Accuracy of the ultrasonic cardiac output monitor in healthy term neonates during postnatal circulatory adaptation

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Keywords: cardiac output measurement; echocardiography; neonatal hemodynamics; ultrasonic cardiac output monitor; point of care ultrasound

Background  Echocardiography is regarded as a gold standard for measuring hemodynamic values. The ultrasonic cardiac output monitor (USCOM) is a new method for measuring hemodynamics and could provide non-invasive point of care guidance. So far, there are no published USCOM reference values for neonates, nor has USCOM’s accuracy been established in this population. We aimed to determine the accuracy and clinical utility of the USCOM in healthy neonates relative to published echocardiographic data, to establish normal hemodynamic parameters that it measures, and to assess the possible role of USCOM as an alternative to echocardiography as a trend monitor.

Methods  Right and left heart hemodynamics of 90 normal neonates were measured during circulatory adaptation over the first three days of life using the USCOM and automated oscillotonometry.

Results  Heart rate showed a significant decline from days one to three, from 126 to 120 ($P<0.001$). Systolic, diastolic and mean arterial pressures all increased significantly from 66 to 71 mmHg, 33 to 38 mmHg and 44 to 49 mmHg, respectively ($P<0.001$ in each case). Right ventricular cardiac index (RV-CI) showed no change with a mean of 5.07 L·min$^{-1}$·m$^{-2}$. Left ventricular cardiac index (LV-CI) declined from 3.43 to 3.00 L·min$^{-1}$·m$^{-2}$ ($P<0.001$). RV-CI exceeded LV-CI on all three days by a mean of 61%. The systemic vascular resistance index (SVRI), based on LV-CI, increased significantly over the three days from 1083 to 1403 dyne·sec·cm$^{-5}$·m$^{-2}$ ($P<0.001$).

Conclusions  Normal neonatal hemodynamic values, as indicated by USCOM, were established. LV-CI measurement showed excellent agreement with published echocardiographic studies. RV-CI was constant and exceeded LV-CI for all three days of this study. It may be falsely high due to flow velocity measurement errors arising from the pulmonary branch arteries, and may represent a limitation of the USCOM method. The progressive rise of arterial pressure and SVRI despite a declining LV-CI may indicate functional closure of the ductus arteriosus, with the greatest change occurring within the first 24 hours. Evidence of closure of the foramen ovale was not observed.

The measurement of hemodynamics has become widespread in the adult population. This is largely due to the introduction of non- and minimally invasive methods of hemodynamic assessment. The ultrasonic cardiac output monitor (USCOM Ltd., Sydney, Australia) has permitted study of normal subjects older than one month old. While neonatal physiology is complex, circulatory dysfunction is still treated by manipulation of preload, afterload, inotropy and other parameters. A non-invasive method which provides point of care guidance for therapy would be attractive to clinicians. However, there are no published USCOM reference values for neonates, nor has USCOM’s accuracy been established in this population.

Invasive hemodynamic measurements are unjustifiable in normal infants. Echocardiography has predominated in neonatal hemodynamic research, but demands considerable technical competence and training, limiting its use by clinicians. The USCOM is a continuous wave Doppler (CWD) based monitor which can measure left and right ventricular outputs from the aortic and pulmonary outflow tracts independently, and could theoretically identify any significant intra- or extra-cardiac shunt. Competence with the USCOM can be achieved in just days of practice with several studies showing good inter- and intra-observer reproducibility. We studied the USCOM in neonates to assess its general accuracy, establish normal hemodynamic values as indicated by this device and to assess its potential role as a trend monitor by determining whether it could identify the normal circulatory adaptations that occur in response to closure of the

DOI: 10.3760/cma.j.issn.0366-6999.2011.15.008
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foramen ovale and the ductus arteriosus.\textsuperscript{8,9,13}

METHODS

Following Institutional Review Board of Guangdong General Hospital approval and formal informed parental consent, ninety singleton full-term healthy neonates were enrolled in the study. Infants with cardiopulmonary disease, meconium-stained amniotic fluid, intrauterine infection or birth asphyxia were excluded, as were maternal hypertension, pre-eclampsia, cardiopulmonary disease or any history of vaso-active medication.

