Abnormal Circulatory Stress Responses of Preterm Graduates

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ABSTRACT: Preterm birth and chronic lung disease may increase the risk of hypertension and cardiovascular disease in infancy and adolescence. Here we looked for evidence of early circulatory dysfunction associated with these perinatal complications. We compared infants born at term (n = 12) with those born preterm with an uncomplicated neonatal course (n = 12) or diagnosed with bronchopulmonary dysplasia (BPD) (n = 10). We measured blood pressure (BP) (Finometer), and heart rate (HR) responses to 4 min of breathing 4% CO2 during quiet sleep. Hypercapnia accelerated HR and increased BP of term infants. Preterm infants either (i) had an exaggerated pressor but little or no HR response to CO2 (healthy or mild-moderate BPD) or (ii) had a diminished pressor response and accompanying decrease in HR (severe BPD). Short-term reflex cardiovascular control was consequently altered by premature birth, with potentially more serious aberrations associated with severe BPD. Most anomalies had not resolved by the time infants born preterm reached term age; some may be early signs of emerging long-term cardiovascular dysfunction. (Pediatr Res 61: 329–334, 2007)

With the impressive increase in survival of very preterm and low birth weight infants come new challenges. Evidence already indicates that this “new generation” of children and adolescents may have accelerated disease onset later in life (1). One factor contributing to their higher risk of cardiovascular disease may be abnormal vascular and circulatory development (2–4). Cardiovascular activity is normally carefully regulated, but if some or all of the central and peripheral regulatory mechanisms involved fail to develop normally, perfusion, growth, and function may be compromised. In exceptional circumstances during infancy, persistent serious dysfunction could result in a sudden catastrophic decrease in BP and HR or prevent autoresuscitative recovery, culminating in sudden infant death syndrome (SIDS) (5,6). In other cases, dysfunction may be relatively benign, although there may still be side effects with adverse consequences of their own.

We know relatively little about how BP and HR control develops, and the potentially adverse effects of fetal and perinatal stress. A better understanding of these issues could lead to new therapies or strategies to prevent neonatal complications and improve long-term outcome. In the study described here, we looked for evidence that development of neonatal circulatory control is altered by common perinatal complications (7). We studied three different groups of newborn infants: those born normally at term, those born preterm but otherwise healthy, and infants born very preterm suffering from chronic lung disease (BPD). Infants with BPD are at particularly high risk of long-term cardiovascular complications and SIDS (8–10). We compared BP and HR responses of these infants to a routine physiologic stress (breathing a low concentration of CO2 for several minutes) commonly used to unmask autonomic anomalies (11). Normally, acute exposure to CO2 increases BP and HR slightly. A heightened/attenuated increase, and/or a failure to recover promptly may indicate that reflexes involved in cardiovascular control have not developed normally. Our hypotheses were (i) short-term control of BP and HR is altered by preterm birth and lung disease; (ii) these functional changes resolve slowly, if at all, and are still evident when infants born preterm reach term age; and (iii) dysfunction is more persistent and serious when associated with BPD.

METHODS

We compared infants born at term (38–42 wk) with healthy infants born preterm (27–34 wk of gestation) and those born preterm (23–33 wk) diagnosed with BPD (Table 1). All were appropriately grown. Term infants were studied 2–5 d after birth, and preterm infants at 36 and 40 wk postmenstrual age. Healthy preterm infants had an uncomplicated neonatal course (no respiratory abnormalities, patent ductus arteriosus, intraventricular hemorrhage, or septicemia). BPD was staged clinically (12) as (a) mild, supplemental O2 for ≥28 d but breathing room air at 36 wk (two infants); (b) moderate, <30% O2 at 36 wk (three infants); and (c) severe, >30% O2 at 36 wk (five infants). None of our subjects required positive airway pressure or ventilation at 36 wk. Two infants with severe BPD were diagnosed with germinal matrix/grade II intraventricular hemorrhage. All infants with BPD received inhalation steroids (Pulmicort 400–600 mg/d) and a bronchodilator (Salbutamol), and those with severe BPD also received diuretics.

Infants slept supine. BP was recorded from a wrist cuff (Finometer, FMS, The Netherlands; for accuracy, the “physiological” function was always enabled) (13). To alleviate venous congestion in the hand, cuff inflations were limited to 10 min (several inflations were needed to complete the protocol). Chest and abdominal movements (Respirtrace), transcutaneous PO2 (TeCO2) and transcutaneous Pco2 (TeCO2) (Radiometer TCM3 electrode, Copenhagen), oxygen saturation (SaO2; finger probe) and an electrocardiogram were recorded (Rembrandt, MediCare Automation, The Netherlands). CO2 (duplicate challenges) was administered during behavioral quiet sleep (14) via a 10-L head box. Tests comprised 2 min of baseline (room air), 4 min of 4% CO2, then 4 min of recovery (air). Head box gas flow was 10 L/min, and supplemental O2 (if required) was delivered via nasal prongs at the prescribed concentration and flow.

