Original Article

Left ventricular dysfunction in the immediate post-natal period

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Background: Our objective was to examine the clinical presentation, echocardiographic findings, and outcomes of newborns presenting with left ventricle (LV) dysfunction in the first 48 hours of life without perinatal asphyxia or structural heart disease. We hypothesize that LV dysfunction may occur due to maladaptation to extrauterine life.

Methods: This is a retrospective cohort analysis including infants born in a quaternary perinatal centre. Late preterm and term neonates who were diagnosed with left ventricular dysfunction at less than 48 hours of life were identified using an echocardiography clinical laboratory's database and extracorporeal life support database. LV dysfunction was defined as m-mode fractional shortening (FS) <28% or ejection fraction (EF) <50% on echocardiography or reduced function reported by a cardiologist. Data extracted included patient & maternal demographics, echocardiogram parameters, clinical status, and medications. The primary outcome measure was time to recovery of LV function based on echocardiography.

Results: Of the 69 patients identified, 19 patients were included in the final analysis. The mean gestational age was 38 weeks. Thirteen (68%) infants did not have an underlying cause identified despite extensive work-up. Four (21%) infants had exposure to maternal illicit drug use during pregnancy. Three infants died, and all infants without identifiable etiologies had recovery of LV function within 14 days of life.

Conclusions: LV dysfunction can occur during the abrupt transition from fetal to neonatal circulation and can be associated with maternal illicit drug use.

Keywords: Left ventricle (LV); dysfunction; fractional shortening (FS); infant; neonate

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Introduction

The successful transition from intrauterine to extrauterine life depends on a series of complex and immediate cardiovascular changes related to the change from a placental circulation to autonomous life sustained by the cardiorespiratory system (1). These changes include rapid alterations in systemic and pulmonary pressures, oxygen tension, adaptations to breathing air, and variations in the endocrine environment within minutes to hours of life (2,3). In particular, the left ventricle (LV) is required to make a significant change in cardiac output at birth, increasing its capacity from 1 to 2 mL/kg/min in a period of minutes to hours (2).

Known causes of LV dysfunction after birth include severe hypoxia, acidosis, congenital cardiomyopathies, and structural congenital heart disease (4). The objective of this retrospective cohort analysis was to study the clinical presentation, echocardiographic findings and outcomes of

newborns who present with echocardiography-confirmed LV systolic dysfunction in the first 48 hours of life, in the absence of the aforementioned factors. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-301/rc).

Methods

The study consisted of a retrospective chart review at British Columbia Children's & Women's Hospital, which provides quaternary perinatal and newborn services to inborn and outborn infants in British Columbia & Yukon Territory, covering an approximate population of four million. Two specific databases collected per standard of clinical care were utilized to identify potentially eligible patients: (I) the echocardiography lab's proprietary data mining software Syngo (Syngo Dynamics, Siemens Healthcare GmbH, Erlangen, Germany). This software was used to identify all neonates who were diagnosed with poor LV function in the first 48 hours of life and (II) the extra corporeal life support (ECLS) database, used to identify newborns put on veno-arterial ECLS for poor cardiac function. Period of review of above databases was between January 1, 2012 through May 31, 2020.

Inclusion criteria consisted of newborns between 33–42 completed weeks of gestation who were less than 48 hours old when diagnosed with LV systolic dysfunction on echocardiography. LV dysfunction was defined as fractional shortening (FS) on m-mode of less than 28%, or ejection fraction (EF) less than 50%, or reduced function reported by a cardiologist. Further subclassification of severity of contractile dysfunction was made modifying a classification of function published by Tissot *et al.* where dysfunction was subdivided into mild (FS 20–28%), moderate (15–19%) and severely reduced (less than 15%) (5). Those with evidence of perinatal asphyxia, as evidenced by a scalp or cord blood pH less than 7 and/or Appearance, Pulse, Grimace, Activity, and Respiration (Apgar) scores of ≤3 at 1 minute and/or 5 minutes after birth, or a clinical diagnosis of perinatal asphyxia made by the intensive care team were excluded. Infants with structural congenital heart disease, other than a patent ductus arteriosus or patent foramen ovale, were also excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for this study was obtained from the University of British Columbia Children's and Women's Health Centre of British Columbia Research Ethics Board (No. H19-02535) and individual consent for this retrospective analysis was waived.

