



Late-Onset Circulatory Collapse and Risk of Cerebral Palsy in Extremely Preterm Infants

Kazuaki Yasuoka, MD^{1,2}, Hirosuke Inoue, MD, PhD^{1,2}, Naoki Egami, MD^{1,2}, Masayuki Ochiai, MD, PhD^{1,2}, Koichi Tanaka, MD^{1,2}, Toru Sawano, MD^{1,2}, Hiroaki Kurata, MD^{1,2}, Masako Ichiyama, MD^{1,2}, Junko Fujiyoshi, MD^{1,2}, Yuki Matsushita, MD, PhD^{1,2}, Yasunari Sakai, MD, PhD¹, Shouichi Ohga, MD, PhD^{1,2}, on behalf of the Neonatal Research Network of Japan*

Objective To investigate whether the development of postnatal, late-onset refractory hypotension, referred to as late-onset circulatory collapse, was associated with an increased risk of developing cerebral palsy (CP) at 3 years of age in extremely preterm infants.

Methods In this historical cohort study, infants who were born at 22-27 weeks of gestation from 2008 to 2012 in the Neonatal Research Network of Japan were eligible. The study sample consisted of 3474 infants (45.6% of 7613 potentially eligible infants) who were evaluated at 36-42 months of age. Late-onset circulatory collapse was defined as a clinical diagnosis of late-onset circulatory collapse requiring treatment with corticosteroids. We compared the neurodevelopmental outcomes between infants with and without late-onset circulatory collapse.

Results Late-onset circulatory collapse was diagnosed in 666 of the infants studied. Infants with late-onset circulatory collapse had a higher incidence of CP than those without late-onset circulatory collapse (18.0% vs 9.8%; $P < .01$). In multivariable logistic analysis, late-onset circulatory collapse was independently associated with CP (aOR, 1.52; 95% CI, 1.13-2.04) and developmental quotient score of <50 (OR, 1.83; 95% CI, 1.23-2.72).

Conclusions Late-onset circulatory collapse may be a relatively common event occurring in extremely preterm infants and an independent risk factor for CP at 3 years of age. (*J Pediatr* 2019;212:117-23).

Refractory hypotension during the early postnatal period is one of the most serious maladaptations of unexpected early transition to extrauterine life in preterm infants, and it is thought to be associated with transient adrenocortical insufficiency.^{1,2} Recently, there have been several reports on refractory hypotension beyond the transitional period among very preterm infants. This condition has been proposed as a new entity called late-onset circulatory collapse.^{3,4} Late-onset circulatory collapse is characterized by hypotension and oliguria emerging after the first week of life in an otherwise generally stable newborn, although the etiology remains elusive.^{3,4} The hypotension does not respond to volume expanders or inotropic agents, but does respond to exogenous corticosteroids, suggesting an underlying transient adrenocortical insufficiency.^{3,4} A previous survey in Japan revealed that 6.3% of infants born at ≤ 1500 grams suffered from late-onset circulatory collapse.⁵ Of particular concern is that the development of late-onset circulatory collapse is associated with periventricular leukomalacia (PVL).⁶⁻⁸ However, there are few reports of neurodevelopmental outcomes of infants with late-onset circulatory collapse. Only 1 small, single-center study demonstrated the association between the development of late-onset circulatory collapse and cerebral palsy (CP) at 3 years of age in preterm infants.⁸

To elucidate the late effects of late-onset circulatory collapse on the preterm survivors, we investigated whether the development of late-onset circulatory collapse was associated with an increased risk of CP at 3 years of age in extremely premature infants using the nationwide cohort database in Japan.

Methods

Study Sample and Data Collection

The Neonatal Research Network of Japan (NRNJ) includes 204 participating neonatal intensive care units ([Appendix](#); available at www.jpeds.com) that register all the clinical information for infants born with a

BPD	Bronchopulmonary dysplasia
CP	Cerebral palsy
DQ	Developmental quotient
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NRNJ	Neonatal Research Network of Japan
PDA	Patent ductus arteriosus
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome

From the ¹Department of Pediatrics, Graduate School of Medical Sciences, and the ²Comprehensive Maternity and Perinatal Care Center, Kyushu University, Fukuoka, Japan

*List of institutions enrolled in the study of the Neonatal Research Network of Japan is available at www.jpeds.com ([Appendix](#)).

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weight of ≤ 1500 grams.^{9,10} This study included the infants who were born at 22^{0/7}-27^{6/7} weeks of gestation between January 1, 2008, and December 31, 2012. We excluded infants who had died at < 3 years of age, those with a major congenital abnormality, and those without available records for diagnosis of late-onset circulatory collapse. The diagnosis of late-onset circulatory collapse was made clinically according to the original diagnostic criteria of the Japanese Study Group for Neonatal Endocrinology^{3,4} as follows: (1) onset at ≥ 1 week after birth; (2) existence of stable period before onset; (3) no apparent causes including sepsis, massive bleeding, or necrotizing enterocolitis (NEC) before onset; (4) a mean blood pressure of $< 80\%$ of that in the previous stable state or a systolic blood pressure < 40 mm Hg; (5) urine volume of < 0.5 mL/kg per hour over the past 8 hours or < 1.0 mL/kg per hour over the past 24 hours; and (6) hypotension and/or oliguria with resistance to intravenous volume expanders or inotropes, but with a response to corticosteroid therapy. In the NRNJ database, late-onset circulatory collapse was defined as meeting the full diagnostic criteria for late-onset circulatory collapse and requiring treatment with corticosteroids. Hydrocortisone of 0.5-2.0 mg/kg was the regular initial dose administered for infants with late-onset circulatory collapse.^{3,4} Corticosteroid therapy then was individualized depending on the clinical response to the initial treatment by the responsible neonatologists.

