Growth Failure and Altered Body Composition Are Established by One Month of Age in Infants with Bronchopulmonary Dysplasia

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ABSTRACT  Long-term growth failure and altered body composition are common consequences of bronchopulmonary dysplasia (BPD). We hypothesized that these chronic findings are preceded by uncompensated, acute early growth failure. The purpose of this study was to evaluate the effects of developing bronchopulmonary dysplasia on body composition and growth of very-low-birth-weight (VLBW) infants during the first six postnatal weeks. Arm muscle and fat accretion and changes in weight, length and head circumference were evaluated in 16 very-low-birth-weight infants who developed bronchopulmonary dysplasia and compared with 16 birth-weight-matched control infants without bronchopulmonary dysplasia. During the 1st wk, both groups experienced similarly low nutritional intakes, wasting of arm muscle and fat stores, and reduced weight, length and head circumference growth velocities, compared with intrauterine growth standards. Between wk 2 and 4, infants with developing bronchopulmonary dysplasia consumed less protein and energy (P < 0.05), accreted less arm fat and muscle (P < 0.05), and grew more slowly than control infants in all measured variables (P < 0.05). When infants with bronchopulmonary dysplasia had achieved full enteral feedings and had similar protein-energy intakes to control infants, they demonstrated similar rates of growth and arm muscle and fat accretion, but did not demonstrate catch-up growth. These data support the speculation that early reductions in muscle and fat accretion and growth velocity contribute to the long-term growth failure in infants with bronchopulmonary dysplasia. Prevention may require greater attention to defining and delivering optimal nutritional therapy to physiologically unstable premature infants in the immediate postnatal period. J. Nutr. 126: 168-175, 1996.

INDEXING KEY WORDS:
- bronchopulmonary dysplasia
- fat accretion
- muscle accretion
- growth
- humans

Long-term growth failure is common in infants with bronchopulmonary dysplasia (BPD) [Davidson et al. 1990, Markestad and Fitzhardinge 1981, O'Shea et al. 1992, Sauve and Singhal 1985, Vohr et al. 1982]. By 40 wk postmenstrual age, infants with BPD have well-established growth failure, characterized by mean weights and lengths more than two standard deviations below the values for term newborns [Davidson et al. 1990, Markestad and Fitzhardinge 1981]. Catch-up growth appears to occur very slowly; follow-up studies have demonstrated that children with BPD had persistently subnormal weights and lengths throughout infancy and into childhood. These children also have reduced subcutaneous fat stores and decreased muscle accretion as evidenced by low triceps skinfold thicknesses and arm muscle areas [Davidson et al. 1990, Markestad and Fitzhardinge 1981, O'Shea et al. 1992, Robertson et al. 1992, Sauve and Singhal 1985, Vohr et al. 1982]. Permanent stunting of growth has been reported in one long-term follow-up study [Northway et al. 1990].

Despite the wealth of information documenting long-term growth failure in infants with BPD, there is little information about the ontogeny of growth failure and altered body composition during the early neonatal period. Documentation of the time of onset, the relationship to nutritional therapy, and the effect on specific body compartments will be necessary to devise strategies to prevent growth failure and the prolonged period of catch-up growth which occurs in infants with BPD. Moreover, it has been hypothesized that inadequate early nutrition may contribute to the pathogenesis of BPD by impeding lung reparative processes in the first month of life [Frank and Sosenko 1988]. Thus, information about the early patterns of

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growth in these infants may ultimately be helpful in reducing the severity of the pulmonary disease itself.

The purpose of this study was to evaluate the effects of developing bronchopulmonary dysplasia on early growth and body composition in very-low-birth-weight (VLBW) infants. We prospectively evaluated a group of infants who developed BPD, comparing them with a group of birth-weight-matched infants who did not develop BPD. To evaluate the quality of growth and the infants' allocation of nutritional resources, we measured arm muscle and fat areas in addition to weight, length and head circumference during the first six postnatal weeks. We hypothesized that slower growth velocities and altered body composition occur early in the neonatal period in infants who are developing BPD.

