B. Simma
M. G. Fritz
R. Trawöger
R. Geiger
C. Fink
I. Hammerer

Changes in left ventricular function in shocked newborns

B. Simma (✉) · R. Trawöger
Pediatric Intensive Care Unit,
Children's Hospital, Anichstrasse 35,
A-6020 Innsbruck, Austria
FAX: + 43 (512) 50 44 911

M. G. Fritz · R. Geiger · C. Fink ·
I. Hammerer
Department of Pediatric Cardiology,
Children's Hospital, Anichstrasse 35,
A-6020 Innsbruck, Austria

Abstract *Objective:* To assess whether the change in cardiac output after volume replacement is due to elevation of stroke volume or heart rate and to determine the effect of mechanical ventilation on the hemodynamic situation.
Design: Prospective study.
Setting: A ten-bed neonatal intensive care unit (level III) at a university hospital.
Patients: 15 consecutive newborns with blood pressure below the 10th percentile related to age and weight.
Interventions: Volume replacement with Ringer's lactate 20 ml/kg body weight.
Measurements and results. Before and after volume replacement, arterial pressure recordings, blood gas analysis, and an echocardiographic study were carried out. Left ventricular and aortic diameters were measured by the two-dimensional M-mode technique and velocity time integral of aortic flow by the pulsed color Doppler technique. From these data, stroke volume and cardiac output were calculated. Cardiac output (703 ± 204 vs 826 ± 166 ml/min, $p < 0.005$) and cardiac index (267 ± 69 vs 302 ± 55 ml/min per kg body weight, $p < 0.01$) changed significantly due to an appreciable elevation in stroke volume (5.2 ± 1.7 vs 5.8 ± 1.7 ml, $p < 0.05$), whereas heart rate was unaltered (140 ± 12 vs 142 ± 20 beats/min; NS). The change in blood pressure (32 ± 5 vs 38 ± 8 mm Hg, $p < 0.01$) was also significant. Cardiac index before and after volume replacement showed a significant inverse correlation with the severity of respiratory disease expressed as alveolar-arterial oxygen difference ($A\text{-}aDO_2$) ($A\text{-}aDO_2$ vs cardiac index before volume replacement: $r = -0.77$, $p < 0.001$; after volume replacement: $r = -0.73$, $p < 0.005$) or oxygenation index (oxygenation index vs cardiac index before volume replacement: $r = -0.73$, $p < 0.005$; after volume replacement: $r = -0.73$, $p < 0.005$). Changes in left ventricular diastolic diameter, left ventricular systolic diameter, and fractional shortening were not significant.
Conclusions: These results indicate that the major regulator of left ventricular output in newborns with hypovolemic or cardiogenic shock is stroke volume and not heart rate and that cardiac output depends on the severity of the respiratory disease.

Key words Cardiac output · Stroke volume · Heart rate · Volume replacement · Shock · Newborn

Introduction

A fundamental aim in the intensive care of neonates is to maintain adequate systemic and pulmonary perfusion. Hemodynamics can be monitored and measured by several direct and indirect techniques. Assessment of cardiac output (CO) provides important information about the hemodynamic situation in hypotensive and shocked newborns, particularly in the immediate post-operative period. It also permits the evaluation of the effect of different therapeutic approaches. The role of heart rate (HR) and stroke volume (SV) in the regulation of CO in newborns is still controversial [1–5]. Studies in animals [5, 6] and term infants [1, 3] have shown that the heart of the newborn works at or near the peak of the Frank-Starling curve and therefore is not able to increase SV in response to bradycardia and hypovolemia [1, 5]. In contrast, several authors [4, 7, 8] demonstrated that both ventricles in animals and sick preterm infants substantially improve their CO by increasing SV when the preload is increased by ductal or atrial shunt. Understanding the changes in CO and its determinants may have direct clinical relevance to the management of hypotension and shock in newborns, because inotropes [3, 9, 10] as well as volume expansion [4, 8] are considered to be the appropriate first-line treatments for such patients. Assessment of CO by pulsed Doppler echocardiography has become a very important tool for measuring hemodynamics and for managing critically ill infants and children, because this technique is noninvasive and has been validated over a wide age range [11–13] which has shown a close correlation with invasive methods [14]. The purpose of this study was to assess the change in left ventricular function due to fluid administration in newborns with hypovolemic or cardiogenic shock by two-dimensional M-mode and pulsed Doppler echocardiographic techniques. We tested the hypothesis that left ventricular output in newborn infants is determined by SV, and not by HR, and that CO is decreased by mechanical ventilation.

