Risk factors and rate of progression for zone I versus zone II type 1 retinopathy of prematurity

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PURPOSE
To compare the risk factors and rate of progression of zone I versus zone II type 1 retinopathy of prematurity (ROP).

METHODS
The medical records of consecutive preterm infants with bilateral type 1 ROP in zone I and age-matched control infants with type 1 ROP in zone II were retrospectively analyzed. Fundus findings at each screening examination and systemic parameters were compared between groups. Univariate and conditional multivariate regression analyses were employed to identify variables significantly associated with zone I ROP.

RESULTS
A total of 30 cases and 30 controls were included. The mean gestational age of included infants was 24.6 weeks in both groups, and the mean birth weights were 685 g in the zone I group and 667 g in the zone II group. The postmenstrual age (PMA) at the time of initial ROP detection did not differ between groups, but the PMA at the time of type 1 ROP detection was significantly earlier in the zone I group (mean, 34.9 vs 37.6 weeks). Conditional multiple logistic regression revealed that mechanical ventilation for 30 days or more was significantly associated with the type 1 ROP in zone I compared with zone II (OR, 3.5; 95% CI, 1.2-10.0).

CONCLUSIONS
Zone I ROP exhibited rapid progression, necessitating close monitoring and prompt treatment. Compromised pulmonary function with associated mechanical ventilation in early life may restrict retinal vascular growth and increase the likelihood of zone I type 1 ROP. (J AAPOS 2014;18:124-128)
ROP in zone I (zone I group) who completed the screening protocol for ROP were identified. The exclusion criteria were as follows: death before or within the screening period, incomplete follow-up, and a lack of adequate systemic information. For each patient with type 1 ROP in zone I, an age-matched control infant with bilateral type 1 ROP in zone II (zone II group) was selected from among the 566 preterm infants. ROP was categorized according to the revised International Classification of Retinopathy of Prematurity.6 The initial timing of and subsequent interval of screening examinations for ROP followed the guidelines proposed by the American Academy of Ophthalmology and the American Academy of Pediatrics and the Association for Pediatric Ophthalmology and Strabismus.9 The treatment criteria were based on the recommendations of the Early Treatment for Retinopathy of Prematurity (ET-ROP) to treat all type 1 ROP eyes, which includes: (1) zone I, any stage ROP with plus disease, (2) zone I, stage 3 ROP without plus disease, and (3) zone II, stage 2 or 3 ROP with plus disease.10

Fundus findings on ROP screening until the development of type 1 ROP or the termination of screening were analyzed. If the two eyes exhibited asymmetry in the rate of progression of ROP, data on the worse eye was included in the analysis. In addition, systemic parameters were retrieved, including birth weight, Apgar score, multiple births, patent ductus arteriosus, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, culture-proven sepsis, early sepsis (defined as the recovery of an organism from blood collected during the first week), use of surfactants, transfusion, duration of total parenteral nutrition, and duration of oxygen therapy, including mechanical ventilation and continuous positive airway pressure.

Mean PMAs at initial ROP detection and at type 1 ROP detection by zone were determined by Kaplan-Meier survival analysis and log-rank test. To find parameters that differed significantly between the two groups, univariate analysis was conducted using the $t$ test, the Fisher exact test, or the $\chi^2$ test on systemic and ocular parameters. A multiple logistic regression analysis was used to identify parameters significantly and independently associated with the zone I group compared with the zone II group. Variables with a significant correlation or a tendency toward an association with zone I group in univariate analysis ($P < 0.2$) and gestational age were included into a conditional multiple logistic regression model. A $P$ value of $<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS for Windows (version 18.0, SPSS Inc, Chicago, IL).

**Results**

The gestational age and severity of ROP in the overall population of 566 infants are presented in Table 1. The demographic and systemic characteristics of the zone I and zone II groups are presented in Table 2. The mean gestational age of the included infants was 24.6 weeks (range, 22.4-26.4 weeks) in both groups, and the mean birth weight was 685 g in the zone I group and 667 g in the zone II group.

The mean postnatal ages (PNAs) and PMAs at the time of detection of any stage ROP and of type 1 ROP are presented in Table 3. The PNAs and PMAs at the time of detection of type 1 ROP was significantly earlier and the interval from the initial detection of ROP to the detection of type 1 ROP significantly shorter in the zone I group (Table 3). However, the PNAs and PMAs at the time of initial ROP detection did not differ between two groups. In the Kaplan-Meier survival plot, PMA at the time of type 1 ROP detection was significantly different between groups (Figure 1).

Univariate analyses revealed that the duration of mechanical ventilation and the proportion of infants treated with mechanical ventilation for 30 days or more were significantly different between the two groups (Table 2). However, other systemic factors such as birth weight, moderate or more severe bronchopulmonary dysplasia, the incidence of sepsis, and so forth, did not differ between groups.

