Left Ventricular Contractility in Extremely Premature Infants in the First Day and Response to Inotropes

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ABSTRACT: The aim was to assess myocardial contractility in infants born <30 wk gestation developing low systemic blood flow (SBF) in the first day, and the effect of dobutamine *versus* dopamine. Superior vena cava (SVC) flow was used as a measure of SBF at 3, 10, and 24 h ($n = 106$). Infants with low SVC flow randomized to dopamine or dobutamine. Myocardial contractility was determined by the relationship between left ventricular (LV) mean velocity of circumferential fiber shortening (mVcfs) and wall stress. Infants who developed low SVC flow had significantly worse myocardial contractility at 3 h, but not 10 h. At 24 h, low-flow infants had lower than expected mVcfs for any given LV stress. In 37 infants randomized to inotrope, there was no significant difference in contractility at 10 $\mu\text{g/kg/min}$. At 20 $\mu\text{g/kg/min}$ ($n = 21$), dopamine increased whereas dobutamine decreased LV stress. Infants on dobutamine had significantly lower than expected mVcfs for any given LV stress compared with infants on dopamine. Contractility was not improved by either inotrope at either dose. In conclusion, infants developing low SVC flow in the first day have worse myocardial contractility at 3 h. Neither inotrope increased contractility, but dopamine increased LV stress at 20 $\mu\text{g/kg/min}$. (*Pediatr Res* 61: 335–340, 2007)

Extremely preterm infants with low brain and upper body blood flow, as measured by SVC flow, in the first day are at increased risk of late peri/intraventricular hemorrhage (1,2), mortality, and subsequent neurodevelopmental impairment (3). Low SVC flow was associated with infants born at lower gestation, with a higher MAP in the first 12 h and a larger diameter DA at 5 h of age (1). Although infants with low SVC flow frequently had normal BP, they had significantly higher calculated UBVR compared with infants with normal flows. However, calculated vascular resistance is not a direct measure of LV afterload. LV stress is affected by LV dimensions, which are affected by preload, and LV wall thickness (4,5).

Although LV shortening fraction has been reported to be reduced in shocked and acidotic preterm infants (6), this measure of LV performance does not take preload or afterload conditions into account and has been reported to be unreliable in preterm infants (7). In contrast, the relationship between LV mVcfs and LV wall stress (LV stress) has been used as a

preload independent measure of LV contractility that takes into account afterload conditions. Myocardial contraction velocity will fall as afterload increases. A steeper negative slope of the regression line of the relationship indicates a more rapidly reducing mVcfs in response to increasing LV stress, or reduced myocardial contractility (4,8). Preterm infants have been documented to have reduced LV contractility in the first days after birth compared with term infants (9), although the relationship to low blood flow states has not been reported. In addition, the effects on myocardial contractility of commonly used inotropes in preterm infants have not been measured in infants with low flow in the first day.

The aim of this study was 1) to examine the relationship between LV mVcfs and wall stress in very preterm infants in the first day with normal and low SVC flows, and 2) to examine the effects of dobutamine and dopamine on this relationship in very preterm infants with low SVC flow in the first day.

METHODS

Cohort study. The study was nested in a two center, prospective cohort study of 128 infants born <30 wk gestation, the clinical outcomes and blood flow findings of which have been reported previously (2,10,11). Infants were eligible for inclusion if born <30 wk gestation, were <12 h after birth, and there was informed parental consent. Infants were excluded if a major congenital or cardiac abnormality was identified, considered by the attending clinician to be nonviable, or if inotrope or indomethacin had been given before enrollment. This report is restricted to 106 infants with an intra-arterial line and who had measurements of LV function performed in the first 24 h. The study was carried out in the Royal Prince Alfred and Royal North Shore Hospital Neonatal Intensive Care Units, Sydney, Australia, between October 1998 and December 1999. The ethics committees of Central Sydney and Northern Sydney Area Health Services approved the study.

