Preterm Birth Is Associated with Altered Myocardial Function in Infancy

Ulf Schubert, MD, Matthias Müller, MD, PhD, Hashim Abdul-Khaliq, MD, PhD, and Mikael Norman, MD, PhD, *Stockholm, Sweden, and Homburg, Germany*

Background: Preterm birth has been associated with myocardial remodeling and accelerated cardiovascular ageing in later life, but the underlying mechanisms are unknown. The investigators used echocardiography to undertake a sequential analysis of myocardial function in preterm infants.

Methods: This study evaluated the cardiac performance of 25 very preterm infants (born at a gestational age of 26–30 weeks), at birth, 3 months (term-equivalent age), and 6 months later (3 months of corrected age). Speckle-tracking echocardiography was used to determine myocardial function, assessing the magnitude of myocardial deformation as longitudinal strain, deformation rate (strain rate), and velocity in both ventricles during systole and diastole. The results were compared with those in 30 infants born at term investigated at birth and at 3 months of age.

Results: At term-equivalent age, the speckle-tracking estimates were similar in both groups. Three months later, very preterm infants exhibited significantly lower left ventricular mean free wall longitudinal strain (−20.0% vs −22.0%, P = .010) and lower left ventricular early diastolic (median, −7.37 vs −10.9 cm/sec, P = .003) and late diastolic (median, −5.11 vs −6.95 cm/sec, P = .009) myocardial velocities than infants born at term. There were no statistically significant group differences in right ventricular or interventricular septal measurements. Conventional echocardiographic variables did not differ significantly between the two groups at any age.

Conclusions: Very preterm infants develop altered left ventricular myocardial function 6 months after birth. Follow-up examinations are needed to determine the implications for cardiovascular health in the growing number of children surviving very preterm birth. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Preterm infant, Cardiac function, Speckle-tracking echocardiography

Each year, approximately 15 million infants are born preterm. Although preterm birth is still a major cause of death worldwide,[1] significant improvements in perinatal care in developed countries mean that it is no longer a fatal pregnancy complication, and a growing number of infants now survive.[2] This development has contributed to an emerging interest in the long-term health and diseases experienced by children and adults who were born preterm.

So far, the significance of preterm birth for cardiac function over the course of a person's lifetime is largely unknown. It is reassuring that premature birth was not associated with increased mortality from ischemic heart disease at an older age in a study that examined births between 1925 and 1949.[3] However, the neonatal survival rates reported for that historic cohort were very limited and selective. In a more contemporary cohort of young adults, preterm birth was associated with structural and functional changes to the left and right sides of the heart, also after adjusting for other risk factors such as blood pressure.[4,5] In a large registry study, the adjusted hazard ratio for cardiovascular mortality in 35- to 45-year-old Swedes decreased by 7% with each additional week of gestation.[6] Given that prematurity has also been associated with adult hypertension,[7,8] diabetes,[9,10] and stroke,[11] it is important to explore and understand the early effects of preterm birth on cardiac function and development.

To our knowledge, no previous study compared the evolution of myocardial function in preterm and term infants beyond the neonatal period into infancy. One animal study involved the delivery of healthy pregnant sheep before they reached full term gestation to study the effects of prematurity in isolation from selection bias and confounding factors. This intervention resulted in irreversible myocardial remodeling in the preterm lambs, with cardiomyocyte hypertrophy and collagen deposition in both ventricles already observed 9 weeks after term-equivalent age.[12] In two recent human studies, altered diastolic myocardial function was reported only weeks after preterm birth, but follow-up ended before or at term-equivalent age.[13,14]

Given significant reductions in longitudinal strain and strain rate previously reported in adults born preterm,[4] we hypothesized that such

From the Division of Pediatrics, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden (U.S., M.N.); and the Department of Pediatric Cardiology, University Hospital Homburg (Saar), Homburg, Germany (M.M., H.A.-K.).

This study was financially supported by the Swedish Heart and Lung Foundation; through a regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, and the Childhood Foundation of the Swedish Order of Freemasons.

Reprint requests: Ulf Schubert, MD, Neonatal Intensive Care Unit K 78, Karolinska Institutet and Karolinska University Hospital, 141 86 Stockholm, Sweden (E-mail: *ulf.schubert@ki.se*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2016.03.011

Abbreviations

IVS = Interventricular septum

LV = Left ventricular

LVM = Left ventricular mass

MPI = Myocardial performance index

PDA = Patent ductus arteriosus

ROI = Region of interest

RV = Right ventricular

SV = Stroke volume

reductions in myocardial function occur in infancy as a consequence of the preterm transition from fetal to neonatal hemodynamics. To test this hypothesis, we used speckle-tracking echocardiography as well as conventional echocardiography to provide serial determinations of cardiac function after very preterm delivery during the first 6 months of postnatal life.