Conditional multiple logistic regression analysis was performed to identify systemic risk factors that were significantly associated with type 1 ROP in zone I compared to zone II.

Variables with a significant correlation or a tendency toward an association with zone I group in the univariate analysis ($P < 0.2$) were as follows: sex, 5-minute Apgar score, use of surfactant twice or more, amount of transfusion, duration of total parenteral nutrition, and mechanical ventilation ≥30 days. These 6 variables and gestational age were entered into a conditional multiple logistic regression analysis performed using SPSS for Windows (version 18.0, SPSS Inc, Chicago, IL).

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<th>Table 1. The gestational ages and severity of retinopathy of prematurity in the overall population of 566 preterm infants of gestational age ≤30 weeks</th>
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model. Among the 7 variables, only mechanical ventilation for 30 days or more was associated with the type 1 ROP in zone I (\(P = 0.022\); OR, 3.5; 95% CI, 1.2-10.0).

### Discussion

This study compared the risk factors between 30 infants with bilateral type 1 ROP in zone I and 30 age-matched control infants with type 1 ROP in zone II. Although the age at detection of any ROP did not differ between groups, rate of progression from the onset of ROP to type I prethreshold ROP was significantly earlier in the zone I group compared to the zone II group. Using the current screening protocol, the time from initial ROP detection to the time of type 1 ROP detection in infants with zone I ROP was short, typically <2 weeks, whereas rate of progression in zone II ROP was variable and not as rapid. Although many case series have reported rapid progression of type 1 ROP in zone I, this is, to our knowledge, the first to report an age-matched comparison of progression between infants with type 1 ROP in zone I and in zone II.

Although risk factors for ROP have been investigated in many studies, risk factors specific for type 1 zone I ROP as...
compared to type 1 zone II ROP have not been identified. In this study, prolonged mechanical ventilation was significantly associated with type 1 ROP in zone I. Infants with type 1 ROP in zone I were 4 times as likely to have had >30 days of mechanical ventilation than matched infants who developed type 1 ROP in zone II. Oxygen that enters into the lung with positive pressure by mechanical ventilation may be a marker for prolonged exposure to high oxygen.11 The supplemental oxygen given during mechanical ventilation contributes to retinal vascular obliteration due to the suppression of oxygen-regulated proangiogenic factors.12 In an oxygen-induced retinopathy model, an animal model of ROP, higher oxygen tension was reported to be associated with larger avascular retinal area.13 Moreover, in some clinical studies, high oxygen saturation in the first postnatal weeks was shown to be associated with an increased incidence of severe ROP.14,15 Recently, high blood concentrations of oxygen in the first 3 postnatal days was reported to be significantly associated with an increased risk of ROP in zone I as well as prethreshold and threshold ROP.16 Thus in infants with prolonged mechanical ventilation with oxygen supplementation, close monitoring for ROP is warranted.

Type 1 ROP in zone I typically develops in extremely preterm infants with low birth weight, which is a well-known risk factor for ROP.17-19 However, in this study, birth weight per se was not found to be a risk factor specific for type 1 ROP in zone I versus zone II. This may be due to the fact that the zone I and zone II infants were matched by gestational age and therefore had similar birth weights as well. Consequently, birth weight would not show up as a distinguishing risk factor.

There are several limitations to this study. This study was retrospective and the sample size was not large. Furthermore, the management protocols of the preterm infants were not consistent during the study period. During the years 2004-2011, there have been considerable advances in neonatal intensive care including improved delivery room management, fluid and electrolyte management, minimal handling, nutritional support, and improved respiratory care. Consequently, during the period, survival rate of extremely preterm infants has increased. In addition, at our center since 2010, lower inspired oxygen level (room air if possible) has been used during resuscitation in delivery room. These differences in the management during the period might also affect development of ROP. However, the fact that this study is an age-matched case–control study to determine risk factors specific for type 1 ROP in zone I is an important strength of our study because it may eliminate some of the potential confounders arising from longitudinal changes in care at our institute.

In conclusion, type 1 ROP in zone I typically developed in infants born before 26 weeks’ gestational age and exhibited rapid progression from the onset of ROP to type 1 ROP, necessitating close follow-up for timely treatment. Infants with type 1 ROP in zone I were more likely to have had mechanical ventilation as compared with zone II ROP.

**Literature Search**

The authors searched PubMed (MEDLINE) without date restriction for English-language only, last on April 30, 2013, using the following search terms and combinations:

- Retinopathy of prematurity AND ROP AND type 1 retinopathy of prematurity
- zone I retinopathy of prematurity.
References


