Impact of Skin-to-Skin Parent-Infant Care on Preterm Circulatory Physiology

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Objectives To ascertain the impact of skin-to-skin care between parents and infants on cardiac function and cerebral blood flow in preterm infants.

Study design We undertook a prospective study of 40 self-ventilating preterm infants at a quaternary center and assessed cardiac performance and cerebral blood flow. Assessments were carried out two hours before skin-to-skin care and then 60 minutes after skin-to-skin care (with the infant still on parent and turned supine).

Results Infants were 30.5 ± 0.6 weeks' gestational age and 1378 ± 133 g birthweight. Axillary temperature noted a nonsignificant increase during skin-to-skin care from 36.7 ± 0.07°C to 36.9 ± 0.07°C (P = .07). Cardiac contractility (right ventricular fractional area change [26.5% ± 0.3% vs 27.8% ± 0.4; P < .001] and tricuspid annular plane systolic excursion [0.73 ± 0.03 cm vs 0.77 ± 0.03 cm; P = .02]) increased significantly, coincident with decreased measures of pulmonary vascular resistance. An increase in systemic cardiac output was associated with increased cerebral blood flow and reduced middle cerebral artery resistive index (0.81 ± 0.02 vs 0.74 ± 0.02; P = .0001).

Conclusions We documented a significant circulatory beneficial adaptation to a common neonatal practice. These findings align with previously documented physiologic benefits in cardiorespiratory stability and cardiac rhythm in preterm infants, and may be mediated through modulation of the autonomic nervous system. *(J Pediatr 2020;222:91-7)*.

Alongside frequent and exclusive breastfeeding, this practice is recommended by the World Health Organization for the routine care of infants with a birthweight (BW) of ≤2000 g.[1] Although much of the published literature attesting to its beneficial physiologic and clinical effects is from low-resource countries, skin-to-skin care has benefits in resource-rich countries as well, such as facilitating the transition to extrauterine life, promoting parent-infant attachment, and improving cardiorespiratory physiology and neurobehavioral stability in preterm infants. A meta-analysis of randomized controlled trials has noted benefits in temperature maintenance with less hypothermia at discharge and higher axillary temperature, lower infection rates and mortality, and better weight gain and parent-infant attachment.[2] A Cochrane analysis of 19 randomized controlled trials comparing kangaroo mother care with conventional care supports these conclusions.[2] In addition to the physiologic benefits, reduced periodic breathing with more regular breathing and fewer bradycardic episodes has been noted.[3]

Heart rate variability (HRV) has been considered a surrogate measure to track cardiac rhythm regulatory changes during kangaroo care. This modality may be clinically useful for capturing the rapidly occurring dynamic changes in autonomic regulation in response to skin-to-skin care. Before, during, and after kangaroo mother care involving 191 sessions in 11 preterm infants, there were significant differences between stable periods during kangaroo care compared with pre-kangaroo care.[4] The salutary impact may be long lasting, as noted by a recent longitudinal study at 10 years of follow-up.[5] Even a small amount of skin-to-skin care, in comparison with those cared for only in an incubator, was associated with beneficial infant and maternal outcomes, such as improved stress response, better organized sleep, and cognitive control. Similar long-lasting effects have been shown by other investigators as well.[6-8]

Early circulatory changes in the neonatal period involve a transition from intrauterine physiology characterized by low left ventricular muscle mass, relative right ventricular (RV) hypertrophy, low systemic (placental during fetal life) vascular resistance, and a high pulmonary vascular resistance (PVR), to a sustained extrauterine physiology which demands almost the exact opposite. Preterm infants are particularly vulnerable because of their inherent autonomic dysregulation and neurobehavioral immaturity, in addition to co-morbidities such as sepsis and the need for respiratory support.

BW	Birthweight
ECHO	Echocardiogram
HRV	Heart rate variability
MCI	Middle cerebral artery
NO	Nitric oxide
PVR	Pulmonary vascular resistance
RV	Right ventricular
SVC	Superior vena cava

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The objective of this study was to ascertain the impact of skin-to-skin care on cardiac function and cerebral blood flow in preterm infants. The hypothesis was that the autonomic and neurobehavioral influences of skin-to-skin care may be reflected in improved regional blood flow and cardiac function.

