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High R/V ratio and vertical P axis in electrocardiography of schoolchildren with BPD

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Brief Report

Short running title: ECG changes in BPD

Persistent elevation in pulmonary artery pressure is frequently observed in severe bronchopulmonary dysplasia (BPD) and it has been suggested that being born preterm is a likely independent risk factor for a novel form of cardiomyopathy (1). Also, preterm birth is associated with higher resting systolic blood pressure later in life than term birth (2).

The gold standard for diagnosing pulmonary hypertension (PH) is catheterisation. Echocardiography is used for non-invasive evaluation of suspected cardiopulmonary disease. However, indirect evidence of PH is also observed in electrocardiography (ECG) when sustained pressure overload leads to increases in right ventricular mass (3).

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High pulmonary artery blood pressure, namely an R/S wave ratio of >1 in lead V1, has been associated with right ventricular hypertrophy in PH adults (3). We hypothesised that schoolchildren born below 32 weeks, particularly those with BPD, would be more likely to present with ECG patterns that suggested higher pulmonary artery blood pressure and also have higher blood pressure levels than term-born peers.

We enrolled 88 schoolchildren born preterm and 88 age- and sex-matched term-born controls. Preterm children were recruited from prospective birth cohorts and term controls from the population register. At 8-14 years they underwent a standard 12-lead ECG using CardioDirect 12V 2.501 software (Spacelabs Healthcare, California, USA). Two blood pressure readings, measured in the right arm while seated, using a Dinamap 9301 Vital Signs Monitor (Morton Medical, London, UK) was used. Children did rest at least 5 minutes before the first reading. BPD was defined as supplementary oxygen requirement for at least 28 days and severity-graded at 36 weeks of post-menstrual age: mild was room air, moderate was <30% and severe was ≥30%. The statistical analyses used SPSS version 25 for Windows (IBM Corp, New York, USA) with independent sample t-tests for continuous variables and the chi-square test for categorical variables. $P<0.05$ was statistically significant. All parents and children gave written, informed consent and assent.

The perinatal characteristics are presented in Table 1. The ECGs were recorded at a mean age of 10.9 ±1.4 years and 11.6 ±1.7 years in the preterm and term groups. None of the children had congenital heart defects and 18/88 (20.5%) preterm and no term children had persistent ductus arteriosus, requiring indomethacin or ligation. Preterm children had shorter P wave duration, PR intervals and shorter QRS durations than term-born peers. Preterm-born children with moderate-to-severe BPD had a more vertical P wave axis ($p=0.044$) and increased R/S wave ratio in V1 ($p=0.035$) than those with mild or no BPD (Table S1).

P axis of >60º was present in 29 (33%) term children and 25 (28%) preterm children ($p=0.513$): this occurred in 17/69 (25%) with no or mild BPD and eight/19 (42%) with moderate-to-severe BPD ($p=0.135$). An R/S ratio of >1 in V1 was found in two (2%) term and in six (7%) preterm recordings ($P=0.148$), including three (4%) with none of mild BPD and three (16%) with moderate-to-severe BPD ($p=0.080$).

There were no detectable differences in blood pressures between the groups and no association to moderate-to-severe BPD (Table S1). Asthma diagnosis or low forced expiratory volume in one second in spirometry was not associated with the ECG changes (data not shown).

Our hypothesis that an increased R/S ratio in V1, an indirect marker of PH (3), would be associated with moderate-to-severe BPD at school age was proved. This finding is in concordance with the growing recognition of the clinical burden attributable to infants with BPD-associated PH. We also found more vertical P wave axes in individuals with moderate-to-severe BPD, which has been associated with emphysema and chronic pulmonary sequelae (4).

The cut-off points for abnormal R/S ratios in V1 (>1) or an abnormal P-axis (>60º) were not associated with either prematurity or BPD, possibly relating to subtler pulmonary and vascular consequence. The shorter ECG time intervals in preterm children were probably due to non-significantly higher heart rates.

PH is a serious condition affecting around one in six extremely premature infants. The highest risks are in those with growth restrictions, higher oxygen requirements at four weeks of age and severe BPD. Interestingly, prospective screening by echocardiography at neonatal period is reported to identified only one-third of infants who developed PH and the remainder were diagnosed later in infancy (5). Our findings suggest the effects may last until early adolescence.

Contrary to our hypothesis and previous studies (2) we found no elevated blood pressure in schoolchildren born preterm with or without BPD. Whether this is explained by improved care, the young age of the children studied, publication bias favouring studies that found the difference between the groups or just lack of power in our study, remains unclear.

The strengths of this study are its prospective nature what it comes to collecting neonatal data, a quite large postsurfactant era cohort from a reginal tertiary centre and matched term controls recruited from the population register. Limitations of our study include the lack of echocardiographic evaluation at school age. In addition, we could not use the data from the neonatal echocardiographic evaluation as it was performed as a part of the routine care at the discretion of the clinician without any predefined echocardiographic criteria.

Our observations suggest that ECG alterations may be a useful biomarker for PH screening. At the very least they indicate that this high-risk group needs to be followed up. Future studies on the long-term cardiopulmonary sequela of preterm birth, particularly in moderate-to-severe BPD, are warranted.

ABBREVIATIONS

BPD, bronchopulmonary dysplasia, PH, pulmonary hypertension, ECG, electrocardiography

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CONFLICTS OF INTEREST

None.

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Table 1. Perinatal characteristics

	Term	Preterm		
		All	None or mild BPD[1]	Moderate to severe BPD[1]
n	88	88	69	19
Gestational age, weeks (SD)	39.9 (1.2)	28.8 (2.1)	29.2 (2.0)	27.0 (1.7)
Birth weight, grams (SD)	3,574 (514)	1,133 (409)	1,211 (412)	838 (231)
Male, n (%)	47 (53)	47 (53)	40 (58)	7 (37)
Apgar score <7 at 5 min, n (%)	0	35 (40)	28 (41)	7 (37)
Antenatal corticosteroid, n (%)	0	74 (84)	58 (84)	16 (84)
Surfactant replacement therapy, n (%)	0	56 (64)	39 (57)	17 (89)
PDA[2], n (%)	0	18 (20)	12 (17)	6 (32)

[1] BPD was defined as supplementary oxygen requirement for at least 28 days and it was severity-graded at 36 weeks post-menstrual age (mild: room air, moderate: requiring <30% and severe: ≥30% of supplemental oxygen)
[2] PDA was treated either with medication (indomethacin) or surgical ligation.
BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus