Title

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Journal

Journal of Perinatology, 35(2)

ISSN

0743-8346

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Publication Date

2015-02-01

DOI

10.1038/jp.2014.151

Peer reviewed

Published in final edited form as:
J Perinatol. 2015 February ; 35(2): 123–127. doi:10.1038/jp.2014.151.

Catecholamine-resistant hypotension and myocardial performance following patent ductus arteriosus ligation

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Abstract

Objective—We performed a multicenter study of preterm infants, who were about to undergo patent ductus arteriosus ligation, to determine if echocardiographic indices of impaired myocardial performance were associated with subsequent development of catecholamine-resistant hypotension following ligation.

Study Design—A standardized treatment approach for hypotension was followed at each center. Infants were considered to have catecholamine-resistant hypotension if their dopamine infusion

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Disclosures: None

Conflict of Interest:
The authors have no conflict of interest.

was >15 μg/kg/min. Echocardiograms and cortisol measurements were obtained between 6 and 14 hours after the ligation (prior to the presence of catecholamine-resistant hypotension).

Results—45 infants were enrolled: 10 received catecholamines (6 were catecholamine-responsive, 4 developed catecholamine-resistant hypotension). Catecholamine-resistant hypotension was not associated with decreased preload, shortening fraction or ventricular output. Infants with catecholamine-resistant hypotension had significantly lower levels of systemic vascular resistance and postoperative cortisol concentration.

Conclusion—We speculate that low cortisol levels and impaired vascular tone may play a more important role than impaired cardiac performance in post-ligation catecholamine-resistant hypotension.

Keywords

cortisol; hydrocortisone; surgery; dopamine; newborn

Introduction

Approximately 30% of preterm infants who undergo surgical ligation of the patent ductus arteriosus (PDA) develop systemic hypotension and receive catecholamine support during the first 6-to-24 hrs after the procedure (1–4). Although catecholamine infusions can usually correct the post-ligation hypotension, approximately half of the hypotensive infants develop catecholamine-resistant hypotension (1, 4). In these infants, a "low stress-dose" of hydrocortisone can normalize their blood pressure (3, 5, 6). Epidemiologic studies have shown that decreased gestational and postnatal age are the strongest predictors of the postoperative hypotension (1–3); in contrast, differences in surgical, anesthetic, and intraoperative fluid management appear to have little effect on the post-surgical hemodynamic decompensation (1, 4, 7).

Changes in myocardial loading conditions and impaired myocardial performance may contribute to the postoperative clinical deterioration since increases in afterload and decreases in preload are observed immediately following PDA ligation (5, 6, 8–11). Although measurements of myocardial performance, made shortly (1–2 hours) after ligation, have not been found to have a strong association with the development of post-ligation hypotension (5, 10, 12), indices of impaired myocardial performance, at 6–8 hours after the operation (closer to the time of clinical deterioration), appear to have a much stronger relationship (6). Prophylactic treatment with milrinone, starting shortly after ligation, has been reported to reduce the incidence of cardiorespiratory instability; however, despite early milrinone treatment, some infants continue to develop post-ligation catecholamine-resistant hypotension (8, 9). To date, no studies have examined the relationship between indices of myocardial performance during the postoperative period and the incidence of catecholamine-resistant hypotension.

We recently conducted a prospective, multicenter study to determine the relationship between an infant's postoperative cortisol response and the development of catecholamine-resistant hypotension (4). We found that infants who developed catecholamine-resistant

hypotension had significantly lower cortisol concentrations than infants who were normotensive or had hypotension responsive to catecholamine infusions and/or volume resuscitation. As part of the parent study, we performed an ancillary study to determine if (A) the development of catecholamine-resistant hypotension and (B) the presence of low postoperative cortisol concentrations were associated with indices of impaired myocardial performance. We report the results of this ancillary echocardiographic study below.

Methods

Eight of the original 12 study sites participating in the main study (4) had the resources to perform the ancillary study. After Institutional Review Board approval, 45 infants were enrolled following parental consent.