Hemodynamic measurements

The USCOM (Uscom Ltd., Sydney, Australia) calculates cross-sectional area (CSA) of the aortic and pulmonary outflow tracts based on validated nomograms derived from height and weight.\textsuperscript{14} These are proprietary, but similar to those described by Nidorf et al.\textsuperscript{15} The predicted valve CSA on the first day was used throughout the study as these would show negligible change over the study period. Blood velocities were measured from the suprasternal notch for the aortic valve and the left parasternal window for the pulmonary valve. The velocity-time profile is automatically traced and integrated to derive the velocity-time integral (vti). Multiplication of the vti by the CSA gives stroke volume (SV). Cardiac output (CO) is calculated using the formula of Dubois et al,\textsuperscript{16} allowing indexed values to be calculated. Systemic vascular resistance (SVR) is calculated from CO and mean arterial pressure (MAP) using the standard formula of SVR=MAP × 80/CO. The USCOM also directly measures peak ejection velocity (Vpk), stroke distance (SD) and systolic flow time (FT), and calculates systemic vascular resistance index (SVRI), cardiac index (CI), stroke volume index (SVI), minute distance (MD) and corrected flow time (FTc) from BSA, SD and HR.

Systolic, diastolic and mean blood pressure (BPsys, BPdia, and Bpmean) were measured using a DINAMAP\textsuperscript{\textregistered} Procare 100 (GE Medical Systems) with neonatal arm cuff. Measurements of blood pressure were made simultaneously with the USCOM measurements and the mean taken as the reference pressure values for that observation.

Timing of measurements

Measurements were made when the infants were quiet, warm and relaxed, and at least 30 minutes after feeding. Examination was performed as nearly as possible at 24-hour intervals for the first three days. Five readings were taken from each of the pulmonary and aortic sites in random order and the results averaged for each site. This would result in an approximately 95% likelihood of observing a difference of under 5% between sets of readings.\textsuperscript{17} To eliminate inter-observer variability, all observations were performed by the same neonatologist who had both completed the recommended USCOM training, and also had considerable experience with USCOM examinations in infants. All USCOM examinations were stored on the hard disk of the monitor and as a hard copy. Examination quality was graded on a twelve point scale with scores of 8/12 or higher being accepted.\textsuperscript{18} For quality control, one third of the 900 stored examinations, chosen at random, were reviewed by a practitioner (BES) with experience of several thousand USCOM examinations.

Subjects positioning

All subjects were examined in the supine or slightly (10°) head-up position. The pulmonary outflow was accessed via the left parasternal approach using the second, third or fourth intercostal space according to the optimum ejection signal quality at each site. The standard 2.2 MHz transducer was used for all measurements.

Statistical analysis

Data were transferred to a Microsoft Excel\textsuperscript{\textregistered} spreadsheet and the Statistical Package for Social Sciences (SPSS) Version 16.0. Data integrity was checked against the original data sources. Normal measurement data were shown as mean and standard deviation (SD). Analysis comprised frequency distribution plotting, Pearson’s coefficient of skewness, independent sample t test, Levene’s test for equality of variances, linear regression and analysis of variance (ANOVA). Statistical significance was taken as $P<0.05$.

RESULTS

All data except sex showed a normal distribution on frequency plotting with Pearson coefficients of skewness less than ± 0.6 in all cases. There were 49 males (54%) and 41 females (46%). The predominance of males over females was not significant ($P=0.079$). Mean gestational age was (38.90±1.00) weeks. Mean birth weight was (3.18±0.36) kg. Crown-heel length was (49.90±1.60) cm. Forty infants (44.4%) were born by normal vaginal delivery, 49 (54.4%) by cesarean section and one (1.2%) by forceps delivery, reflecting the tertiary referral centre nature of the hospital practices in China. Apgar scores were recorded as 9 or 10 at one minute and as 10 at 5 minutes, in all subjects.

Measurements were made on the first day between 1.9 and 23 hours after birth, (mean 7.4 hours); 24 in the first four hours (mean 3.10±0.58) hours, 42 between 4 and 8 hours (mean 5.30±1.13) hours and 24 between 8 and 23 hours (mean 15.30±5.42) hours. Measurements on subsequent days were made as close as possible to 24 hours after the initial measurement (mean 23.60±1.81) hours.

As all the scalar data showed a normal distribution, we computed a normal range for the data, defined as mean ± 1.96 standard deviations (SD), which encompassed 95% of the total observations. The values for each are shown
in Table 1. SVR and SVRI were calculated from BPmean: systemic vascular resistance; SVRI: systemic vascular resistance index. The values for these measurements in Table 1 are therefore applicable to days 2 and 3.

