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Closure time of ductus arteriosus after birth based on survival analysis

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ABSTRACT

Objectives: The correct ductus arteriosus (DA) closure time is somewhere between the opening and closing time confirmed on echo, not on examination. We investigated DA closure time and factors affecting DA closure time using interval censoring analysis.

Methods: This was an observational, retrospective study including 2611 healthy neonates. Echo was performed every 12–24 h after birth until DA closure. We investigated the DA closure time using interval censoring analysis. If the DA was closed on echo, we assumed that the DA was open at birth. We evaluated clinical factors affecting DA closure time.

Results: Median DA closure time was 13.5 h (range, 7.7–18.7 h) after birth. DA closure time was associated with primipara status, maternal prostaglandin E2 (PGE2) administration, < 2500 g birth weight, and diagnosis of congenital ductus arteriosus aneurysm (DAA). Using proportional hazards regression models, the interval-censored data (primipara, hazard ratio [HR] = 1.099, $P = 0.04$; PGE2, HR = 0.823, $P = 0.03$; < 2500 g, HR = 1.413, $P < 0.01$; DAA, HR = 0.570, $P < 0.01$) were found to be significantly associated with DA closure time.

Conclusions: Estimation of DA closure time by interval censoring analysis is helpful to determine the optimal time to perform echo and to predict risk factors for patent DA.

1. Introduction

The ductus arteriosus (DA) is a fetal vascular connection between the main pulmonary artery and the aorta that diverts blood away from the pulmonary bed. After birth, the abrupt increase in oxygen tension and falling prostaglandin (PGE2) levels from the placental source inhibit ductal smooth muscle voltage-dependent potassium channels, resulting in an influx of calcium and ductal constriction [1]. The medial smooth muscle fibers in the ductus contract, which results in wall thickening, lumen obliteration, and shortening of the ductus arteriosus. Functional complete closure usually occurs within 24 to 48 h of birth in term neonates and in most term neonates with no lung disease, the DA closes within 3 days of life based on echocardiography (echo) [2]. Within the next 2 to 3 weeks, infolding of the endothelium along with subintimal disruption and proliferation result in fibrosis and a permanent seal [3]. The resulting fibrous band with no lumen persists as the ligamentum arteriosum. A patent DA (PDA) occurs when the DA fails to completely close postnatally. The diagnosis of PDA is usually based on its characteristic clinical findings, and is typically confirmed by echo. Echo is the main diagnostic imaging modality used to evaluate PDA severity in the neonatal period, and quantification of shunt volume is a major goal of the hemodynamic evaluation of patients with PDA.

Survival analysis is the analysis of time-to-event data. Such data describe the length of time from a time origin to an endpoint of interest [4]. For example, individuals may drop out of a study, or they might have a different event, such as death due to an accident, which is not part of the endpoint of interest. These incomplete observations cannot be ignored, but need to be handled differently. The objectives of survival analysis include the analysis of patterns of event times, the comparison of distributions of survival times in different groups of individuals, and examining whether and by how much some factors affect the risk of an event of interest. Interval-censored data arise when the event or failure of interest is known only to occur within a time interval. Such data are commonly encountered in disease research, where the ascertainment of an asymptomatic event is costly or invasive and thus can take place only at a small number of monitoring times. An important special case of interval-censored data is the so called current status data [5,6]. The correct DA closure time can address interval

Abbreviations: DA, ductus arteriosus; PDA, patent ductus arteriosus; PGE2, prostaglandins E2 (PGE2); DAA, congenital ductus arteriosus aneurysm; echo, echocardiography; NICU, neonatal intensive care unit

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Table 1
Study participant characteristics (n = 2611).

Characteristics of mothers and neonates (n = 2611)			
Pregnancy	Primipara/multipara	1302	1309
Delivery	Cesarean section/vaginal	487	2124
Sex	Male/female	1293	1318
Conception	AC/SC	417	2194
Administration of PGE	Admit/no admit	165	2446
PDA type of DAA	Diagnosis/no diagnosis	219	2392

	Median	IQR
Maternal age (y)	32 y	28–35 y
Ga (week, day)	39 w3 d	38 w1 d–40 w5 d
Weight (g)	3004	2792–3234

Cord blood analysis			
pH	(n = 2559)	7.308	7.270–7.344
pCO_2 (mm Hg)	(n = 2544)	46.6	40.9–51.7
pO_2 (mm Hg)	(n = 2520)	18.8	15.4–22.6
Hb (g/dL)	(n = 2520)	15.7	14.7–16.7
SO_2 (%)	(n = 2495)	31.5	22.1–43.6
O_2 Hb (%)	(n = 2518)	31.2	21.8–34.1
COHb (%)	(n = 2519)	0	0.0–0.3
HHb (%)	(n = 2520)	67.8	55.7–77.5
MetHb (%)	(n = 2517)	0.9	0.8–1.1
Na (mmol/L)	(n = 2517)	133	132–135
K (mmol/L)	(n = 2547)	4.2	3.9–4.4
Ca^{2+} (mmol/L)	(n = 2547)	1.42	1.37–1.46
BS (mg/dL)	(n = 2545)	89	70–109
Lactate (mmol/L)	(n = 2541)	3.6	2.6–4.8
HCO_3^- (mmol/L)	(n = 2531)	22.5	20.8–24.1
BE (mmol/L)	(n = 2534)	−3.5	−5.3 to −2.1
Anion gap	(n = 2534)	4.1	1.8–6.7