Echocardiography was performed on 122 infants at 3 h, 126 infants at 10 h, and 119 infants at 24 h after birth. Invasive BP monitoring was required for calculation of LV wall stress but was unavailable for 25 infants at 3 h, 19 infants at 10 h and 20 infants at 24 h. Measurements of LV function including mVcfs and LV wall stress were available for a total of 106 infants in the first 24 h, including 94 at 3 h, 104 at 10 h, and 97 at 24 h. Technical difficulties with echocardiography or videotape recordings accounted for lost measurements on 3 infants at 3 and 10 h and 2 infants at 24 h.

Randomized trial of dobutamine versus dopamine. Forty two infants with low SVC flow (<41 mL/kg/min) were enrolled in a blinded randomized trial of volume and dobutamine *versus* volume and dopamine, from which the effects on blood flow and clinical outcomes have been reported previously (11). After normal saline, 10 mL/kg, infants were randomized to dobutamine

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Abbreviations: BP, blood pressure; DA, ductus arteriosus; LV stress, left ventricular wall stress; MAP, mean airway pressure; mVcfs, mean velocity of circumferential fiber shortening; RVO, right ventricular output; SBF, systemic blood flow; SVC flow, superior vena cava flow; UBVR, upper body vascular resistance

or dopamine, initially at 10, increasing to 20 $\mu\text{g/kg/min}$ if SVC flows failed to be maintained >40 mL/kg/min in the first 24 h. Invasive arterial monitoring using umbilical or peripheral arterial catheters was available in 37 of the 42 infants enrolled. Measurements of myocardial contractility were available for 21 of 22 infants randomized to volume and dobutamine, and 16 of 20 infants randomized to volume and dopamine.

Physiologic and echocardiographic measurements. Physiologic measurements including heart rate, mean BP, and MAP were taken immediately before echocardiography. All BP measurements were taken from an umbilical arterial or peripheral arterial catheter. Mean airway pressure was recorded from the Dräger Babylog 8000 ventilator measured pressure.

Echocardiographic monitoring was performed routinely at 3, 10, and 24 h (cohort study). Echocardiography was also performed on infants enrolled in the trial of volume and inotrope immediately before and after normal saline, and immediately before and 30 min after commencement of inotrope, or change in dose of inotrope. All measurements were performed blind to treatment allocation. An Acuson (Mountain View, CA) 128/XP10 ultrasound scanner was used with a 7 MHz vector array transducer incorporating colour flow and pulsed wave Doppler. The scan was recorded on to VHS videotape and the measurements then taken from the videotape. Structural normality of the heart was established on the initial scan. All eligible infants had echocardiographic measurements of SVC flow, right ventricular output (RVO), color Doppler DA diameter, mVcfs, and LV stress at 3, 10, and 24 h after birth. RVO, SVC flow, and DA diameter were measured as previously reported (12–14). Upper body systemic vascular resistance was calculated from BP and SVC flow measurements:

UBVR [mm Hg/mL/kg/min]

$$= \text{mean BP (mm Hg)} \div \text{SVC flow (mL/kg/min)}.$$

Left ventricular mean velocity of circumferential fractional shortening (mVcfs) was determined by the method described by Berdjis *et al.* (15) using following formula:

$$\text{mVcfs (circumferences/s)} = (\text{Ced} - \text{Ces}) \div (\text{Ced})(\text{ETc}),$$

where Ced = end-diastolic circumference; Ces = end-systolic circumference; and ETc = left ventricular ejection time corrected for heart rate [ETc = ET/RR interval]. Ced and Ces were measured by tracing the internal circumference of the left ventricle from a two-dimensional image using a short axis view of the left ventricle at the level of the mitral valve leaflets. ETc and the RR interval were measured from the arterial pulse wave trace.

The LV stress was calculated by the method described by Grossman *et al.* (16) using the following formula:

$$\text{LV stress} = 0.34 (\text{Des})(\text{ESP}) \div h [1 + (h/\text{Des})],$$

where Des = end-systolic diameter calculated by dividing Ces by π to minimize errors due to irregularity of the left ventricular shape; ESP = end-systolic pressure; and h = left ventricular posterior wall thickness. ESP (mm Hg) was interpreted from the arterial pulse tracing as the pressure at the dicrotic notch. The left ventricular wall thickness (h) was measured from the M-mode short axis view of the left ventricle at the level of the mitral valve leaflets.