There were significant changes in all the left heart values and in the right heart values for Vpk, Pmn, Vti, FT, and FTc as shown in Table 2.
Figure. Changes in hemodynamic parameters on day one. Age in hours, 0−4, 4−8 and >8 means time in hours from birth to hemodynamic measurement. For 0−4 hours (n=24), for 4−8 hours (n=42), for >8 hours (n=24). BPmean: mean blood pressure gradient; CO: cardiac output; CI: cardiac index; SVRI: systemic vascular resistance index. It shows increased BPmean despite falling cardiac output. Together with increased SVRI this may indicate PDA constriction. n/s: not significant.

HR showed a significant fall over three days, whilst BPsys, BPdia, BPmean, SVR and SVRI all increased significantly (P<0.001 in each case), most of the change occurred between days one and two. Only BPsys showed a further significant increase between days two and three (P=0.027). Left heart SV and SVI showed significant reductions over three days from 6.0 to 5.5 ml and 27.5 to 26.5 ml/m² respectively (P=0.033 and 0.011). LV-CO and CI decreased from 0.23 to 0.20 L·kg⁻¹·min⁻¹ and 3.43 to 3.00 L·m⁻²·min⁻¹ respectively (P<0.001 for both). In contrast, right ventricular SV, SVI, CO and CI showed no significant change, as shown in Table 2.

The data from day one were split into three groups where measurements were made between zero and four hours, four to eight hours and over eight hours. Significant changes were found for HR, BPmean, CO, CI and SVRI between groups one and two, and between groups two and three as shown in Figure.

Peak velocity reduced significantly for both the pulmonary and aortic valves. For the pulmonary valve the mean±SD Vpk was (1.38±0.15) m/s for 0−4 hours, (1.31±0.18) m/s for 4 to 8 hours and (1.27±0.16) m/s for 8 to 24 hours, P<0.01 in each case. The corresponding figures for the aortic valve were (1.19±0.18) m/s, (1.14±0.16) m/s and (1.08±0.17) m/s, P<0.01 in each case.

DISCUSSION

Our primary goal was to determine the accuracy of the USCOM relative to published echocardiographic data and to establish normal hemodynamic values in neonates as indicated by this instrument. The normal distribution of our data provides both basic reference values for the USCOM, and allowed identification of a normal range of values for this population with this monitor.

Pulsed or continuous wave Doppler

While Doppler-derived hemodynamic values for neonates have been presented before, these studies typically used pulsed-wave Doppler (PWD), not stand alone continuous wave Doppler (CWD) transducers and modal Doppler flow profile tracing methodologies, which may deliver greater accuracy. PWD can underestimate SV and CO by up to 22%.17 The USCOM device adheres to the guidelines of the American Society of Echocardiography,11 which theoretically should optimize reliability and reproducibility, but could also result in higher values for CO and SV than previously reported.

Left ventricular cardiac output (LV-CO)

Mean LV-CO on days 1 and 3 at 230 ml·kg⁻¹·min⁻¹ and 200 ml·kg⁻¹·min⁻¹ correlates well with published echocardiographic studies. Day one LV-CO has been reported to be 235−243 ml·kg⁻¹·min⁻¹ and 187 ml·kg⁻¹·min⁻¹ on day three.8 A further study,16 using both PWD and CWD, found day one LV-CO was 230 ml·kg⁻¹·min⁻¹. A PWD study via the suprasternal notch20 found LV-CO was 236 ml·kg⁻¹·min⁻¹. Other published values are 241 ml·kg⁻¹·min⁻¹ and 240 ml·kg⁻¹·min⁻¹.21,22 The latter group reported the day three value as 190 ml·kg⁻¹·min⁻¹, and attributed this to constriction of the patent ductus arteriosus (PDA). The LV-CO findings of our study are therefore consistent with the published data.

Right ventricular cardiac output (RV-CO)

Mean day one RV-CO was 340 ml·kg⁻¹·min⁻¹, and did not change significantly during the study. There is a paucity
of echocardiographic data for RV-CO in normal neonates and, unsurprisingly, little pulmonary artery catheter data.23,24 RV-CO should be similar to LV-CO in the absence of a significant shunt, but the difference between RV-CO and LV-CO of 110 ml·kg⁻¹·min⁻¹ in this study seems excessively high. Interatrial shunt contributes only 10%–15% of the RV volume load, or 35–50 ml for our subjects. However, one study,25 comparing duplex Doppler against USCOM, found mean RV-CO was 319 ml·kg⁻¹·min⁻¹ for echocardiography against 327 ml·kg⁻¹·min⁻¹ for USCOM, a difference of less than 3%. A study in children 2 to 122 days old showed LV-CO was 233 ml·kg⁻¹·min⁻¹ for USCOM and 251 ml·kg⁻¹·min⁻¹ for echocardiography, a 7% difference.26 The figures for RV-CO were 338 and 279 ml·kg⁻¹·min⁻¹, a 21% difference. Both showed RV-CO to be greater than LV-CO with USCOM showing higher values than echocardiography.