Inclusion/exclusion criteria, surgical, and postoperative management, as well as other details of the parent study can be found in our previous report (4). Infants were eligible for the study if they were 1) delivered between $23^{0/7}$ – $31^{6/7}$ weeks gestation, and 2) were about to have a PDA ligation. Although all infants had either a moderate or large left-to-right PDA shunt, there was no attempt to standardize the criteria used to determine the need for ligation (4).

Since catecholamine-resistant hypotension during the postoperative period was the primary outcome (see below), a standardized approach to management was agreed upon by all participating centers. The standardized approach outlined when volume expanders and vasopressors would be initiated, and the rate at which they would be increased. An arterial line and transducer were used to measure blood pressure continuously in all infants receiving catecholamine infusions or hydrocortisone for blood pressure support.

Hypotension was defined as "*mean BP* less than the 3rd percentile for postmenstrual age (13, 14) that lasted more than 15 minutes". Operationally this meant that infants were considered to be hypotensive, and require treatment for their hypotension, if their mean blood pressure was less than [(postmenstrual age in mm Hg) − (3 to 4 mm Hg)]. When infants failed to maintain an *adequate* BP (defined as "BP greater than the hypotensive range"), 2–3 boluses of isotonic saline (10 mL/kg per bolus) could be given to correct presumed hypovolemia, before catecholamine support was initiated. Infusion of dopamine or dobutamine (the choice was left to the clinical neonatologist) was started at 5 μg/kg/min and increased by 2.5 μg/kg/min every 15 minutes until an *adequate* BP was achieved. Combinations of dopamine and dobutamine could be used. Milrinone was not used to treat post-ligation hypotension (however, at one study site (7 infants), a milrinone infusion was started shortly after ligation as part of an institutional protocol designed to prevent postoperative hypotension (8, 9).

If a dopamine infusion >15 μg/kg/min failed to maintain an adequate BP, a “low stress dose” of intravenous hydrocortisone (starting at 1 mg/kg/day) could be added. The “low stress dose” of hydrocortisone could not be used unless the dopamine infusion was >15 μg/kg/min. The collective experience, shared by the centers prior to the study, was that infants who failed to maintain an *adequate* BP, with dopamine infusions =15 μg/kg/min, usually required dopamine infusions >20 μg/kg/min before *adequate* BPs were achieved. Therefore, we

classified infants as having *Catecholamine-resistant hypotension* if they received a dopamine infusion >15 μg/kg/min. In our study, all of the infants, who failed to maintain an *adequate* BP with dopamine infusions =15 μg/kg/min, were started on hydrocortisone (in addition to increasing the amount or number of catecholamine infusions).

We used a *Catecholamine Score* (calculated as the sum of all catecholamines corrected for potency: 1 × dopamine (μg/kg/min) + 1 × dobutamine) to measure the amount of catecholamine support an infant was receiving to maintain an *adequate* BP (15). A *Vasoactive Inotropic Score* (*Catecholamine Score* + 10 × milrinone (μg/kg/min)) was also calculated for each infant. (16).

We defined the severity of the hypotension by the maximum support needed to maintain an infant's BP above the hypotensive range: *mild* = volume boluses alone; *Catecholamine-responsive hypotension* = maximum Inotrope Score less than or equal to 15; and *Catecholamine-resistant hypotension* = maximum dopamine infusion >15 μg/kg/min.

Echocardiograms

We planned to perform our echocardiographic studies during the early stages of post-ligation hypotension, prior to the onset of *Catecholamine-resistant hypotension* (if it occurred). The decision to perform the study echocardiogram at this time point was based on several considerations. Prior studies have shown that echocardiograms performed either prior to, or 60 minutes after the surgery, are not associated with the development of post-ligation hypotension (5, 10, 12). On the other hand, echocardiographic measurements made at 6–8 hours after the operation (6) (when infants have already started to develop hypotension) have a strong relationship to the presence of postoperative hypotension. Unfortunately, the interpretation of measurements made in the presence of hypotension can be confounded by the need for and administration of inotropic drugs during the echocardiographic study. Since our goal was to determine if there was a relationship between measurements of impaired myocardial performance and the development of *catecholamine-resistant hypotension*, we planned to perform our studies between 6 and 14 hours after the ligation, at a time when hypotension was likely to be present, but before the onset of *catecholamine-resistant hypotension*.