Gestational age was calculated based on an ultrasound examination in early pregnancy and the date of the last menstrual period. Small for gestational age was defined as a birth weight of < 10 th percentile for gestational age.¹¹ Clinical chorioamnionitis was diagnosed based on clinical symptoms, including maternal fever, a tender uterus, and an elevated white blood cell count. Antenatal steroid use was defined as the maternal administration of steroids to promote fetal lung maturity. Respiratory distress syndrome (RDS) was diagnosed based on clinical and radiographic findings. Moderate to severe bronchopulmonary dysplasia (BPD) was defined as receiving supplemental oxygen or positive pressure at 36 weeks' postmenstrual age.¹² Treatment with surgical ligation was performed for closure of patent ductus arteriosus (PDA) diagnosed based on both the echocardiographic and clinical findings. Severe intraventricular hemorrhage (IVH) was defined according to the classification of Papile et al as grades III and IV.¹³ Cystic PVL was diagnosed by cranial ultrasound examination or head magnetic resonance imaging. Sepsis was defined as culture-proven septicemia or bacteremia during the neonatal intensive care unit stay. NEC was defined as Bell stage II or greater.¹⁴ Severe retinopathy of prematurity was treated by laser coagulation or cryocoagulation therapy. In agreement with the original concept of late-onset circulatory collapse,^{3,4} we did not consider infants as having late-onset circulatory collapse when they concurrently developed sepsis, severe IVH, NEC, or any other acute illness. Thus, the eligibility of late-onset circulatory collapse reflected the high stringency of the diagnosis when the participants were registered in the NRNJ database.

This study was approved by the internal review board of Tokyo Women's Medical University. Written informed consent was obtained from the parents or guardians of all infants in the NRNJ.

Neurodevelopmental Outcomes

The primary objective of this study was to investigate whether the development of late-onset circulatory collapse was associated with CP at age 3 years of extremely preterm infants. Comprehensive neurodevelopmental assessments were performed on the infants at 36-42 months of chronological age at each participating institution. CP was defined as abnormal muscle tone in ≥ 1 extremity and abnormal control of movement and posture.¹⁵ The presence or absence of CP was diagnosed by board-certified pediatricians specialized in child neurology. Profound CP was defined as a Gross Motor Function Classification System level of 4 or 5,¹⁵ and infants with an unknown level were classified as having CP instead of profound CP. Trained psychometricians performed developmental testing by using the Kyoto Scale of Psychological Development, a standard developmental scoring system in Japan.¹⁶ According to the protocol, the developmental function was categorized as 'severely delayed (developmental quotient [DQ] of < 50), delayed (DQ of < 70), subnormal (DQ of 70-84), and normal (DQ of ≥ 85).¹⁶ Visual impairment was defined as blindness with no functional vision in one or both eyes. Hearing impairment was defined as the need for amplification.

Statistical Analyses

Continuous and categorical variables were compared using the Wilcoxon rank-sum test and the χ^2 test, respectively. We estimated ORs with 95% CIs for developing CP and other neurodevelopmental outcomes with and without adjustment for potential confounders using logistic regression models. The following variables were examined as potential confounders influencing the development of CP: gestational age, birth weight, small for gestational age, clinical chorioamnionitis, antenatal steroid, sex, Apgar score at 5 minutes, RDS, moderate to severe BPD, PDA requiring surgical ligation, severe IVH, sepsis, NEC, and severe retinopathy of prematurity.^{17,18} According to the previous reports,⁶⁻⁸ we considered cystic PVL as a potential intermediate variable between late-onset circulatory collapse and CP and therefore we did not include cystic PVL in the main model. Results with a P value of $< .05$ were considered significant. Statistical analyses were performed using the software program JMP 13.0 (SAS Institute, Cary, North Carolina).

Results

Characteristics of the Study Sample

Among a total of 24 704 infants with a birth weight of < 1500 grams, 9297 were born at 22-27 weeks of gestation

during the study period (Figure). Of these, the following infants were excluded: 1258 infants who had died before 3 years of age, 232 infants with a major congenital abnormality, and 194 infants without available records of diagnosis of late-onset circulatory collapse. Consequently, a total of 7613 infants were eligible to participate in a follow-up evaluation at age 3 years. These infants were born at a median gestational age of 26^{0/7} weeks (IQR 24^{5/7}-27^{0/7} weeks) and a birth weight of 769 grams (IQR, 632-924 grams). A median length of neonatal intensive care unit stay was 118 days (IQR, 97-145 days). A total of 1399 infants (18.4%) were diagnosed with late-onset circulatory collapse among eligible infants. We excluded 4139 infants: 3909 were lost during the follow-up period with variable reasons, and follow-up data were missing for 230 infants who were followed until age 3 years. The study sample consisted finally of 3474 infants (45.6% of the eligible infants) who were evaluated at 3 years of age (Figure). In the study sample, the birth weight and the incidences of PDA requiring surgical ligation, severe IVH, and NEC were significantly lower, and the incidences of small for gestational age, clinical chorioamnionitis, antenatal steroid, and moderate to severe BPD were significantly higher than in the nonevaluated infants (Table I). There was no difference in the other variables between the study sample and the nonevaluated infants.