Methods

The study was approved by the Health Research Ethics Board (approval number RES-19-0000-553A). Informed written parental consent was obtained. The study was conducted at a quaternary center, caring for infants ≥23 weeks of gestational age onward as well as providing surgery as required. This neonatal intensive care unit with a total bed strength of 64 cots (with one-half providing respiratory support), admits approximately 200 infants <32 weeks of gestational age annually, ∼80 of which have a BW of <1000 g. This study enrolled self-ventilating (not needing any respiratory support) infants between 28 and 36 weeks of corrected gestational age and >7 days of age with normal cranial ultrasound examinations. Infants with congenital heart disease were excluded. The parents had been performing skin-to-skin care for >3 days at recruitment. All the infants in this cohort were being administered breast milk. The study design included an assessment of cardiac performance and cerebral blood flow by bedside ultrasound examination conducted between periods of feeding. Assessments were done 2 hours before skin-to-skin care and supine in the cot/incubator (echocardiogram [ECHO]-I) and then after 60 minutes of having skin-to-skin care (with the infant still on parent and turned supine, ECHO-II). (**Figure 1**; available at www.jpeds.com) shows the positioning of a mother and infant during skin-to-skin care. The infants had ongoing continuous cardiorespiratory monitoring during skin-to-skin care. Disposable and prewarmed single use gel sachets were used to reduce skin contamination and to maintain body temperature. The ECHO parameters are summarized in (**Table I**; available at www.jpeds.com).[9-12] Briefly, these parameters included measures of cardiac output, contractility, and PVR (by measuring the ratio of time to peak velocity to RV ejection time). The latter is a noninvasive surrogate for PVR and correlates well with invasive cardiac catheterization measures as well as with measures of RV contractility (ventriculoarterial coupling).[13,14] An increase in this ratio a signifies lowering of PVR. Patent ductus arteriosus was an a priori exclusion criterion; it was reassessed for closure in 1 weeks' time if found patent, but continued patency excluded the infant from recruitment. Superior vena cava (SVC) velocity time integral was taken as a surrogate of systemic blood flow and was measured as described previously.[15,16] The straight midportion of the middle cerebral artery (MCA) was visualized by color Doppler ultrasound examination from the temporal view; velocity recordings were done using pulse wave Doppler. The angle of insonation was kept to <15° in all cases. An average from 5 cycles was obtained. The velocity time integral (area under the curve [in centimeters]) and resistive index were measured; the latter was calculated by the formula (peak systolic velocity-end diastolic velocity)/peak systolic velocity. **Figure 2** depicts the MCA Doppler and velocity time integral recordings as surrogates of blood flow. All ECHO evaluations were performed by a single operator on the Vivid E95 cardiovascular ultrasound system (GE Medical Systems, Milwaukee, Wisconsin) using a 12-MHz phased array transducer probe that allowed image acquisition at a rate of 120-180 frames per second. Data were analyzed offline on *EchoPac* (Horten, Norway). Images were acquired by a single investigator and analyzed offline. Demographic and clinical data such as gestational age, BW, corrected gestational age, and current weight, sex, and day of life were collected.

Continuous variables were compared using the Student t test and categorical variables were compared using χ^2 or Fisher exact tests. Analyses were performed using Stata software version 114.0 (StataCorp, College Station, Texas). Significance was set at a P value of < .05.

Results

Forty infants met the inclusion criteria. The mean gestational age and BW of the study cohort were 30.5 ± 0.6 weeks and 1378 ± 133 g, respectively, and 35 of the 40 caregivers were mothers. **Table II** depicts demographic details of the cohort. Most of the infants were inborn, and 80% (32/40) were appropriate for gestational age. Thirteen infants (32%) required no respiratory support beyond initial stabilizing continuous positive airway pressure at the time of delivery. Two infants were intubated and mechanically ventilated at birth for a brief period (2 and 5 days), followed by continuous positive airway pressure. For the remaining 25 infants, continuous positive airway pressure was the maximal respiratory support required during hospitalization. The unit practices minimally invasive surfactant therapy for surfactant replacement, which was administered to 8 of the infants (20%). None of the infants had received inotropes in the previous 72 hours or blood transfusions in the preceding 1 week. No sedation was used during the study. Most of the infants (22/40 [55%]) were in the second week of life and 10 (25%) infants were 3-4 weeks of age. Eight infants were >4 weeks of age; the oldest being 8 weeks of age at assessments.