Two-dimensional echocardiograms were performed by trained operators at each study site. All of the de-identified data recordings were analyzed by two of the authors who were unaware of the infants' degree of catecholamine support (SN, PM). The following echocardiographic measurements were made as previously described (5, 6): left ventricular output (LVO), stroke volume (SV), shortening fraction (SF), heart rate-corrected velocity of circumferential fiber shortening (VCFc), and LV end-diastolic diameter (LVEDD). Mean arterial BP (recorded at the time of the echocardiogram) was used to calculate wall stress (WS). We used mean BP because it is more representative of the entire cardiac cycle, and previous studies have shown an excellent correlation between mean arterial pressure and end-systolic pressure (17). Mean BP was also used to calculate systemic vascular resistance (SVR). We calculated the myocardial performance index (MPI), a widely used measure of global myocardial function, by dividing the sum of isovolumic contraction and relaxation times with the ejection time (18). MPI is inversely related to myocardial function. We were

especially interested in indicators of impaired left ventricle systolic performance (SF ≤25% and LVO <150 ml/kg/min) (19, 20) since these have previously been reported to be associated with post-ligation hypotension and need for inotropic support (6).

Steroid measurements

Echocardiographic measurements were compared with serum cortisol measurements made between 8–14 hours after the surgery. If hydrocortisone was started before the 8–14 hour time point, the cortisol measurement was obtained before the first hydrocortisone dose was administered. Cortisol assays were performed by ultra-performance liquid chromatography tandem mass spectrometry (4, 21). Values obtained by this technique have correlation coefficients between 0.7 and 0.99 when compared with those obtained by radioimmunoassy (22). The cortisol results were not available during the study and were not used in the decision to start hydrocortisone treatment.

Since the adequacy of an infant's cortisol response for maintaining blood pressure depends on both the circulating cortisol level and the stress experienced by the infant, we defined a "decreased cortisol response" as one in which the cortisol level was in the lower quintile of the postoperative cortisol concentrations found in the study population. By using this definition we could match the appropriateness of the cortisol response to the level of stress that the infant was experiencing since all infants underwent the same operation.

Statistics

Data were analyzed using Student's t-test, Chi-Square or Fisher's Exact, and the Mann-Whitney test as appropriate. Data are reported as mean ± standard deviation or median (interquartile range).

Results

Forty-five infants were enrolled in the ancillary echocardiographic study. Mean gestational age, birth weight, and postnatal age at ligation were 25.5±1.6 weeks, 782±190 grams, and 3.5±1.9 weeks, respectively. Forty percent (18/45) met criteria for hypotension: 8 were treated with volume boluses alone; 10 received catecholamines (dopamine, with or without dobutamine) in addition to volume boluses. Six of the 10 infants who received catecholamines were Catecholamine-responsive (normalized their blood pressure with *Catecholamine Scores* ≤15); 4 developed catecholamine-resistant hypotension (with dopamine infusion >15 μg/kg/min) and received hydrocortisone plus catecholamine infusions to normalize their blood pressure. As we observed in the parent study (4), infants in the ancillary study, who developed post-ligation hypotension (n=18), were more likely to be younger and weigh less at the time of ligation (27.9±2.6 versus 29.5±2.2 weeks post-menstrual age, $p<0.04$; 2.6±1.6 versus 4.1±1.9 weeks post-natal age, $p<0.02$; and, 910±338 versus 1162±353 grams, $p<0.02$, respectively) (1, 3).

Infants who received catecholamines to maintain an *adequate* BP, had them started within the first 12 hours after ligation. Maximal *Catecholamine Scores* were reached by 18 hours after ligation (Table 1). Among the infants who developed Catecholamine-resistant hypotension, *Catecholamine Scores* >15 did not occur until at least 10 hours after ligation

(Table 1). All of the echocardiograms were performed prior to the presence of catecholamine-resistant hypotension and before maximal *Catecholamine Scores* were reached (Table 1).

Infants who developed post-ligation hypotension were more likely than normotensive infants to have echocardiographic measurements consistent with decreased myocardial performance (Table 2-Part A): hypotensive infants were more likely to have shortening fractions less than or equal to 25%, and, there was a trend for LVO to be lower and MPI to be higher in the hypotensive group as well (Table 2-Part A).