Late-Onset Circulatory Collapse and Risk of CP

Table II presents the neonatal characteristics of the infants with late-onset circulatory collapse (n = 666) and non-late-

onset circulatory collapse (n = 2808). The gestational ages and birth weights were significantly lower in infants with late-onset circulatory collapse than in infants without late-onset circulatory collapse. Infants with late-onset circulatory collapse had significantly higher incidence of small for gestational age, clinical chorioamnionitis, male sex, Apgar score of <4 at 5 minutes, RDS, moderate to severe BPD, PDA requiring surgical ligation, severe IVH, cystic PVL, sepsis, and severe retinopathy of prematurity compared with infants without late-onset circulatory collapse. Regarding neurodevelopmental outcomes at 3 years of age (Table III), infants with late-onset circulatory collapse had significantly higher incidence of CP, profound CP, a DQ of <70, and a DQ of <50 than infants without late-onset circulatory collapse. Multivariable logistic regression analysis revealed that late-onset circulatory collapse was significantly and independently associated with CP (aOR, 1.52; 95% CI, 1.13-2.04) and a DQ of <50 (aOR, 1.83; 95% CI, 1.23-2.72). We asked further whether sepsis, severe IVH, NEC, or a combination of these acute illness had a confounding effect on the development of late-onset circulatory collapse. We therefore examined the relationship between late-onset circulatory collapse and CP in 2875 infants (516 with late-onset circulatory collapse and 2359 without late-onset circulatory collapse) by removing infants who had any histories of sepsis, severe IVH, or NEC (Table IV; available at www.jpeds.com). We obtained the same result in the relationship between late-onset circulatory collapse and CP (aOR, 1.45; 95% CI, 1.01-2.08), even after excluding these

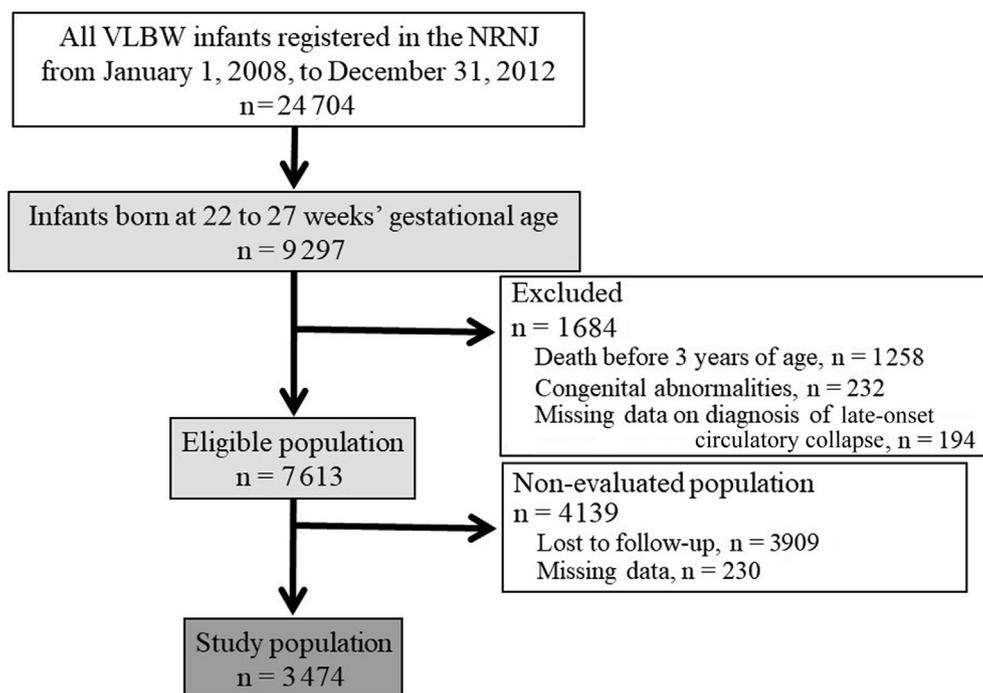


Figure. Enrolled patients of extremely preterm infants in the present study. VLBW, Very low birth weight.