Abbreviations: AC, assisted conception; Ap, Apgar score; BS, blood sugar; BE, base excess; Ca^{2+}, calcium ion; COHb, carboxyhemoglobin; DAA, ductus arteriosus aneurysm; GA, gestational age; Hb, hemoglobin; HCO_3^-, bicarbonate ion; HHb, deoxidized hemoglobin; IQR; interquartile range; K, potassium; MetHb, methemoglobin; Na, sodium; O_2Hb, oxyhemoglobin; PGE2, oral or infusion of prostaglandin E2 (dinoprostone); SC, spontaneous conception; SO_2, oxygen saturation.

censoring of the data because the DA closing time is defined as the time of DA opening and the time of DA closing as confirmed on echo, not at the examination.

The goal of the present study was to investigate, chronologically and the various maternal and neonate factors affecting DA closure time in normal neonates using interval censoring analysis.

2. Patients and methods

2.1. Study population

The study population comprised 2611 normal neonates, including 20 twins, admitted to two institutions, the Maternal-Fetal and Neonatal Care Center of Hamamatsu University School of Medicine and Chutoen Medical Center, between September 2010 and December 2016. Mothers, neonates, and cord blood characteristics are summarized in Table 1. Exclusion criteria were admission to the neonatal intensive care unit (NICU) for treatment of disease, preterm birth with gestational age < 37 weeks, congenital heart disease, diagnosis of small for gestational age (SGA) or large for gestational age (LGA), as defined by a birth weight below or above the 10th and 90th percentile for gestational age [7], and chromosomal abnormalities.

The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine and Chutoen Medical Center and was conducted according to the principles of the Declaration of Helsinki (approval date: 1 March 2017; approval number: 17-038 at Ethics Committee of Hamamatsu University School of Medicine, 3 March 2017; approval number: 44 at Ethics Committee of Chutoen Medical Center). Informed consent were obtained as opt-out and inclusion agreements based on 'Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects'. We posted the explanation of this study on the web homepage of both institutions. When a participant showed intention of the disagreement, we excluded data from this study.

2.2. Analysis

Since this study was an observational, retrospective, historical cohort study, the results required validation using prospective evaluation in a small cohort of patients. In the present study, we retrospectively reviewed medical records to determine the experience of the two institutions. At these two institutions, screening of the neonates was performed with two-dimensional and color Doppler echo [8,9].

2.2.1. Echo evaluation

For data acquisition, a Vivid q or Vivid-S5 cardiac ultrasound system (GE Healthcare Japan, Tokyo, Japan) with a 6S, 7S, or 12S sector array transducer was used. Echo was performed at rest. All neonates underwent routine echo evaluation, including cross-sectional and M mode ultrasonography, pulse and continuous wave Doppler imaging, and Doppler color flow imaging studies. Routine echo was performed every 12–24 h after birth until confirmation of DA closure. Color Doppler images of the DA were optimally obtained from parasternal DA long-axis views in each infant. The maximum duration of the ultrasound was limited to 15 min in each case. DA closure was defined when echo could not detect DA color Doppler flow or left pulmonary artery diastolic Doppler flow. The stored digital scans were analyzed by a reader blinded to the patient's details (K.S., T.I., M.U., and S.I.). K.S., T.I., M.U., and S.I. performed the echocardiography and interpreted the echocardiogram. We almost estimated DA assessment from parasternal DA long-axis views but a few infant could not reviewed from parasternal views. These infants were reviewed from subcostal DA views. Finally, one reviewer (S.I.) confirmed DA closure from the medical record and echocardiogram.

2.3. Data analysis

2.3.1. Definitions of DA closure time

We investigated DA closure time after birth. We supposed the ductus arteriosus closure time was when we confirmed the disappearance of ductus color on the Doppler flow at echo examination; however, the correct ductus arteriosus closure time was somewhere between the opening and closing time confirmed at echo, because, when we detected ductus closure on examination, the ductus was already closed. For example, we performed a screening echocardiography 6 h after birth, and detected left to right ductus flow. After 24 h from birth, we repeated the echocardiography, and we could not detect ductus flow. The correct ductus arteriosus closure time is between 6 and 24 h after birth, not 24 h after birth. We investigated the time of echo examination based on medical records. We divided DA closure time into two types. In the first type, called 'interval-censored,' we assumed DA was open at birth or at the time of DA patency demonstrated on echo; we then confirmed time of DA closure diagnosed by echo examination. In the second type, called the 'right-censored,' we could not confirm the time of DA closure during the study period or it is presumed that the closure time of DA was after the examination period. Our dataset contained 2595 (99.4%) neonates with interval-censored data and 16 (0.6%) neonates with right-censored data.