox.ac.uk/bandolier/band70/b70-5.html> [Accessed 2004].
- Berton, C. & Cholley, B. (2002). 'Equipment review: new techniques for cardiac output measurement--oesophageal Doppler, Fick principle using carbon dioxide, and pulse contour analysis', *Crit Care*, 6 (3), 216-221
- Boldt, J. (2002). 'Clinical review: hemodynamic monitoring in the intensive care unit', *Crit Care*, 6 (1), 52-59
- Chand, R., Mehta, Y. & Trehan, N. (2006). 'Cardiac output estimation with a new Doppler device after off-pump coronary artery bypass surgery', *J Cardiothorac Vasc Anesth*, 20 (3), 315-319
- Chaney, J. C. & Derdak, S. (2002). 'Minimally invasive hemodynamic monitoring for the intensivist: Current and emerging technology', *Critical Care Medicine*, 30 (10), 2338
- Cholley, B. P. & Payen, D. (2005). 'Non-invasive techniques for measurements of cardiac output', *Current Opinion in Critical Care*, 11 (5), 424
- CSANZ (2005). *Competency in Diagnostic Cardiac Catheterization and Coronary Angiography* [Internet]. Cardiac Society of Australia and New Zealand. Available from:

http://www.csanz.edu.au/guidelines/training/Angiography_Guidelines.pdf
[Accessed 27th November 2006].

De Maria, A. N. & Raisinghani, A. (2000). 'Comparative overview of cardiac output measurement methods: has impedance cardiography come of age?' *Congest Heart Fail*, 6 (2), 60-73

Dey, I. & Sprivulis, P. (2005). 'Emergency physicians can reliably assess emergency department patient cardiac output using the USCOM continuous wave Doppler cardiac output monitor', *Emergency Medicine Australasia*, 17 (3), 193-199

DHA (2006). *Medicare Benefits Schedule Book* [Internet]. Australian Government. Available from: [http://www.health.gov.au/internet/wcms/publishing.nsf/Content/B444E30202CBDD93CA2570A400097806/\\$File/Complete%20MBS%20for%20download%20\(PDF%206716%20KB\).pdf](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/B444E30202CBDD93CA2570A400097806/$File/Complete%20MBS%20for%20download%20(PDF%206716%20KB).pdf) [Accessed 5th December 2006].

Engoren, M. & Barbee, D. (2004). 'Accurate, noninvasive continuous monitoring of cardiac output by whole-body electrical bioimpedance', - *American-Journal-of-Critical-Care*, - 125, - 40-45

FDA (2005). *510(k) Summary* [Internet]. United States Food and Drug Administration. Available from: <http://www.fda.gov/cdrh/pdf4/K043139.pdf> [Accessed

Gibbs, N. & Borton, C. (2006). *Safety of Anaesthesia in Australia - A review of anaesthesia related mortality 2000-2002*, Australian and New Zealand College of Anaesthetists, <http://www.anzca.edu.au/pdfdocs/Final%20Report%202002%20Website%20Version.pdf>.

Haas, L. E. M., Tjan, D. H. T. et al (2006). 'Validation of the USCOM-1A cardiac output monitor in hemodynamic unstable intensive care patients', Conference Paper: Annual Intensive Care Society Congress, Netherlands. http://www.uscom.com.au/abstracts/09_Netherlands_study_Feb06.pdf.

Harvey, S., Young, D. et al (2006). 'Pulmonary artery catheters for adult patients in intensive care', *Cochrane Database Syst Rev*, 3, CD003408

Hett, D. A. & Jonas, M. M. (2004). 'Non-invasive cardiac output monitoring', *Intensive Crit Care Nurs*, 20 (2), 103-108

Klabunde, R. E. (2006). *Cardiovascular Physiology Concepts* [Internet]. Available from: <http://cvphysiology.com/index.html> [Accessed 4th December 2006].

Knobloch, K., Hubrich, V. et al (2006). 'Feasibility of preclinical cardiac output and systemic vascular resistance in HEMS in thoracic pain--the ultrasonic cardiac output monitor', *Air Med J*, 25 (6), 270-275

Knobloch, K., Hubrich, V. et al (2005a). 'Non-invasive determination of cardiac output by continuous wave Doppler in air rescue service', *Anesthesiologie Intensivmedizin Notfallmedizin Schmerztherapie*, 40 (12), 750