Table I. Neonatal characteristics of the study sample

Characteristics	Study sample (n = 3474)	Nonevaluated sample (n = 4139)	P value
Gestational age, weeks	26 ^{0/7} (24 ^{5/7} -27 ^{0/7})	26 ^{0/7} (24 ^{5/7} -27 ^{1/7})	.81
Birth weight, grams	760 (625-922)	777 (638-926)	<.01
Small for gestational age	733/3474 (21.1)	762/4139 (18.4)	<.01
Clinical chorioamnionitis	1069/3383 (31.6)	1123/3860 (29.1)	.02
Antenatal steroid	1995/3446 (57.9)	2186/4052 (54.0)	<.01
Male sex	1876/3474 (54.0)	2197/4139 (53.0)	.43
Apgar score <4 at 5 min	260/3439 (7.6)	331/3979 (8.3)	.25
RDS	2709/3471 (78.1)	3186/4131 (77.1)	.35
Moderate to severe BPD	1364/3469 (39.3)	1457/4110 (35.5)	<.01
PDA requiring surgical ligation	475/2742 (17.3)	667/3277 (20.4)	<.01
Late-onset circulatory collapse	666/3474 (19.2)	733/4139 (17.7)	.10
Severe IVH	203/3469 (5.9)	292/4128 (7.1)	.03
Cystic PVL	137/3467 (4.0)	162/4125 (3.9)	>.99
Sepsis	431/3466 (12.4)	509/4118 (12.4)	.94
NEC	58/3471 (1.7)	102/4122 (2.5)	.02
Severe retinopathy of prematurity	1134/3417 (33.2)	1351/3997 (33.8)	.59

Data are presented as the number/number with available information (percentage) or as the median (IQR). P values were obtained using the Wilcoxon rank-sum test (continuous variables) and χ^2 test (dichotomous variables).

infants (Table V; available at www.jpeds.com). To assess the impact of selected variables including late-onset circulatory collapse on CP, we compared the neonatal characteristics between infants with and without CP in our study sample. All variables except small for gestational age, clinical chorioamnionitis, Apgar score of <4 at 5 minutes, and RDS were significantly different between both groups, as expected (Table VI; available at www.jpeds.com). We found that severe IVH (aOR, 10.2; 95% CI, 7.07-14.7) had the greatest impact on CP among confounding variables (Table VII, model A; available at www.jpeds.com). Late-onset circulatory collapse had a mild but significant impact on the risk of CP. When cystic PVL was additionally entered into the logistic model, cystic PVL had the highest odds ratio for CP (aOR, 11.6; 95% CI, 7.31-18.5) among selected variables, and late-onset circulatory collapse (aOR, 1.34; 95% CI, 0.98-1.83) was not a significant risk factor for CP (Table VII, model B).

Discussion

Our study demonstrates a novel risk of CP from late-onset circulatory collapse among premature infants. Late-onset circulatory collapse was independently associated as a risk factor for CP and neurodevelopmental delay at 3 years of age in extremely premature infants. Late-onset circulatory collapse has not been recognized worldwide; however, a considerable proportion of surviving extremely preterm infants in Japan experienced this seemingly idiopathic hypotension. This study highlights the importance of recognizing late-onset circulatory collapse because it is associated with long-term neurodevelopmental problems.

The survival rate of extremely preterm infants has improved, and the morbidity has been recognized in developed countries.^{9,19-21} In the past 2 decades, late-onset circulatory collapse has been reported, increasingly principally from Japan,^{5,8,10,22,23} but also Korea²⁴ and Taiwan.²⁵ Recent

Table II. Neonatal characteristics in infants with and without late-onset circulatory collapse

Characteristics	Late-onset circulatory collapse (n = 666)	Non-Late-onset circulatory collapse (n = 2808)	P value
Gestational age, weeks	25 ^{2/7} (24 ^{0/7} -26 ^{4/7})	26 ^{1/7} (24 ^{6/7} -27 ^{1/7})	<.01
Birth weight, grams	676 (570-848)	777 (641-940)	<.01
Small for gestational age	168/666 (25.2)	565/2808 (20.1)	<.01
Clinical chorioamnionitis	229/643 (35.6)	840/2740 (30.7)	.01
Antenatal steroid	393/665 (59.1)	1602/2781 (57.6)	.51
Male sex	395/666 (59.3)	1481/2808 (52.7)	<.01
Apgar score <4 at 5 min	68/661 (10.3)	192/2778 (6.9)	<.01
RDS	565/666 (84.8)	2144/2805 (76.4)	<.01
Moderate to severe BPD	323/665 (48.6)	1041/2804 (37.1)	<.01
PDA requiring surgical ligation	115/531 (21.7)	360/2211 (16.3)	<.01
Severe IVH	51/664 (7.7)	152/2805 (5.4)	.03
Cystic PVL	49/666 (7.4)	88/2801 (3.1)	<.01
Sepsis	109/665 (16.4)	322/2801 (11.5)	<.01
NEC	17/665 (2.6)	41/2806 (1.5)	.06
Severe retinopathy of prematurity	321/660 (48.6)	813/2757 (29.5)	<.01

Data are presented as the number/number with available information (percentage) or as the median (IQR). P values were obtained using the Wilcoxon rank-sum test (continuous variables) and χ^2 test (dichotomous variables). Infants with late-onset circulatory collapse do not have sepsis, severe IVH, NEC, or other acute illness during the active phase of late-onset circulatory collapse.