Materials and methods

Fifteen newborns were examined in this study. Fluid administration was indicated when the blood pressure was $< 10^{th}$ percentile related to age and weight [15] and was then ordered by the doctor responsible for resuscitation. Patients with a congenital heart malformation were not included. An infusion of Ringer's lactate 20 ml/kg body weight or 5% plasma protein was given over 1 h. During this period, ventilatory and inotropic support was unaltered. The study design was approved by the Institutional Review Board.

In all patients, a 24-gauge arterial catheter was inserted into the radial artery for continuous monitoring of systemic arterial pressure (MAP) (SMU SVO, Hellige, Freiburg, Germany) using a pressure transducer (Combitrans, B. Braun, Melsungen, Germany) and for intermittent determination of arterial blood gases (288

Blood gas system, Ciba Corning Diagnostics, Medfield, Mass., USA). Echocardiographic examination and blood gas analysis were performed before and immediately after the end of fluid administration by the same investigator.

All patients were ventilated by a pressure-controlled, time-cycled ventilator (Babylog 8000, Draeger, Lübeck, Germany). Alveolar-arterial oxygen difference (A-aDO$_2$) was derived from standard formulae:

$$PAO_2 = PiO_2 - PaCO_2/RQ$$

where PiO_2 = barometric pressure – saturated water vapor pressure × FIO_2, and RQ = 1.0, and therefore A-aDO$_2$ = 713 × FIO_2 – $PaCO_2$ – PaO_2. Oxygenation index (OI) was calculated as mean airway pressure × FIO_2/PaO_2 × 100.

Echocardiographic data collection

An ultrasound imaging system equipped with a 5.0 MHz transducer (CFM 750, Vingmed, Trondheim, Norway) was used in the echocardiographic studies. A baseline two-dimensional and color Doppler assessment was performed to rule out structural heart disease. Two-dimensional M-mode measurements of the aorta and the left ventricle were made from a parasternal short axis view according to the guidelines for M-mode echocardiography of the American Society of Echocardiography [16]. The examination included the aortic diameter at the level of the valvular annulus (AoD) and the left ventricular cavity dimensions at end-diastole (LVDD) and end-systole (LVDS). An apical transducer position was used to record the aortic flow signal by placing a pulsed-wave Doppler sample at the level of the AoD and aligning it along the direction of blood flow to accomplish maximum flow velocities. No angular correction techniques were used. The velocity time integral of the systolic aortic flow (VTIAo) was derived from planimetric measurement of the area under the aortic flow curve. HR was measured from the intervals of the systolic aortic Doppler signals. Echocardiographic images were downloaded to a magneto-optical disc and analyzed off-line using a commercially available software package (Echo-disp 4.0, Vingmed Sound, Trondheim, Norway). Measurements of four to six cardiac cycles were averaged to determine the following values: fractional shortening (FS, %) = (LVDD – LVDS)/ LVDD × 100; SV = VTIAo × 3.1416 × AoD^2/4; CO = SV × HR; and cardiac index (CI) = SV × HR/kg body weight. These calculations were made by one observer who was blinded to the study.

Statistical analysis

Analysis of data before and after volume administration was performed with the Wilcoxon signed-rank test for nonparametric values using StatView SE Graphics (v1.03, 1988, Abacus, Berkeley, Calif., USA). Results are shown as median and range. A p-value of < 0.05 was considered to be statistically significant.

Results

Fifteen consecutive newborn patients were included in this study. Table 1 shows the demographic and clinical data. Median gestational age was 38 (range 35–41) weeks, median birthweight was 2690 (range 1980–

Table 1 Demographic and clinical data for 15 patients before and after volume administration. Values are median and range

Gestation (weeks)	38 (35–41)	
Birth weight (g)	2690 (1980–3850)	
Male/female	7/8	
Apgar score		
1 min	6 (1–9)	
5 min	8 (4–10)	
10 min	8 (5–10)	
Age at study entry	22 (3–264)	