Statistics. Data were analyzed using SPSS (SPSS Inc., Chicago, IL). Categorical variables were compared using a two-sided χ^2 test or Fisher exact test where appropriate. Continuous variables were compared using a two-sample *t* test for parametric and Mann-Whitney *U* test for nonparametric variables. Myocardial contractility was assessed by examining the scatter plots of mVcfs versus LV stress and determining the slope of best fit using two-stage least squares linear regression analysis. Regression analyses were performed comparing infants who developed low SVC flow (<41 mL/kg/min) in the first 24 h to those who maintained SVC flows, and comparing infants who initially received dobutamine to those who received dopamine from before, at 10 and 20 $\mu\text{g/kg/min}$. A second analysis was performed using regression modeling in SAS exploring for possible interactions between inotrope and dose using a model that combined observations across time periods. This allowed the analyses to determine whether changes in contractility were due to changes in slope or position of the regression lines, representing the difference between inotropes for expected value of mVcfs for any given value of LV stress. In both sets of analyses, one extreme outlier was excluded. The combined regression analysis model used terms to adjust for inotrope, difference between inotrope, and dose of inotrope allowing for interactions between inotrope and dose. As not all infants had the dose of inotrope increased to 20 $\mu\text{g/kg/min}$, the final analysis was adjusted for risk factors for failure of response to inotropes including lack of antenatal corticosteroids, gestational age, MAP, and baseline SVC flow (11).

Table 1. Demographic and respiratory data comparing infants maintaining normal (≥ 41 mL/kg/min) or low (<41 mL/kg/min) SVC flow in first 24 h

	Normal SVC flow	Low SVC flow	p Value
No.	66	40	
Mean gestation, wk (SD)	27.1 (1.7)	25.8 (1.8)	<0.001
Mean birth weight, g (SD)	999 (290)	924 (277)	0.2
Birth weight ≤ 10 th percentile	9 (14%)	0	0.01
Male	36 (55%)	18 (45%)	0.3
Antenatal steroids	63 (95%)	33 (83%)	0.04
Maternal antihypertensives	18 (27%)	1 (3%)	0.001
Vaginal delivery	25 (38%)	21 (53%)	0.1
<i>Ex utero</i> transfer	4 (6%)	8 (20%)	0.054
Apgar ≤ 4 at 1 min	26 (39%)	22 (55%)	0.1
Ventilated	64 (97%)	40 (100%)	0.5
Average MAP first 12 h (SD)	7.6 (2.5)	8.7 (2.5)	0.03
DA >1.6 mm at 3 h	44 (67%)	28 (70%)	0.7

RESULTS

Cohort study. One hundred and twenty eight infants were enrolled. Measurements of LV function including mVcfs and LV wall stress were available for a total of 106 infants in the first 24 h, including 94 at 3 h, 104 at 10 h, and 97 at 24 h (Table 1). Forty (42%) of 106 infants developed low SVC flow in the first 24 h. These infants were of significantly lower gestational age, and less likely to be growth restricted, born to mothers who had received antenatal steroids or were on antihypertensives. They were more likely to be transferred *ex utero* and to have a higher average MAP in the first 12 h.

At 3 h, there was a poor correlation (Pearson $r = 0.15$, $p = 0.2$) between mean BP and SVC flow, but a strong inverse correlation (Pearson $r = -0.90$, $p < 0.001$) between the log of the calculated UBVR and SVC flow. At 3 h (Table 2), infants who developed low SVC flow in the first 24 h had a significantly lower mean BP, RVO, and SVC flow, and higher calculated UBVR (0.649 versus 0.414 mm Hg per mL/kg/min). There was no significant difference in mVcfs or LV stress. However, infants who developed low SVC flow had significantly worse myocardial contractility as measured by the increased slope of the regression equation between LV stress and mVcfs ($p = 0.005$) (Table 3, Fig. 1).