Table III. Neurodevelopmental outcomes at 3 years of age in infants with late-onset circulatory collapse

Outcomes	Late-onset circulatory collapse (n = 666)	Non-late-onset circulatory collapse (n = 2808)	P value*	Crude OR (95% CI)	P value†	aOR‡ (95% CI)	P value†
CP	120/666 (18.0)	276/2808 (9.8)	<.01	2.02 (1.60-2.55)	<.01	1.52 (1.13-2.04)	<.01
Profound CP	34/487 (7.0)	62/1996 (3.1)	<.01	2.34 (1.52-3.60)	<.01	1.31 (0.75-2.30)	.34
Cognitive impairment							
DQ of <70	192/570 (33.7)	557/2453 (22.7)	<.01	1.73 (1.42-2.11)	<.01	1.16 (0.91-1.49)	.23
DQ of <50	62/570 (10.9)	111/2453 (4.5)	<.01	2.57 (1.86-3.56)	<.01	1.83 (1.23-2.72)	<.01
Visual impairment	5/577 (0.9)	10/2600 (0.4)	.17	2.26 (0.77-6.65)	.14	2.25 (0.70-7.26)	.18
Hearing impairment	7/492 (1.4)	23/2055 (1.1)	.64	1.28 (0.54-2.99)	.58	1.51 (0.61-3.77)	.37

*P values were obtained using the χ^2 test.

†ORs with 95% CIs and P values were obtained from logistic regression analysis.

‡Adjusted values were obtained from logistic regression analysis after adjusting for all variables listed in Table II except cystic PVL.

awareness of the disorder has led to a steady increase in the number of reported cases of late-onset circulatory collapse from 8.5% in 2006¹⁰ to 13.1% in 2012⁵ among infants with a birth weight of <1000 grams, and this study showed that approximately 1 in 5 extremely preterm infants suffered from late-onset circulatory collapse. These results imply that the development of late-onset circulatory collapse is not uncommon in very preterm infants. In preterm infants, the biological prematurity in combination with increased demands in critical illness may result in inadequate cortisol production for the degree of illness or stress.^{2,26} The transient adrenocortical insufficiency of prematurity was usually used to describe the acute clinical scenario within the first week of life.^{2,26} In contrast, recent studies have demonstrated that relative adrenocortical insufficiency can persist after the transitional period in preterm infants, which has been thought to be one of the major causes of late-onset circulatory collapse.^{22,27,28} The endocrine function of premature infants remains unclear, and definitive diagnostic criteria for late-onset circulatory collapse have not yet been defined.^{3,4} Therefore, late-onset circulatory collapse is defined as symptoms and signs of “late-onset” circulatory failure without obvious causes that responds to glucocorticoids. Our extended analysis provided evidence that the complications of sepsis, severe IVH, or NEC had negligible effects on the pathogenic process of CP in infants with late-onset circulatory collapse. However, we cannot exclude the possibility that these complications contributed to the development of late-onset circulatory collapse, because we had only limited information regarding the time of their onsets. Further research is needed to establish the pathophysiology and diagnostic criteria for late-onset circulatory collapse.

One of the leading causes of CP is PVL, which results mainly from 2 major mechanisms, namely, hypoxia/ischemia and infection/inflammation.^{17,29} We could not determine whether these mechanisms were present in the pathogenic process of PVL partly because no information was available for the onset or duration of cystic PVL, severe IVH, and late-onset circulatory collapse in the database.

Several reports have supported our argument that the development of late-onset circulatory collapse increases the risk of PVL.^{6-8,24} An ultrasound study revealed that the

diastolic blood flow velocity in cerebral and renal arteries was decreased, despite an increased ejection fraction, in patients with late-onset circulatory collapse, which resembled distributive shock.³⁰ In this regard, late-onset circulatory collapse and PVL might be linked to each other in their pathogenic mechanisms and potentially to the long-term deficits of CP. From an opposing perspective, however, we cannot exclude the possibility that there were still unidentified causal factors, rather than late-onset circulatory collapse that contributed to the development of PVL and CP. For these reasons, we have not fully demonstrated the cause-and-effect relationship between late-onset circulatory collapse and CP.

It has been suggested that late-onset circulatory collapse, which is likely to be associated with permanent problems, should be treated as early as possible.^{4,8} In most cases, hydrocortisone is effective for the treatment of late-onset circulatory collapse.^{3,4,25} In contrast, the possibility of adverse effects, especially neurodevelopmental toxicity, from systemic corticosteroids should also be taken into account. Meta-analyses of studies in preterm infants have shown that early dexamethasone is associated with an increased risk of neurodevelopmental disabilities, whereas early hydrocortisone and late dexamethasone or hydrocortisone are not associated with obvious long-term problems.^{31,32} In the present study, although actual data of kind, timing, and dosage of exposure were not recorded in our NRNJ database, there might not be a direct association between corticosteroid administration and CP because it was speculated that infants with late-onset circulatory collapse received hydrocortisone during a late phase. However, an experimental study has shown that hydrocortisone can have detrimental effects on the developing brain via binding to glucocorticoid receptors, even though that steroid has fewer neurotoxic effects than dexamethasone.³³ Recent clinical studies have also indicated that early or late hydrocortisone is associated with undesired effects on neurodevelopment in premature infants.³⁴⁻³⁷ These studies are important warnings to discourage the liberal use of even relatively low-dose corticosteroids in these vulnerable infants with actively developing brain. Further studies are needed to provide a definitive assessment of the neurodevelopmental safety of hydrocortisone in infants with late-onset circulatory collapse.