SUBJECTS AND METHODS

Subjects. The study was approved by the Human Subjects Committees of the University of Minnesota Hospital and the Children's Health Care-St. Paul. All subjects were newborn infants admitted to the neonatal intensive care units at the University-Variety Hospital for Children or Children's Health Care-St. Paul. Groups of VLBW infants with and without BPD followed longitudinally were the focus of this study. However, to establish a reference curve for arm muscle and fat areas from 24–41 weeks gestation, we also studied a cross-sectional group of premature and term infants near the time of birth.

Cross-sectional group. One hundred fifteen infants with birth weights which were appropriate for gestational age at 24–41 wk gestation were studied within 72 h of birth. Gestational age was determined by obstetric criteria and confirmed by neonatal physical examination using a modified Dubowitz assessment of gestational age [Constantine et al. 1987]. Infants were excluded if they had multiple congenital anomalies or other abnormalities preventing accurate measurement. Data from 22 subjects had been used in a previous publication [Georgieff et al. 1989a].

Longitudinal group. All appropriate for gestational age infants with birth weights between 750 and 1500 g were prospectively entered into the study until 16 infants with BPD and 16 matching control subjects were enrolled. This number was selected on the basis of pilot data which demonstrated that BPD and control infants differed by ~one standard deviation in weight at 1 mo of age. Gestational age determination and early exclusion criteria were the same as those used for the cross-sectional group. Infants were also excluded if they were discharged prior to 6 wk of age or if diagnosed with a chronic illness, unrelated to BPD, which would affect growth. One infant who had BPD developed post-hemorrhagic hydrocephalus; her head measurements were excluded after 1 wk of age when ventriculomegaly was diagnosed using cranial ultrasonography.

At 28 d of age each subject was assigned to the BPD or the control group. The diagnosis of BPD was established if the infant had received positive-pressure ventilation during the first 2 wk of life, had persistently abnormal chest radiographs consistent with BPD [Edwards 1988], and required supplemental oxygen at 28 d. Each subject entered into the BPD group was matched with the next-born infant without BPD whose birth weight was within 250 g. Fifteen infants were excluded after enrollment into the study because of death, discharge or transfer to another hospital before 6 wk of age (n = 2 BPD, 9 control), lack of a matching control subject (n = 3 BPD), or development of necrotizing enterocolitis with short bowel syndrome (n = 1 control).

Anthropometric measurements. Cross-sectional group. Measurements were made in duplicate by two of four trained study personnel who measured infants at both hospitals. The mid-arm circumference, estimated to the nearest 0.25 cm, was measured at the midpoint of the upper left arm as described by Sasanow et al. (1986). Triceps skinfold thicknesses, estimated to the nearest 0.25 mm, were measured using Lange calipers (Cambridge Scientific Industries, Cambridge, MD) and recorded within 15 s after application and again when a stable measurement was obtained [Brans et al. 1974]. Mid-arm muscle, water and fat areas were calculated by the method described by Sann et al. (1988).

Longitudinal groups. Unclothed infants were weighed on admission and daily thereafter by the nursing staff. All other measurements (length, head circumference, mid-arm circumference and triceps skinfold thickness) were done in duplicate by two of four study personnel. Measurements were taken initially within 72 h of birth and once per week thereafter. Arm measurements were performed as described for the cross-sectional group. Length and head circumference were measured using paper measuring tapes (Ross Laboratories, Columbus, OH) using methods described by Miller and Hassanein (1971). Weight, length and head measurements were z-transformed for postmenstrual age using the growth curves described by Babson and Benda (1976) for premature infants.

To compare rates of growth at similar energy intakes, gains in weight, length, head circumference, arm muscle and fat areas were computed for the first 2 wk after the infant had reached full enteral feedings [≥460 kJ/(kg·d)]. For weight, length, and head circumference, changes in z-scores over the 2-wk period were also calculated.

