THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Cardiopulmonary Adaptation During First Day of Life in Human Neonates

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Objective To characterize the natural history of cardiopulmonary physiology in the first 24 hours after birth.

Study design A prospective observational study of healthy newborns was conducted at a large tertiary perinatal center. Echocardiography was performed at <0.5, 2-3, 7-10, and 22-24 hours of age. Specifically, assessment of pulmonary vascular resistance (PVR) (pulmonary artery acceleration time [PAAT], right ventricular ejection time, right ventricular ejection time:PAAT [PVR index], and PAAT indexed to heart rate [PAATi]), ventricular outputs (right and left), and ventricular function (tricuspid annular planar excursion, right ventricular [RV] fractional area change [FAC], RV/left ventricular [LV] global peak longitudinal strain, and LV ejection fraction) were performed. One-way repeated-measures ANOVA analysis was performed for time-dependent variables.

Results In total, 15 neonates (9 males), born at 40 ± 0.8 weeks and 3.5 ± 0.5 kg, respectively, were studied. We observed increased PAATi ($P < .05$) by 2-3 hours, followed by a subsequent decline in all indices of PVR (PVR index, PAATi, midsystolic notching, and right-to-left ductal flow [$P < .0001$]). Although right and left ventricular stroke volume increased over the study interval ($P < .001$), LV output remained stable. All indices of RV function (tricuspid annular planar excursion, RV fractional area change 4-chamber, and RV global peak longitudinal strain-3 chamber [$P < .001$]) increased during the study interval.

Conclusion The immediate transition after birth is characterized by lower PVR, reversal of the transductal shunt, and increased biventricular stroke volume. The differential adaptive response of the RV and LV is novel and may relate to loading conditions and patent ductus arteriosus closure. *(J Pediatr 2018;■■:■■-■■).*

The transition from intrauterine to extrauterine life represents a critical phase of physiological adaptation, impacting many organ systems, most notably the heart and the lungs. Most neonates complete this transition without complications; however, dysregulation of normal postnatal adaptation may lead to acute cardiopulmonary instability, necessitating advanced intensive care support.[1] In some situations, death or adverse neurosensory impairment may ensue.[2,3] The approach to cardiovascular care in these patients is limited by the lack of reliable or readily available physiologic measures of cardiopulmonary health and suboptimal thresholds for therapeutic interventions, driven in part by a paucity of information regarding physiological cardiac adaptation after birth and the interaction with changes in pulmonary circulation.

Experiments in animals have demonstrated a progressive decrease in pulmonary vascular resistance (PVR) over the first 48-72 hours after birth in response to lung recruitment and increased alveolar paO_2.[4] As PVR decreases, the direction of flow across the ductus arteriosus (DA) and foramen ovale becomes increasingly left-to-right, and the shunts eventually close. The

DA	Ductus arteriosus
FAC-3C	Fractional area change measured from RV-focused apical 3-chamber view
FAC-4C	Fractional area change measured from RV-focused apical 4-chamber view
GLS	Global peak longitudinal strain
LV	Left ventricular
LVO	Left ventricular output
LVSV	Left ventricular stroke volume
PAAT	Pulmonary artery acceleration time
PAATi	Pulmonary artery acceleration time index
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PVR	Pulmonary vascular resistance
PVRi	Pulmonary vascular resistance index
RV	Right ventricular
RVET	Right ventricular ejection time
RVO	Right ventricular output
RVSV	Right ventricular stroke volume
S:D	Systole:diastole
SVR	Systemic vascular resistance
TAPSE	Tricuspid annular plane systolic excursion
TDI	Tissue Doppler imaging

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Funded by the Canadian Institutes of Health Research (CIHR; MOP #93596 and 84290 [to R.J.]). A.J. was supported by a Sick Kids Research Training Centre Clinician Scientist Training Program Doctoral Award. P.M. and A.J. serve on the advisory board of Mallinckrodt Pharmaceuticals. The other authors declare no conflicts of interest.

Portions of this study were presented as a poster at the Pediatric Academic Societies annual meeting, May 6-9, 2017, San Francisco, California.

