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PUBTEXTO

Minimally Invasive Technique for Direct Measurement of Neonatal Hemodynamic Utilizing the COstatus Monitor

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Abstract

Background: The objective of this study is to establish feasibility of directly measuring cardiac output in a neonatal population using the COstatus Monitor (Transonic Systems, Ithaca, NY USA).

Methods: The COstatus Monitor utilizes an extracorporeal loop attached to arterial and venous lines to measure cardiac output using ultrasound dilution. Injections of 1mL/kg of body temperature saline were injected into the loop. Up to two measurement sessions were performed daily for a maximum of four days for each patient.

Results: Cardiac output was measured 54 times in 12 neonates with no adverse events. Infants ranged in weight (0.72 to 3.74 kg), gestational age (24 to 41.3 weeks), and day of life (1 to 13 days). The mean cardiac output was 0.43 L/min with a mean cardiac index of 197 mL/kg/min.

Conclusions: Direct measurement of cardiac output by the COstatus monitor is feasible in a neonatal population. Minimal variance was exhibited for all parameters in consecutive measurements.

Keywords: Cardiac output; Neonatal; COstatus

Introduction

Knowledge of cardiac output is a valuable tool in the treatment of critically ill patients. Often in the Neonatal Intensive Care Unit (NICU) setting, cardiac output is indirectly measured using blood pressure, heart rate, urine output, and other indirect markers. Indirect measurement, however, can often be inaccurate in the pediatric population [1]. Direct calculation of cardiac output in pediatric patients has typically required respiratory mass spectrometry or invasive catherization [2-4]. These methods involve considerable risk or are often not feasible in the neonatal population. Less invasive methods utilizing Doppler or bioimpedance exist but are also inaccurate [5-7]. The COstatus Monitor (Transonic Systems, Ithaca, NY USA) utilizes ultrasound dilution for measurement of cardiac output and is suitable for use in the neonatal population, requiring only the presence of arterial and central venous access, which is prevalent among many neonates admitted to the NICU [8]. The COstatus Monitor's safety [9], and accuracy was extensively validated in neonatal animal models [10-12], and has been validated in various pediatric populations [13-16]. However, no neonatal cardiac output study was performed.

Purpose

The purpose of this pilot study was to establish the feasibility of directly measuring cardiac output and other hemodynamic parameters in a neonatal population using the COstatus Monitor.

Materials and Methods

Ultrasound Dilution

The COstatus Monitor utilizes the technique of ultrasound dilution (UD). UD was initially used in hemodialysis starting in 1995 and has been used extensively in this field [17]. The underlying concept is that the ultrasound velocity of blood decreases with an injection of saline, producing a dilution curve. The ultrasound velocity of blood is 1580m/s while that of normal saline is 1533m/s. The COstatus monitor utilizes a system of an extracorporeal loop (arteriovenous AV loop) primed with a standard NICU flush (1:1 heparinized normal saline), or the patient's blood, which is connected to the arterial and venous catheters. The venous line of the AV loop is connected to the umbilical venous catheter or peripherally inserted central catheter line of the patient, while the arterial line is connected to the umbilical arterial catheter or peripheral arterial line of the patient. On the AV loop are two clamp-on flow/dilution sensors and a small pump that circulates blood at 9mL/min. In a measurement session, typically two injections of 1mL/kg body temperature isotonic solution are injected into the venous loop, allowing for two measurements of hemodynamic parameters: cardiac output (CO), cardiac index (CI), active circulating volume index (ACVI), central blood volume index (CBVI), and systemic vascular resistance index (SVRI) (Figure 1).

Study population

We recruited neonates from the 58 bed Level IV Neonatal

Intensive Care Unit at Children's National Medical Center. Any infant with central venous and arterial access was invited to participate in this study. Infants were excluded if appropriate vascular access was not in place, or if access was being used for continuous life-saving medications that could not be temporarily paused.