Nutritional intakes. Weekly protein and energy intakes were calculated from each infant's parenteral and enteral nutritional intakes using the manufacturer's specifications of nutritional content for commer-
cial formulas and parenteral nutrition, and using the nutrient composition of preterm breast milk described by Lemons et al. (1982).

Patient care was similar in both neonatal intensive care units. Parenteral and enteral nutrition was prescribed according to the nutritional recommendations for premature infants by the American Academy of Pediatrics (1993). The ultimate goals of nutritional therapy were to provide ~500 kJ/kg of body weight per day and 3.0–3.6 g/(kg·d) of protein enterally or 360–380 kJ/(kg·d) and 2.5–3.0 g/(kg·d) of protein parenterally. All infants received parenteral nutrition until enteral feedings were established. Parenteral nutrition was usually initiated at 2–3 d of age using energy intakes of 60–100 kJ/(kg·d) and protein intakes of 0.5–1.0 g/(kg·d) and advanced as tolerated according to the published recommendations (American Academy of Pediatrics 1993). Enteral feedings with preterm infant formula [Enfamil Premature Formula, Mead Johnson, Evansville IN or Special Care Formula, Ross Laboratories, Columbus, OH] or fortified breast milk (Human Milk Fortifier, Mead Johnson) were introduced when the infant was clinically stable and advanced as tolerated. Premature formula or fortified breast milk was fed until a weight of 1500–1800 g was reached or concentrated formula was no longer needed.

Data analysis. Cross-sectional group. Polynomial regression analyses were used to construct standard curves for arm muscle area and arm fat area.

Longitudinal group. Clinical characteristics were compared between groups using Student’s t test for continuous variables and chi-square test for non-continuous variables. Arm muscle area and arm fat area, weight, length and head circumference z-scores, and protein and energy intakes were compared between groups over the 6-wk study period using repeated measures ANOVA. Significant differences were further analyzed using Newman-Keuls’ multiple range tests (Bruning and Kintz 1977). In the BPD group, 13 of 16 infants remained hospitalized and were measured at wk 7–9; these data were not used in any statistical analyses, but are shown to depict trends.

Growth velocities for arm muscle area, arm fat area, weight, length and head circumference during the first 2 wk of full enteral feedings were compared between groups using Student’s t tests.

Statistical comparisons were considered significant at P < 0.05. All data are presented as the mean ± 1 SD.

RESULTS

Cross-sectional group. Arm muscle area and arm fat area were significantly correlated with increasing gestational age (Fig. 1). The values obtained for the term infants are consistent with those obtained by Sann et al. (1988), who studied healthy full-term French infants, whereas the curves for preterm infants are unique.

Longitudinal groups. The clinical characteristics of the longitudinal groups are shown in Table 1. Infants with BPD remained in supplemental oxygen and were mechanically ventilated longer than the control infants.

Although the infants in the two groups were of comparable size at birth, repeated measures ANOVA demonstrated significant effects of BPD group [P < 0.01] and time [P < 0.001] on weight, length, and head circumference z-scores as well as arm muscle area and arm fat area. Post-hoc testing demonstrated that by 2–4 wk of age, infants with BPD were smaller than control infants in all measured variables and remained so (with the exception of length z-score) for the duration of the study period (Fig. 2, 3).

The significant effects of BPD group [P-values < 0.05] and time [P-values < 0.001] on protein and
TABLE 1
Gestational age, birth measurements, and respiratory status of bronchopulmonary dysplasia (BPD) and control groups

