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Running Title: In-vitro evaluation of an USCOM device

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Abstract

Purpose

Non-invasive cardiac output monitoring techniques provide high yield, low risk mechanisms to identify and individually treat shock in the emergency setting. The non-invasive ultrasonic cardiac output monitoring (USCOM) device uses an ultrasound probe applied externally to the chest; however limitations exist with previous validation strategies. This study presents the in-vitro validation of the USCOM device against calibrated flow sensors and compares user variability in simulated healthy and septic conditions.

Methods

A validated mock circulation loop was used to simulate each condition with a range of cardiac outputs (2-10 l/min) and heart rates (50-95 bpm). Three users with varying degrees of experience using the USCOM device measured cardiac output and heart rate by placing the ultrasound probe on the mock aorta. Users were blinded to the condition, heart rate and cardiac output which were randomly generated. Results were reported as linear regression slope (β).

Results

All users estimated heart rate in both conditions with reasonable accuracy ($\beta=0.86-1.01$), while cardiac output in the sepsis condition was estimated with great precision ($\beta=1.03-1.04$). Users generally overestimated the cardiac output in the healthy simulation ($\beta=1.07-1.26$) and reported greater difficulty estimating reduced cardiac output compared with higher values. Although there was some variability between users, particularly in the healthy condition ($P<0.01$), all estimations were within a clinically acceptable range.

Conclusions

In this study the USCOM provided a suitable measurement of cardiac output and heart rate when compared with our in-vitro system. It is a promising technique to assist with the identification and treatment of shock.

Keywords

USCOM, cardiac output, mock circulation loop

Introduction

Ideal treatment for shock should be based on individualized optimization of oxygen delivery based on cardiac output (CO), heart rate (HR) and stroke volume (SV). The thermodilution technique, via the pulmonary artery catheter (PAC), remains the gold standard for measuring CO in critical patients. However, it does entail many risks such as infection, arrhythmias on insertion, cardiac valve damage during prolonged use, catheter knotting, pulmonary artery rupture and pulmonary embolism [1]. The ideal system for cardiac output monitoring would be non-invasive, easy to use, reliable and compatible from patient to patient [1].

Non-invasive cardiac output monitoring is a subject of great interest to the emergency medicine community [2, 3]. While less invasive techniques (in comparison to the PAC) such as pulse contour analysis, transpulmonary thermodilution, lithium dilution and central venous oxygen saturation exist, they all require placement of a venous / arterial line [1, 4]. Oesophageal Doppler and the Fick Principle gas rebreathing techniques provide technically simple alternatives, yet could still be considered invasive and come with inherent risks [1]. The only truly non-invasive techniques for measuring CO currently consist of transthoracic electrical bioimpedance, Nexfin finger arterial pulse contour analysis, and transthoracic continuous wave Doppler ultrasound [1]. Transthoracic electrical bioimpedance is limited by interference from arrhythmias, patient movement, patient body size variation and electric conductivity between the electrodes [5]. Meanwhile, the Nexfin device lacks an initial patient-specific calibration process and has shown to be associated with error [6]. while transthoracic Doppler ultrasound has traditionally been technically challenging and limited to those with extensive formal training [7].

The ultrasonic cardiac output monitoring (USCOM) device provides a more simple technique which measures CO via a Doppler ultrasound probe applied supra-sternally [8]. The USCOM algorithms are based on data from neonates of 23 weeks gestational age to 86 year old adults, and have been specifically validated for cardiac outputs ranging from 0.12 to 18.7 l/min [9]. An algorithm incorporated into the software estimates the valve cross sectional area so that the CO can be calculated from the measured velocity across the aortic or pulmonary valve. Alternatively, a valve diameter can be manually selected if previously determined by echocardiography, or similar techniques. The ultrasound probe is positioned in the supra sternal notch to measure the blood velocity in the ascending aorta.

Validation of these non-invasive CO measurement techniques is vital to ensure their clinical use is justified. While the USCOM device has been validated against flow sensors in in-vivo models [10] and against thermodilution [8, 11-13] and echocardiography [14] techniques in humans, these techniques are associated with their own variability and imprecision [15]. Hence there is a clear need for an independent study to validate the device against calibrated flow sensors in an in-vitro setting. In addition, user variability must be evaluated to ensure clinical findings are consistent between operators. Therefore, the aim of this study was to evaluate, in-vitro, the accuracy and variability of the USCOM device with various flow rates and users. The results of this study provide a guide to clinicians on the reliability of the USCOM device when measuring various flow rates and heart rates, and how users of different clinical backgrounds adapt to the device.