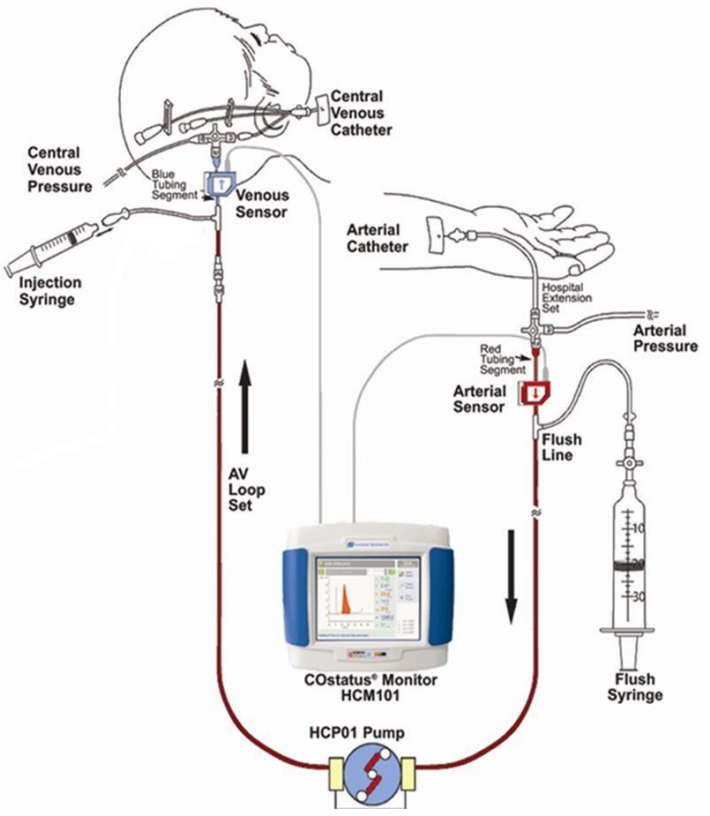


Figure 1: *Schematic presentation of COstatus monitor attached to an infant.*

Study design

After Institutional Review Board approval, enrolled infants underwent up to two measurement sessions per day for up to four days. Each measurement session consisted of two to three readings with the COstatus Monitor. Measurements were stopped prior to four days if lines needed to be changed per nursing regulations or if central vascular access was no longer medically indicated. Data was collected for CO, CI, ACVI, CBVI, and SVRI. In addition to hemodynamic parameters, we collected demographic data for gestational age, postmenstrual age, chronological age, medications, diagnoses, and respiratory support. Infants were closely monitored for any complications, including central line occlusion, malfunction, loss, or infection.

Data analysis

Variance was calculated for each hemodynamic marker by computing the mean and standard deviation (SD) between measurements taken in one session. We then quantified reproducibility as the coefficient of variation (SD/mean*100%) of consecutive measurements.

Results

A 54 measurements of cardiac hemodynamics were performed in 12 neonates. Weight ranged from 720g to 3740g with gestational ages between 24 and 41.3 weeks. Chronological age ranged from 1 to 13 days. All infants had an umbilical venous catheter for central venous access. Arterial access was via umbilical arterial catheter or peripheral arterial line. There were no incidences of line malfunction, loss, clot, or infection. The mean cardiac output calculated for this cohort was 0.43L/min (SD 0.26). The mean cardiac index was 197mL/kg/min (SD 72). Cardiac output increased with gestational age in a linear fashion. A best-fit line and R- squared value were calculated for this association (Figure 2). Cardiac index, however, showed little change with increasing maturity. A best-fit line estimates a cardiac index of approximately 200mL/kg/min, independent of gestational age. (Figure 2).

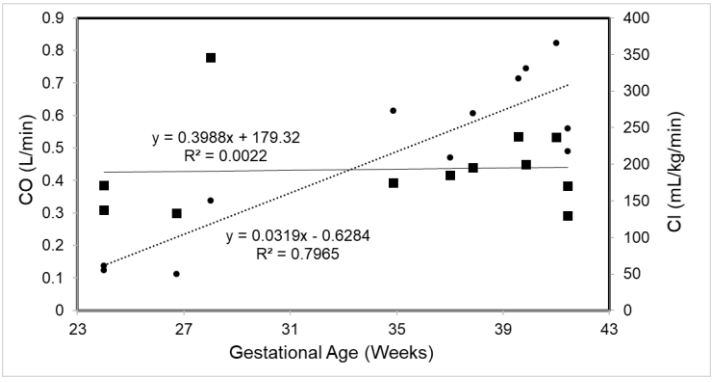


Figure 2: *Cardiac output (circles, dotted line) and cardiac index (squares, solid line) as functions of gestational age.*