Abbreviations: BPD, bronchopulmonary dysplasia; HVR, hypercapnic ventilatory response; TeCO2, transcutaneous Pco2

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Age (babies with mild and moderate BPD (hypercapnic ventilatory response (HVR) was the slope of the line relating against the corresponding change in TcCO2. We took into account the time breathing were expressed as relative changes from baseline and were plotted

breathing amplitude (tidal volume, VT), and the product (ventilation; V = RR × VT) were calculated from the frequency and amplitude, respectively, of chest and abdominal movements. VT was proportional to the sum of chest and abdominal amplitudes (15). Increases in the rate (ΔRR) and depth (ΔVt) of breathing were expressed as relative changes from baseline and were plotted against the corresponding change in TcCO2. We took into account the time lag in response of the TcCO2 electrode (approx 15 s). The strength of the hypercapnic ventilatory response (HVR) was the slope of the line relating instantaneous V and TcCO2.

Statistics. Cardiovascular data were normally distributed and analyzed via two-way analysis of variance (ANOVA) to test for significant main (time, group) and interaction effects, followed by pairwise comparisons of means using multiple range tests with the Bonferroni correction. Respiratory data were not normally distributed and hence were analyzed using nonparametric tests. We tested for differences between HRVs (Kruskal-Wallis test) and analyzed whether the HVR was due to changes in amplitude or rate of breathing (or both; Spearman’s rank correlation test). We also tested for a positive or negative (or no) association between BP, HR, and ventilatory response by pairwise ranking of slopes (Spearman’s rank correlation test). A p value ≤0.05 indicated significant differences/correlations at the 95% confidence level. Measurement error is presented as standard deviations (SDs) in the text, and (for clarity) standard error of the mean (SEM) in the figures.

The Karolinska University Hospital Ethics Committee approved all procedures, and written informed consent was obtained from parents of infants who participated.

RESULTS

Baseline data: Asleep, breathing air. We analyzed data from 94 CO2 tests (35 for preterm, 39 for BPD, and 20 for full-term infants). Babies with severe BPD had a higher resting TcCO2 and respiratory rate at 36 wk than did infants with mild-moderate or no disease; HRs and transcutaneous O2 levels were comparable for all infants born preterm; however, the SaO2 was slightly lower in severe BPD (Table 2A). At term, the respiratory rate and TcCO2 of infants with severe BPD had decreased slightly. Preterm infants in general had higher resting HR and respiratory rates than did infants of the same age born at term (Table 2B).

BP and HR responses: healthy infants. Our purposes here was to determine whether cardiovascular responses to CO2 were altered after preterm birth. All groups received a comparable CO2 load (∆TcCO2 = mean during 4th min – baseline = 1.0 ± 0.6 kPa, 1.3 ± 0.4 kPa, and 1.1 ± 0.5 kPa for term versus preterm at 36 and 40 wk, respectively). The resulting increase in mean BP (the pressor response) was exaggerated at 36 wk, but had normalized by term (Fig. 1A,D). The pressor response always outlasted the stimulus, with BP remaining elevated long after TcCO2 returned to baseline (Fig. 1A,D). Pulse pressure returned to baseline more quickly than mean BP (Fig. 1B,E). The HR of term infants increased promptly during CO2 exposure and slowly returned to baseline during recovery, a response that was relatively subdued and delayed (“phase-shifted”) for infants born preterm (Fig. 1C,F).

BP and HR response of infants with BPD. Here we analyzed how lung disease influenced cardiovascular control. Baseline TcCO2 was elevated in severe BPD, but the increase in CO2 during hypercapnia was comparable across the BPD spectrum (∆TcCO2 = 1.1 ± 0.5 kPa versus 1.0 ± 0.5 kPa for mild-moderate versus severe BPD, respectively; Fig. 2A). Infants with mild-moderate BPD had a comparable pressor response to that of healthy preterm infants, but in severe BPD, the pressor response was markedly diminished (Fig. 2B,C).