At 10 h (Table 2), 6 of 39 infants who developed low SVC flow in the first 24 h were on inotropes compared with 1 of 65 who maintained SVC flow. The infants who developed low SVC flow in the first 24 h had a significantly lower mean BP, larger diameter DA, and lower SVC flow and RVO at 10 h. Calculated UBVR was significantly higher in the infants with low SVC flow (0.933 versus 0.509 mm Hg per mL/kg/min). There was no significant difference in mVcfs but a significantly lower LV stress (34.98 versus 42.16 g/cm², $p = 0.02$). The difference in LV stress is similar in magnitude (36.42 versus 42.39 g/cm²) but no longer significant if the six infants on inotropes are excluded. Myocardial contractility was no longer significantly different with the slope of the regression equation nearly identical ($p = 0.06$) (Table 3, Fig. 1).

At 24 h (Table 2), all 32 infants who developed low SVC flow were on inotropes with only 3 of these infants still having

Table 2. Cardiorespiratory variables [mean (SD)] at 3, 10, and 24 h in infants that maintained normal or had low SVC flow in the first 24 h

	3 hours			10 hours			24 hours		
	Normal flow	Low flow	<i>p</i> Value	Normal flow	Low flow	<i>p</i> Value	Normal flow	Low flow	<i>p</i> Value
No.	59	35		65	39		65	32	
MAP $\ddagger$	8.0 (2.2)	9.2 (2.8)	0.03	7.1 (2.6)	7.8 (2.2)	0.1	6.4 (2.5)	7.3 (2.0)	0.1
FiO ₂ (%)	32 (14)	41 (22)	0.03	29 (10)	38 (21)	0.02	28 (9)	34 (23)	0.2
Mean BP (mm Hg)	32.3 (5.6)	28.4 (5.6)	0.002	35.5 (6.3)	28.7 (7.7)	<0.001	37.7 (6.3)	37.0 (8.2)	0.6
Ducal diameter (mm)	2.1 (0.7)	2.2 (0.9)	0.5	1.2 (0.7)	1.6 (0.7)	0.008	0.4 (0.7)	0.5 (0.7)	0.3
RVO (mL/kg/min)	217.7 (67.0)	148.0 (50.4)	<0.001	195.9 (64.0)	127.6 (44.5)	<0.001	255.0 (62.6)	238.8 (92.7)	0.4
SVC flow (mL/kg/min)	87.1 (27.6)	51.0 (22.7)	<0.001	77.3 (31.5)	33.3 (10.5)	<0.001	92.8 (32.7)	76.2 (32.9)	0.02
mVcfs (circ/s)	1.052 (0.187)	0.960 (0.313)	0.1	0.957 (0.197)	0.929 (0.252)	0.6	0.928 (0.220)	0.792 (0.191)	0.005
LV stress (g/cm ²)	36.56 (15.98)	35.54 (14.58)	0.8	42.16 (14.43)	34.98 (15.54)	0.02	48.10 (17.79)	52.97 (19.41)	0.2
Calculated UBVR $\ddagger$	0.414 (0.169)	0.649 (0.299)	<0.001	0.509 (0.170)	0.933 (0.378)	<0.001	0.453 (0.161)	0.634 (0.436)	0.03
Dobutamine (<i>n</i>)				0	3		0	24	
Dopamine (<i>n</i>)				1	3		3	17	

¶cm H₂O; ‡mm Hg per mL/kg/min.