- Knobloch, K., Lichtenberg, A. et al (2005b). 'Non-invasive cardiac output determination by two-dimensional independent Doppler during and after cardiac surgery', *Annals Of Thoracic Surgery*, 80 (4), 1479
- Kotake, Y., Suzuki, T. et al (2006). 'Evaluation of non-invasive cardiac output monitor with transthoracic Doppler method in the ICU', Conference Paper: American Society of Anesthesiology Annual Meeting, Chicago, USA. http://www.uscom.com.au/abstracts/Keio_ASA_abstract.pdf.
- Lichtenthal, P., Phillips, R. et al (2005). 'USCOM: an accurate system for cardiac output measurement?' Conference Paper: 25th International symposium on intensive care and emergency medicine, Brussels. *Critical Care*, 2005; Vol 9; Suppl 1, <http://ccforum.com/supplements/9/S1/?page=3>.
- Lijmer, J. G., Mol, B. W. et al (1999). 'Empirical evidence of design-related bias in studies of diagnostic tests.' *Journal of the American Medical Association*, 282 (11), 1061 - 1066
- Losey, T., Nguyen, H. B. et al (2005). 'Inter-rater agreement of a non-invasive ultrasound cardiac output monitoring (USCOM) device in emergency department patients', *Annals Of Emergency Medicine*, 46 (3), S18
- Medicare Australia (2006). *Medicare Benefits Schedule (MBS) Item Statistics Reports* [Internet]. Australian Government. Available from: http://www.medicareaustralia.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml [Accessed 5th December 2006].
- NHS (2006). *National Research Register* [Internet]. National Health Service, United Kingdom. Available from: <http://www.nrr.nhs.uk/search.htm> [Accessed 6th November 2006].
- Norton, L. & Slater, A. (2005). *Australian and New Zealand Paediatric Intensive Care Registry, 2004*, Australian and New Zealand Paediatric Intensive Care Society, Melbourne,
- NZHS (2006a). *Selected Morbidity Data for Publicly Funded Hospitals 1 July 2002 to 30 June 2003* [Internet]. New Zealand Health Information Service. Available from: <http://www.nzhis.govt.nz/publications/public.html> [Accessed 5th December 2006].
- NZHS (2006b). *Selected Privately Funded Morbidity Data 2002* [Internet]. New Zealand Health Information Service. Available from: <http://www.nzhis.govt.nz/publications/privatemorbidity02.pdf> [Accessed 5th December 2006].
- O'Driscoll, G., Wright, J. J. et al (2005). 'Cardiac output measurement with the USCOM ultrasonic cardiac output monitor', Conference Paper: 2nd Asian Pacific Congress of Heart Failure, Singapore. http://www.uscom.com.au/abstracts/05_RPH_Abstract.pdf.
- Phillips, B., Ball, C. et al (2001). *Levels of Evidence and Grades of Recommendations* [Internet]. Centre for Evidence-Based Medicine, Oxford, UK. Available from: Available from: http://www.cebm.net/levels_of_evidence.asp [Accessed 28th January 2004].

Phillips, R., Paradisis, M. et al (2006a). 'CO measurement in preterm neonates: validation of USCOM against echocardiography', Conference Paper: International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium.

http://www.uscom.com.au/abstracts/15_Neonates_Study_Brussels.pdf.

Phillips, R. A., Lichtenthal, P. J. et al (2006b). 'Non-invasive cardiac output measurement in children and adults in the cardiac surgical environment', Conference Paper: European Society of Intensive Care Medicine, Barcelona, Spain. http://www.uscom.com.au/abstracts/CardiacSurgery_abstract.pdf.

Smartt, S. (2005). 'The pulmonary artery catheter: gold standard or redundant relic', *J Perianesth Nurs*, 20 (6), 373-379

Stow, P. J., Hart, G. K. et al (2006). 'Development and implementation of a high-quality clinical database: the Australian and New Zealand Intensive Care Society Adult Patient Database', *J Crit Care*, 21 (2), 133-141

Tam, M. K., Tang, C. O. et al (2006). 'Observer agreement of non-invasive cardiac output measurement in the emergency department using portable continuous wave Doppler device (USCOM)', Conference Paper: Emergency Medicine Scientific Symposium, Hong Kong.

http://www.uscom.com.au/abstracts/ObserverAgreementPWH_SSEM2006.pdf

Tan, H. L., Pinder, M. et al (2005). 'Clinical evaluation of USCOM ultrasonic cardiac output monitor in cardiac surgical patients in intensive care unit', *British Journal of Anaesthesia*, 94 (3), 287-91

Tibby, S. M. & Murdoch, I. A. (2003). 'Monitoring cardiac function in intensive care', *Arch Dis Child*, 88 (1), 46-52

USCOM (2004). *CE Certificate* [Internet]. USCOM Pty Ltd. Available from: http://www.uscom.com.au/data/CE_Certificate%20.pdf [Accessed 28th November 2006].

USCOM (2006). *Non-invasive haemodynamics* [Internet]. USCOM Pty Ltd. Available from: <http://www.uscom.com.au/> [Accessed 28th November 2006].

White S.M. (2004) 'Consent for anaesthesia', *J Med Ethics*, 30 (3):286-90.

Wikipedia (2006). *Dyne* [Internet]. Wikipedia. Available from: <http://en.wikipedia.org/wiki/Dyne> [Accessed 30th November 2006].