Our study has several limitations. First, the results of this study must be interpreted with caution because it was a retrospective study with a high loss to follow-up rate, although we tried to overcome this limitation partially by using a large nationwide database. The validation studies using a replication set of extremely preterm cohort are needed to verify the present findings. Second, the relation between late-onset circulatory collapse and mortality was not investigated because there was not sufficient information on the detailed causes of death in each subject in the NRNJ database. Third, we could not fully adjust for other potential confounding factors related to prematurity or associated with neurodevelopmental disability, such as socioeconomic variables (eg, parental education level) and other neonatal interventions (eg, the strategy of nutritional support or ventilation). Last, we did not use the Bayley Scales of Infant Development III, which is used worldwide, but used the Kyoto Scale of Psychological Development instead, which is only used in Japan. However, a previous study showed that this scale correlated well with the Bayley III scale.¹⁶

We have identified that the development of late-onset circulatory collapse in extremely preterm infants is an independent predictor of adverse neurodevelopmental outcomes at 3 years of age. To confirm our findings, further prospective studies are needed. Until then, late-onset circulatory collapse should be recognized as one of the important complications of extremely preterm infants, because it may be associated with subsequent CP. ■

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Reprint requests: Hirosuke Inoue, MD, PhD, Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan, 812-8582. E-mail: hinoue@pediatr.med.kyushu-u.ac.jp

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Appendix

List of Institutions enrolled in the study of the Neonatal Research Network of Japan include: Sapporo City General Hospital, Asahikawa Kosei General Hospital, Engaru-Kosei General Hospital, Kushiro Red Cross Hospital, Obihiro-Kosei General Hospital, Tenshi Hospital, NTT Higashinihon Sapporo Hospital, Nikko Memorial Hospital, Nayoro City General Hospital, Sapporo Medical University, Asahikawa Medical University, Aomori Prefectural Central Hospital, Iwate Medical University, Iwate Prefectural Ofunato Hospital, Iwate Prefectural Kuji Hospital, Iwate Prefectural Ninohe Hospital, Sendai Red Cross Hospital, Akita Red Cross Hospital, Tsuruoka Municipal Shonai Hospital, Yamagata University, Yamagata Prefectural Central Hospital, Fukushima Medical University, Takeda General Hospital, Fukushima National Hospital, Tsukuba University, Tsuchiura Kyodo Hospital, Ibaraki Children's Hospital, Dokkyo Medical University, Jichi Medical University, Ashikaga Red Cross Hospital, Gunma Children's Medical Center, Kiryu Kosei General Hospital, Fuji Heavy Industries Health Insurance Society Ota Memorial Hospital, Gunma University, Saitama Children's Medical Center, Nishisaitama-chuo National Hospital, Saitama Medical University Saitama Medical Center, Kawaguchi Municipal Medical Center, Jichi Medical University Saitama Medical Center, Asahi General Hospital, Chiba Kaihin Municipal Hospital, Kameda Medical Center, Tokyo Women's Medical University Yachiyo Medical Center, Junendo University Urayasu Hospital, Tokyo Metropolitan Children's Medical Center, Tokyo Women's Medical University, Aiiku Hospital, Nihon University Itabashi Hospital, National Center for Global Health and Medicine, Tokyo Medical University, Teikyo University, Showa University, Japan Red Cross Medical Center, National Center for Child Health and Development, Tokyo Metropolitan Otsuka Hospital, Toho University, Tokyo Metropolitan Bokuto Hospital, Tokyo Jikei Medical University, Tokyo Medical and Dental University, Saint Luku's International Hospital, Junendo University, Sanikukai Hospital, Katsushika Red Cross Hospital, Yokohama Rosai Hospital, Yokohama City University Medical Center, St. Marianna University School of Medicine Hospital, Kanagawa Children's Medical Center, Tokai University, Kitazato University, Odawara Municipal Hospital, Nippon Medical School Musashi Kosugi Hospital, Saiseikai Yokohamashi Tobu Hospital, National Hospital Organization Yokohama Medical Center, Yamanashi Prefectural Central Hospital, Nagano Children's Hospital, Shinshu University, Iida Municipal Hospital, National Hospital Organization Shinshu Ueda Medical Center, Saku General Hospital, Niigata University, Niigata Prefectural Central Hospital, Niigata Municipal Hospital, Nagaoka Red Cross Hospital, Koseiren Takaoka Hospital, Toyama Prefectural Central Hospital, Toyama University, Ishikawa Medical Center for Maternal and Child Health, Kanazawa Medical University,

