



Original article

What echocardiographic indices are predictive of patent ductus arteriosus surgical closure in early preterm infants? A prospective multicenter cohort study[☆]



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ABSTRACT

Background: No echocardiographic indices for predicting the need for preterm patent ductus arteriosus (PDA) surgery have been tested with an adequate sample size. We tested the hypothesis that some echocardiographic indices have better predictive ability for the need for PDA surgery.

Methods: We prospectively collected data from infants with gestational ages between 23 and 29 weeks at 34 Japanese neonatal intensive care units over 14 months. Data points were 1, 3, 7, and 14 days of age and, if applicable, before PDA surgery. We assessed five echocardiographic indices. Volume and dimension indices were adjusted for birth body weight (BBW). For each echocardiographic index, the worst value among all data points in nonsurgical patients or the value just before surgery in surgical patients was used.

Multivariate logistic regression was applied with adjustment for clinical status.

Results: In total, 691 patients were analyzed, of whom 61 (8.8%) underwent surgery, as guided using the criteria in the protocol. The areas under the receiver-operating characteristic curve for PDA diameter (0.86) and PDA diameter/BBW (0.86) were the largest, followed by those of left pulmonary artery end-diastolic velocity (LPAedv) (0.80), and left atrial volume/BBW (0.80).

Conclusions: Considering the measurement's easiness and independence of body size, PDA diameter and LPAedv may serve as useful indices for assessing the need for PDA surgery in early preterm infants.

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Introduction

Patent ductus arteriosus (PDA) is a major complication in preterm infants, with symptomatic PDA being particularly associated with death [1], intraventricular hemorrhage [2], chronic lung disease [3], and necrotizing enterocolitis [4]. Thus, appropriate management of PDA is crucially important to improve the prognosis in preterm infants. The management of PDA currently shows wide interinstitutional and international variations [5–7]. Moreover, the optimal timing for interventions for PDA or even whether PDA surgical closure could improve patient outcomes has been a matter of international debate [8]. Arguing on different grounds would be attributable to differences in the method of diagnosing significant PDA, including a lack of concrete definition of clinically symptomatic PDA [9] and hemodynamically significant PDA [10]. Hemodynamically significant PDA is diagnosed by echocardiography regardless of the existence of apparent symptoms. A study comparing PDA management strategies between Canadian and Japanese neonatal databases has indicated the usefulness of proactive echocardiography in enabling the early diagnosis of hemodynamically significant PDA to improve the outcome in preterm infants with PDA [11].

The aorta-to-pulmonary artery shunt via the ductus arteriosus increases the pulmonary blood flow and left heart dimension. Previous studies reported several echocardiographic parameters for the assessment of PDA severity such as the left atrial-to-aortic root ratio (LA/Ao) [12], left atrial volume (LAV) [13,14], pulmonary arterial blood flow pattern and velocities [12], PDA diameter (PDAd), and left ventricular diastolic dimension (LVDD) [15]. Specifically, our previous pilot study indicated that LAV may be more useful than LA/Ao in evaluating for the prediction with PDA surgical closure [13]. However, none of these indices has been tested with adequate sample size for their ability to predict the need for PDA therapies. This study was undertaken to test the hypothesis that some echocardiographic indices have better predictive ability for the need for PDA surgical closure in early preterm infants. In addition, we assessed whether LAV has better predictive ability than LA/Ao.

Methods

Study design and patients

We performed a prospective multicenter observational study [Patent ductus arteriosus and Left Atrial Size Evaluation study in preterm infants (PLASE)] at 34 neonatal intensive care units (NICUs) in Japan. We predefined the inclusion criteria as follows: (1) having a gestational age at birth between 23 weeks & 0 day and 29 weeks & 6 days, (2) being admitted to the NICUs participating in this study up to 24 h after birth, and (3) surviving at 24 h after birth. We excluded patients with (1) chromosomal abnormalities; (2) multiple anomalies, apparent clinical syndrome, or congenital anomalies that required surgery during infancy; (3) congenital heart disease other than PDA, patent foramen ovale, and persistent left superior vena cava; (4) congenital metabolic, endocrine, neuromuscular, or systemic bone disease; (5) family history of severe hereditary diseases such as neuromuscular disease or cardiomyopathy; and (6) critical conditions deemed ineligible for this study by attending physicians.

This study was approved by the ethical committees of Kanagawa Children's Medical Center and Saitama Medical University and the institutional review board of each participating institute. According to the regulatory policy of each institution, consents from parents or guardians for their infants' participation in this study were assured by either obtaining written informed

consents or excluding infants whose parents did not agree on providing their infants' data to the study.