Table III summarizes the cardiac function and cerebral blood flow parameters before and after 60 minutes of having skin-to-skin care (with the infant still on the parent and turned supine). The ductus arteriosus was noted to be spontaneously closed in all infants. Significant changes were noticed in RV global (fractional area change) and longitudinal contractility (tricuspid annular plane systolic excursion) and measure of PVR. Stroke volume was significantly increased. Among the systemic circulatory changes, SVC flow increased at repeat assessments coincident with a significant decline in MCA resistive index. The MCA area under the curve reflecting cerebral blood flow increased from 8.5 ± 0.2 cm to 9.4 ± 0.3 cm (P < .001). Cranial ultrasound examinations 1-2 weeks subsequent to the study noted no intraventricular hemorrhages.

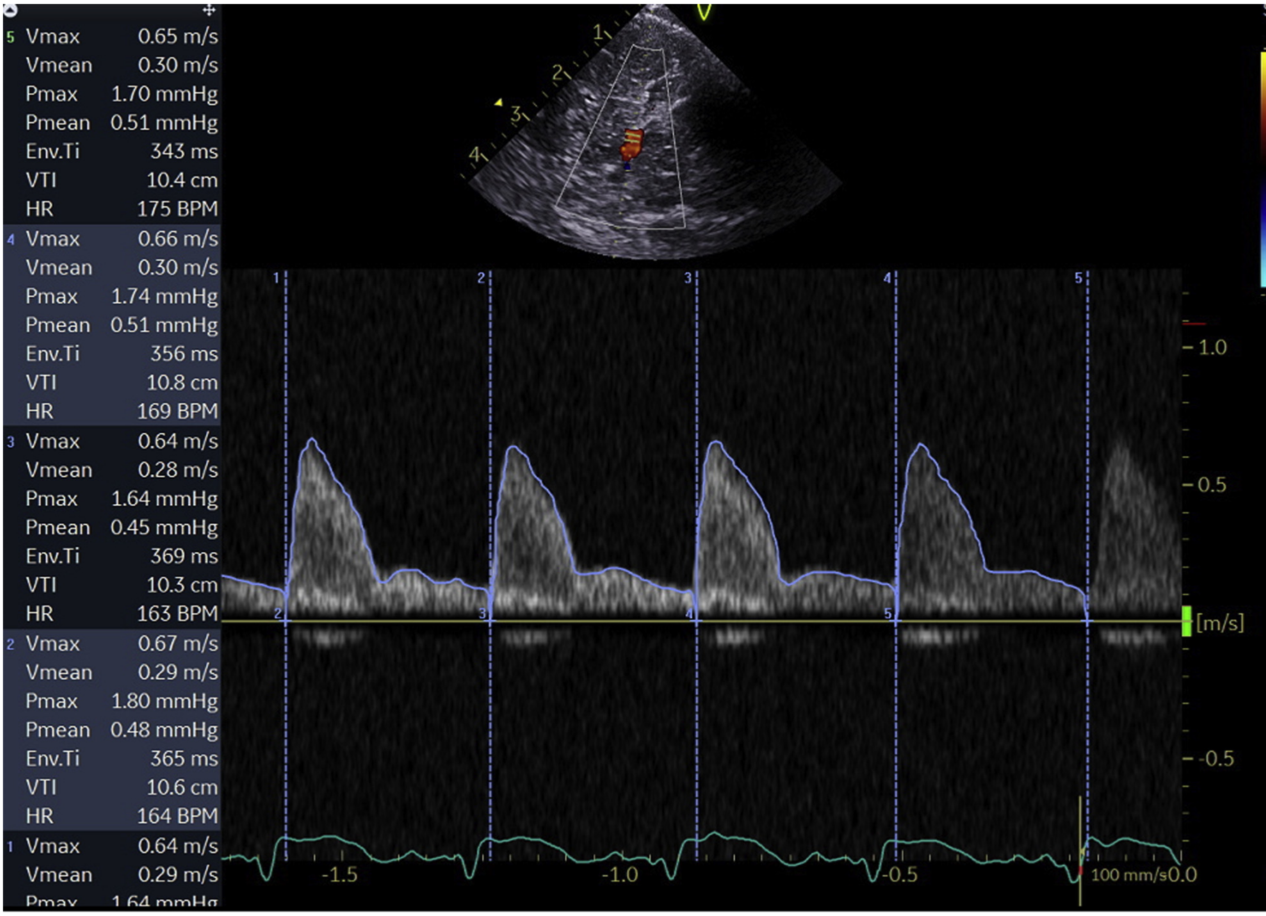

Figure 2. Pulse wave Doppler of MCA and velocity time integral tracing.