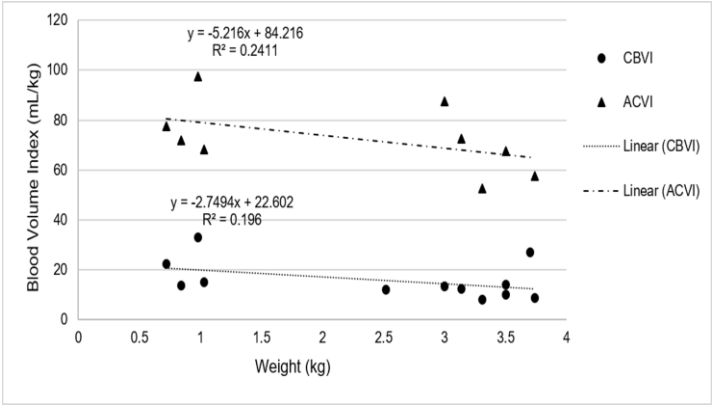


Figure 3: *Central blood volume (circles, dotted line) and active circulation volume (triangles, solid line) indices as functions of weight.*

In contrast, indices for both active circulating volume and central blood volume had negative trends with increasing weight (Figure 3). Two of the study patients were enrolled while undergoing therapeutic hypothermia protocol for Hypoxic-Ischemic Encephalopathy (HIE). Measurements were taken while hypothermic and after rewarming was completed. During the hypothermic state, the measured cardiac output and cardiac index was nearly half of the normothermic state (Figure 4), with similar

findings in the second patient. The results of three days of hemodynamic monitoring in a 1.03 kg patient are presented in (Figure 5). (Table 1) presents patient data and results of shunt evaluations by COstatus. (Table 2) presents statistical data including reproducibility of consecutive measurements of COstatus hemodynamic parameters.

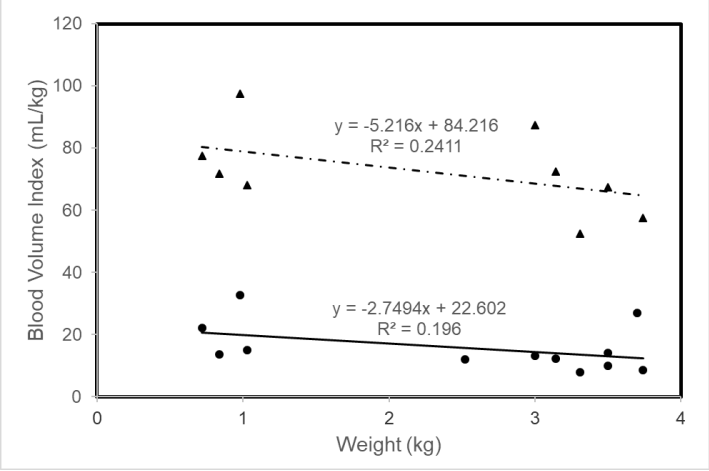
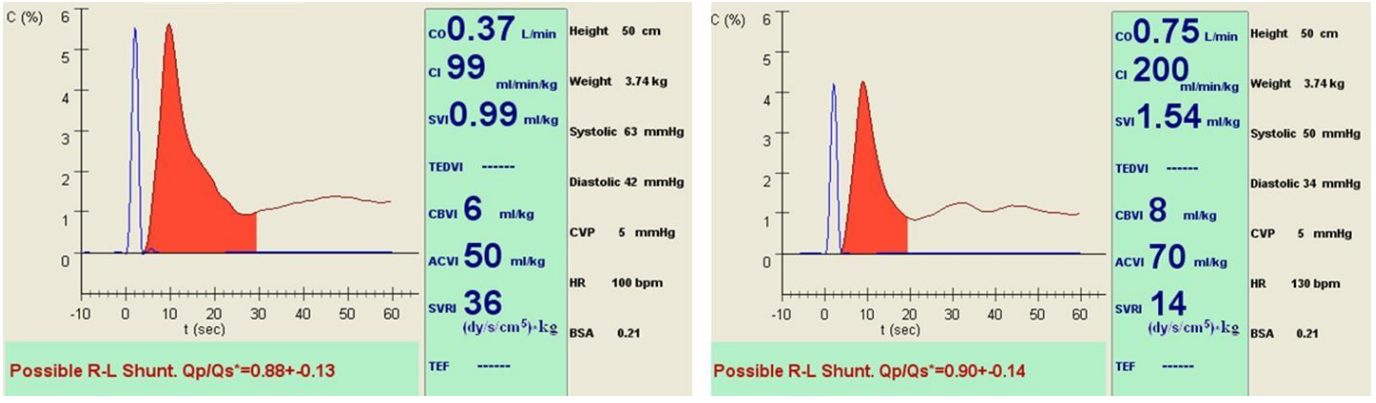