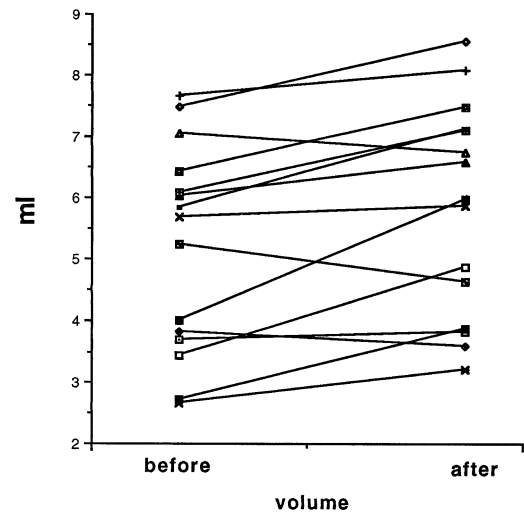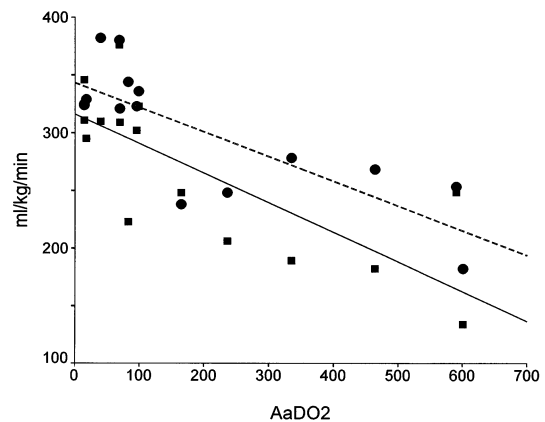|	Volume administration		p-value[a]
	Before	After	
pH	7.39 (7.2–7.53)	7.4 (7.22–7.5)	NS
PaO_2	68 (32–109)	64 (53–93)	NS
$PaCO_2$	36 (23–45)	38 (29–46)	< 0.02
BE	–2.9 (8.4–8.0)	–2.7 (–8.6–7.5)	NS

[a] Wilcoxon signed-rank test

Table 2 Hemodynamic and echocardiographic data before and after volume administration. Values are median and range

	Before	After	p-value[a]
HR (bpm)	140 (125–164)	139 (119–187)	NS
MAP (mm Hg)	33 (22–40)	37 (31–60)	< 0.005
VTIAo (cm)	10.1 (6.0–12.6)	11.1 (7.2–14.4)	< 0.01
SV (ml)	5.7 (2.6–7.7)	6.0 (3.2–8.6)	< 0.05
CO (ml/min)	726 (400–990)	890 (580–1030)	< 0.005
CI (ml/min/kg)	295 (134–376)	323 (182–382)	< 0.01
LVDS (cm)	1.0 (0.9–1.3)	1.0 (0.8–1.2)	NS
LVDD (cm)	1.6 (1.3–1.7)	1.6 (1.3–1.7)	NS
FS (%)	33 (23–40)	32 (23–44)	NS

[a] Wilcoxon signed-rank test

Fig. 1 Stroke volume values for the 15 patients before and after volume administration (5.2 ± 1.7 vs 5.8 ± 1.7 ml, $p < 0.05$)

Fig. 2 Correlation between A-aDO$_2$ and cardiac index before (*squares, solid line; $r = -0.77$, $p < 0.001$*) and after administration (*circles, dotted line; $r = -0.73$, $p < 0.005$*) volume administration

3850) g, and median age at entry to the study was 22 (range 3–264) h. The clinical diagnosis in the study sample was gastroschisis in 4, asphyxia in 3, sepsis and congenital diaphragmatic hernia (CDH) in 2, and omphalocele in 1. Three patients were examined twice. pH, arterial oxygen tension, and base excess did not differ before and after volume administration, whereas arterial carbon dioxide tension significantly rose but remained within the normal range.

VTIAo significantly increased in these shocked infants as a result of volume administration (Table 2). Individual SV values for each patient before and after volume administration are given in Fig. 1. At study entry, SV ranged from 2.6 to 7.7 ml, and the mean increased significantly due to volume administration (median 6.0 ml, range 3.2–8.6 ml, $p < 0.05$) (Table 2). SV did not increase in 3 of the 15 patients and there was no particular reason for these nonresponders to differ from the others. The changes in left ventricular CO and CI were statistically significant. The improvement in SV, left ventricular CO, and CI corresponded with a statistically significant increase in blood pressure (Table 2). There

was no difference in SV, CO, CI, and MAP between subgroups of patients, i.e., those with congenital diaphragmatic hernia (CDH; $n = 3$) and those with gastroschisis ($n = 4$). The number of patients, however, is too small to determine any significance. Mean basic heart rat, LVDS, LVDD, and FS did not change significantly following volume administration (Table 2).

CI before volume administration showed a significant inverse correlation with the degree of mechanical ventilation expressed as OI (OI vs CI: $r = -0.73$, $p < 0.005$) and with the severity of respiratory disease expressed as A-aDO$_2$ (A-aDO$_2$ vs CI: $r = -0.77$, $p < 0.001$). Fluid administration improved CI, but the inverse correlation with OI (OI vs CI: $r = -0.73$, $p < 0.005$) and A-aDO$_2$ (AaDO$_2$ vs CI: $r = -0.73$, $p < 0.005$) persisted (Fig. 2).