Data extracted included patient & maternal demographics, echocardiogram parameters, clinical status, and medications used. The primary outcome was time to recovery of LV function based on echocardiographic findings. Recovery of function was defined as normal FS of ≥28% or EF of ≥50%. A diagnosis of persistent pulmonary hypertension of the newborn (PPHN) was made after accounting for parameters of pulmonary artery pressure such as patent ductus arteriosus flow direction and velocity, tricuspid regurgitation velocity, and flattening of the interventricular septum in systole. Markers of right ventricle (RV) systolic function included tricuspid annular plane systolic excursion, subjective visual assessment of RV function, myocardial performance index, and qualitative visual inspection of RV function. Parameters of diastolic function such as tissue doppler indices were also recorded. All patients underwent a cardiology consultation and final diagnosis was assigned by the on call cardiologist with clinic-echocardiographic correlation. The echocardiograms were also reviewed by the reading cardiologist, which is normal standard operating procedure at this centre. No significant conflict was noted between the echocardiography reading and consulting cardiologist. All echocardiograms were reviewed by the study team and results agreed with the reports by the cardiologists.

Statistical analysis

Descriptive statistics for patient characteristics and outcomes are reported. Normality of the data was tested using the Kolmogorov-Smirnov test. Categorical data are presented as frequencies (percentages), and continuous data as mean ± standard deviation or median with interquartile ranges after testing for normality.

Results

A total of 69 patients were identified as per inclusion criteria. Twenty were excluded due to a gestational age of less than 33 weeks, 15 had structural heart disease, 11 had perinatal asphyxia, 3 babies echocardiograms were found to be normal on review, and 1 was excluded due to incomplete records. Nineteen patients were included in the final data analysis, with a mean gestational age of 38 weeks (range: 35–41 weeks) and a mean birth weight of 3,100 grams (range: 1,800–4,200 grams). Twelve infants were male

Table 1 Maternal demographics and comorbidities, including antenatal drug usage

Patient number	Maternal age (years)	Maternal health conditions	Maternal drug and substance use
1	38	Severe preeclampsia	Aspirin
2	36	Nil	Nil
3	39	Nil	Nil
4	29	Asthma	Flovent
5	31	Nil	Nil
6	30	Gestational diabetes mellitus	Nil
7	23	Multiple sclerosis	Nil
8	32	Morbid obesity (body mass index >40 kg/m^2)	Nil
9	34	Hepatitis C	Heroin, methamphetamine, alcohol, smoking
10	25	HIV, gonorrhoea, chlamydia	Heroin, methamphetamine, alcohol, smoking, methadone, abacavir, lamivudine, atazanavir, ritonavir
11	24	Depression, post-traumatic stress disorder, urinary tract infection	Heroin, methamphetamines, marijuana, smoking
12	34	Gestational diabetes mellitus	Nil
13	31	Nil	Heroin, methadone, over the counter drug abuse: codeine, dimenhydrinate, acetaminophen
14	30	Nil	Nil
15	26	Hepatitis B	Nil
16	37	Nil	Nil
17	32	Depression	Venlafaxine
18	29	Nil	Nil
19	30	Anxiety, depression	Sertraline

Nil, not in the list; HIV, human immunodeficiency virus.

(64%) and 2 (10%) were small for gestational age (defined as <10th percentile for gestational age). One was large for gestational age (defined as >90th percentile for gestational age). All infants were born to non-consanguineous parents and were products of spontaneous conception. Apgar scores were performed in all patients and at 1 minute, 18 of the 19 patients were 7 or above and all 19 patients were 8 or above at 5 minutes. Initial rooming in with the mother was advised by the pediatrician/midwife for 11 of the 19 and the remaining 8 patients were advised to be transferred to the intensive care unit (ICU) or a special baby unit at birth. However, 10 of the roomed in babies were subsequently transferred to the ICU. Nine babies were transferred on day 1 and 1 on day 2 of life. Only 1 baby was nursed in a maternal unit until recovery of cardiac function. Echocardiogram was performed on day 1 in 12 and on day 2 in 7 newborns.

In our cohort, 68% (n=13) of the mothers were diagnosed to have significant physical or mental health disorders (*Table 1*). Eight mothers (42%) in this study were on medications for various reasons and 4 (21%) reported illicit drug use during pregnancy. Seven infants were born via Caesarean Section (indications: placenta previa, triplet gestation, increased body mass index, repeat lower section caesarean section, and abnormal heart rate tracing).

