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Retinopathy of Prematurity Is Associated with Increased Systolic Blood Pressure in Adults Who Were Born Preterm

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Preterm · Retinopathy of prematurity · Blood pressure · Salivary cortisol

Abstract
Background: Adults born preterm are at risk of developing cardiovascular morbidities. ***Objective:*** The aim of this study was to evaluate the relationship between retinopathy of prematurity (ROP) and blood pressure (BP) and salivary cortisol levels during adulthood. ***Methods:*** Sixty-nine subjects (mean age 22.6 years) were included. Subjects were adults who were: (a) ex-preterm infants with severe ROP ($n = 22$), born at gestational age (GA) <30 weeks with a birth weight (BW) <1,000 g, (b) ex-preterm infants with no/mild ROP ($n = 21$), born at GA <28 weeks with a BW <1,000 g, or (c) full-term controls ($n = 26$). Anthropometric data, office BP, ambulatory BP, and morning and evening salivary cortisol were analyzed. ***Results:*** As adults, ex-preterm infants with severe ROP had on average 7.4 mm Hg higher systolic office BP than those with no/mild ROP ($p = 0.019$) and controls ($p = 0.007$). A high cortisol level, tall height, and severe ROP were independent predictors of higher ambulatory systolic BP during adulthood in forward stepwise regression analysis, independent of GA. ***Conclusion:*** Our results indicate that preterm infants with severe abnormal retinal vascular development during the neonatal period may be at an increased risk for increased BP during adulthood. We found no differences between those with no/mild ROP as infants and controls with regard to BP data.

Introduction

Preterm birth is associated with an increased risk of high blood pressure (BP) in young adulthood [1]. Immaturity and being born small for gestational age (GA) [1] are proposed to explain this association. Neonatal complications such as retinopathy of prematurity (ROP) [2] have also been associated with hypertension in children who were born preterm.

The present study evaluated the relationship between severe ROP during infancy and adult BP, physical activity, and salivary cortisol levels. Results were compared with individuals born very preterm without severe ROP and full-term controls. All study participants were part of a cohort born between 1988 and 1993 in Stockholm, Sweden.

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Table 1. Peri- and neonatal characteristics and current characteristics in adults born preterm with different grades of ROP during their early neonatal weeks (preterms), or born at full term with a normal BW (controls)