### Table 1. Population data

<table>
<thead>
<tr>
<th>Group</th>
<th>Gestation at birth (wk)</th>
<th>Birth weight (g)</th>
<th>Weight (g)</th>
<th>Age (d)</th>
<th>Age (wk)</th>
<th>Weight (g)</th>
<th>Age (d)</th>
<th>Age (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full term (n = 12)</td>
<td>40 (38–42)</td>
<td>3575 (3065–4645)</td>
<td>2140 (1886–2960)</td>
<td>28 (13–64)</td>
<td>36 (34–37)</td>
<td>3575 (3065–4645)</td>
<td>5 (2–10)</td>
<td>41 (39–41)</td>
</tr>
<tr>
<td>Preterm (n = 12)</td>
<td>32 (27–34)</td>
<td>1530 (1144–2640)</td>
<td>2412 (1400–2955)</td>
<td>63 (15–90)</td>
<td>36 (36–36)</td>
<td>3060 (2546–3480)</td>
<td>62 (41–85)</td>
<td>40 (40–40)</td>
</tr>
<tr>
<td>BPD (n = 10)</td>
<td>26 (23–33)</td>
<td>875 (500–2342)</td>
<td>2412 (1400–2955)</td>
<td>63 (15–90)</td>
<td>36 (36–36)</td>
<td>3150 (2400–3660)</td>
<td>93 (46–117)</td>
<td>40 (39–40)</td>
</tr>
</tbody>
</table>

Details of the three infant study groups. The median and range (min-max) are shown. Note that full-term infants were only studied once. PMA, postmenstrual age (* = postconceptual age + postnatal age).

### Table 2. Baseline data

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (min⁻¹)</th>
<th>RR (min⁻¹)</th>
<th>TcCO2 (kPa)</th>
<th>TcO2 (kPa)</th>
<th>SaO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Baseline data at 36 wk PMA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Preterm (n = 12)</td>
<td>144 ± 7</td>
<td>52 ± 4</td>
<td>5.8 ± 0.1</td>
<td>8.3 ± 0.9</td>
<td>98 ± 1</td>
</tr>
<tr>
<td>Mild BPD (n = 5)</td>
<td>145 ± 1</td>
<td>51 ± 7</td>
<td>5.8 ± 0.1</td>
<td>8.0 ± 0.9</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>Severe BPD (n = 5)</td>
<td>147 ± 5</td>
<td>61 ± 4</td>
<td>6.7 ± 0.1*</td>
<td>8.2 ± 0.4</td>
<td>94 ± 2*</td>
</tr>
<tr>
<td>B. Baseline data at term PMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full term (n = 12)</td>
<td>121 ± 6</td>
<td>41 ± 3</td>
<td>5.3 ± 0.2</td>
<td>9.4 ± 0.7</td>
<td>96 ± 1</td>
</tr>
<tr>
<td>Preterm (n = 12)</td>
<td>137 ± 5†</td>
<td>44 ± 2</td>
<td>5.6 ± 0.2</td>
<td>8.9 ± 0.6</td>
<td>98 ± 1</td>
</tr>
<tr>
<td>Mild BPD (n = 5)</td>
<td>144 ± 8‡</td>
<td>52 ± 5‡</td>
<td>5.8 ± 0.2</td>
<td>8.3 ± 1.0</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>Severe BPD (n = 5)</td>
<td>146 ± 5†‡</td>
<td>58 ± 3‡</td>
<td>6.1 ± 0.3‡</td>
<td>9.1 ± 1.0</td>
<td>95 ± 1</td>
</tr>
</tbody>
</table>

Baseline values measured in air, during quiet sleep at PMA 36 wk (A) and 40 wk (B). Values are mean ± SD. There was significant CO2 retention in babies with severe BPD at 36 wk (A); preterm infants had higher HRs compared with term babies at the same age (B).

* Significantly different from preterm and mild BPD.
† Significantly different from term.
‡ Significantly different from preterm (ANOVA).
The increase (and subsequent dramatic decrease) in pulse pressures was due principally to changes in systolic pressure (Fig. 3). CO₂ exposure always caused mild bradycardia in BPD (Fig. 2D). Baseline TcCO₂ levels fell slightly with age in severe BPD (Table 2), but circulatory responses of both BPD groups to CO₂ did not change between 36 and 40 wk. There was no correlation between gestational/postnatal age and the pressor response of infants with BPD.

HVRs. Because breathing has mechanical and reflex effects on BP and HR, we looked for evidence of an association between the cardiovascular and ventilatory responses to CO₂, i.e. did babies with the most vigorous ventilatory responses have the most (or least) vigorous BP or HR responses? As expected, CO₂ consistently augmented breathing (Fig. 4A,B). The net increases in ventilation and breathing strategies were comparable, irrespective of gestation, age, or BPD grade (Fig. 4C,D) and hence could not explain the dramatically reduced pressor response in severe BPD (Figs. 3D and 4D). There was a strong correlation between HR and systolic (p = 0.006) but not diastolic BP (p = 0.06) responses, indicating that only systolic BP increased in parallel with HR. There was no association between the ventilatory and HR or BP responses to CO₂ (p = 0.77 and 0.66, respectively).