Therapeutic decision-making

The decision-making for the surgical closure of PDA was left at the discretion of the physicians or surgeons and was based on clinical conditions such as hemodynamic instability, feeding problems, and further renal or respiratory impairment. For the preparation of this study, a preliminary questionnaire survey was sent to the director or representative of each participating NICU to assess the clinical management of PDA. Prophylactic indomethacin [16] was used in 25 institutes (74%). With respect to the therapeutic administration of cyclooxygenase (COX) inhibitors, intravenous indomethacin [17,18] and oral mefenamic acid [19] were used in 33 institutes (97%) and 1 institute (3%), respectively.

Data acquisition

Clinical investigators at each institute entered the data into Excel-based electronic case report forms (eCRFs), which did not include personal information (anonymization in a linkable fashion). eCRFs were electronically sent to a data coordinating center (T.K.) and were analyzed by a statistical team (E.I., M.M., T.I.) after data cleaning, both of which were independent of principal investigators (K.T., S.M.). Only clinical investigators at each institute and data coordinating center could directly access each eCRF.

Demographic and clinical data

We collected data on sex, in-hospital birth, delivery modes, use of antenatal steroid and postnatal hydrocortisone, type of pregnancy (singleton or not), gestational age, birth body weight (BBW) and height, Apgar score at 1 and 5 min after birth, small for gestational age status, and patients' status (dead/alive) at discharge. With respect to the management of PDA, we collected data on the use of prophylactic indomethacin (routine administration within 24 h after birth regardless of PDA severity), pharmacological treatment with COX inhibitors, and PDA surgical closure as the primary outcome.

Echocardiographic measurements

Furthermore, we collected data on echocardiographic measurements at days 1, 3, 7, and 14 as required data points and allowed the following evaluation intervals: 18–30 h for day 1, 60–84 h for day 3, 6–8 days for day 7, and 12–16 days for day 14. Data were obtained just before the initial therapeutic administration of COX inhibitor, if given, and before (within 6 h) and at 1 day (18–30 h) after PDA surgical closure, if performed. We decided the required data points as 1, 3, 7, and 14 days of age because each time point almost represents the timing of stabilization after delivery (day 1), post-circulatory adaptation [20] after birth (day 3), adaptation to enteral nutrition (day 7), and the stable phase (day 14) in most preterm infants with a good clinical course. We also acquired the data before PDA surgery, if applicable, so as not to miss the information on the most loaded condition.

The following echocardiographic variables were measured: LVDD (mm) and left ventricular systolic dimension (LVDS, mm) using M-mode in the short-axis view, left atrial (LA) diameter (mm) and aortic diameter (mm) in the long-axis view employing the leading edge method [21], LA area (cm²) and LA long-axis length (LA length, cm) in the four-chamber view, narrowest internal diameter of the PDA (PDAd, mm) in the ductal long-axis view, PDA flow pattern (left to right, right to left, bidirectional, none), and left pulmonary artery end-diastolic velocity (LPAedv, cm/s) [12,22]. We calculated LAV using the single-plane

area-length method with the following equation [23–25]: $LAV = 0.85 \times (LA \text{ area})^2 / (LA \text{ length}) \text{ (cm}^3\text{)}$.

When the echo window did not allow for clear M-mode in the short-axis view, LVDd and LVDs were measured in the long-axis view. We employed M-mode measurement because it has high reproducibility and temporal resolution, and wealth of published data although care is required for measuring the accurate perpendicular angle [21].

Quality control of echocardiography

Upon planning this study, no established guideline on echocardiographic measurements in preterm infants had been published. Therefore, before data acquisition, we developed a manual that specified how to measure each echocardiographic index in this study by modifying the standard recommendation for echocardiographic measurements in adults [21,23] to match the circumstances in preterm infants. The manual is available in the PLASE website (http://square.umin.ac.jp/plase/data/echo_measurement6-26-15.pdf). Specifically, to avoid disturbing the fragile preterm infants in this study, echocardiography was performed without changing the infants' position, except for prone position. In preparation for this study, we evaluated the accuracy of measurements in all participating echocardiographers using standard still images to measure LA/Ao, LAV, LVDd and LVDs, and PDA diameter. In the event that each measurement was out of the predefined range ($< -1.5SD$ or $> 1.5SD$ of all participants), the study office chair (S.M.) inspected the measurement images, evaluated the deviation from the standard measurement described in the manual, and advised on how to correctly measure it until the measurement was within the range. Detail on this quality control of echocardiographic measurements was previously published [26]. After passing this quality control test, each echocardiographer was allowed to initiate data acquisition for this study. In addition, echocardiographic images of the first case in each institute were sent to the study office, and qualities of measurements were inspected. Following the completion of these quality control procedures, patient enrollment was initiated.