	No/mild ROP (n = 21)	Severe ROP (n = 22)	Controls (n = 26)	p	1 vs. 2	1 vs. 3	2 vs. 3
Male/female, *n*	11/10	10/12	9/17				
Neonatal anthropometrics							
BW, g	850 (719, 986)	830 (699, 960)	3,440 (3,323, 3,563)	<0.001			
BW SDS	−0.83 (−1.31, −0.35)	−0.34 (−0.86, 0.09)	−0.18 (−0.61, 0.26)	0.13			
GA, weeks	26.0 (25.5, 26.5)	25.5 (25.0, 26.0)	39.6 (39.1, 40.1)	<0.001			
Perinatal characteristics							
Maternal age, years	34 (32, 36)	31 (28, 33)	31 (28, 33)	0.07			
Paternal age, years	34 (29, 39)	36 (33, 40)	34 (30, 38)	0.76			
Maternal height, cm	165 (162, 168)	169 (166, 172)	165 (162, 168)	0.06			
Paternal height, cm	181 (179, 184)	179 (176, 181)	178 (175, 181)	0.21			
Target height cm	175 (171, 179)	173 (169, 177)	174 (170, 187)	0.77			
Maternal education level, mean 2–7	4.0 (3.4, 4.6)	4.2 (3.6, 4.8)	4.0 (3.5, 4.6)	0.85			
Paternal education level, mean 2–7	4.6 (3.9, 5.2)	4.2 (3.5, 4.8)	4.1 (3.5, 4.7)	0.51			
Maternal pregnancies, *n*	2.8 (2.2, 3.4)	2.5 (1.9, 3.1)	1.9 (1.3, 2.4)	0.09			
Siblings, *n*	0.65 (0.3, 1.0)	0.91 (0.5, 1.3)	0.73 (0.4, 1.1)	0.60			
Maternal smoking during pregnancy (no/yes), %	88/13	88/13	95/5	0.67[a]			
Fertility problems (no/yes), %	89/11	88/13	95/5	0.70[a]			
Maternal diabetes(no/yes), %	100/0	95/5	100/0	0.35[a]			
Maternal preeclampsia (no/yes), %	84/16	74/26	100/0	0.06[a]			
Mode of delivery (vaginal/ section), %	32/68	80/20	100/0	<0.001[a]			
Prenatal cortisol (no/yes), %	84/16	79/21	100/0	0.07[a]			
BPD (no/yes), %	67/33	27/73	100/0	<0.001[a]			
IVH (no/yes), %	62/38	55/45	–	0.62[a]			
PVL (no/yes), %	71/29	77/23	–	0.66[a]			
Current anthropometrics							
Age at follow-up, years	22 (21.86, 22.7)	23 (22.3, 23.3)	23 (22.0, 23.0)	0.21			
Height, cm	170 (166, 175)	170 (166, 175)	175 (172, 180)	0.12			
Difference from target height, cm	−3.7 (−6.0, −1.5)	−3.4 (−5.6, −1.2)	2.2 (0.2, 4.1)	<0.001	0.84	<0.001	<0.001
Weight, kg	63 (57, 69)	67 (62, 73)	73 (67, 78)	0.07			
BMI, kg/m^2	22 (20.2, 23.2)	23 (21.6, 24.5)	24 (21.2, 24.9)	0.17			
Head circumference, cm	55 (54, 56)	56 (55, 57)	57 (56, 58)	0.007			
Waist circumference, cm	83 (79, 88)	89 (85, 93)	86 (82, 90)	0.21			
Waist-to-height ratio	0.49 (0.47, 0.52)	0.52 (0.50, 0.55)	0.49 (0.47, 0.51)	0.09			
Hip circumference, cm	91 (86, 95)	95 (91, 100)	97 (93, 101)	0.09			
Current characteristics							
Current smoking or snuff use (no/yes/missing), %	83/17/3	82/18/0	72/28/0	0.45[a]			
Physical activity, h/week	5.3 (3.3, 7.3)	2.2 (0.3, 4.0)	4.8 (3.2, 6.5)	0.07			
Self-reported wakening period, h	16.3 (15.5, 17.1)	15.7 (14.9, 16.5)	15.5 (14.9, 16.5)	0.35			
Self-reported sleeping period, h	7.7 (6.9, 8.5)	8.3 (7.5, 9.1)	8.5 (7.8, 9.3)	0.30			

Values are presented as the mean (95% CI). Statistical analysis: analysis of variances (ANOVA), followed by post hoc Fischer test unless stated otherwise. BMI, body mass index; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; SDS, standard deviation score. [a] Pearson χ^2 test.

Materials and Methods

Subjects

Follow-up BP measurements at age 20–25 years were performed in 69 individuals. Study participants included ex-preterms (n = 43) with a postmenstrual age of ≤30 weeks and full-term normal-weight controls (n = 26) born in Stockholm between 1988 and 1993. In the initial cohort, infants with birth weights (BW) <1,500 g were included. During the neonatal period, 51 of 291 infants died.

All 28 subjects treated for severe ROP in the primary cohort were invited to participate in the present study and 22 accepted. In total, 125 controls were included in the primary cohort, 55 were randomly selected and invited, and 26 participated.

Infants with no/mild ROP and GA <28 weeks at birth were included as preterm controls (n = 42). Twenty-one agreed to par-