Although evidence suggests CWD is superior to PWD, CWD has one significant disadvantage. With PWD, a specific discrete sample volume is interrogated which can be positioned anywhere within the ventricular outflow tract. With CWD all velocities within the insonation field are detected, be they subvalvular, valvular or supravalvular.27 In neonates it is possible to detect the flow velocities of the left and right pulmonary branch artery (PBA). The flow velocity in the PBAs can exceed that in the pulmonary artery by a factor of 1.27.28 This could result in an apparent RV-CO of 340 ml·kg⁻¹·min⁻¹ when the true value is 285 ml·kg⁻¹·min⁻¹. Further, while PDA persists, there is an extra blood volume entering the pulmonary artery distal to the pulmonary valve which increases the flow velocity in the PBAs but not the transvalvular velocity. The day one pulmonary Vpk values support this, with Vpk declining from 1.38 to 1.31 to 1.27 m/s in the three groups.

**Outflow tract diameter (OTD)**

An error in estimation of the pulmonary OTD by either USCOM or echocardiography of less than 1 mm produces a volume calculation error of over 50 ml·kg⁻¹·min⁻¹. Measurement of the OTD is the largest single source of error in Doppler volume measurements.17 While CWD cannot overestimate flow velocities, it can underestimate them if the insonation angle relative to the line of flow increases beyond about 20°.29 This may explain the lower RV-CO of 282 ml·kg⁻¹·min⁻¹ found by Meyer et al.13 We therefore recommend that RV-CO values from the USCOM be interpreted with some caution.

Our study identifies normal values for USCOM. Others26 have also found no change in RV-CO over the first 3–4 days, so changes or deviations from these values will still be of clinical importance. While absolute values are questionable, use of USCOM as a trend monitor on the right heart appears justifiable.

**Closure of patent ductus arteriosus (PDA)**

LV-CO fell by 76 ml/min over the first day, yet BPsys, BPdia, BPmean and SVRI increased over the same period. This may represent closure of the PDA. One study found that with a PDA, flow fell from 62 ml·kg⁻¹·min⁻¹ at 2 hours old to 14 ml·kg⁻¹·min⁻¹ at 12 hours.22 They observed similar changes in LV-CO to our study, concluding this was due to ductal closure. Similar findings have been reported by others.9–20,25 In a study of therapeutic closure,20 LV-CO fell by 91 ml·kg⁻¹·min⁻¹ after closure. All the cited studies agree that PDA closes in the first 24 hours in the majority of subjects with closure becoming apparent in the 12–24 hours period. However, ductal constriction has been observed as early as 4 hours in 80% of normal neonates.20 Our data fits with this view, with a significant rise in BPmean and SVRI occurring between the 4–8 hours and 8–24 hours periods while CO, CI, HR and SV showed no change.

Closure of the ductus arteriosus reportedly results in decreased left ventricular preload and increased SVRI leading to decreased SV and CO.31,32 Our day1 results showed no evidence of this. The reduction in LV-CO in the first eight hours resulted from reduced HR. This could be due to either an overall reduction in cardiac preload, or equally, closure of the PDA increasing BP leading to reduced sympathetic drive and slowing of HR. However, USCOM tracked the hemodynamic changes during this period, supporting its use as a trend monitor.

**Patent foramen ovale (PFO)**

Textbooks state closure of the PFO occurs soon after birth. The evidence does not support this view. One study33 showed 47% of neonates had PFO on days four and five. Others found PFO in 82% of normal neonates at a mean of 57 hours. It is of course possible that functional closure of the PFO could occur very soon after birth, with minimal change thereafter. Against this background it is unsurprising that USCOM could not identify PFO closure.

In conclusion, the normal range for USCOM values in the neonatal population has been established. USCOM results were consistent with published echocardiographic data as regards LV-CO. USCOM RV-CO should be interpreted with caution. The trends resulting from PDA closure were identified. PFO closure was not identified. Our study, in a challenging study group, suggests that USCOM is a reasonably accurate and practical alternative to echocardiography as a screening tool and treatment monitor.

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(Received February 12, 2011) Edited by CHEN Li-min