In our cohort, 6 patients had definitive diagnoses (2 with early-onset neonatal infection, 1 with suspected inborn error of mitochondrial metabolism, 1 with Barth syndrome, and 2 with arrhythmia), and the remainder of the cohort had isolated LV dysfunction without any

Table 2 Patient course and outcomes

Patient number	Intensive cardiopulmonary assistance	Respiratory assistance (days)	Final diagnosis	Time to endpoint	Function reduction on initial scan (FS %)	FS % on day of recovery/ endpoint
1	Milrinone ×4 d	NPO ×5 d	Resolved LV dysfunction (? cause)	Functional recovery 8 d	Mild (visually reported to be poor)	Day 8–41%
2	Epinephrine ×1 d	CV ×2 d	Inborn error of mitochondrial metabolism	Death 2 d	Moderate (15%)	Last echo on day 2–17%
3	Dopamine ×1 d, ECLS ×4 d	CV ×4 d, CPAP ×1 d	Resolved LV dysfunction (? cause)	Functional recovery 4 d	Mild (23%)	33%
4	Nil	Nil	Resolved LV dysfunction (? cause)	Functional recovery 14 d	Mild (24%)	29%
5	Milrinone ×6 d	Nil	Resolved PPHN	Functional recovery 4 d	Mild (24%)	40%
6	Dobutamine ×1 d	CV ×1 d, CPAP ×1 d	Resolved LV dysfunction (? cause)	Functional recovery 3 d	Moderate (19.4%)	29.4%
7	Dobutamine ×3 d + epinephrine ×1 d	CV ×4 d	Maternal enterovirus with transplacental infection, severe cardiac dysfunction	Death 4 d	Moderate (12.5%)	Last echo day 4–29.4%
8	Milrinone ×162 d + dopamine × 2 d, ECLS ×13 d	CV ×92 d, CPAP ×1 d	Barth syndrome	Progress to cardiomyopathy	Moderate (12%)	Day 128–38%. Significant diastolic dysfunction
9	Epinephrine ×3 d	CV ×6 d, CPAP ×1 d	Resolved PPHN	Functional recovery 5 d	Severe (13%)	33%
10	Nil	CPAP ×1 d	Diastolic dysfunction (? cause)	Functional recovery 87 d	Severe (13%)	31%
11	Norepinephrine ×4 d + dopamine ×5 d	CV + JET + iNO ×9 d, CPAP ×2 d	Resolved PPHN	Functional recovery 3 d	Moderate (18%)	49%
12	Dopamine ×3 d + norepinephrine ×3 d	CV ×4 d	Fulminant E coli sepsis with meningitis	Death 4 d	Mild (27%)	Last echo day 2–28%
13	Nil	Hi flow + CPAP ×5 d	? Impaired function due to premature closure of PDA	Functional recovery 9 d	Severe (13%)	40%
14	Nil	Nil	Premature ventricular ectopics and poor LV function	Functional recovery 9 d	Mild (23%)	32%
15	Nil	Nil	Resolved LV dysfunction (? cause)	Functional recovery 4 d	Mild (23%)	37%
16	Nil	Nil	Panhypopituitarism; LV dysfunction	Clinical recovery 6 d	Mild (22%)	Repeat echo not performed due to complete clinical recovery
17	Milrinone ×4 d + prostaglandin ×1 d	CPAP ×2 d	Resolved PPHN	Functional recovery 3 d	Severe (13%)	35%
18	Nil	CPAP ×1 d	Ectopic atrial tachycardia	Functional recovery 5 d	Mild (23%)	36%
19	Milrinone ×4 d	CPAP ×1 d	Resolved PPHN	Functional recovery 6 d	Mild (visually reported to be poor)	31%

FS, fractional shortening; NPO, nasal prongs oxygen therapy; d, days; LV, left ventricle; CV, conventional ventilation; ECLS, extracorporeal life support; CPAP, continuous positive airway pressure; Nil, not in the list; PPHN, pulmonary hypertension of the newborn; JET, jet ventilation; iNO, inhaled nitric oxide; PDA, patent ductus arteriosus.

Table 3 Clinical indications for echocardiography

Indication(s) for echocardiography	Number of patients
Cyanosis	7
Shock/hypotension/metabolic acidosis	4
Respiratory distress	2
Antenatal possibility of congenital heart disease	2
Irregular pulse	2
Pathological murmur/gallop	2
Significant pre/post ductal saturation difference	1
Post cardiac arrest	1
Hypertension	1
Antenatal poor cardiac function	1

specific diagnoses (*Table 2*). The clinical indications that prompted an echocardiogram in babies where no clear cause was found are summarized in *Table 3*. Most common indications included cyanosis, shock, hypotension, and metabolic acidosis. Twelve infants required inotropic support, 2 required ECLS and 3 died. All survivors, except 2, had recovery of LV function within 14 days of life. The FS on the initial scan for all patients was a mean of 20.26%±7.25%. Infants were found to have functional recovery at a median of 5 days [interquartile range (IQR): 4 days]. FS at final follow-up scan was 35.46%±8.63%. All infants without clear etiologies recovered function within 14 days of life with or without advanced cardiac support. Although an attempt was made to collect RV function parameters, due to inconsistencies with laboratory reporting, we were not able to procure any useable RV data. As well, the cardiologists' reports did not mention RV dysfunction. The babies with poor function underwent a viral panel which included a standard myocarditis workup. No specific viruses were identified other than enterovirus, as mentioned. Cardiac magnetic resonance imaging (MRI) was not performed at the time or during follow-up.