Table 3. Regression analyses of the relationship between mVcfs and LV wall stress in infants at 3, 10, and 24 h that maintained or had low SVC flow in the first 24 h

	3 hours	mVcfs (circ/s) =	<i>n</i>	<i>p</i> Value	<i>r</i> ²	<i>p</i> Value (difference)
Normal flow		1.19 – 0.004 * LV stress (g/cm ²)	59	0.004	0.13	
Low flow		1.46 – 0.014 * LV stress (g/cm ²)	35	<0.001	0.43	0.005
10 h						
Normal flow		1.24 – 0.007 * LV stress (g/cm ²)	65	<0.001	0.25	
Low flow		1.19 – 0.007 * LV stress (g/cm ²)	39	0.008	0.16	0.06
24 h						
Normal flow		1.18 – 0.005 * LV stress (g/cm ²)	64	<0.001	0.27	
Low flow		1.05 – 0.004 * LV stress (g/cm ²)	30	0.001	0.48	0.009

Figure 1. Myocardial contractility (mVcfs vs LV stress) at 3, 10, and 24 h in infants maintaining normal SVC flow (◆) and developing low SVC flow (○) in the first 24 h. Regression lines (95% confidence intervals) showing infants with low flow (dashed lines) had significantly worse contractility at 3 h, but not 10 or 24 h, compared with infants maintaining normal flows (solid lines).

low SVC flow. Three of 65 infants who had not developed low SVC flow were on inotropes for hypotension. Infants who developed low SVC flow in the first 24 h still had significantly lower SVC flow at this time but had similar mean BP. They had significantly lower mVcfs (0.792 *versus* 0.928 circ/s) but not significantly different LV stress. The calculated UBVR was significantly higher (0.634 *versus* 0.453 g/cm²). Myocardial contractility was significantly different although the slope of the regression equation was similar (*p* = 0.009) (Table 3, Fig. 1). The difference is due to a lower mVcfs than predicted for any given LV stress at this time in the infants who had developed low SVC flow.

Trial of dobutamine versus dopamine. Twenty-one infants randomized to volume and dobutamine and 16 infants to volume and dopamine had myocardial contractility measurements performed before and after a dose of 10 μ g/kg/min was reached. Ten infants randomized to dobutamine and 11 to dopamine had measurements before and after inotrope at a dose of 20 μ g/kg/min. There were no significant differences between infants randomized to dobutamine and dopamine in baseline cardiorespiratory variables and measures of myocardial contractility (Table 4).

At 10 μ g/kg/min, infants randomized to dobutamine had a reduction in calculated UBVR compared with an increase for

Table 4. Baseline and change in cardiorespiratory variables [mean (SD)] before and after inotrope at 10 and 20 $\mu\text{g/kg/min}$

	Dobutamine			Dopamine		
	Before	Change after 10 $\mu\text{g/kg/min}$	Change after 20 $\mu\text{g/kg/min}$	Before	Change after 10 $\mu\text{g/kg/min}$	Change after 20 $\mu\text{g/kg/min}$
No.	21	21	10	16	16	11
MAP (cm H ₂ O)	8.6 (2.4)	0.2 (0.6)	0.0 (0.2)	8.1 (1.9)	0.1 (0.9)	0.1 (1.2)
FiO ₂ (%)	38 (24)	-1 (3)	-1 (2)	45 (23)	-2 (11)	7 (25)
Mean BP (mm Hg)	30.6 (5.1)	0.4 (4.3)	0.9 (3.2)*	26.8 (8.9)	4.1 (7.1)	5.1 (5.7)*
Ducal diameter (mm)	1.3 (0.8)	-0.2 (0.4)	0.1 (0.6)	1.6 (0.8)	0 (0.4)	-0.1 (0.4)
RVO (mL/kg/min)	159.6 (63.1)	6.9 (35.2)	-5.2 (19.2)	136.3 (52.9)	4.1 (40.9)	-7.0 (44.9)
SVC flow (mL/kg/min)	42.8 (18.9)	5.2 (12.1)	6.9 (18.8)	48.1 (22.0)	-0.9 (16.5)	-5.6 (15.8)
mVcfs (circ/s)	0.905 (0.226)	-0.044 (0.224)	-0.038 (0.190)	0.904 (0.263)	-0.006 (0.258)	0.059 (0.225)
LV stress (g/cm ²)	36.06 (11.34)	1.39 (11.06)	-4.53 (9.67)¶	33.39 (19.30)	4.16 (11.41)	13.13 (11.94)¶
Calculated UBVR‡	0.920 (0.619)	-0.164 (0.435)*	0.013 (0.308)	0.634 (0.298)	0.079 (0.192)*	0.436 (0.606)