Discussion

Important autonomic physiologic modulation in response to skin-to-skin care has been previously demonstrated.[3,17] The practice of skin-to-skin care in comparison with conventional care (ie, no skin-to-skin care), has shown benefits including improved body temperature and cardiorespiratory stability. Our study on premature infants noted significant improvements in cerebral blood flow and cardiovascular performance with skin-to-skin care. The findings complement previous conclusions of beneficial effects on HRV and oxygenation. Regular skin-to-skin care seems a simple yet powerful intervention with significant hemodynamic impact, supporting its routine use in neonatal units.

Echocardiography remains the backbone of noninvasive assessment of cardiac function and regional blood flow in this age group.[9-12] With respect to pulmonary circulation, we noted significant changes in RV contractility and PVR. We assessed RV function by way of global contractility

Table II. Demographics of the study population

Variables	n = 40
Gestational age at birth (weeks)	30.5 ± 0.6
BW (g)	1378 ± 133
Postnatal age at the time of study (days)	12 (9-25)
Weight at the time of study (g)	1700 ± 385
Antenatal steroids	35 (87.5)
Mode of delivery (cesarean)	28 (70)
Inborn	32 (80)
Male sex	18 (45)
Apgar score at 5 minutes	8 (8, 9)

Values are mean ± SD, median (IQR) or number (%).

Table III. Comparison of parameters before and after 60 minutes of having skin-to-skin care (with the infant still on parent and turned supine)

Variables	Echo-I	Echo-II	*P* Value
Axillary temperature (°C)	36.7 ± 0.07	36.9 ± 0.07	.07
Heart rate (bpm)	154 ± 2	146 ± 2	<.001
RV stroke volume (mL/kg)	1.26 ± 0.04	1.41 ± 0.05	<.001
RV fractional area change (%)	26.5 ± 0.3	27.8 ± 0.4	<.001
TAPSE (cm)	0.73 ± 0.03	0.77 ± 0.03	.02
TPV/RVETc	0.27 ± 0.007	0.3 ± 0.008	<.001
LV stroke volume (mL/kg)	1.24 ± 0.04	1.37 ± 0.04	.0001
Fractional shortening (%)	27.8 ± 0.1	29.2 ± 0.1	.054
SVC VTI (cm)	8.3 ± 0.3	9.3 ± 0.3	<.001
MCA resistive index	0.81 ± 0.02	0.74 ± 0.02	.0001

LV, left ventricular; *TAPSE*, tricuspid annular plane systolic excursion; *TPV/RVETc*, time to peak velocity to RV ejection time; *VTI*, velocity time integral.
Values are mean ± SD.