Sample size estimation

The sample size for this study was estimated using data from the previous pilot study [13]. The areas under the receiver-operating characteristic (ROC) curve using the worst LA/Ao and LAV/BBW values in each patient throughout the study period to differentiate those who underwent PDA surgical closure from those who did not were 0.804 for LA/Ao and 0.955 for LAV/BBW. We assumed that the ratio of patients treated with PDA surgical closure to those who were not is 1:8, with the α error and power being equal to 0.05 and 0.8, respectively. Given these data and assumptions, the estimated sample size was 32 surgical closure cases, with 317 cases in total. When we assume that 15% of cases were ineligible, the estimated sample size would be 400. Further, we considered the difference between the previous (single observer in a single institute) and present studies (34 NICUs and >200 observers) and increased the sample size by 20% up to 500 cases.

Statistical analysis

Descriptive statistics [e.g. mean \pm standard deviation, median (minimum, maximum)] were used to summarize the demographic or clinical data of infants who underwent or did not undergo PDA surgery. Differences between the two groups were analyzed using unpaired *t*-test for continuous variables or chi-squared test for categorical data. Regarding echocardiographic data, the worst value among all data points in nonsurgical patients or the value

just before surgery in surgical patients was used for analysis in this study because the echocardiographic indices can be influenced by treatments. Echocardiographic indices with body size dependency (LAV, PDA_d, and LVD_d) were divided by BBW to standardize the body size. Accurate body weight measurement is invasive for early preterm and thus is not frequently performed in the early neonatal period, except just after birth in real-world practice. Although the typical adaptation process after birth significantly reduces edema and thus body weight, this occurs mainly due to excretion of water, and actual body size does not change to a great extent during the first two weeks. Further, body weight is more commonly used and thus easier to use than body height or body surface area in the neonatal intensive care unit. Given the non-invasive nature of this study, we employed birth body weight for the representative value of body size during the first two weeks. We employed univariate and multivariate logistic regression models adjusted for gestational age, sex, and small for gestational age status to predict the need for PDA surgical closure and calculated the estimated areas under the ROC curve of the models. We described area under the curve (AUC) values of 0.9–1.0, 0.8–0.9, 0.7–0.8, 0.6–0.7, and 0.5–0.6 as excellent, good, fair, poor, and fail, respectively [27]. The AUC of LAV/BBW (preplanned primary exposure) and other echocardiographic indices including PDA_d/BBW, LVD_d/BBW, and LPA_{edv} (secondary exposures) was compared with that of LA/Ao (preplanned control exposure) using the nonparametric approach of DeLong [28]. R version 3.3.2 (pROC package; R Foundation for Statistical Computing, Vienna, Austria) was used to estimate the sample size, and SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) was used to analyze the data for other statistics.

Results

Demographics

During the 14-month registration period from October 6, 2015, to December 31, 2016, a total of 737 preterm infants were enrolled in this study, of whom 691 were included in the analyses (Fig. 1). Among them, 61 patients underwent PDA surgical closure (8.8%); 45 patients with hemodynamic instability and 16 patients without; 24 patients in whom the use of COX inhibitor was contraindicated and 37 patients in whom it was not (Table 1). The major indication for PDA surgery was hemodynamic instability ($n = 45$), followed by feeding problems ($n = 13$, milk restriction or intestinal impairment). The other 3 patients underwent PDA surgery because of renal impairment ($n = 2$) and respiratory impairment ($n = 1$). The demographics of patients who underwent or did not undergo PDA surgical closure are summarized in Table 2. Infants who underwent PDA surgical closure had lower gestational age and BBW, lower proportion of singletons, and higher proportion treated with therapeutic COX inhibitors than those who did not. No differences in Apgar scores and death rates were observed.