* $p < 0.05$; ¶ $p < 0.01$; ‡mm Hg per mL/kg/min.**Table 5.** Linear regression analyses of the relationship between mVcfs and LV wall stress in infants before and after inotrope at 10 and 20 $\mu\text{g/kg/min}$

Before inotrope	mVcfs (circ/s) =	No.	p Value	r^2	p Value (difference)
Dobutamine	$1.57 - 0.018 * \text{LV stress (g/cm}^2\text{)}$	21	<0.001	0.77	
Dopamine	$1.15 - 0.007 * \text{LV stress (g/cm}^2\text{)}$	16	0.09	0.20	0.8
Inotrope 10 $\mu\text{g/kg/min}$					
Dobutamine	$1.21 - 0.009 * \text{LV stress (g/cm}^2\text{)}$	21	0.02	0.26	
Dopamine	$1.31 - 0.011 * \text{LV stress (g/cm}^2\text{)}$	16	<0.001	0.65	0.7
Inotrope 20 $\mu\text{g/kg/min}$					
Dobutamine	$1.00 - 0.003 * \text{LV stress (g/cm}^2\text{)}$	10	0.1	0.29	
Dopamine	$1.32 - 0.010 * \text{LV stress (g/cm}^2\text{)}$	11	0.01	0.65	0.02
Inotrope at highest dose					
Dobutamine	$1.20 - 0.010 * \text{LV stress (g/cm}^2\text{)}$	21	0.002	0.23	
Dopamine	$1.26 - 0.010 * \text{LV stress (g/cm}^2\text{)}$	16	0.001	0.46	0.4

infants randomized to dopamine, with the difference between inotropes being significant (Table 4). Changes in mVcfs and LV stress were not significantly different. In regression analysis of LV stress and mVcfs, there was no significant difference in myocardial contractility comparing dobutamine and dopamine at 10 $\mu\text{g/kg/min}$ (Table 5, Fig. 2). In addition, there was no significant difference between the regression equations for mVcfs and LV stress from before inotrope to after inotrope at 10 $\mu\text{g/kg/min}$ for either dobutamine or dopamine.

At 20 $\mu\text{g/kg/min}$, 10 infants randomized to dobutamine had a reduction in LV stress compared with an increase for 11 infants randomized to dopamine with the difference between inotropes being significant (-4.53 versus $+13.13$ g/cm², $p < 0.01$) (Table 4). Changes in mVcfs and calculated UBVR were not significantly different (Table 4). In regression analysis of LV stress and mVcfs (Table 5, Fig. 2), there was a significant difference in myocardial contractility between infants on dobutamine and infants on dopamine ($p = 0.02$). These findings were not affected by adjusting for gestational age, a complete course of antenatal corticosteroids, and baseline MAP and SVC flow.

An analysis of myocardial contractility at the highest dose reached included all infants (Table 5). At the highest dose of inotrope reached (10 or 20 $\mu\text{g/kg/min}$), there was no significant difference ($p = 0.4$) in myocardial contractility (relationship between mVcfs and LV stress) between infants receiving dobutamine or dopamine (Fig. 2).

Dopamine versus dobutamine: combined regression analysis—mVcfs versus LV Stress. Using the combined regres-

Figure 2. Regression lines (95% confidence intervals) demonstrating relationship between mVcfs and LV stress for infants receiving dobutamine (◆, solid lines) and dopamine (○, dashed lines) at 0, 10, and 20 $\mu\text{g/kg/min}$, and the highest dose reached.

sion model described in methods, there was no significant difference between inotrope groups before infusion (difference between inotropes = -0.055 circ/s, SE = 0.073, $p = 0.5$) or at 10 $\mu\text{g/kg/min}$ (difference = 0.092 circ/s, SE = 0.083, $p = 0.3$), but there was a significant difference at 20 $\mu\text{g/kg/min}$