The goal of our study was to determine if echocardiographic indices of myocardial performance were more impaired in infants who developed catecholamine-resistant hypotension than in those who developed milder forms of hypotension (i.e., those with volume-bolus responsive or catecholamine-responsive hypotension). We found that most of the myocardial and cardiac output measurements were similar between the two groups of hypotensive infants (Table 2-Part B). There were, however, significant differences between the two groups in the magnitude of their heart rates and systemic vascular resistances (Table 2-Part B). There was also a trend for wall stress to be lower in the catecholamine-resistant hypotension group (Table 2-Part B).

Infants who developed catecholamine-resistant hypotension had lower postoperative cortisol concentrations than infants who developed milder forms of hypotension (i.e., hypotension that responded to catecholamine infusions and/or volume boluses) (Table 2-Part B). We defined a “decreased cortisol level” as one in which the post-ligation cortisol level was in the lower quintile of the distribution of postoperative cortisol concentrations. Seventy-five percent of the infants who developed catecholamine-resistant hypotension had cortisol concentrations in the lower quintile compared with only 12% of those who never developed catecholamine-resistant hypotension ($p<0.02$). Infants who developed catecholamine-resistant hypotension were younger and weighed less at the time of ligation. However, as we previously observed in the parent study, low cortisol concentrations were a significant and independent risk factor for developing catecholamine-resistant hypotension even when demographic differences were included in a multivariable model (4).

We compared infants with postoperative cortisol concentrations in the lower quintile with infants whose cortisol concentrations were above the bottom quintile (Table 3). We found that the two groups differed only in indices of afterload (wall stress) and heart rate (Table 3).

Discussion

Prior studies have noted that myocardial performance appears to be impaired (decreased LVO, decreased SF, and increased MPI) following PDA ligation (5, 6, 8, 9). Our findings are consistent with the prior reports, and support the hypothesis that impaired myocardial performance may contribute to the development of postoperative hypotension. We found a significant association between decreased shortening fraction and the development of post-ligation hypotension. Similarly, there was a trend for hypotension to be associated with decreased LVO and increased MPI (Table 2-Part A).

The goal of our study was to determine if indices of impaired myocardial performance were also associated with a specific subset of hypotensive infants - those whose hypotension is refractory to catecholamine treatment. Our findings do not support an association between impaired myocardial performance and catecholamine-resistant hypotension (Table 2-Part B). Nor do they support a relationship between indices of impaired performance and the presence of decreased postoperative cortisol levels (which is associated with catecholamine-resistant hypotension) (Table 3). Infants in our study, who had decreased postoperative cortisol levels and catecholamine-resistant hypotension, had lower levels of systemic vascular resistance and afterload (Table 2-Part B and Table 3). These findings are more consistent with the hypothesis that low cortisol levels and catecholamine-resistant hypotension may be related to impaired vascular tone rather than to impaired cardiac performance. The fact that hydrocortisone treatment of preterm infants with catecholamine-resistant hypotension increases blood pressure by increasing systemic vascular resistance and afterload/wall stress (without altering cardiac output) is consistent with our findings and supports our hypothesis (23). We speculate that low postoperative cortisol concentrations may lead to down-regulation of vascular adrenergic receptors, which, in turn, may contribute to the failure of catecholamine infusions to maintain vascular tone and blood pressure (24, 25).

Our study has some important limitations:

In addition to the limitations inherent in the use of functional echocardiography in preterm infants, echocardiograms in our study were acquired by different sonographers - at different sites. However, the echocardiograms were analyzed by the same two authors who were unaware of the infants' need for catecholamine support.

In our study there were low numbers of infants who developed catecholamine-resistant hypotension. This is not an unexpected finding since only 8–15% of preterm infants undergoing PDA ligation develop this condition (1, 5, 6). However, the low numbers may have underpowered the study to determine a true difference in myocardial performance.

The study was designed so the echocardiograms would be performed close to the time the infants were expected to develop catecholamine-resistant hypotension. However, this meant that 80% of the infants who received catecholamines during the postoperative period were already receiving low-dose catecholamine infusions at the time of their echocardiogram. Although the level of catecholamine support during the echocardiogram varied between patients, all of the patients were studied before their maximum *Catecholamine Score* was reached and prior to the development of catecholamine-resistant hypotension. Nevertheless, the variation in inotropic support at the time of the echocardiogram may have confounded our analyses and altered our ability to detect significant differences in myocardial performance between the groups.