Cardiovascular control at term equivalent age. The principal findings at term are summarized in Figure 5. Infants born at this age responded to CO₂ by increasing both BP and HR, but those born preterm responded with either (i) a normal pressor but weak HR response (mild-moderate or no BPD) or (ii) an abnormally low pressor response confounded by mild cardiac depression (severe BPD).

DISCUSSION

Our data reveal that preterm birth is associated with persistently altered HR and in some circumstances abnormal pressor responses to mild stress (Fig. 5). These findings are remark-

Figure 1. Cardiovascular responses of to CO₂ during sleep. Preterm infants at 36 and 40 wk are compared at left [A–C; 36 wk (○), 40 wk (●); n = 12] and preterm and term infants at the same age at right [D–F; preterm at 40 wk (●); full term (○), n = 12]. The increase (and subsequent decrease) in BP was exaggerated at 36 wk (A; p = 0.05), but had normalized by term (D; p = 0.5). Pulse pressure of preterm infants increased more rapidly during CO₂ exposure (B, p = 0.4; E, p = 0.02). Only term infants had increased BP and HR when exposed to CO₂ (C, p = 0.09; F, p < 0.001). Mean ± SEM; p values (two-way ANOVA) refer to group comparisons; *p < 0.05.

Figure 2. Cardiovascular responses to CO₂ in BPD. TcCO₂ levels were elevated in severe BPD [A: mild-moderate BPD (●), n = 5; severe BPD (○), n = 5; p < 0.001 for group × time ANOVA interaction]. Mean BP and pulse pressure were exaggerated in mild-moderate BPD, and attenuated in severe BPD (B, C; p = 0.04 and 0.01 for group comparisons, respectively). HR decreased during CO₂ exposure, then increased transiently (D; p = 0.2 for group comparisons). Values are mean ± SEM.
body stores which buffer changes in CO₂ are correspondingly much smaller in infancy. At both ages, the pressor response outlasts the stimulus, most likely due to residual adrenergic stimulation by catecholamines released into the blood from the adrenal (21). The similarities between adults and infants suggest that (i) this cardiovascular chemoreflex arc is normally well developed at or soon after birth and (ii) elements of it may be fine-tuned as the heart and nervous systems mature, but the response itself changes little with age.

Although term infants exposed to CO₂ increase both BP and HR (22), infants born preterm increase BP with little or no change in HR (Fig. 1). In fact, the preterm heart already beats 10% or so faster at rest, partly to compensate for lower systemic vascular resistance: because blood flows out of low-resistance (preterm) arteries more rapidly, this maintains diastolic pressure (both lower in preterms; Fig. 3) (23). Under such circumstances, peripheral vasoconstriction (which boosts venous filling pressure and end-diastolic ventricular volume) may be the principal means of increasing BP during the initial minutes of CO₂ exposure. The accompanying hyperpnea may also help because it lowers pleural pressure, which draws blood into the right side of the heart (24,25). An exceptionally strong preterm vasoconstrictor reflex may compensate for the delayed cardioacceleratory response of the preterm infant to CO₂. The latter suggests that preterm cardiac adrenergic receptors are stimulated mainly by circulating (adrenal) catecholamines rather than directly by sympathetic nerve terminals within the heart (22,26). The younger the gestation, the steeper was the acute increase and subsequent decrease in, particularly, pulse pressure (Fig. 1). Acute changes in BP are buffered by the baroreflex, which adjusts HR and sympathetic tone to keep pressure changes within a narrow range. This reflex is active but functionally immature at 36 wk and still relatively weak at 40 wk (27). If the threshold for baroreflex activation is slow to reset to the usual postnatal range, dynamic variations in pressure may be wider than expected and remain so for much longer than is normal after birth, as we observed (28).

**BPD.** BPD is a pathologic response of the immature lung to medical treatments used to support breathing and combat
hypoxia. It occurs in approximately 30% of infants born extremely preterm, many of whom may remain symptomatic for months or years (12). Neonatal cardiovascular dynamics has not been studied systematically, although known complications of the severest forms of BPD include pulmonary hypertension, cardiac hypertrophy, and systemic hypertension (8,9,29). Variations in practice, guidelines, and endpoints make it difficult to standardize grading of the severity of BPD. The criteria we used, O2 dependency at 36 wk (12), is useful for several reasons: (i) it is used clinically to define BPD; (ii) O2 support ≥30% (severe) or <30% (mild-moderate BPD) correlates reasonably well with the underlying hypoxia (measured by the decrease in saturation during O2 withdrawal), and (iii) prolonged O2 dependency correlates with long-term (respiratory) dysfunction (30).