Methods

Mock Circulation Loop

A mechanical representation of the heart and circulatory system, known as a mock circulation loop (MCL) (Figure I), was used for this study [16, 17]. Atrial and ventricular chambers were represented by clear, vertical polyvinyl chloride (PVC) pipes with tee sections connecting the inflow, outflow and heart chambers. Arterial and venous sections were simulated through horizontally placed PVC pipes, connected to form systemic and pulmonary circulations. Forward flow was generated through simulated ventricular systole and controlled pneumatically through a series of compressed air regulators (ITV2030-012BS5, SMC Pneumatics, Brisbane, Queensland, Australia) and solenoid valves (VT325-035DLS, SMC Pneumatics) to provide passively filled heart chambers and variable contractility, HR and systolic time. A Starling response was implemented in both left and right ventricles which actively controlled ventricular contractility based on ventricular preload [18]. Mechanical valves (flap, not cusp shaped) were used to simulate the mitral, aortic, tricuspid and pulmonary valves. Four independent, air-filled Windkessel chambers were employed to simulate systemic and pulmonary arterial and venous compliance. Variable resistance valves (VMP025.03X.71, Convair Engineering, Epping, Australia) allowed easy manipulation of systemic and pulmonary vascular resistance. The working fluid throughout this study was a water/glycerol mixture (60/40% by mass) which, at a room temperature of 22°C, demonstrated similar viscosity (3.5 mPa.s) and density (1100 kg.m⁻³) to that of blood at 37°C.

Figure I - Schematic of the MCL setup for USCOM evaluation. LA - left atrium, MV - mitral valve, LV - left ventricle, AoV - aortic valve, AoC - aortic compliance chamber, SQ – systemic flow meter, SVR - systemic vascular resistance valve, SVC - systemic venous compliance chamber, RA - right atrium, TV - tricuspid valve, RV - right ventricle, PV - pulmonary valve, PAC - pulmonary arterial compliance chamber, PQ – pulmonary flow meter, PVR - pulmonary vascular resistance valve, PVC - pulmonary venous compliance chamber, USCUM – ultrasonic cardiac output monitoring device. Arrows indicate direction of flow.

USCOM Evaluation

The MCL was initially configured to a known flow rate (5.0 l/min) through manual manipulation of left ventricular contractility and systemic vascular resistance (SVR). The continuous wave ultrasound transducer (2.2MHz, USCOM, Coffs Harbour, NSW, Australia) was placed on the 90 degree aortic bend, facing directly towards the aortic valve at a distance of approximately 16 cm from the valve. An AquaFlex ultrasound gel pad (Parker Laboratories, Fairfield, NJ, USA) of 2 mm thickness was placed between the probe and the 25 mm diameter mock aorta to improve the transmission of the ultrasonic signal. The USCOM aortic valve diameter selection was then adjusted through trial and error until MCL and USCOM flow rates matched. This process was completed for two additional flow rates (3.0 and 7.0 l/min) to ensure the selected aortic valve diameter could be used in all cases. An aortic valve of diameter 1.8 cm giving a valve area of 2.54 cm² was chosen for this study.

Left ventricular contractility and SVR were then manipulated to represent a healthy condition with a mean aortic pressure (MAP) of 90 mmHg and a mean CO between 3.5 and 8.0 l/min. CO was varied in 0.5 l/min increments primarily through manipulation of HR (50 – 95 bpm) and minor adjustments in SVR. The operator of the USCOM device then placed the probe on the mock aorta and recorded the CO and HR for ten cardiac cycles. The operator manually removed any cycles deemed to be ‘outliers’ (at their own discretion) before taking the average CO and HR from the remaining cycles. If less than six cycles remained after ‘outliers’ were removed, the test was repeated. CO and HR were then varied, randomly, until each level of CO had been evaluated once.

This process was then repeated with simulation of a sepsis condition with CO varied between 2.0 and 10.0 l/min in 1.0 l/min increments. The simulated sepsis conditions were achieved through manipulation of SVR and MCL volume, which subsequently varied MAP between 40 and 110 mmHg while HR was maintained at 80 bpm. Again, the USCOM operator removed any results deemed ‘outliers’ and recorded the CO and HR.