Despite the small sample size and variation in inotropic support at the time of the echocardiogram, we did observe a significant difference between the groups in measures of systemic vascular resistance and afterload. We speculate that following PDA ligation, impairment of myocardial performance may contribute to the development of postoperative

hypotension. However, once hypotension does occur, low cortisol concentrations and abnormal vascular tone may play a more important role than impaired cardiac performance in the development of refractory catecholamine-resistant hypotension. Only a randomized controlled trial, that examines the utility of cortisol replacement in hypotensive infants with low serum levels, will be able to elucidate the true contribution of low cortisol and low vascular tone on the severity of post-ligation hypotension.

Acknowledgement

This study was supported in part by grants from the Thrasher Research Fund, NIH/NCRR UCSF-CTSI Grant Numbers UL1 TR000004 and UL1 TR000445-06, NHLBI (HL109199), and a gift from the Jamie and Bobby Gates Foundation. Mass spectrometry was supported by grants for the Michigan Nutrition Obesity Center (DK089503) and Michigan Regional Comprehensive Metabolomics Research Core (U24DK097153).

Abbreviations

PDA	Patent ductus arteriosus
BP	Blood pressure
LVO	Left ventricular output
SF	Shortening fraction
SV	Stroke volume
VCFc	velocity of circumferential fiber shortening (corrected for heart rate)
LVEDD	Left ventricular end-diastolic diameter
WS	Wall stress
SVR	Systemic vascular resistance
MPI	Myocardial performance index
HR	Heart rate

References

1. Moin F, Kennedy KA, Moya FR. Risk factors predicting vasopressor use after patent ductus arteriosus ligation. Am J Perinatol. 2003; 20:313–320. [PubMed: 14528401]
2. Harting MT, Blakely ML, Cox CS Jr, Lantin-Hermoso R, Andrassy RJ, Lally KP. Acute hemodynamic decompensation following patent ductus arteriosus ligation in premature infants. J Invest Surg. 2008; 21:133–138. [PubMed: 18569433]
3. Teixeira LS, Shivananda SP, Stephens D, Van Arsdell G, McNamara PJ. Postoperative cardiorespiratory instability following ligation of the preterm ductus arteriosus is related to early need for intervention. J Perinatol. 2008; 28:803–810. [PubMed: 18615091]
4. Clyman RI, Wickremasinghe A, Merritt TA, Solomon T, McNamara P, Jain A, Singh J, Chu A, Noori S, Sekar K, Lavoie PM, Attridge JT, JR S, Gillam-Krakauer M, Reese J, DeMauro S, Poindexter B, Aucott S, Satpute M, Fernandez E, Auchus RJ. Hypotension following patent ductus arteriosus ligation: The role of adrenal hormones. J Pediatr. 2014; 164:1449–1455. [PubMed: 24636853]
5. Noori S, Friedlich P, Seri I, Wong P. Changes in myocardial function and hemodynamics after ligation of the ductus arteriosus in preterm infants. J Pediatr. 2007; 150:597–602. [PubMed: 17517241]