0022-3476/$ - see front matter. Crown Copyright © 2018 Published by Elsevier Inc. All rights reserved.
https://doi.org10.1016/j.jpeds.2018.04.051

cardiovascular impact of the transitional period on myocardial function and cardiac output is not well understood. We recently published normative echocardiography data for right ventricular (RV) and left ventricular (LV) function, pulmonary hemodynamics, and shunt characteristics in a cohort of 50 healthy neonates born at term.[5,6] We demonstrated a reduction in PVR during the first 2 days of age, without any discernible change in heart function. The study lacked evaluation of infants within the first 12 hours of life, a critical time period during which the adaptive physiologic changes are expected to be greatest. The primary aim of this study was to characterize cardiopulmonary changes associated with adaptation to postnatal life in healthy humans. We determined the natural history of PVR, cardiac output, myocardial function, and transitional shunts over the first 24 hours following birth.

Methods

A prospective observation study was conducted in the postnatal ward at Mount Sinai Hospital, a tertiary care teaching hospital. The study was approved by the institutional research ethics board. Women with singleton, low-risk pregnancies who presented in labor between 37 and 42 completed weeks of gestation were approached for consent before delivery. A qualitative, time-specific, post-hoc comparative analysis with data obtained in a previous prospective observational study of healthy neonates born at term aged <48 hours was performed.[5,6]

Exclusion criteria included maternal diabetes, hypertension, use of antidepressant medications, abnormal results of first trimester screen, any congenital anomaly on anatomy ultrasound scan, known genetic anomaly, abnormal Doppler profile in umbilical artery, or clinical suspicion of chorioamnionitis. We also excluded infants with arterial or venous cord pH <7.0, Apgar score ≤5 at 5 minutes of age or who required any active resuscitation other than drying and stimulation, were noted to have dysmorphic features, or required admission to the neonatal intensive care unit. In addition, we excluded any infant with congenital heart disease except patent foramen ovale (PFO) and/or a patent ductus arteriosus (PDA).

We obtained serial echocardiography-derived measures of PVR, pulmonary and systemic blood flow, cardiac function, and shunts within 24 hours of birth. Each infant underwent 4 sequential echocardiograms at <0.5 hours, 2-3 hours, 7-10 hours, and 22-24 hours of age. Images were acquired via an E9 ultrasound system with a 12-MHz neonatal transducer (GE Medical Systems, Milwaukee, Wisconsin). The first echocardiogram was performed in the delivery room and completed by 30 minutes of age. Subsequent scans were performed in the postnatal ward and lasted <20 minutes. All infants were assessed at rest with simultaneous electrocardiogram recording. All scans were recorded in RAW DICOM data format, digitally stored, and analyzed off-line in a random order with a dedicated workstation (EchoPAC, version BT10; GE Medical Systems). All imaging and analyses were performed according to published American Society of Echocardiography guidelines.[7,8] All echocardiographic indices are listed in **Table I** and described in the **Appendix** (available at www.jpeds.com).

Assessment of PVR was performed by measuring pulmonary artery acceleration time (PAAT) and pulmonary vascular resistance index (PVRi = right ventricular ejection time

Table I. List of echocardiography-derived indices used in this study

PVR	• PAAT • PVRi = RVET/PAAT • PAATi
Pulmonary blood flow	• RVSV • RVO
Systemic blood flow	• LVSV • LVO
Shunts	• PDA • PFO
RV function	Systolic function • TAPSE • FAC-4C • FAC-3C • TDI-derived peak systolic myocardial velocity measured on RV lateral wall just below the tricuspid annulus (RV s′) • GLS measured using speckle tracking echocardiography from the RV lateral wall (GLS-4C) and inferior wall (GLS-3C) Diastolic function • Isovolumic relaxation time measured using TDI (IVRT′) • Ratio of tricuspid valve early (TvE) and late (TvA) inflow velocities
LV function	Systolic function • Ejection fraction measured with the Simpson biplane method • TDI-derived peak systolic myocardial velocity measured on LV lateral wall just below the mitral annulus (LV s′) • Average of the peak longitudinal strain measured using speckle tracking echocardiography from LV-focused apical 4-, 3-, and 2-chamber views (LV GLS) Diastolic function • IVRT′ • Ratio of mitral valve early (MvE) and late (MvA) inflow velocities
Global systolic and diastolic function (calculated for both ventricles)	• Myocardial performance index measured using TDI (= [IVRT′ + isovolumic contraction time]/duration of systole) • Ratio of total duration of systole and diastole measured using TDI (S′:D′)

FLA 5.5.0 DTD ■ YMPD9972_proof ■ May 23, 2018

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