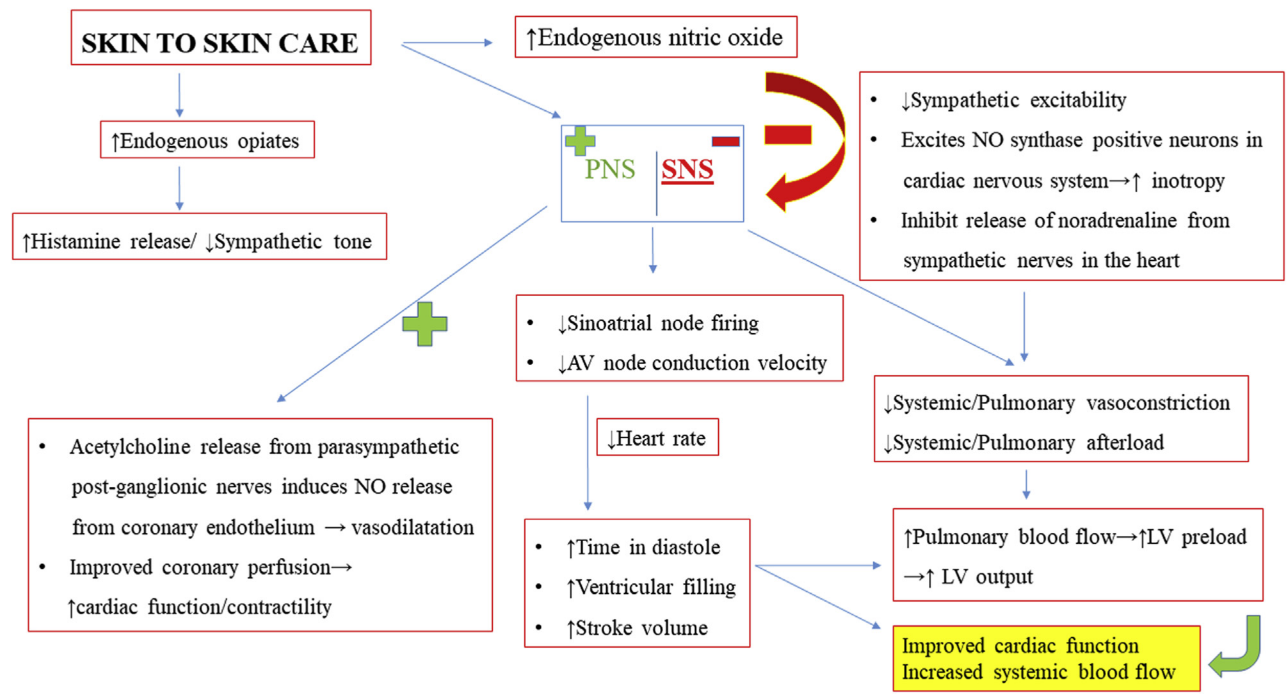

Figure 3. Putative mediators of the effect of skin-to-skin contact on cardiovascular system. *AV*, atrioventricular; *LV*, left ventricular; *PNS*, peripheral nervous system; *SNS*, sympathetic nervous system.

(fractional area change), longitudinal contractility (tricuspid annular plane systolic excursion), and output (stroke volume). The net effect of increased RV contractility and decreased PVR is increased pulmonary blood flow, which consequently would increase left ventricular inflow and output, provided there is no underlying congenital heart or cardiogenic disease. The systemic effects of skin-to-skin care are further noted by a significant increase in cerebral and SVC blood flow. In premature infants, SVC flow is a sensitive marker of systemic blood flow.[15] Low SVC flow in the first 48 hours of life is linked with the development of severe intracranial hemorrhage in premature infants.[18] Although we did not directly measure cerebral oxygen delivery, an increase in cerebral blood flow may improve perfusion/oxygenation at the organ/tissue level. This finding may be true for the lungs as well, and this observation may be one putative explanation for improved saturations noticed in previous studies after skin-to-skin care.

Korraa et al examined changes in cerebral blood flow before and after 30 minutes of kangaroo care in 60 preterm infants of 32 ± 2 weeks gestation and 2080 ± 270 g BW.[19] This study did not mention ductal patency status (which may affect cerebral blood flow), the age at assessment, or whether skin-to-skin care was still being done at the second Doppler assessment. Nonetheless, a significant decrease in resistive index and increased cerebral blood flow was noted, accompanied by a significant reduction in heart rate and an increase in oxygen saturation.[19] Our study, although performed in more premature and lower BW infants, additionally assessed cardiac function. The changes in MCA Doppler in our study mirrored previous findings. In contrast with earlier work, the second assessment was done after 60 minutes of skin-to-skin care (with the infant still on the parent and turned supine). A decrease in the heart rate has been a consistent feature in previous studies, and the same was noted in our cohort as well. In summary, the widely prevalent practice of skin-to-skin care has a significant beneficial impact on preterm circulatory physiology. The physiologic plausibility of our findings may have multiple mechanistic constructs. Figure 3 depicts various pathways that might mediate the effects of skin-to-skin care on cardiac function and organ blood flow.

Neurobehavioral Influences on the Autonomic System and Associated Circulatory Physiology