A summary of the haemodynamic conditions evaluated with the USCOM device in the MCL is shown in Table I. Healthy and sepsis conditions were evaluated over the complete range of flow rates in the MCL by three users. User 1 was a Consultant in Emergency Medicine with research experience and clinical application using the USCOM in over 200 patients. User 2

was a Clinical Nurse in Emergency Medicine with research experience and extensive application using the USCOM device in over 100 patients. User 3 was a Clinical Nurse in Intensive Care with extensive application using the USCOM device in an in-vivo research facility (over 50 animals). All users were blinded to the randomly generated CO and HR values and no feedback was given until the end of the entire study.

Condition	MAP	CO	HR	SVR
	<i>mmHg</i>	<i>l/min</i>	<i>bpm</i>	<i>Dyne.s.cm⁻⁵</i>
Healthy	90	3.5 – 8.0	50 – 95	1000 - 1500
Sepsis	40-110	2.0 - 10	80	700 - 1000

Table I – Haemodynamic parameters for healthy and sepsis conditions. MAP – mean aortic pressure, CO – cardiac output, HR – heart rate, SVR – systemic vascular resistance.

Data Acquisition

Haemodynamic MCL parameters were captured at 100 Hz using a dSPACE acquisition system (DS1103, dSPACE, Wixom, MI, USA). Systemic and pulmonary flow rates were recorded using magnetic flow meters (IFC010, KROHNE, Duisburg, Germany). Circulatory pressures were recorded using silicon-based transducers (PX181B-015C5V, Omega Engineering, Stamford, CT, USA).

Statistics

Statistical analysis was completed using STATA (Version 12.0, StataCorp LP, College Station, Texas, USA). Data were checked for completeness and validity and assessed for normality using the Shapiro-Wilk test. For non-normal data, general comparisons between groups (eg. control vs septic simulation) were made using two-tailed Mann-Whitney-Wilcoxon U-test or if normally distributed, a standard two-tailed t-test. Ordinary least squares regression was used to test associations between variables. In this case, regression analysis was preferred over the Bland-Altman method because the latter cannot be applied when estimating agreement between two measurement methods repeated on separate occasions, as was the case with these data. The resulting regression slopes (β) and their 95% confidence intervals were tabulated. Regression slope confidence intervals including the value 1.0 indicate perfect statistical agreement. All models were assessed for degree of fit to the data using the reported R^2 value (coefficient of determination). Model residuals were examined

for heteroscedasticity and normality. The level of significance was set at $P < 0.05$ for all analyses.

Results

Results were obtained to compare the CO estimated by the USCOM device with that measured in the MCL. Example flow rate (MCL) and velocity (USCOM) traces at a CO of 5.0 l/min are shown in Figure II. As expected, the USCOM velocity trace was more pulsatile in comparison to the MCL flow rate trace, where instantaneous flow rate generally oscillated between approximately 4.7 and 5.3 l/min. This can be attributed to the varied placement of each sensor, with the USCOM directed close to the aortic valve while the MCL flow sensor was placed downstream of a compliance chamber. The USCOM velocity trace, which precisely simulated the 5.0 l/min CO in this case, generally showed consistent results over the ten second measurement period. However, some of the velocity profiles produced unexpected results, such as the example in Figure II, and were removed prior to calculating cardiac output. This was particularly noticeable at the lower flow rates (ie. CO<4.0 l/min) evaluated in this study.

Figure II – Example flow rate / flow velocity traces produced by the mock circulation loop (top) and the ultrasonic cardiac output monitoring device (USCOM) (bottom) with mean flow rates of 5.0 L/min. Note the last cycle was removed from the USCOM trace as an outlier, leaving nine remaining cycles to determine cardiac output. CO – instantaneous cardiac output, MCO – mean cardiac output.

Graphical comparisons between the estimated USCOM CO and HR with those measured in the MCL for healthy and sepsis conditions are displayed in Figure III while regression slopes for individual users are presented in Table II. As both HR and CO data were significantly different for the two simulated conditions (control vs septic) ($P < 0.01$ in each case), data from the two simulations were analysed separately.