Discussion

This study was designed to test the hypothesis that CO in newborns with hypovolemic or cardiogenic shock is determined by SV and not by HR. We found that additional fluid administration significantly increases CO due to improved SV and not to a change in HR. Our results confirm that even at a rapid HR, the left ventricle responds to volume loading due to the Frank-Starling mechanism.

There were no preterm infants enrolled in this study, because the first-line treatment of arterial hypotension in these infants included the elevation of maintenance fluid in steps of 20 ml/kg per day followed by the administration of inotropes [10] until blood pressure values returned to normal. Therefore, the study sample primarily consisted of postoperative or asphyxiated term infants and cardiac function in this population may be different to that of premature infants.

Another problem of studying this group of term and near-term babies is the heterogeneous nature of clinical conditions that the babies have. In those with gastroschisis, the cause of preload problems would have been hypovolemia, whereas in those with CDH, high ventilatory pressures and high pulmonary vascular resistance limit left ventricular preload. Therefore, it may be assumed that these babies respond to volume administration in a different way. We, however, did not observe any difference in hemodynamic data between patients with gastroschisis and those with CDH.

Regulation of blood pressure is based on a complex interaction between HR, SV, and systemic vascular resistance. SV itself is dependent on a number of factors, one of which is the Frank-Starling relationship, but other important determinants include contractility and afterload.

One of the major problems in animal studies evaluating the effect of changes in preload on CO has been the fact that volume administration directly affects preload. Left ventricular SV responds to increase in preload up to a mean left atrial pressure of 10 mm Hg. The lack of increase in SV above this level due to volume administration is related to a simultaneous increase in MAP and afterload [17]. The measurement of left atrial pressure in preterm and newborn infants is not a routine procedure in neonatal intensive care, however. In our patients the increase in SV would have been greater had afterload not increased and these results may also explain the lack of improvement or even decrease in SV after volume administration in some patients. The neonatal heart also might not be able to respond as well to volume loading as an older heart does, because the increase in left ventricular preload at birth may expend most of the immature heart's Frank-Starling reserve [1, 5, 7]. These above studies were performed in animals or healthy term newborns.

The question in sick infants in neonatal intensive care, however, is how much perfusion has to be established in order to prevent ischemia and which parameters provide reliable information about the true hemodynamic situation [18]? As the symptoms are similar, it is difficult to establish by usual monitoring in the neonatal intensive care unit which value is responsible for the infant's hypotension. Measurement of CO by Doppler echocardiography may provide the answer to this. There is evidence that myocardial dysfunction may play an important role in preterm infants who become hypotensive [3]. In these infants, FS and CO were significantly lower compared to a control group. Our data demonstrate an increase in SV and CO but no change in FS. The assessment of CO by pulsed Doppler echocardiography has been validated by several authors [12, 13, 19] who have found a close correlation between those values and values obtained by invasive methods such as thermodilution. In adult patients, intraobserver variability ranges between 2 and 12% and interobserver variability between 3 and 6% [20]. One study in term infants [11] revealed considerable errors in the comparison of various infants, which were reduced by having serial measurements performed by one observer in the same group of infants. Another advantage of echocardiography is that in contrast to the direct Fick method, dye dilution, and thermodilution, CO measurements by pulsed Doppler technique are taken over a longer period of time and not just one heart beat. However, evaluation of the left ventricular systolic function using fractional shortening obtained by M-mode echocardiography assumes uniform contraction of the left ventricle [21] and provides little information about global cardiac performance in newborns [22]. Therefore, as in our study, a change in CO is not necessarily accompanied by a change in FS [8] and a low FS does not always indicate poor left ventricular function [3].

Another finding of this study was the wide range of CO in these infants (136–376 ml/kg per min). Preterm and term babies usually have a left ventricular CO of 200–300 ml/kg per min [8]. CO, however, is affected not only by hypovolemia, myocardial dysfunction, and systemic vascular resistance, but also by other factors like mean airway pressure due to mechanical ventilation [23]. Calculating CI and severity of respiratory disease, we were able to demonstrate that a low CI significantly correlates with worsening respiratory disease evidenced by an increase in A-aDO$_2$ and OI. Fluid administration corrected some of the preload deficit resulting from mechanical ventilation and improved CO, but the correlation between respiratory disease severity and CI remained unaltered. Other authors have also reported evidence that in shocked preterm [4, 8, 24] and adult [25] patients who are being mechanically ventilated volume expansion can improve

CO for a short time, whereas FS and HR remain unaltered [4].

In conclusion, volume replacement in shocked newborns improves left ventricular CO by increasing SV and not by increasing HR, and CO significantly correlates with the severity of respiratory disease.

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