Kanazawa Medical Center, Fukui Prefectural Hospital, Fukui University, Gifu Prefectural General Medical Center, National Hospital Organization Nagara Medical Center, Takayama Red Cross Hospital, Seirei Hamamatsu Hospital, Shizuoka Saiseikai Hospital, Shizuoka Children's Hospital, Hamamatsu Medical University, Numazu Municipal Hospital, Yaizu City Hospital, Fujieda Municipal General Hospital, Nagoya Red Cross Daini Hospital, Nagoya University, Nagoya Red Cross Daiichi Hospital, Toyohashi Municipal Hospital, Nagoya City West Medical Center, Anjo kosei Hospital, Tosei General Hospital, Komaki Municipal Hospital, TOYOTA Memorial Hospital, Okazaki Municipal Hospital, Konan Kosei Hospital, National Mie Central Medical Center, Ise Red Cross Hospital, Yokkaichi Municipal Hospital, Otsu Red Cross Hospital, Shiga University of Medical Science Hospital, Nagahama Red Cross Hospital, Uji Tokushukai Hospital, The Japan Baptist Hospital, Kyoto University, Kyoto Red Cross Daiichi Hospital, National Maizuru Medical Center, Fukuchiyama City Hospital, Kyoto Prefectural University of Medicine Hospital, Kyoto City Hospital, Mitsubishi Kyoto Hospital, Yodogawa Christian Hospital, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka University, Takatsuki General Hospital, Kansai Medical University, Osaka City General Hospital, Osaka City Sumiyoshi Hospital, Aizenbashi Hospital, Toyonaka Municipal Hospital, National Cerebral and Cardiovascular Center, Kitano Hospital, Saiseikai Suita Hospital, Chifune Hospital, Belland General Hospital, Rinku General Medical Center, Osaka Red Cross Hospital, Yao Municipal Hospital, Osaka General Medical Center, Osaka City University, Hyogo Prefectural Kobe Children's Hospital, Kobe University, Kakogawa West City Hospital, Saiseikai Hyogoken Hospital, Kobe City Medical Center General Hospital, Hyogo College of Medicine Hospital, Himeji Red Cross Hospital, Toyooka Public Hospital, Hyogo Prefectural Awaji Medical Center, Nara Medical University, Wakayama Medical University, Tottori Prefectural Central Hospital, Tottori University, Shimane Prefectural Central Hospital, Matsue Red Cross Hospital, Kurashiki Central Hospital, Tsuyama Central Hospital, Kawasaki Medical School Hospital, National Hospital Organization Okayama Medical Center, Okayama Red Cross Hospital, Hiroshima City Hiroshima Citizens Hospital, Hiroshima Prefectural Hospital, Hiroshima University, Tsuchiya General Hospital, National Hospital Organization Kure Medical Center, Yamaguchi University, Yamaguchi Grand Medical Center, Tokushima University, Tokushima Municipal Hospital, Kagawa University, National Hospital Organization Kagawa Children's Hospital, Matsuyama Red Cross Hospital, Ehime Prefectural Central Hospital, Kochi Health Science Center, St. Mary's Hospital, National Kyushu Medical Center, Kurume University, Kitakyushu Municipal Medical Center, University of Occupational and Environmental Health, Fukuoka University, Kyushu University, Iizuka Hospital, National Hospital Organization Kokura Medical

Center, National Hospital Organization Saga Hospital, National Hospital Organization Nagasaki Medical Center, Kumamoto City Hospital, Kumamoto University, Oita Prefectural Hospital, Almeida Memorial Hospital, Nakatsu Municipal Hospital, Miyazaki University, National Hospital

Organization Miyakonojo Medical Center, Kagoshima City Hospital, Imakiire General Hospital, Okinawa Prefectural Nanbu Medical Center & Children's Medical Center, Okinawa Prefectural Chubu Hospital, Naha City Hospital, Okinawa Red Cross Hospital.

Table IV. Neonatal characteristics in infants with and without late-onset circulatory collapse (excluding infants with sepsis, severe IVH, and NEC)

Characteristics	Late-onset circulatory collapse (n = 516)	Non-late-onset circulatory collapse (n = 2359)	P value
Gestational age, weeks	25 ^{4/7} (24 ^{2/7} -26 ^{5/7})	26 ^{2/7} (25 ^{0/7} -27 ^{1/7})	<.01
Birth weight, grams	701 (581-855)	788 (653-950)	<.01
Small for gestational age	135/516 (26.2)	486/2359 (20.6)	.01
Clinical chorioamnionitis	179/500 (35.8)	707/2306 (30.7)	.03
Antenatal steroid	313/515 (60.8)	1378/2338 (58.9)	.44
Male sex	307/516 (59.5)	1238/2359 (52.5)	<.01
Apgar score <4 at 5 min	49/513 (9.6)	140/2337 (6.0)	.01
RDS	437/516 (84.7)	1781/2357 (75.6)	<.01
Moderate to severe BPD	240/515 (46.6)	834/2355 (35.4)	<.01
PDA requiring surgical ligation	84/406 (20.7)	274/1845 (14.9)	<.01
Cystic PVL	29/516 (5.6)	52/2352 (2.2)	<.01
Severe retinopathy of prematurity	237/511 (46.4)	613/2315 (26.5)	<.01

Data are presented as the number/number with available information (percentage) or as the median (IQR).

P values were obtained using the Wilcoxon rank-sum test (continuous variables) and χ^2 test (dichotomous variables).