6. McNamara PJ, Stewart L, Shivananda SP, Stephens D, Sehgal A. Patent ductus arteriosus ligation is associated with impaired left ventricular systolic performance in premature infants weighing less than 1000 g. J Thorac Cardiovasc Surg. 2010; 140:150–157. [PubMed: 20363478]
7. Lemyre B, Liu L, Moore GP, Lawrence SL, Barrowman NJ. Do intra-operative fluids influence the need for post-operative cardiotropic support after a pda ligation? Zhongguo Dang Dai Er Ke Za Zhi. 2011; 13:1–7. [PubMed: 21251376]
8. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr. 2012; 160:584–589. e581. [PubMed: 22050874]
9. El-Khuffash A, McNamara PJ, Lapointe A, Jain A. Adrenal function in preterm infants undergoing patent ductus arteriosus ligation. Neonatology. 2013; 104:28–33. [PubMed: 23635520]
10. Kimball TR, Ralston MA, Khoury P, Crump RG, Cho FS, Reuter JH. Effect of ligation of patent ductus arteriosus on left ventricular performance and its determinants in premature neonates. J Am Coll Cardiol. 1996; 27:193–197. [PubMed: 8522694]
11. Takahashi Y, Harada K, Ishida A, Tamura M, Tanaka T, Takada G. Changes in left ventricular volume and systolic function before and after the closure of ductus arteriosus in full-term infants. Early Hum Dev. 1996; 44:77–85. [PubMed: 8821898]
12. Lindner W, Seidel M, Versmold HJ, Dohlemann C, Riegel KP. Stroke volume and left ventricular output in preterm infants with patent ductus arteriosus. Pediatr. Res. 1990; 27:278–281. [PubMed: 2320395]
13. Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: A prospective multicenter study. Philadelphia neonatal blood pressure study group. J Perinatol. 1995; 15:470–479. [PubMed: 8648456]
14. Watkins AM, West CR, Cooke RW. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. Early Hum Dev. 1989; 19:103–110. [PubMed: 2737101]
15. Skippen PW, Krahn GE. Acute renal failure in children undergoing cardiopulmonary bypass. Crit Care Resusc. 2005; 7:286–291. [PubMed: 16539583]
16. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, Charpie JR, Hirsch JC. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med. 2010; 11:234–238. [PubMed: 19794327]
17. Rowland DG, Gutgesell HP. Use of mean arterial pressure for noninvasive determination of left ventricular end-systolic wall stress in infants and children. Am J Cardiol. 1994; 74:98–99. [PubMed: 8017319]
18. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive doppler-derived myocardial performance index: Correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr. 1997; 10:169–178. [PubMed: 9083973]
19. Gill AB, Weindling AM. Echocardiographic assessment of cardiac function in shocked very low birthweight infants. Arch Dis Child. 1993; 68:17–21. [PubMed: 8439190]
20. Walther FJ, Siassi B, King J, Wu PY. Echocardiographic measurements in normal preterm and term neonates. Acta Paediatr Scand. 1986; 75:563–568. [PubMed: 3751552]
21. Taylor LK, Auchus RJ, Baskin LS, Miller WL. Cortisol response to operative stress with anesthesia in healthy children. J Clin Endocrinol Metab. 2013
22. Kulle AE, Welzel M, Holterhus PM, Riepe FG. Implementation of a liquid chromatography tandem mass spectrometry assay for eight adrenal c-21 steroids and pediatric reference data. Horm Res Paediatr. 2013; 79:22–31. [PubMed: 23328487]
23. Noori S, Friedlich P, Wong P, Ebrahimi M, Siassi B, Seri I. Hemodynamic changes after low-dosage hydrocortisone administration in vasopressor-treated preterm and term neonates. Pediatrics. 2006; 118:1456–1466. [PubMed: 17015536]
24. Seri I, Evans J. Controversies in the diagnosis and management of hypotension in the newborn infant. Curr Opin Pediatr. 2001; 13:116–123. [PubMed: 11317051]
25. Ng PC, Lee CH, Lam CW, Ma KC, Fok TF, Chan IH, Wong E. Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed. 2004; 89:F119–F126. [PubMed: 14977894]

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Table 1

Relationship between study measurements and the amount and timing of catecholamine support

	Normotension	Hypotension		
	None (n=27)	Volume-boluses alone (n=8)	Catecholamine-responsive (n=6)	Catecholamine-resistant (n=4)
Time after ligation when:				
Study Echocardiogram performed (hr)	10.0±5.0	9.5±3.1	11.1±4.5	7.4±1.5
Serum Cortisol measured (hr)	12.2±3.4	10.3±2.2	10.9±1.5	10.1±1.2
Catecholamine infusion started (hr)	-	-	6.0±5.0	2.5±2.4
Catecholamine Score >15 first reached (hr)	-	-	-	11.8±1.7
Maximum *Catecholamine Score* reached (hr)	-	-	13.3±5.1	14.8±3.0
Rate of catecholamine/inotropic administration at the time of the Echocardiogram				
Catecholamine Score	-	-	3.0±2.3	10±0
Vasoactive Inotropic Score	0.5±1.1	1.5±1.6	3.6±2.9	10±0

Definitions: Volume-boluses, infants who received volume-resuscitation/boluses alone; Catecholamine-responsive Hypotension, infants whose maximum *Catecholamine Score* was ≤15; Catecholamine-resistant Hypotension, infants whose maximum dopamine infusion was >15 μg/kg/min.