Figure III – Data and line of identity (solid line) for the (i) cardiac output comparison in the healthy condition, (ii) heart rate comparison in the healthy condition and (iii) cardiac output comparison in the sepsis condition between the mock circulation loop and USCOP device for users 1 (left), 2 (middle) and 3 (right). USCOP CO – estimated cardiac output by the USCOP device, USCOP HR – estimated heart rate by the USCOP device, MCL CO – cardiac output measured by the mock circulation loop, MCL HR – heart rate measured by the mock circulation loop.

Cardiac output	User 1	User 2	User 3
Healthy	1.26 (0.82, 1.69)	1.44 (1.25, 1.63)	1.07 (0.91, 1.23)
Sepsis	1.04 (0.91, 1.16)	1.04 (0.89, 1.19)	1.03 (0.86, 1.20)
Heart rate			
Healthy*	0.86 (0.50, 1.23)	Perfect fit	1.01 (0.87, 1.15)
Sepsis	-	-	-

Table II – Regression slopes for individual users comparing mock circulation loop and USCOP data in healthy and sepsis conditions. In each model, $R^2 > 0.95$ and the residuals were homoscedastic and normally distributed. *Note that heart rate comparisons in the sepsis condition were not assessed as heart rate was fixed at 80 bpm.

In the healthy condition, all users generally overestimated CO ($\beta = 1.26, 1.44$ and 1.07 for users 1, 2 and 3 respectively), particularly at increased flow rates (Figure III(i)). For instance, at a CO of 4.0 l/min, users 1, 2 and 3 estimated CO at 3.7, 4.1 and 4.1 l/min respectively with the USCOM device. However when CO was increased to 8.0 l/min, the same users estimated CO at 9.4, 9.5 and 8.5 l/min. While this result indicates improved USCOM performance at lower CO, all users commented on increased difficulty to obtain ten seconds of consistent data at lower CO. HR measurements with the USCOM were, however, estimated with great accuracy ($\beta = 0.86, 1.00$ and 1.01 for users 1, 2 and 3 respectively). This was evident at high and low HR, with very few incorrect readings throughout the experiment (Figure III(ii)).

During the sepsis condition, users generally estimated CO with considerable precision ($\beta = 1.04, 1.04$ and 1.03 for users 1, 2 and 3 respectively). Users 1 and 3 tended to slightly overestimate CO, while user 2 generally underestimated this value. For instance, at a CO of 5.0 l/min, users 1 and 3 estimated CO at 5.7 and 5.6 l/min respectively while the estimation of user 2 was 4.7 l/min. Again, all users commented on the increased difficulty to obtain consistent CO estimation at lower flow rates (Figure III(iii)).

Comparative statistics between users (Table III) demonstrated no statistically significant difference in performance between users, except in the case of user 3 who predicted CO in the healthy simulation with high precision ($P < 0.01$). In this case, users 1 and 2 significantly overestimated CO. Users 1 and 3 tended to occasionally overestimate HR, though the result in each case was not significantly different from perfect prediction. Meanwhile, user 2 was the only candidate to predict HR with absolute precision.

Simulation	Cardiac output	Heart rate
Healthy	$P < 0.01$	$P = 0.17$
Sepsis	$P = 0.12$	$P = 0.37$

Table III – Comparative statistics between users for heart rate and cardiac output in healthy and sepsis simulations.

Discussion

Volume expansion is frequently used in critically ill patients [19]. This is often initiated with little objective evidence of circulatory status and may be given based on the potentially incorrect assumption that patients with circulatory insufficiency will benefit from fluid administration. Data indicates that 28 to 60% of fluid interventions in critically ill patients are ineffective as measured by increasing SV or CO [19]. In fact, fluid boluses have been shown to significantly increase early mortality in critically ill children with impaired perfusion [20]. Therefore, the accurate estimation of CO is vital in the emergency setting, with non-invasive and reliable CO monitors providing particular benefit. The reliability of these devices must be assessed in-vitro, in-vivo and through extensive human studies prior to clinical acceptance. The USCOM device is a non-invasive technique of measuring CO, HR and SV. The device allows beat to beat measurement of these parameters and, therefore, produces personalised, physiologically based fluid management protocols which may contribute to the rational and objective guideline of circulatory management. Because of its reported accuracy, the USCOM monitor is useful for diagnosing circulatory abnormalities and guiding the standard interventions of fluid inotropes and vaso-active therapies [21]. However, it may be unsuitable for patients with significant valvular stenosis [1].