Table 2. BP data

	No/mild ROP (n = 21)	Severe ROP (n = 22)	Controls (n = 26)	p	1 vs. 3	2 vs. 3	1 vs. 2
Office BP							
Mean systolic BP right arm	124 (119, 129)	131 (127, 136)	124 (120, 127)	0.015	0.82	0.007	0.019
Mean systolic BP left arm	125 (120, 129)	131 (126, 136)	123 (119, 127)	0.042	0.63	0.017	0.06
Mean diastolic BP right arm	75 (72, 78)	77 (74, 81)	75 (72, 78)	0.38			
Mean diastolic BP left arm	75 (72, 79)	77 (73, 80)	74 (71, 77)	0.45			
Ambulatory BP							
24-h systolic BP	123 (120, 127)	127 (122, 131)	124 (120, 127)	0.40			
24-h diastolic BP	72 (70, 74)	73 (69, 76)	70 (68, 72)	0.33			
24-h pulse pressure	51 (49, 54)	54 (51, 58)	52 (50, 55)	0.33			
24-h heart rate, beats/min	74 (69, 78)	71 (67, 76)	73 (69, 77)	0.72			
24-h systolic recordings above 140 mm Hg, %	19 (9, 28)	28 (16, 40)	15 (9, 21)	0.10[a]			
Day systolic BP	127 (123, 131)	130 (126, 135)	126 (123, 128)	0.22			
Day systolic hypertension, %	19 (7, 37)	38 (15, 61)	4 (0, 12)	0.012[a]			
Day diastolic BP	76 (73, 79)	76 (73, 79)	74 (71, 76)	0.35			
Day diastolic hypertension, %	5 (1, 15)	14 (0, 31)	0	0.11[a]			
Day pulse pressure	51 (48, 54)	54 (51, 57)	52 (50, 55)	0.37			
Night systolic BP	114 (110, 119)	118 (113, 124)	113 (109, 117)	0.18			
Night systolic hypertension, %	19 (7, 37)	43 (20, 66)	15 (0, 30)	0.07[a]			
Night diastolic BP	62 (59, 65)	63 (59, 67)	60 (57, 63)	0.50			
Night pulse pressure	53 (50, 56)	56 (52, 59)	53 (50, 55)	0.31			
Night systolic recordings above 120 mm Hg, %	25 (13, 37)	42 (26, 58)	25 (15, 34)	0.09[a]			
Nocturnal dipping, %	48 (24, 71)	45 (21, 69)	58 (37, 78)	0.65[a]			
WCH, %	19 (1, 37)	33 (11, 55)	27 (9, 45)	0.57[a]			
Morning cortisol, μg/L	21 (16, 26)	22 (16, 27)	22 (15, 28)	0.84			
Evening cortisol, μg/L	6.8 (5.3, 8.2)	9.6 (7.6, 11.7)	7.9 (6.8, 9.0)	0.035	0.30	0.11	0.012

Data are presented as mm Hg (95% CI) unless otherwise stated. The 2 ROP groups were born before gestational week 28, except for 3 individuals in the severe ROP group, born before week 30 (birth weight <1,250 g), between 1988 and 1993. Statistical analysis: analysis of variances (ANOVA), followed by post hoc Fischer test unless stated otherwise. BP, blood pressure; WCH, white coat hypertension. [a] Pearson χ^2 test.

ticipate in the study. Participants and nonparticipants showed no differences in GA and BW within the groups.

The study protocol was approved by the ethics committee at Karolinska Solna, Stockholm. All subjects provided written informed consent.

Definitions

GA was determined by ultrasound during early pregnancy. Standard deviation scores (SDS) were based on the Swedish reference curve at birth [3] and adulthood (Tables 1, 2).

Morbidity Examination: ROP Evaluation

ROP was classified according to an international classification [4]. Each child was classified according to the most advanced ROP stage observed.

Subjects were divided into 2 groups according to ROP staging; no/mild ROP (stage ≤2; n = 21) or severe ROP (stage ≥3; n = 22; Table 1). All individuals with severe ROP were treated with retinal ablation (cryotherapy) according to guidelines current at the time of the study [5].

Maternal and Heredity Factors, Neonatal Information, Self-Reported Physical Activity, and Smoking Habits

The maternal medical history and neonatal information was obtained at the time of the initial study (Table 1). Current subject characteristic information was obtained at the time of the study (Table 1). Two subjects in the severe ROP group took antihypertensive medication.

Data Collection: BP Measurements

An experienced nurse recorded each subject's office BP in both arms and was unaware which group the participant represented. An oscillometric automatic BP monitor (Omron HEM-7201; Omron Healthcare, Kyoto, Japan) was used, with the subject in a supine position after 10 min of rest. Office BP was calculated as the mean of 2 recordings.

Each subject's ambulatory BP was obtained using a noninvasive oscillometric system (Spacelabs 90207, Spacelabs Inc., Redmond, WA, USA) applied on the nondominant arm. The measurement period was at least 24 h, with readings every 20 min. Means were calculated over the entire 24-h period, and for day (6 a.m. to 11 p.m.) and night (11 p.m. to 6 a.m.).

Morning and evening salivary cortisol (immunochemistry, radioimmunoassay, and reference morning [10–46 nmol/L] and evening [3.2–15 nmol/L] levels) were obtained 1 day prior to the BP measurements.