Figure 4: *COstatus measurement during and after therapeutic hypothermia for HIE.*



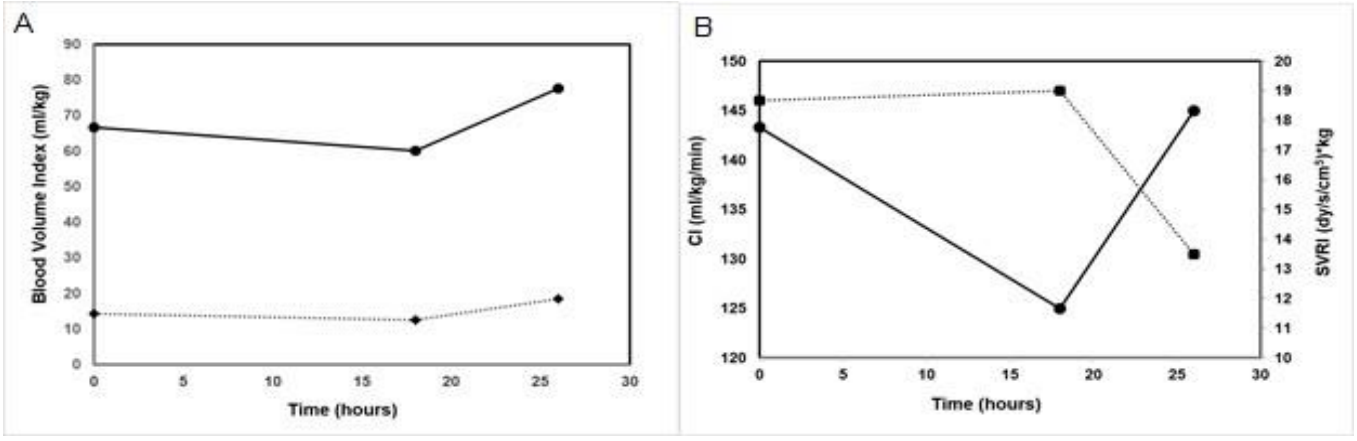


Figure 5: *a.) Central Blood Volume Index (A - dotted line), Active Circulation Volume Index (A - solid line), Cardiac Index (B - solid line), and Systemic Vascular Resistance Index (B - dotted line) measurements over a 3-day period in 1.03 kg patient.*

Table 1: *Patient data including shunt values.*

pt. #	Diagnosis	Weight (kg)	Gestational Age (weeks)	Shunt, by Dilution	Qp/Qs Range

1	Persistent Pulmonary Hypertension Respiratory Distress Syndrome	3.5	34	Right to left	0.9
2	Right Heart Failure, Premature Closure of Ductus Arteriosus in utero Respiratory Distress Syndrome	3.13	37	Right to left	0.9
3	Respiratory Distress Syndrome	0.98	28	Bidirectional	0.79 ; 3
4	Respiratory Distress Syndrome	0.72	24	Left to right	1.3 - 1.9
5	Respiratory Distress Syndrome	1.03	24	Left to right	1.4- 1.8
6	Respiratory Distress Syndrome	0.84	26	Bidirectional	0.67 ; 3
7	Mild Hypoxic-Ischemic Encephalopathy Respiratory Distress Syndrome	3.7	41	Left to right	1.7
8	Mild Hypoxic-Ischemic Encephalopathy Persistent Pulmonary Hypertension, s/p ECMO Respiratory Distress Syndrome	3	39	No shunt*	n/a
9	Moderate Hypoxic-Ischemic Encephalopathy, s/p Therapeutic Hypothermia Persistent Pulmonary Hypertension, s/p ECMO Respiratory Distress Syndrome	3.5	41	No shunt*	n/a
10	Moderate Hypoxic-Ischemic Encephalopathy, Therapeutic Hypothermia Respiratory Distress Syndrome	3.74	41	Right to left	0.88-0.9
11	Moderate Hypoxic-Ischemic Encephalopathy, Therapeutic Hypothermia Respiratory Distress Syndrome	3.31	42	Right to left	0.88-0.9
12	Respiratory Distress Syndrome Multiple Congenital Anomalies, No Syndrome Identified	2.52	37	No shunt*	n/a