Others have evaluated the accuracy of similar CO measurement techniques, such as oesophageal Doppler, which has shown an 86% clinical agreement with PAC thermodilution methods when measuring changes in CO. However, only a 52% agreement was achieved when measuring absolute cardiac output values [22]. The USCOM, however, has shown varied results [3] with some reporting excellent correlation with PAC thermodilution methods [23-25], and others reporting poor correlation [26]. Tan et al. [8], who compared the USCOM and PAC in 22 intensive care patients, reported that the correlation between the two techniques worsened as CO was increased. In this study, the USCOM device tended to underestimate CO compared to PAC at high flow rates, while the authors concluded that low CO states also required further validation. In our study, we also noted difficulty in obtaining consistent measurements at low and high CO; however users tended to overestimate CO at higher flow rates. In fact, the frequency of failed measurement attempts (ie. less than six consistent beats per 10 cardiac cycles) was noticeably higher in cases of low CO. While HR was generally estimated with very high precision, there were some instances of measurement errors and, therefore, HR estimation with the USCOM device should not be treated as a

definitive measurement. Nevertheless, the results achieved in our study generally showed high statistical agreement between the CO and HR estimated by the USCOM and that measured by the MCL.

Our study also showed a generally good correlation between users, except in the case of the healthy simulation where two users significantly overestimated CO while the other user demonstrated greater precision. This was particularly promising due to the varied nature and level of training of our users (ie. emergency medicine consultant / clinical nurse in emergency medicine / in-vivo research nurse), and demonstrated the ease with which users of different backgrounds can become familiar with the USCOM. Nevertheless, this study would benefit from a larger sample size of users with various backgrounds. Corley et al. [7] reported the time to optimal USCOM signal acquisition was reduced by over 50% after just 30 examinations with non-echocardiographically trained users. Meanwhile, Dey et al. [27] reported that emergency department physicians with no prior ultrasound experience could be trained to obtain reliable CO measurements via the USCOM over the course of just 20 patient assessments. This study reported an average inter-assessor difference in CO of just 0.2 l/min and inter-assessor correlation (R^2) of 0.96, similar to the value reported by Nguyen et al. [28] ($R^2 = 0.87$). Although our results also demonstrated good correlation between users, the average inter-assessor difference in CO was slightly larger than reported previously at 0.67 and 0.61 l/min for the healthy and sepsis conditions respectively.

While our study compared the USCOM device with accurate flow measurement systems in-vitro, there are some obvious limitations. Firstly, while our in-vitro test rig produces an excellent representation of circulatory haemodynamics, the aortic valve is simulated by a mechanical swing check valve rather than a native trileaflet valve which may alter the velocity profile detected by the ultrasound probe. Meanwhile, the valve diameter was manually selected in our study based on a series of calibrations, thus eliminating the potentially inaccurate nomogram typically used in the USCOM to estimate aortic valve size based on patient characteristics [1]. The design of our in-vitro circuit allowed almost perfect alignment of the ultrasound beam with the blood flow, thus eliminating the potential misalignment factor in humans. Future studies may benefit from an improved, and enclosed / blinded representation of the aorta and aortic valve while a greater range of HR and CO should be evaluated. Although the 90 degree bend and the distance from the USCOM probe

to the simulated aortic valve (16cm) in-vitro may not represent the depth from the aorta to the suprasternal notch, the MCL still proved an excellent tool for evaluation of the USCOM device, which displayed high correlation with accurate flow sensors between various users. The MCL, constructed of PVC which has a similar acoustic impedance to water [29], should not have had a significant effect on the Doppler signal quality. The use of a MCL as a training tool for USCOM should be explored, as it provides an ideal platform to become familiar with the device, sensor placement and selecting / removing unsuitable data to achieve reliable CO and HR estimations.

In conclusion, this in-vitro evaluation of the USCOM device demonstrated strong correlation between the non-invasive estimation of CO and HR with those measured in a MCL. While HR was measured with great accuracy in all cases; users tended to overestimate CO at high flow rates and reported difficulty in recording consistent measurements at low flow rates. There was also a good correlation between users with different backgrounds and experience levels with the USCOM. Therefore, the USCOM is a promising technique for the estimation of CO and HR in the clinical setting.

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