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>BPD group</th>
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<tbody>
<tr>
<td></td>
<td>$n = 16$</td>
<td>$n = 16$</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>28.4 ± 1.3</td>
<td>28.0 ± 1.9</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1136.3 ± 131</td>
<td>1132.0 ± 183</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>37.3 ± 1.9</td>
<td>37.1 ± 3.1</td>
</tr>
<tr>
<td>Birth head circumference, cm</td>
<td>26.3 ± 1.2</td>
<td>25.9 ± 1.6</td>
</tr>
<tr>
<td>Respiratory distress syndrome, n</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Mechanical ventilation, d</td>
<td>6.5 ± 11.0</td>
<td>22.4 ± 18.3*</td>
</tr>
<tr>
<td>Supplemental oxygen, d</td>
<td>9.2 ± 9.6</td>
<td>52.0 ± 31.1*</td>
</tr>
</tbody>
</table>
| Supplemental oxygen at ≥36 wk postmenstrual age, n | 0 | 4

1 Data are expressed as the mean ± SD or the number of infants per group; * indicates significant difference between BPD and control groups ($P < 0.05$).

energy intakes were also evident by repeated measures ANOVA. Post-hoc testing showed that infants with BPD had lower protein intakes from wk 2 to 4 and lower energy intakes during wk 2–3 compared with the control group (Fig. 4). Infants with BPD took 2 wk longer than control infants to achieve full enteral feedings (Table 2). During the 2 wk period following achievement of full, equicaloric enteral feedings, both groups demonstrated similar gains in weight, length, head circumference and arm fat accretion. Infants in the BPD group demonstrated greater changes in weight gain z-scores and arm muscle are a gain compared with the control group (Table 2).

DISCUSSION

This study indicates that growth failure accompanied by muscle and fat stores in infants with BPD occurs early in the postnatal period, at a time when chronic pulmonary disease is still developing. Although both groups of infants in this study demonstrated loss of arm muscle and fat stores as well as significant decelerations in growth during the first postnatal week, persistently poor growth in the first postnatal month was characteristic only of the infants who were developing BPD. When infants with BPD were able to tolerate full enteral feedings, growth and muscle and fat accretion were similar to that seen in infants without BPD, but significant catch-up growth did not occur. Overall, these changes in growth velocity and body composition place the infant who is developing BPD at a growth disadvantage soon after birth because in this study, the early reductions in growth velocity and alterations in body composition remained uncompensated during the hospital course. The results of the study are consistent with previous studies of infants and children with BPD which described a high incidence of subnormal weight and length at 40 wk postmenstrual age. In those studies subnormal weight and length persisted throughout infancy and into childhood (Davidson et al. 1990, Markestad and Fitzhardinge 1981, O'Shea et al. 1992, Robertson et al. 1992, Sauve and Singhal 1985, Vohr et al. 1982). On the basis of these data, we speculate that very early, uncompensated growth failure is the predecessor to long-term growth failure observed in many infants with BPD.

The growth patterns of the two groups of infants can be compared and contrasted during three phases of postnatal weeks.

**FIGURE 2** Weight, length and head circumference z-scores as a function of postnatal age for the bronchopulmonary dysplasia (BPD, $n = 16$) and control groups ($n = 16$). Data are presented as the mean ± 1 SD; * denotes a significant difference between the groups ($P < 0.05$).
groups of infants received an average of 1.5 g/[kg · d] of protein and 251 kJ/[kg · d] for the 1st wk. These intakes were associated with wasting of arm muscle and fat areas, indicating depletion of already scarce protein and energy reserves. As in a previous study, these data indicate that early weight loss was not limited to loss of extravascular body water (as occurs in full-term infants), but was also associated with wasting of muscle and fat stores (Georgieff et al. 1989). Although these early changes in weight and body composition are often thought to be normal or physiologic, they have significant consequences for the premature infant because of the rapid pace of in utero growth. For example, the infants in both groups of this study were one standard deviation below the mean in weight, length, and head circumference for postmenstrual age by the end of the first wk. Although slowly advancing parenteral and enteral nutritional intakes are recommended for preterm infants, our data have shown that even a brief period of nutritional intake not meeting expected energy expenditure in the immediate neo-

FIGURE 3 Arm muscle area (AMA) and arm fat area (AFA) of the bronchopulmonary dysplasia (BPD, n = 16) and control groups (n = 16) as a function of postnatal age, plotted over the mean (solid line) and 95% confidence limits (dashed lines) established by the cross-sectional control group for 28–37 wk gestation. Data are presented as the mean ± 1 SD; *denotes a significant difference between groups (P < 0.05).