Such influences have been previously assessed in infants with complex congenital heart disease. These infants are characterized by an abnormally reduced parasympathetic activity and abnormally high sympathetic activity.[20-22] In the 4 weeks after daily skin-to-skin care for 14 days, the baseline high-frequency HRV, reactivity to challenge, and recovery after challenge improved significantly. When the environment, for example, an intensive care unit for a preterm infant, elicits primarily sympathetic effects, pathways in the brain are developed with sympathetic dominance.[22] The close physical contact (primary interaction between newborn infants and their mothers) may well dampen the sympathetic drive. According to the Schore regulation theory, the development of patterns of response of the components of the autonomic nervous system is directly influenced by the mother's interactions with her infant.[22-24] These precisely coordinated interactions in turn regulate physiology. Feldman et al studied 35 premature infants who received ≥1 hour of skin-to-skin care daily for 14 consecutive days beginning at 32 weeks' gestational age.[25] On assessment at 37 weeks (~3 weeks after the intervention ended), infants in the intervention (skin-to-skin care) cohort exhibited more rapid maturation of baseline HRV compared with the control group. Investigators noted that the quality of parent-infant attachment is relevant as well. Increased heart rates were noted during separations and heart rate recovery during reunions was faster in securely attached infants than in their insecurely attached counterparts.[26] Zelenko et al observed 41 adolescent mother-infant dyads and noted increased behavioral distress in the insecure/resistant infants compared with the secure group, indicating a strong neurobehavioral component to the physiologic changes.[27] A recent randomized crossover study on 28 stable preterm infants noted significant correlations between parental engagement and salivary oxytocin and cortisol levels.[28] We suggest that skin-to-skin care is an evidence-based strategy that enhances developing relationships by increasing oxytocin levels and synchronous, responsive parent-infant interactions. Oxytocin modulates autonomic functions such as heart rate.

The findings in our study involve cardiac function and the vascular effects (cerebral blood flow and PVR). The vasculature is under a predominant sympathetic effect to produce a state of maintained tone.[29-31] In contrast, heart rate and rhythm are dominantly under parasympathetic effect via the sinoatrial node and the atrioventricular node conduction velocity. In a previous study, infants demonstrated higher vagal tone after skin-to-skin care in comparison with the controls.[25] The sympathetically innervated arterioles, which constitute the major resistance vessels, also play a key role in regulating regional blood flows. Hence, sympathetic neural control of arteriolar resistance and its dampening by mediators such as nitric oxide (NO) offers a powerful regulatory mechanism. The improvement in cardiac function, temporally coincident with increased regional (cerebral) blood flow noted in our study, should be viewed in this context. A decrease in heart rate allowing a longer diastole and greater ventricular filling possibly leads to higher stroke volume (in keeping with Frank-Starling curve).

Role of NO

NO relaxes pulmonary vascular arteriolar smooth muscle thereby producing a significant decrease in PVR. As a direct vasodilator, essentially acting as a functional antagonist of the sympathetic vasoconstrictor tone, it plays a key role in regulating blood flow at the microvasculature level.[32,33] The slow conducting unmyelinated afferent nerve fibers respond to touch and skin-to-skin contact during kangaroo care.[19,34,35] Their activation in turn stimulates the limbic system to produce neurohormonal mediators, including endorphins, neuropeptide, and calcitonin gene-related peptide, which enhance postsynaptic NO synthase (the neuronal NO synthase). In vitro experimental data indicate that neuronal NO synthase-derived NO is important in the local regulation of vascular tone, independently of the central nervous system.[36]

The Role of Cortisol and Opiates

Chronic exposure to stress in the neonatal intensive care unit causes a dominant, overactive and unstable sympathetic nervous system.[37-40] Importantly, maternal contact and awareness of the mother's heart-beat promoted autonomic stability and reduced stress among preterm infants.[41,42] Decreased stress may be 1 pathway to better cardiorespiratory parameters. Decreased stress and increased physiologic stability may also reflect in reduced cortisol levels. In a study on preterm infants (mean gestational age of 29 weeks, mean BW of 1400 g), Gitau et al noted a consistent and significant reduction in salivary cortisol levels before and after 20 minutes of skin-to-skin care.[43] The use of salivary cortisol level as a stress marker has been used previously in adults and infants.[44-46] Significant correlations between plasma and salivary cortisol levels have been documented in preterm infants.[46,47] Mooncey et al noted a significantly reduced plasma cortisol in human preterm infants after a 20-minute period of skin-to-skin care.[48] There is experimental evidence from studies in rhesus monkeys that the distress reducing effects of nonsedating doses of morphine (administered during separation) are similar to the calming influence of mother and infant reunion.[49] Vasodilatation via histamine release and a reduction of sympathetic nervous system tone may be additional mediators.[50]

Skin-to-skin care is perhaps the normal physiologic state. The stress response of being separated, although a universal part of the experience in the neonatal intensive care unit, is a negative intervention causing increased stress. These pathways show strong biological plausibility as to how parent-infant contact can exert powerful influences with a bearing on autonomic functions affecting cardiovascular performance and organ blood flow.