Table 2: *Mean, SD, range and reproducibility of hemodynamic parameters measured by the COstatus Monitor.*

Parameters	**CO, (L/min)**	**CI (mL/min/kg)**	**CBVI, (mL/kg)**	**ACVI (mL/kg)**	**SVRI, (dy/s/cm^5)*kg**
Mean ± SD	0.43 ± 0.26	197 ± 72	16.6 ± 8.1	76 ± 13	16.4 ± 4.8
Range	0.11 - 0.82	125 - 435	8 - 40	53 - 100	5 - 22.5
Reproducibility	8.16%	8.13%	8.95%	8.32%	8.59%

Discussion

Currently there is no "gold standard" technology to measure CO in neonatal patient population. COstatus ultrasound dilution method was extensively validated in neonatal animal model. To our knowledge it is the first clinical study applying this technology in neonatal patients. The safety of injections of saline and starting and stopping the pump was addressed in piglet study [9]. This study found that no clinically relevant cerebral or systemic hemodynamic changes occurred while using the COstatus Monitor. The absolute accuracy of COstatus was successfully compared with blood flow measured by perivascular probe on pulmonary artery (gold standard transit time technology) at different clinical animal models like blood loss [10], lung injury [11], and in presence of shunts [12]. COstatus CO measurements in pediatric patient populations showed acceptable agreements to other more invasive reference techniques. These included perivascular transit time flow probes on pulmonary artery and ascending aorta [13,14] (during surgery), Fick [15], and pulmonary artery thermodilution [16]. There have been no clinical validation studies using COstatus technology in the neonatal population as the methods of validation used previously are not as feasible in this population. Our study demonstrates that the COstatus Monitor, which utilizes ultrasound dilution, can be safely utilized in the neonatal population and is feasible for measuring neonatal cardiac hemodynamics. The monitor is also capable of reliably measuring intracardiac shunts, increasing its utility in the neonatal ICU setting [13,18]. This is the first study clinical study of COstatus monitor in neonatal patent population.

In our study, each measurement session was comprised of two to three individual measurements. This allowed us to determine the reproducibility of measurements taken by the monitor (Table 2). We calculated reproducibility as the coefficient of variation of consecutive measurements in a single session. These values ranged from 8.13% to 8.95% for the various parameters measured, indicating good internal validity.

Each measurement session returned a set of mean values from the individual readings. All enrolled infants underwent at least one session with a maximum of three sessions. We plotted the mean values of all sessions for an individual patient to elucidate trends in cardiac hemodynamics (Figures 2 and 3).

Cardiac output

Cardiac output increased with gestational age while cardiac index remained steady at approximately 200mL/kg/min. Knowledge of this constant is valuable for quick estimation of CO of infants of varying weight and has been validated in previous animal models. The COstatus monitor also provides data for ACVI, which approximately is the total blood volume in neonates. Knowledge of total blood volume can help to tailor therapy when deciding between fluid resuscitation and initiation of vasopressors.

Central blood volume index

Central blood volume consists of the blood volume in the heart, lungs and larger central blood vessels as it measures the blood volume between the injection site and the recording site. CBVI normally is expected to be in the range of 17-20 ml/kg for an older patient population [19]. The observed average CBVI in this population was 16.6 ml/kg. While this is the average of the population, separating out the four patients with right to left shunts gives a much smaller CBVI of 9.6 ± 1.8 ml/kg versus the CBVI of the rest of the population of 19.7 ± 9.7 ml/kg. This may be explained by the fact that in patients with a right to left shunt, part of their blood volume bypasses the lungs leaving a small volume in the lungs and central circulation.

Active circulation volume index

Active circulation volume is amount of that indicator mixed within one minute after the injection. In other words, it is amount of blood that actively supports cardiac output.

This is consistent with the strong negative correlation (R2= 0.50) observed between ACVI and SVRI. With regard to the absolute value of ACVI, these patients often have a heart rate of 100 bpm or more, and unlike adults do not have large amounts of blood volume in their peripheral veins. Therefore, one minute after injecting saline indicator will allow for enough time for mixing with the volume close to total amount of patient's blood. The observed range of ACVI (50-100 ml/kg) confirms this assumption. The negative trend of ACVI with weight/age (Figure 3) also confirms that the total blood volume decreases with age [20].