of their hospitalization: the 1st wk, wk 2–4, and following 4 wk. The 1st wk was characterized by suboptimal intakes of energy and protein by both groups. Although the protein and energy requirements of acutely ill premature infants have not been unequivocally established, it is known that healthy premature infants require between 2.0 and 2.5 g/[kg · d] of protein and 251 kJ/[kg · d] to meet basal metabolic requirements and prevent catabolism of protein stores (Anderson et al. 1979). Substantially greater energy needs can be anticipated in infants with acute pulmonary disease because cellular oxygen consumption and therefore total energy expenditure increases with severity of respiratory distress (Wahlig et al. 1994).

In this study, parenteral nutrition generally was initiated by the 2nd or 3rd postnatal day and slowly advanced using the recommendations of the American Academy of Pediatrics (1993). Because slow advances in protein and lipid intakes are recommended, both

FIGURE 4 Protein and energy intakes of the bronchopulmonary dysplasia (BPD, n = 16) and control groups (n = 14, 2 hospital feeding records were lost) as a function of postnatal age. Data are presented as the mean ± 1 SD; *denotes a significant difference between groups (P < 0.05).
natal period was associated with significant reductions in growth velocity and alterations in body composition for both groups of infants.

During the intermediate time period (2–4 wk), a significant disparity in growth patterns developed between the two groups. Whereas the control group infants (whose acute lung disease had resolved) began to grow at rates parallel to the intruterine growth curve, the infants who were developing BPD continued to diverge from the expected norm. The finding of reduced weight, length and head circumference velocities in the group with BPD was expected, and is consistent with previous studies which have described subnormal weight and length percentiles in older premature infants and children with BPD (Davidson et al. 1990, Markestad and Fizhachurdis 1981, Northway et al. 1990, O'Shea et al. 1992, Robertson et al. 1992, Sauve and Singhal 1985, Vohr et al. 1983). The finding that infants with BPD demonstrated a 20% loss of arm muscle and fat by as early as 2 wk of age suggests that this group was receiving little excess fuel above basal requirements to support tissue fat and muscle accretion. No apparent preferential loss of muscle or fat stores occurred during this time period, implying that both may have been catabolized for energy production.

The possibility that the early growth failure in the BPD group was due to a relative lack of energy compared with total energy expenditure was supported by the fact that this group received significantly less energy and protein per kilogram of body weight during wk 2–4 compared with the control group. This finding should be viewed with some caution because infants received a combination of enteral and parenteral feedings during this time period, and most of the control infants received at least some breast milk, for which the nutrient composition was assumed on the basis of prior research (Lemons et al. 1982) and not known with certainty. However, only 3 of 16 infants in the BPD group received breast milk, making it unlikely that erroneous estimation of nutrient composition was responsible for poor growth in this group of infants. In addition, the finding of decreased nutritional intakes in infants with BPD has been previously reported and attributed to the need for fluid restriction to prevent pulmonary edema, difficulties in introducing enteral feedings because of recurrent episodes of feeding intolerance and cardiopulmonary instability, and associated complications of patent ductus arteriosus and sepsis (Vohr et al. 1982, Yeh et al. 1989). It would be tempting to speculate that this reduced intake was further complicated by potentially higher protein and energy demands in that group. Previous studies of infants with BPD have demonstrated increased energy expenditures by 1–3 mo of age (deGarmara 1992, Weinstein and Oh 1981, Yeh et al. 1989). However, these studies generally focused on selected populations of infants with established severe BPD (Weinstein and Oh 1981, Yeh et al. 1989). No studies have evaluated rates of oxygen consumption in infants during the first four postnatal weeks, as they were developing BPD, prior to the establishment of the diagnosis at 28 d.