Table V. Neurodevelopmental outcomes at 3 years of age in infants with late-onset circulatory collapse (excluding infants with sepsis, severe IVH, and NEC)

Outcomes	Late-onset circulatory collapse (n = 516)	Non-late-onset circulatory collapse (n = 2359)	P value*	Crude OR (95% CI)	P value†	aOR‡ (95% CI)	P value†
CP	67/516 (13.0)	173/2359 (7.3)	<.01	1.89 (1.40-2.54)	<.01	1.45 (1.01-2.08)	.04
Profound CP	19/374 (5.1)	38/1670 (2.3)	.01	2.30 (1.31-4.03)	<.01	1.33 (0.64-2.75)	.45
Cognitive impairment							
DQ of <70	139/459 (30.3)	404/2081 (19.4)	<.01	1.80 (1.44-2.26)	<.01	1.22 (0.92-1.62)	.16
DQ of <50	40/459 (8.7)	70/2081 (3.4)	<.01	2.74 (1.83-4.10)	<.01	2.04 (1.26-3.32)	<.01
Visual impairment	4/454 (0.9)	6/2190 (0.3)	.09	3.24 (0.91-11.5)	.07	2.73 (0.71-10.5)	.14
Hearing impairment	4/384 (1.0)	17/1728 (1.0)	.92	1.06 (0.35-3.17)	.92	1.20 (0.38-3.78)	.76

*P values were obtained using the χ^2 test.

†ORs with 95% CIs and P values were obtained from logistic regression analysis.

‡Adjusted values were obtained from logistic regression analysis after adjusting for all variables listed in Table IV except cystic PVL.

Table VI. Neonatal characteristics in extremely preterm infants with and without CP

Characteristics	CP (n = 396)	Non-CP (n = 3078)	P value
Gestational age, weeks	25 ^{4/7} (24 ^{1/7} -27 ^{3/7})	26 ^{1/7} (24 ^{6/7} -27 ^{1/7})	<.01
Birth weight, grams	717 (586-890)	765 (632-924)	<.01
Small for gestational age	96/396 (24.2)	637/3078 (20.7)	.10
Clinical chorioamnionitis	121/384 (31.5)	948/2999 (31.6)	>.99
Antenatal steroid	209/394 (53.1)	1786/3052 (58.5)	.04
Male sex	238/396 (60.1)	1638/3078 (53.2)	.01
Apgar score <4 at 5 min	39/394 (9.9)	221/3045 (7.3)	.07
RDS	322/396 (81.3)	2387/3075 (77.6)	.11
Moderate to severe BPD	206/396 (52.0)	1158/3073 (37.7)	<.01
PDA requiring surgical ligation	80/319 (25.1)	395/2423 (16.3)	<.01
Late-onset circulatory collapse	120/396 (30.3)	546/3078 (17.7)	<.01
Severe IVH	109/396 (27.5)	94/3073 (3.1)	<.01
Cystic PVL	87/395 (22.0)	50/3072 (1.6)	<.01
Sepsis	79/396 (20.0)	352/3070 (11.5)	<.01
NEC	14/396 (3.5)	44/3075 (1.4)	<.01
Severe retinopathy of prematurity	196/394 (49.8)	938/3023 (31.0)	<.01

Data are presented as the number/number with available information (percentage) or as the median (IQR).

P values were obtained using the Wilcoxon rank-sum test (continuous variables) and χ^2 test (dichotomous variables).

Table VII. Risk factors for CP at 3 years of age in extremely preterm infants

Variables	Model A*		Model B†	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Cystic PVL	–	–	11.6 (7.31-18.5)	<.01
Severe IVH	10.2 (7.07-14.7)	<.01	8.41 (5.69-12.4)	<.01
NEC	2.27 (1.04-4.94)	.04	2.16 (0.95-4.90)	.07
Small for gestational age	1.86 (1.13-3.07)	.02	1.85 (1.10-3.12)	.02
Moderate to severe BPD	1.76 (1.34-2.31)	<.01	1.81 (1.37-2.40)	<.01
Late-onset circulatory collapse	1.52 (1.13-2.04)	<.01	1.34 (0.98-1.83)	.07
PDA requiring surgical ligation	1.51 (1.11-2.07)	<.01	1.50 (1.08-2.08)	.01
Severe retinopathy of prematurity	1.49 (1.13-1.96)	<.01	1.44 (1.09-1.92)	.01
Male sex	1.20 (0.92-1.57)	.18	1.28 (0.97-1.69)	.09
Birth weight, per 100 grams	1.15 (1.00-1.32)	.06	1.15 (0.99-1.33)	.07
Sepsis	1.10 (0.77-1.57)	.61	1.09 (0.75-1.58)	.65
Antenatal steroid	1.01 (0.78-1.32)	.91	1.08 (0.82-1.42)	.58
RDS	0.97 (0.69-1.36)	.87	0.93 (0.66-1.31)	.68
Clinical chorioamnionitis	0.96 (0.72-1.29)	.80	0.98 (0.72-1.32)	.87
Apgar score <4 at 5 min	0.91 (0.57-1.46)	.71	0.98 (0.61-1.57)	.94
Gestational age, per week	0.87 (0.73-1.03)	.10	0.83 (0.70-1.00)	.05

aORs and P values were obtained from the logistic regression analysis.

*Model A was adjusted for all variables listed in Table II except cystic PVL.

†Model B was adjusted for the all variables included in the model A plus cystic PVL.