Prediction of the need for PDA surgical closure by echocardiographic parameters

As shown in Table 3 and Fig. 2, the predictive ability of univariate logistic regression models was good for PDA_d/BBW (AUC, 0.84); fair for LAV/BBW (AUC, 0.75), LVD_d/BBW (AUC, 0.74), and LPA_{edv} (AUC, 0.75); but poor for LA/Ao (AUC, 0.67). In comparison, the predictive ability of multivariate logistic regression models adjusted for gestational age, sex, and small for gestational age status was good for LAV/BBW (AUC, 0.80), PDA_d/BBW (AUC, 0.86), and LPA_{edv} (AUC, 0.80), and fair for LVD_d/BBW (AUC, 0.77) and LA/Ao (AUC, 0.75). The difference in AUCs between each echocardiographic index and LA/Ao was statistically

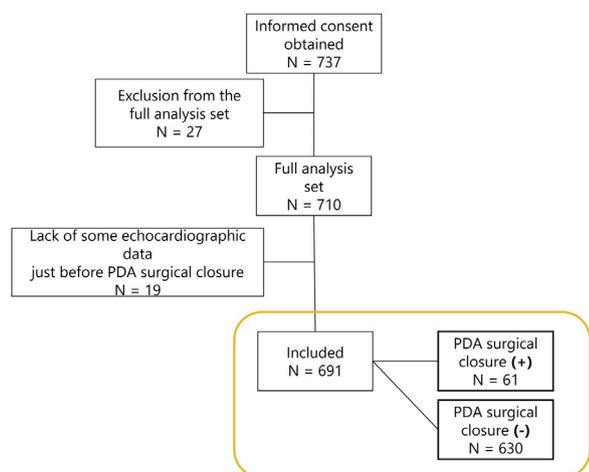


Fig. 1. Flow chart of this study. A total of 737 preterm infants were enrolled, of whom 27 were excluded from the full analysis set and subsequently 19 were excluded owing to the lack of some echocardiographic data just before PDA surgical closure. Finally, 691 patients were included in the analysis, of whom 61 underwent PDA surgical closure (8.8%). PDA, patent ductus arteriosus.

Table 1
Indication of PDA surgical closure.

| | Cox inhibitor contraindication + | Cox inhibitor contraindication – | Total |
|---------------------------|-------------------------------------|-------------------------------------|-------|
| Hemodynamic instability + | 20 | 25 | 45 |
| Hemodynamic instability – | 4 | 12 | 16 |
| Total | 24 | 37 | 61 |

PDA, patent ductus arteriosus.

significant only for PDA/BBW ($p < 0.001$). The predictive ability of LAV and LVDd was slightly poorer without BBW correction than that with BBW correction, whereas the predictive ability of PDA without BBW correction (Online Table 1) was similar to that with BBW correction.

Table 2
Demographics of included patients.

| | PDA surgical closure | No PDA surgical closure | p-Value |
|--|---------------------------------|---------------------------------|---------|
| Number of patients | 61 | 630 | |
| Gestational age (weeks) | 25.6 ± 1.7 25.1 (23.0, 29.6) | 27.0 ± 1.9 27.1 (23.0, 29.9) | <0.0001 |
| Birth weight (g) | 743 ± 172 715 (305, 1207) | 880 ± 268 859 (297, 1817) | <0.0001 |
| Birth height (cm) | 31.4 ± 2.7 31.5 (23.7, 38.0) | 33.3 ± 3.5 33.3 (23.5, 42.5) | <0.0001 |
| Small for gestational age | 10 (16.4%) | 147 (23.3%) | 0.26 |
| Singleton (%) | 41 (67.2%) | 515 (81.7%) | 0.01 |
| Male sex (%) | 29 (47.5%) | 351 (55.7%) | 0.23 |
| In-hospital birth (%) | 61 (100.0%) | 617 (97.9%) | 0.62 |
| Cesarean section (%) | 54 (88.5%) | 518 (82.2%) | 0.29 |
| No antenatal steroid (%) | 12 (19.7%) | 155 (24.6%) | 0.44 |
| Apgar score, 1 min | 3.9 ± 2.1 4.0 (2, 5) | 4.2 ± 2.1 4.0 (2, 6) | 0.34 |
| Apgar score, 5 min | 6.3 ± 1.8 7.0 (1, 9) | 4.2 ± 2.1 7.0 (0, 10) | 0.18 |
| Prophylactic indomethacin (%) | 25 (41.0%) | 187 (29.7%) | 0.08 |
| Therapeutic cyclooxygenase inhibitor (%) | 57 (93.4%) | 308 (49.0%) | <0.0001 |
| Postnatal hydrocortisone during the first 3 days after birth (%) | 25 (41.0%) | 230 (36.5%) | 0.49 |
| Death | 1 (1.6%) | 9 (1.4%) | 0.61 |

Data are presented as mean ± standard deviation, range (median) for continuous variables, or number (percent). Wilcoxon rank-sum test (Mann–Whitney *U* test) and Fisher's exact test were used for continuous and categorical variables, respectively.