(difference = 0.231 circ/s, SE = 0.105, $p = 0.03$). The slope was constant across all time periods, and was estimated to be $mVcfs = -0.00981 \times \text{LV stress}$ (SE = 0.00176, $p < 0.0001$). Hence, the expected value of mVcfs decreases 0.00981 circ/s per 1 g/cm² increase in LV stress. The difference between inotropes at 20 $\mu\text{g/kg/min}$ is due to a reduction in expected mVcfs in infants on dobutamine for any given LV stress compared with infants on dopamine. These findings were not affected by adjusting for gestational age, a complete course of antenatal corticosteroids, and baseline MAP and SVC flow.

DISCUSSION

This study has shown that infants who develop low SBF in the first day have significantly worse LV contractility in response to higher wall stress. We have previously reported that very premature infants are at high risk of developing low SBF in the first 24 h (1,2,13). To overcome the problem of shunts across the adapting heart confounding ventricular outputs as a measure of SBF (13,14,17), we have used SVC flow as a measure of upper body and brain blood flow that is not affected by these shunts (1,12). Low SVC flow was a consistent and significant risk factor for infants developing late peri/intraventricular hemorrhage, neonatal mortality (1,2) and subsequent neurodevelopmental impairments (3). These low SVC flows were associated with lower gestation age at birth, higher MAP, and larger diameter DA in the first hours, as well as a high calculated UBVR (1,2). However, it has been unclear as to whether the higher calculated UBVR is a compensatory mechanism for low SBF to maintain blood flow to vital organs ("compensated shock"), or whether the increased vascular resistance is a contributory factor with high vascular resistance leading to low cardiac output and organ blood flow in extremely premature infants with poor myocardial contractility. For this reason, in this study we decided to use direct preload independent measures of myocardial contractility that account for afterload to directly measure the response of the left ventricle to varying after-loads in a population of infants, many of who developed low SBF as measured by SVC flow. It has previously been reported that preterm infants have lower myocardial contractility than term infants at 6 h of age (9). However, the relationship to SBF and response to inotropes has not been reported in extremely preterm infants.

Infants who developed low SVC flow in the first 24 h had significantly worse myocardial contractility at 3 h of age as measured by an increased negative slope of relationship between mVcfs and LV stress. This was despite there being no significant difference in the average mVcfs and average LV stress between infants with and without low flow. This strongly suggests that the problem in extremely premature infants who develop low flow is inability to maintain left ventricular velocity of contraction against the increased afterload found in the early postnatal period. High systemic vascular resistance may be a compensatory mechanism for low SBF, but the presence of poor myocardial contractility at 3 h before many developed low flow suggests it is also a contributing factor. The difference in myocardial contractility was also significant at 24 h, but did not reach significance at 10 h.

The relationship is confounded at these times by the use of inotropes and the potential for myocardial adaptation over time. At 3 h, low-flow infants had a greater than expected reduction in mVcfs as LV stress increased (*i.e.* increased slope of the regression line). However, by 24 h the difference in contractility is associated with a lower than expected mVcfs at all levels of LV stress (change in position of regression line). This suggests there has been a global deterioration in myocardial function over time in infants with low SVC flow. This may reflect myocardial immaturity (18–20) or injury.