Shunts

Dilution methods have long time been known to identify and quantify shunts based on the shape of dilution curves [21-23]. Ultrasound dilution uses the same concept of measuring Qp/Qs that has been validated against direct flow measurement of the aorta and pulmonary artery [13]; as well as compared to ECHO in a 73-patient study [24], color-flow Doppler transthoracic echocardiogram (TTE), and oximetry and angiography measured in the cath lab for right to left shunts [25]. In our study, nine patients had shunts: four right to left, three left to right, and two bidirectional (Table 1). It is important to note that dilution methods identify and calculate Qp/Qs for hemodynamically functioning shunts. It is possible that an anatomical shunt with low blood flow (0.9 <Qp/Qs<1.1) may not be identified by dilution measurements, due to a low or no flow, consider low-pressure gradients.

Therapeutic hypothermia

Several studies have indirectly measured cardiac output in infants undergoing therapeutic hypothermia for Hypoxic-Ischemic Encephalopathy, showing varying degrees of decreased cardiac output during hypothermia followed by increases during rewarming ranging from approximately 15-45% [26-29]. These

studies reported a mean cardiac index varying from 83-180mL/kg/min during hypothermia, and 120-260ml/kg/min when normothermic. Our findings utilizing direct measurement by ultrasound dilution confirm this reported trend, however elucidated a more stark increase in cardiac index of 58% (Figure 4). Mean cardiac index during hypothermia in our study was 117mL/kg/min (range 105-130), increasing to 185mL/kg/min (range 170-200) during normothermia. Values during normothermia are consistent with a mean cardiac index of approximately 200mL/kg/min across our cohort. We believe this to be the first report of direct measurement of cardiac output of neonates undergoing therapeutic hypothermia for HIE. Our findings suggest that prior reports utilizing indirect techniques such as echocardiography to estimate cardiac output may have underestimated the effect of hypothermia on hemodynamics.

Three day monitoring

This 1.03kg patient was monitored over three days after transitioning from a conventional ventilator (SIMV) to High Frequency Oscillatory Ventilation (HFOV) for worsening hypoxia due to Respiratory Distress Syndrome secondary to extreme prematurity (Figure 5). The decrease in CO seen on the second day of observation correlates with an increase in the required Mean Airway Pressure (MAP) on the oscillator. Fluids were also restricted at this time due to concern for a Patent Ductus Arteriosus (PDA) confirmed on ECHO, correlating with the decreased CBVI and ACVI. On the final day of observation, the infant had increased CO, CBVI, and ACVI. This is consistent with the MAP being weaned and the infant having decreased urine output with dilutional hyponatremia due to poor renal perfusion from the worsening PDA. There was worsening left to right shunt noted on measurements with increasing Qp/Qs during this time. Of note, the heart rate remained similar across all readings during this observation period, indicating that changes in CO during were predominantly driven by changes in stroke volume, presumably from changing intrathoracic pressures (MAP) and preload (CBVI and ACVI). Infants who would benefit most from direct monitoring of cardiac hemodynamics often have the central access necessary to utilize the COstatus monitor due to their inherent acuity. Use of the COstatus monitor in this population would allow the clinical team to tailor care based on current hemodynamic status. There is minimal fluid introduced to the patient during measurements, and blood used to prime the system is returned to the patient at the end of each session. The AV loop which attaches to the patient's central lines is disposable and can be used up to four days, or until IV tubing needs to be changed.

Limitations

This study is limited by a small sample size. There is no feasible "Gold Standard" available for comparison. Further work will focus on increasing sample size across gestational ages and weights to establish normative ranges for cardiac hemodynamics in neonates as measured by ultrasound dilution. The disadvantage of the COstatus technology is that during the three to five minutes of taking the measurements, arterial pressure monitoring is not available. During that time, an automatic cuff pressure measurement should be implemented.

Conclusion

Cardiac output can be safely and accurately measured in neonates utilizing ultrasound dilution via the COstatus monitor in a neonatal population. Our study demonstrates that cardiac output is positively correlated with increasing gestational age, while cardiac index remains approximately 200mL/kg/min, independent of gestational or postnatal age. Indices for circulating blood volume and active circulating volume show an inverse Correlation with increasing weight. Reported results demonstrate good internal validity and high precision. This technology may allow for more precise and individualized care of the critically ill neonate, as well as examine the effects of various disease states and therapies on central hemodynamics.

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Disclosure Statement

The authors have no vested interests in the COstatus Monitor or Transonic Systems, Inc. (Ithaca, NY USA). The COstatus monitor and disposable AV loops were loaned for the duration of the study.

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