* $p < 0.05$ for the comparison between those who underwent and did not undergo PDA surgical closure.

PDA, patent ductus arteriosus.

Discussion

This prospective multicenter study employing a cohort of 691 early preterm infants assessed the ability of five echocardiographic indices to predict the need for PDA surgical closure after full consideration of all clinical conditions and data. Without adjustment, only the PDA/BBW had good predictive ability (AUC, 0.84), whereas the other echocardiographic indices had fair to poor predictive ability (AUC, 0.67–0.75). After adjustment, LAV/BBW, PDA/BBW, and LPAedv had good predictive ability (AUC, 0.80–0.86), whereas LVDd/BBW and LA/Ao had fair predictive ability (AUC, 0.75–0.77). There was no significant difference in AUCs between LA/Ao (AUC 0.75) and other echocardiographic indices except for PDA/BBW, which showed a significantly larger AUC than LA/Ao.

Abilities of echocardiographic indices to predict the need for PDA surgical closure

The finding that the predictive ability of five echocardiographic indices was good to fair is reasonable because all of them reflect the degree of left-to-right PDA shunt volume, which is the main factor causing adverse clinical effects. The large PDA increases the left-to-right PDA shunt after postnatal reduction in pulmonary vascular resistance, and the increase in the left-to-right PDA shunt leads to LA and left ventricular (LV) enlargement and increases the LPAedv.

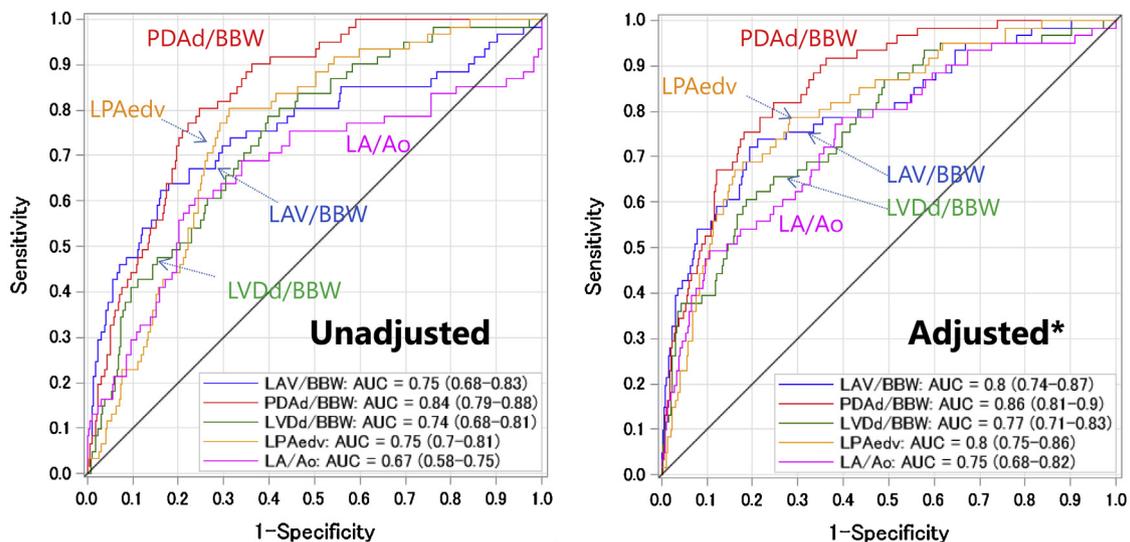
PDA size had the best predictive values among indices. Although the high predictive ability of PDA to predict the need for PDA surgical closure seems a matter of course, that is not the case. We have to point out two aspects. First, the hemodynamic severity (or shunt volume) of PDA is determined by not only the PDA size but also the relative balance between pulmonary and systemic vascular resistance. Nevertheless, the PDA size per se showed the best predictive ability for PDA surgical closure. This may be due to the time points of echocardiographic measurements in this study, which did not include those just after birth but were started after day 1. At day 1, the reduction in pulmonary vascular resistance and narrowing of ductus

Table 3
Univariate and multivariate logistic regression analyses of the predictive ability of echocardiographic indices (worst values) for the need for PDA surgical closure, with adjustment for gestational age, sex, and small for gestational age status.