There were 3 deaths in our cohort. The mean FS at first scan for the babies who died was 18.5%±8.32% and at last scan was 24.93%±6.93%. The causes for death in the 3 patients were (I) presumed inborn error of metabolism; (II) trans-placental transmission of enteroviral infection; and (III) Escherichia coli sepsis. EF was not found to correlate with LV systolic function.

The babies did not have any comorbidities other than those mentioned in *Table 2*. Babies who died had very high lactate levels and low pH as markers of poor microcirculation. As it is well established that these are markers of poor circulation, we did not elaborate on them further.

Discussion

Our study aimed at characterizing LV systolic dysfunction in newborns born between 33–42 weeks gestation without obvious risk factors. In our cohort, less than one-third of patients had definitive diagnoses despite extensive testing. Of those without a clear underlying etiology, recovery of LV function occurred in all within 14 days, with the exception of a baby born to a human immunodeficiency virus (HIV) positive mother on anti-retrovirals. In our cohort of newborns with LV dysfunction, 21% of mothers reported illicit drug use during the pregnancy. Echocardiographic parameters were not statistically significant predictors of death.

Poor LV function at birth is usually attributed to congenital heart disease and intra-partum asphyxia. In addition, sepsis and septic shock have been associated with LV dysfunction (6,7). There have been some studies exploring the effects of maternal HIV and anti-retroviral drugs on poor LV function after birth, none statistically significant (8-10). The significance of the severity of LV dysfunction in a cohort of newborns with PPHN was demonstrated by AbdelMassih *et al.* (11). Various possible etiologies such as hypoxia, pressure and volume overload, and LV-RV interactions were suggested.

Maternal drug abuse has been shown to cause various pathologies in the fetus and child, ranging from miscarriage to long term neurocognitive disabilities (12). From a cardiovascular standpoint, selective serotonin reuptake inhibitors have recently been implicated to cause PPHN, as shown in a recent meta-analysis (13). Use of illicit drugs has been shown to be a causative factor for intrauterine growth retardation (14) and there is evidence of echocardiographically detectable subclinical changes in LV stroke volume, LV cardiac output, and indices of diastolic function noted in babies born to intrauterine growth restriction mothers (15). In total, 21% of mothers in our study reported illicit use of drugs. This appears to be out of proportion from the national average of 5% (16). Going forward at our institution, we have been more aggressive with performing cardiac MRIs. The authors now consider that performing a cardiac MRI might be prudent keeping in

mind the clinical scenarios. We consider an echocardiogram and basic myocarditis workup, including a sepsis and viral screen, as important work up for this cohort of patients.

Limitations

Our study has several limitations. This is a convenient sample in a referral center to study LV dysfunction in newborns without obvious risk factors. The causation of LV dysfunction and outcomes of infants may vary across different centres. The maternal health conditions were largely self-reported without going into detailed toxicology screening. We cannot rule out the possibility that exposure to drugs and other high risk behaviors were under-reported. The impact of prenatal exposure to illicit drugs is not conclusive, as studies often failed to adjust for poor prenatal care and nicotine exposure (17). We were unable to track babies with maternal exposure to illicit drugs. A comparison to a cohort of babies born to mothers with illicit drug exposure who underwent an echocardiogram in the first 48 hours of life would provide useful data. This subgroup will have missed the asymptomatic or minimally symptomatic patients, making this a highly susbselected population and hence any power derived from the study will not have much objective value. Further, this was a sample of convenience. Future prospective studies with a larger sample size are warranted.

Conclusions

The results from this cohort study revealed that there is a subgroup of babies who are born with poor cardiac function at birth without an identified etiology. A proposed mechanism for this finding is delayed cardiovascular adaptation to extrauterine life. There is a disproportionately high number of mothers using illicit drugs during pregnancy in this group of patients. In addition, 12 mothers (63%) had significant antenatal comorbidities, which suggests that the maternal milieu might be a factor in determining successful transition of the LV to postnatal life.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-301/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-301/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-301/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for this study was obtained from the University of British Columbia Children's and Women's Health Centre of British Columbia Research Ethics Board (No. H19-02535) and individual consent for this retrospective analysis was waived.

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