METHODS

This observational, longitudinal study measured cardiac function in very preterm infants at birth, at term-equivalent age, and at 3 months of corrected age. For comparison, we studied a healthy control group of term infants at birth and at 3 months of age. Both groups were recruited in parallel, and they represent a randomly selected, convenience sample in which a total of 135 echocardiographic investigations were performed during a study period of 2 years. Parental informed consent was obtained before each examination, and the study protocol was approved by the regional ethical review board in Stockholm, Sweden. All the parents who were invited to take part agreed to participate in the study, and there were no dropouts because of pregnancy or postnatal complications, fetal or infant death, or withdrawal of parental consent.

Subjects

The study group comprised 25 very preterm singleton infants, 13 boys and 12 girls, born at the Karolinska University Hospital in Stockholm. The gestational age of the infants varied between 26 and 30 weeks. According to Swedish sex- and gestational age–specific reference data for normal fetal growth,[15] 21 preterm infants were appropriate for gestational age, with birth weights within ±2 SDs of the mean, and four were small for gestational age, with birth weights of >2 SDs below the mean. There were no cases of chromosomal disorders, congenital syndromes or infections, or malformations.

We included 30 healthy infants born at term with normal birth weights as control subjects. This reference group was recruited at routine antenatal visits in the second trimester at three primary health care maternity clinics in Stockholm.

Gestational age was prospectively determined in all pregnancies by fetal ultrasound examinations at 17 to 18 postmenstrual weeks, according to Swedish recommendations for antenatal care. The parents were interviewed about their family histories of cardiovascular disease, and a positive history was defined as a report of myocardial infarction, stroke, treated hypertension, or hyperlipidemia among the parents' first-degree relatives.

Umbilical artery blood flow velocity measurements had been performed before delivery, on the basis of clinical indications, in 10 of the 25 pregnancies that ended very preterm, and the pulsatility index was found to be normal in all cases, within ±2 SDs for gestational length. There were no data or measurements on fetal umbilical blood flow in the control subjects born at term.

None of the mothers had diabetes. The most common reasons for premature delivery were premature rupture of membranes ($n = 9$), preterm labor ($n = 7$), and vaginal bleeding ($n = 7$). In addition, one mother needed a cesarean delivery because she developed preeclampsia, and another delivery was medically indicated because the mother had a liver tumor.

Table 1 Maternal and infant characteristics

	Preterm infants (n = 25)	Term control infants (n = 30)	P
Maternal data			
Age (y)	32.6 ± 4.2	31.1 ± 4.3	.20
Parity	1.7 ± 1.0	1.9 ± 1.0	.46
Family history of CVD	3/25 (12%)	5/30 (17%)	.62
Smoking in pregnancy	5/25 (20%)	1/30 (3.3%)	.048
Perinatal data			
Gestational age (wk)	27.7 ± 1.2	39.0 ± 1.4	—
Boys	13/25 (52%)	10/30 (33%)	.16
Birth weight (g)	1,153 ± 258	3,456 ± 437	—
Birth-weight SDS	−0.82 ± 1.01	0.09 ± 1.10	.003
Birth length (cm)	37.2 ± 2.7	50.3 ± 1.9	—
Infant data at final assessment			
Corrected age (wk)*	13.7 ± 2.1	13.0 ± 1.4	.13
Weight (kg)	5.61 ± 0.48	6.09 ± 0.62	.003
Length (cm)	59.8 ± 2.5	61.2 ± 2.7	.072
Body surface area (m^2)†	0.305 ± 0.018	0.321 ± 0.021	.004
Heart rate (beats/min)	144 ± 17	143 ± 15	.90
Systolic blood pressure (mm Hg)	91 ± 13	94 ± 9	.41
Diastolic blood pressure (mm Hg)	59 ± 11	63 ± 12	.32

CVD, Cardiovascular disease; *SDS*, SD score.
Data are expressed as mean ± SD or as proportion (percentage).
*Corrected age = chronological age reduced by the number of weeks born before 40 weeks of gestation.[16]
†Calculated according to the Mosteller formula.[20]

The infant and maternal characteristics are presented in Table 1.

Neonatal Characteristics and Morbidity among Very Preterm Infants

In the very preterm group, 22 of 25 infants (88%) received antenatal steroids for induction of lung maturation, and 10 infants (40%) needed ventilator support during their initial hospitalization. Twenty (80%) had umbilical artery catheters inserted after birth, with the catheter tip located in the lower thoracic aorta (Th6–Th10). All umbilical catheters were removed before the first ultrasonographic assessment. Five infants (20%) were pharmacologically treated with ibuprofen for hemodynamically significant patent ductus arteriosus (PDA), but none of the infants needed surgical ligation for this condition. Ten infants (40%) had septicemia; three (12%) had diagnoses of mild intraventricular hemorrhage (grades 1 and 2); four (16%) had bronchopulmonary dysplasia, defined as needing supplementary oxygen at 36 weeks of postmenstrual age; and one infant (4%) had retinopathy of prematurity stage 1. There were no cases of necrotizing enterocolitis.

Study Protocol

In accordance with recommendations of the American Academy of Pediatrics,[16] participants' age is reported as "postmenstrual age"