We have previously reported that over 40% of infants with low SVC flow failed to respond or maintain SVC flow on either dopamine (32%) or dobutamine (55%) (11). The use of inotropes did not change the slope of the relationship between mVcfs and LV stress at 10 or 20 $\mu\text{g/kg/min}$. At 20 $\mu\text{g/kg/min}$ there was evidence that the expected mVcfs for any given LV stress was lower for infants on dobutamine, but this analysis is restricted to 21 infants with persisting low SVC flow who progressed to the higher dose. When infants were compared at the highest dose reached, there was again no difference in myocardial contractility between infants on dobutamine or dopamine. Of note is that there was no improvement in myocardial contractility in infants on either inotrope, with trends to deterioration at increasing dose. In addition, dobutamine produced a significant decrease in calculated UBVR at a dose of 10 $\mu\text{g/kg/min}$, whereas dopamine produced a significant increase in LV stress at 20 $\mu\text{g/kg/min}$. At this dose, there was a trend to falling SVC flow. These were short-term assessments of the effects of inotropes on flow and contractility. At 24 h, infants on dobutamine had a significantly greater RVO than infants on dopamine (11). Further research is needed to determine whether treating hypotension with higher doses of dopamine is safe over the first day, or whether this strategy will lead to a subsequent reduction in systemic and organ blood flows due to poor myocardial contractility resulting in "decompensated" shock.

Methodological strengths of this study include the relatively large sample size for an echocardiographic study in preterm infants, measurements of myocardial contractility at 3 h preceded the development of low SVC flow for most infants, and inotrope interventions were blinded by use of identically labeled syringes resulting in contractility measurements being blinded to treatment allocation. However, not all infants randomized to inotrope had the dose increased to 20 $\mu\text{g/kg/min}$ making these observations potentially biased. We have exercised caution in interpreting differences in effect at this dose although adjusting this analysis for risk factors for nonresponse (lower gestation, incomplete antenatal steroids, baseline MAP and SVC flow) did not affect this conclusion. Infants had echocardiographic measurements 30 min after change of dose of inotrope. We speculate that substantially increasing LV stress in extremely premature infants in the first day is likely to result in substantial falls in systemic and organ blood flows. Further blinded, randomized studies are needed to determine the effect of inotropes over the first day. Finally, measurements of LV dimensions in extremely premature infants are difficult, although intra- and interobserver reliability have previously been reported to be good. Intra- and interob-

server reliability could not be conducted in the context of this interventional study given the small size of the infants and the frequency of echocardiography. The substantial variability in measurements is evidenced in the scatter plots of mVcfs versus LV stress (Figs. 1 and 2) and the wide standard deviations for mVcfs and LV stress (Table 2 and Table 4). This variability will include both substantial between infant variability and measurement error. Difficulties with measurement include the elliptical shape of the extremely preterm infant left ventricle and variability of LV topography impacting on accuracy of tracings of LV circumferential dimensions and wall thickness. The differences in contractility between infants with low and normal flows are unlikely to be biased by measurement. However, important differences between inotropes may not have been detected by measurements with substantial variability.

Identification of the mechanisms of low SBF in extremely preterm infants in the first day offers a therapeutic opportunity. Infants who develop low SVC flow are born more immature, ventilated with higher MAP (1,2,13) and have a larger diameter DA (1,21) in the first hours. They have higher systemic (1,2) and pulmonary (13) vascular resistances and poor myocardial contractility. Many do not respond to inotropes (11), with no improvement in myocardial contractility observed with either inotrope in this study, suggesting an immaturity of the extremely preterm infant's myocardium (18). Infants that fail to respond are less likely to have received a complete course of antenatal steroids (11). Potential therapeutic options are limited with a need to identify antenatal strategies for maturing the infant's myocardium, postnatal strategies to reduce the effect of ventilatory management on SBF, and the use of cardiovascular treatments to prevent low SBF. We are currently studying the effect of milrinone (a phosphodiesterase inhibitor with "inodilator" properties) with the goal of preventing SBF (22), given that milrinone has been used to treat (23) and prevent (24) low cardiac output syndrome after cardiac surgery, a condition that shares many of the hemodynamic features with that found in the extremely premature infant in the first day.

In conclusion, infants who develop low SVC flow in the first day have significantly worse myocardial contractility. Neither dopamine nor dobutamine produces an improvement in myocardial contractility in preterm infants in the first day after birth. At 20 $\mu\text{g/kg/min}$, dopamine substantially increases LV afterload. Further research is required to validate the accuracy of these measurements of myocardial contractility in preterm infants, and to reproduce these findings in another preterm infant population with low SBF.

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