Table 2

Cardiac function, hemodynamics, and serum cortisol in study infants (n=45)

	Part A		**Part B**		
	Normotension	***Hypotension***	**Hypotension**		
	No Hypotension (n=27)	***Hypotension (all types) (n=18)***	**Volume- boluses alone (n=8)**	**Catecholamine-responsive (n=6)**	**Catecholamine-resistant (n=4)**
LVO (ml/kg/min)	240±58	***216±79***§	201±40	224±132	235±38
LVO <150 ml/kg/min (%)	8	***17***	13	33	0
Shortening Fraction ≤25% (%)	15	***50****	63	33	50
MPI	0.42±0.12	***0.47±0.21***	0.47±0.12	0.41±0.23	0.58±0.30
MPI >2z (%)	11	***33***§	25	33	50
LVEDD (cm/kg)	1.32±0.37	***1.36±0.31***	1.42±0.28	1.29±0.41	1.33±0.25
LA/Ao	1.51±0.34	***1.44±0.53***	1.54±0.49	1.32±0.33	1.39±1.02
SVR (mm Hg/L/kg/min)	167±74	***187±99***	202±78	216±132	110±44**
Heart Rate (beats/min)	155±13	***162±19***	153±14	160±24	180±5**
Stroke Volume (ml/kg)	1.56±0.42	***1.34±0.46***	1.33±0.33	1.36±0.72	1.31±0.24
VCFc (Circ/sec)	1.24±0.30	***1.25±0.36***	1.18±0.39	1.33±0.22	1.25±0.51
Wall Stress (g/cm2)	31±19	***29±19***	41±23	20±5	17±7§§
Cortisol (ng/ml) median (interquartile range)	24 (10–54)	***42 (10–84)***	60 (22–100)	51 (33–367)	8 (2–12)**

Definitions: *Hypotension (all types),* all hypotension groups combined (i.e., infants who received volume-resuscitation/boluses alone, catecholamine-responsive infants, and catecholamine-resistant infants).

LVO, left ventricular output; MPI, left ventricular myocardial performance index; MPI >2z, MPI greater than 2 standard deviations above the normative mean; LVEDD, left ventricular end-diastolic diameter; LA/Ao, ratio of left atrium to aortic root dimension; SVR, systemic vascular resistance; VCFc, velocity of circumferential fiber shortening (corrected for heart rate);

Values represent mean ± standard deviation or percent (%);

* p-value <0.05,

§<0.15: For comparisons between infants with No Hypotension and infants with *Hypotension (all types)*

** p-value <0.05,

§§<0.15: For comparisons between infants with Catecholamine-resistant hypotension and infants with milder types of Hypotension (Volume-resuscitation/boluses-alone and Catecholamine-responsive infants)

Table 3

Cardiac Function and Hemodynamics in infants with Low Post-ligation Cortisol concentrations

	Post-ligation Serum Cortisol concentrations in Lower Quintile	
	No (n=36)	**Yes (n=9)**
LVO (ml/kg/min)	224±71	251±54
LVO <150 ml/kg/min (%)	15	0
Shortening Fraction <25% (%)	25	11
MPI	0.43±0.14	0.43±0.24
MPI >2z (%)	20	22
LVEDD (cm/kg)	1.37±0.32	1.21±0.40
LA/Ao	1.53±0.43	1.29±0.36
SVR (mm Hg/L/kg/min)	183±89	146±64
Heart Rate (beats/min)	154±15	172±12*
Stroke Volume (ml/kg)	1.46±0.46	1.47±0.37
VCFc (Circ/sec)	1.22±0.32	1.32±0.34
Wall Stress (g/cm^2)	33±19	17±6*

Definitions: see Table 2

Values represent mean ± standard deviation or percent (%).

* p-value <0.05,

§ <0.15