We identified several reflex anomalies associated with BPD, including mild, hypercapnia-induced cardiac depression (bradycardia). This immature, fetal-like vagal response to CO2 is normally blocked/reversed after birth because lung inflation is cardioexcitatory. In BPD, however (irrespective of its severity), HR decreased despite a seemingly brisk ventilatory response to CO2 (Fig. 4). Why? One problem faced in this disease is that the lungs are stiff and difficult to inflate and keep inflated, so breathing tends to be rapid and shallow (31). If lung expansion is restricted and cardioexcitatory lung inflation afferents are only weakly activated in BPD, it may be difficult to counteract rapid, CO2-induced cardiac depression (32,33). The slow, secondary increase in HR which occurred in healthy preterms exposed to CO2 was also largely absent in BPD; this may indicate impaired adrenal catecholamine release or altered cardiac adrenergic receptor activity caused by chronic sympathetic overactivation, both of which are complications of BPD (34–36). A strong cardiodepressant reflex of the sort we describe is a poor prognostic sign: it could trigger or deepen asphyxial coma or prevent cardiovascular autoresuscitation and may be a factor contributing to the high SIDS rate in BPD (6,10,37).

Unlike HR, disturbances in BP control varied with severity of lung disease. In mild-moderate BPD, the pressor response to CO2 was exaggerated. Whether this is a side effect of lung disease per se is not clear because infants with BPD tend to be younger and smaller at birth than healthy preterms. BP may increase more when these infants are exposed to CO2 due to a combination of factors related to immaturity: strong sympathethic vasoconstrictor tone, a persistent cardioinhibitory reflex (a decrease in HR allows the heart more time to fill with blood, increasing cardiac output), and poor buffering of sudden increases in output and pressure due to a weak baroreflex. At the other end of the BPD spectrum, however, we observed a diminished pressor response and dramatic recovery fall off in pulse pressure. This suggests that the challenge in severe BPD may be to maintain pressure and perfusion and prevent it from decreasing (rather than increasing) too much, too quickly. A weak pressor response to stress may be a symptom of immaturity confounded by pathophysiological adaptations to chronic disease. Why short-term BP control is compromised in this way and why babies with severe BPD seem so close to failure is difficult to say. Chemoreceptor-mediated responses to hypercapnia may be diminished in severe BPD due either to chronic CO2 retention, or weakening of the sympathoadrenal system (18,35,38). Furthermore, because the head and upper body of these babies is often disproportionately large (39,40), cerebral vasodilation during CO2 exposure could profoundly reduce systemic vascular resistance. Combined with an already high HR (which limits the heart’s capacity to increase the volume and force of ventricular ejection) and a fast shallow breathing pattern (which does not facilitate venous return), stroke volume and pulse pressure may actually decrease (Fig. 2C). The decrease may be especially difficult to arrest or counteract because the baroreflex is still immature. These infants could consequently be vulnerable to episodes of spontaneous hypotension and hypoperfusion, a potentially serious situation given their rapid metabolism and precarious energy balance (35,41).

**Longer term consequences.** The persistent differences that we observed between groups at term age indicate that circulatory control must develop more slowly or diverge from normal when babies are born too early. Ultimately, these changes can be traced to the sudden growth arrest occurring immediately after premature birth (40). Infants born preterm may eventually catch up to their counterparts born at term, although to what extent presumably depends on whether key events occur at the proper time and in the correct sequence, e.g. changes in baroreflex control (which normally strengthens), cardiovagal inhibition (which weakens), metabolism (which slowly decreases), vascular resistance (which increases), and within the heart itself (27,42,43). Because the HR of the preterm infant is often elevated at 6 mo, central and peripheral mechanisms involved in cardiac (and perhaps circulatory) control may be quite slow to reset or normalize (if at all) (44). Presumably, and this requires long-term follow-up, the more severe and persistent the dysfunction (e.g. severe BPD), the slower will be the path to recovery and the more likely it is that there will be enduring, perhaps serious, side effects. Dysfunction of the sort we describe may be further worsened by hypoxia (which amplifies the effects of hypercapnia, and is a complication of BPD) or nicotine exposure due to maternal tobacco use (45–47).

**CONCLUSION**

Short-term control of HR and BP is altered by preterm birth and superimposed chronic lung disease. Some of the reflex changes we describe could predispose to episodes of sudden hypotension and may be early signs of emerging long-term dysfunction.

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