We acknowledge certain limitations. Our study assessed a relatively small number of preterm infants. For logistical reasons, we did not perform assessments after skin-to-skin care beyond the 1 hour because some parents continue to perform skin-to-skin care for a longer period of time. Blood pressure or saturations were not recorded in this study. Finally, the person performing the ECHO was not masked to the intervention or the study.

In conclusion, we found significantly improved cardiac function and regional blood flow in preterm infants after skin-to-skin care. Skin-to-skin care between parents and newborn infants is a powerful influence with multiple mediators affecting the autonomic nervous system and physiologic regulation and adaptation. The data provide a scientific rationale to an old and widespread neonatal practice, aligning with information on cardiorespiratory stability and heart rate rhythm. ■

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Familial Hyperphosphatasia with Mental Retardation, Seizures, and Neurologic Deficits

Mabry C, Bautista A, Kirk RFH, Dublilier LD, Braunstein H, Koepke JA. J Pediatr 1970;77:74-85.

Mabry et al reported the first 4 patients with hyperphosphatasia with mental retardation syndrome (HPMRS) to present with generalized seizures and facial dysmorphism. The syndrome can be distinguished from other developmental disabilities by the stable elevation of alkaline phosphatase without bone disease.[1] Few published reports of the syndrome appeared before we identified a patient whose seizures responded to pyridoxine.[2] Improved syndromology[1] made it possible to use next-generation sequencing to identify the recessive mutations that cause what became known as Mabry syndrome (OMIM 239300).[2] There are at least 6 phenotypes. HPMRS 1, 2, 5, and 6 result from disruption of 4 genes encoding phosphatidylinositol glycan (PIG) anchor biosynthesis enzymes that act in the endoplasmic reticulum: type V (*PIGV*) type O (*PIGO*), type W (*PIGW*), and type Y (*PIGY*). HPMRS 4 and 3 result from disruption of 2 genes encoding postattachment to proteins (PGAP) enzymes that stabilize glycosylphosphatidylinositol attachment to proteins in the golgi: *PGAP3* and *PGAP2*.[3] The report by Mabry et al describes the first of at least 21 inherited glycosylphosphatidylinositol biosynthesis defects (GPIBDs) that together compose approximately 0.15% of all developmental disabilities.[4] The HPMRS3 (GPIBD8 [MIM: 614207]) phenotype presented by Mabry et al, resulting from biallelic inheritance of PGAP2 mutations, is the prototypical HPMRS phenotype among GPIBDs.[5] This work demonstrates the value of case studies to basic science, clinical innovation, and patient follow-up.

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Figure 1. Mother-infant position for ECHO II (with written parental permission).

Table I. Summary of hemodynamic assessments

Parameters	Mode	View	Cursor position	Comment
RV stroke volume (mL/kg)	PWD	Oblique pulmonary artery view	Aligned with the flow, sample at the tips of pulmonary leaflets	VTI × CSA indexed to weight
RV fractional area change (%)	2D	Apical 4-chamber view	Include full view of the RV (base to apex)	[(RV 4-chamber area at end-diastole – RV 4-chamber area at end-systole)/RV 4-chamber area at end-diastole] x 100%
TAPSE (mm)	M-mode	Apical 4-chamber view	Lateral tricuspid annulus	Measure of longitudinal contractility
TPV/RVETc	PWD	Oblique pulmonary artery view	Aligned with the flow, sample at the tips of pulmonary leaflets	1/(TPV/RVETc) acts as a surrogate for pulmonary vascular resistance
LV stroke volume (mL/kg)	PWD	Five-chamber apical view	Aligned with the flow, sample at the tips of aortic leaflets	VTI × CSA indexed to weight
Fractional shortening (%)	M-mode	Parasternal long axis	Just distal to mitral valve leaflet tips at end-diastole	(LVEDD – LVESD)/LVEDD

2D, 2-dimensional; *CSA*, cross-sectional area; *LVEDD*, left ventricular end diastolic dimension; *LVESD*, left ventricular end systolic dimension; *PWD*, pulse wave Doppler; *RVET*, RV ejection time; *TAPSE*, tricuspid annular plane systolic excursion; *TPV*, time to peak velocity; *TPV/RVETc*, ratio of time to peak velocity to RV ejection time; *VTI*, velocity time integral.