The majority of infants in this study had milder BPD than described in previous studies (Weinstein and Oh 1981, Yeh et al. 1989); most were weaned from supplemental oxygen by 36 wk postmenstrual age. deGarmara (1992) recently demonstrated increased energy expenditures only in infants with severe BPD, whereas infants with milder BPD had energy expenditures which were within the range of normal values seen in healthy premature infants. Kurzner et al. (1988) studied infants with BPD at 6 mo corrected age and found that infants with normal growth did not have increased energy expenditures. The finding of similar growth velocities (and even higher for arm muscle accretion and weight z-score) in infants with BPD compared with control infants during a 2-wk period of equicaloric intakes supports the concept that suboptimal nutrient delivery or inefficient utilization of delivered nutrients, rather than increased energy requirement, most likely accounted for the diverging growth patterns documented in wk 2–4.

After 4 wk of age, protein and energy intakes equalized between the two groups, and growth rates became similar. Using fortified breast milk or standard preterm formulas at 494 kJ/(kg·d), catch-up growth did

| Age at full enteral feeds, wk | 3.3 ± 2 | 5.6 ± 2* |
| Weight gain, cm/14 d | 1.6 ± 1.0 | 1.5 ± 1.0 |
| Head circumference gain, cm/14 d | 2.0 ± 1.0 | 2.0 ± 1.0 |
| Arm muscle area gain, mm²/14 d | 0.12 ± 0.5 | 0.16 ± 0.5 |
| Arm fat area gain, mm²/14 d | 25.5 ± 19 | 18.7 ± 21 |

**Table 2**

Growth patterns on full enteral feeds

1 Data are expressed as the mean ± SD or the number of infants per group, * indicates significant difference between BPD and control groups (P < 0.05).

2 Two infants' hospital feeding records were lost.
not occur. By 6 wk of age, the BPD group had arm muscle areas (as well as weights and lengths) which were below the normal range for postmenstrual age. Reduced rates of arm muscle accretion relative to in utero norms continued until the eighth postnatal week in the BPD group. In contrast, the control group demonstrated arm muscle accretion rates which paralleled the normal curve by the third postnatal week.

Although infants with BPD demonstrated much poorer growth in all measured variables, both groups of infants demonstrated a similar pattern of sparing of arm fat accretion and head circumference relative to weight, length and arm muscle growth. Fat accretion in control infants showed complete catch-up to the mean of the standard curve by 6 wk. Fat accretion rates were slower in infants with BPD than in the control group, but arm fat areas never fell below the 95% confidence limits established by the cross-sectional group, suggesting that fat accretion was also prioritized (though to a lesser extent) in this group of infants.

The rapid development of subcutaneous fat stores has been previously reported in healthy growing preterm infants (Kashyap et al. 1986, Reichman et al. 1981). Reichman et al. (1981) noted that postnatal fat deposition in preterm infants was greater than that seen in utero and resembled early postnatal fat deposition in full-term infants. The finding of relative preservation of fat accretion, even in infants with BPD who had growth failure, is consistent with Reichman's speculations that fat deposition after birth is important for thermoregulation and does not simply represent storage of excess energy (Reichman et al. 1981).

The results of this study indicate that growth failure and alterations in body composition in infants with developing chronic lung disease occur early, predating the diagnosis of BPD at 28 d. These findings were associated with significantly lower protein and energy intakes, and occurred in spite of the relatively mild nature and ultimately short duration of their chronic lung disease. The alterations in body composition persisted until hospital discharge, implying that these infants were discharged with significantly lower protein and energy reserves. This finding is important because of previous reports documenting persistently reduced arm muscle and fat areas in very-low-birth-weight infants throughout the first postnatal month (Georgieff et al. 1989b). Further investigation into optimal nutrient delivery to physiologically unstable premature infants in the immediate neonatal period may be useful in preventing growth deceleration and loss of protein-energy stores in all VLBW infants, and may be particularly helpful in preventing growth failure in those infants who later develop bronchopulmonary dysplasia.

**LITERATURE CITED**