Definitions

The target height (in centimeters) was defined as the maternal height + paternal height (adding 13 [male]/subtracting 13 [fe-

male]) divided by 2. Hypertension was defined as the mean systolic daily ambulatory BP >135 mm Hg and/or under BP medication or a mean systolic nighttime BP >120 mm Hg [6]. Diastolic hypertension was defined as daily ambulatory BP >85 mm Hg [6]. Nocturnal dipping was defined as a mean nighttime systolic BP 10% or more below that of the mean daytime systolic BP. White coat hypertension was considered present when the office systolic BP level was at the 95th percentile or higher, with a systolic ambulatory average BP at the 90th percentile or lower and compared with Swedish reference values [7].

Statistics

Individuals' anthropometric data, BP, and salivary cortisol levels are presented as the mean and 95% confidence intervals (CI). The comparison between groups was made by analysis of variance and post hoc Fischer test. The Pearson χ^2 test was used. Forward stepwise multiple regression analysis was performed with systolic BP as a dependent variable. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using Statistica StatSoft, version 10 (Statistica, Tulsa, OK, USA).

Results

Table 1 shows data for the 69 subjects at birth and adulthood. The 2 ex-preterm groups did not reach their target height compared with the controls.

Subjects with no/mild ROP had lower evening cortisol levels compared with those with severe ROP. The adult severe ROP group had approximately 7.4 mm Hg higher systolic office BP than the no/mild ROP ($p = 0.019$) and control ($p = 0.007$) groups (Table 2). Additionally, the severe ROP group had a higher incidence of daily systolic hypertension and trended towards a difference in nighttime systolic hypertension (Table 2).

In forward stepwise regression analysis with systolic daily ambulatory BP as the dependent variable, morning cortisol levels ($\beta = 0.268$, $p = 0.024$), height ($\beta = 0.239$, $p = 0.043$), and severe ROP ($\beta = 0.235$, $p = 0.047$) were included as independent predictors (adjusted $r^2 = 0.15$, $p < 0.005$, $n = 65$). GA, BW SDS, neonatal bronchopulmonary dysplasia (BPD), and graded physical activity had no impact when included in the analysis. With left arm office systolic BP as a dependent variable, severe ROP ($\beta = 0.331$, $p = 0.004$), height ($\beta = 0.400$, $p < 0.001$), and morning cortisol levels ($\beta = 0.236$, $p = 0.029$) were significant predictors (adjusted $r^2 = 0.29$, $p < 0.0001$, $n = 65$) independent of GA, BW SDS, or BPD. Less physical activity was a nonsignificant predictor ($\beta = -0.169$, $p = 0.14$).

Discussion

Subjects with severe ROP as infants, indicating severe early abnormal retinal vessel development, had increased office systolic BP and higher incidences of hypertension in daily systolic ambulatory BP as adults. However, adults born preterm with no/mild ROP did not differ from controls in office or ambulatory BP recordings. Higher morning salivary cortisol, taller height, and severe ROP were related to higher ambulatory daily systolic BP independent of GA, BW SDS, and neonatal BPD.

Morning salivary cortisol was weakly related to office and daytime ambulatory systolic BP. Nearly all of the subjects had salivary cortisol within the normal range. In older men born at term, high salivary cortisol has been associated with hypertension [8].

In the Express study, approximately 70% of extremely preterm infants born at GA <27 weeks developed ROP and one-fifth needed laser therapy [4]. Low weight or poor weight gain, hyperglycemia, and other neonatal morbidities correlate with more severe ROP [9]. Infants with severe ROP experience an early catabolic period with metabolic derangement that may affect cardiovascular development.

We found differences in systolic but not in diastolic BP. This is in accordance with BP findings in another group of preterm children with severe ROP. At the age of 4 years, these infants presented with higher mean office arterial pressure [2]. In a large retrospective meta-analysis, however, ROP was not associated with increased BP in ex-preterm subjects [10].

In our study, about 40% of severe ROP subjects had systolic daytime and nighttime hypertension. In a retrospective study, at a mean age of 52 years, nighttime mean systolic BP was the most significant predictor of cardiac events [6]. Although the sample was small, our results indicate that subjects with severe ROP need early follow-up for BP control and, if required, treatment.

One limitation of this study was the relatively low participation rate, although no simple signs of selection bias were detected between the participating and non-participating subjects. The causal relationship of these findings, as well as the effect on future morbidity, should be investigated in greater depth.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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