| Covariant | Unadjusted | | Adjusted | | Comparison of AUC between each index and LA/Ao p-Values |
|--------------------------------|------------|-----------|----------|-----------|---|
| | AUC | 95% CI | AUC | 95% CI | |
| LAV (mL)/BBW (kg) | 0.75 | 0.68–0.83 | 0.80 | 0.74–0.87 | 0.07 |
| PDA _d (mm)/BBW (kg) | 0.84 | 0.79–0.88 | 0.86 | 0.81–0.90 | <0.001 |
| LVD _d (mm)/BBW (kg) | 0.74 | 0.68–0.81 | 0.77 | 0.71–0.83 | 0.46 |
| LPA _{edv} (cm/s) | 0.75 | 0.70–0.81 | 0.80 | 0.75–0.86 | 0.06 |
| LA/Ao | 0.67 | 0.58–0.75 | 0.75 | 0.68–0.82 | Control |

PDA, patent ductus arteriosus; AUC, area under the curve; CI, confidence interval; LA/Ao, left atrial-to-aortic root ratio; LAV, left atrial volume; BBW, birth body weight; PDA_d, PDA diameter; LVD_d, left ventricular diastolic dimension; LPA_{edv}, left pulmonary artery end-diastolic velocity.
* p-values for the comparison of AUC of adjusted regression models between each index and LA/Ao (control).

Prediction of PDA surgical closure



* Adjusted for gestational age, sex, and small for gestational age status

Fig. 2. ROC analysis for the prediction of the need for PDA surgical closure. Left panel: ROC curves derived from univariate logistic regression. The predictive ability of univariate logistic regression models was good for PDA_d/BBW, fair for LAV/BBW, LVD_d/BBW, and LPA_{edv}, but poor for LA/Ao. Right panel: ROC curves derived from multivariate logistic regression with adjustment for gestational age, sex, and small for gestational age status. The predictive ability was good for LAV/BBW, PDA_d/BBW, and LPA_{edv} and fair for LVD_d/BBW and LA/Ao.

ROC, receiver-operating characteristic; PDA, patent ductus arteriosus; PDA_d, PDA diameter; BBW, birth body weight; AUC, area under the curve; LAV, left atrial volume; LVD_d, left ventricular diastolic dimension; LPA_{edv}, left pulmonary artery end-diastolic velocity; LA/Ao, left atrial-to-aortic root ratio.

arteriosus should have already progressed in most cases. Thus, the worst PDA_d value after day 1 may reflect the shunt volume induced by PDA opening or the patent tendency of ductus arteriosus, resulting in PDA_d/BBW having the highest predictive ability for PDA surgical closure. Second, potential difficulties in accurate PDA_d measurement did not hamper the prediction of the need for PDA surgical closure. Accurate PDA_d measurement is difficult [29] and challenging, particularly in small or trivial shunts. However, because PDA_d measurement would become much easier as the ductus increases in size, the difficulty in measurement did not prevent the PDA_d/BBW from having the best predictive ability for the need for PDA surgical closure among all indices.

Previous reports have indicated the usefulness of ductal diameter in predicting therapeutic intervention [30–32] or

subsequent significant PDA [33]. Their findings were consistent with that of our study. However, their sample size was small, with only 6–16 infants who underwent PDA surgical closure being included, and was not adequate to specifically assess the prediction of PDA surgical closure. Because not only PDA_d but also PDA length may affect the shunt volume through the PDA, it is important to reveal all echocardiographic views of PDA. Although we did not assess the PDA length in this study, its effect on PDA severity may merit future investigations.

LPA_{edv} had good predictive ability for the need for PDA surgical closure. The echocardiographic beam direction toward LPA is straight from the echo transducer; hence, it is simple and does not require special skills to accurately measure LPA_{edv} using pulse-wave Doppler [34]. Accordingly, current results indicate that easily measurable LPA_{edv} can serve as one of the useful

echocardiographic indices for predicting the need for PDA surgical closure.

The LAV/BBW and LA/Ao were indices representing the blood volume load on the left atrium. Although LAV/BBW had a larger AUC than LA/Ao, the difference was not significant, with 95% confidence intervals overlapping. Theoretically, the LAV is considered superior to LA/Ao because, unlike LAV, LA/Ao represents only the anteroposterior dilation of the left atrium, ignoring the dilation at the other two directions. However, our previous study reported that the measurement error of LAV was larger than that of LA/Ao, which may reduce the superiority of LAV to LA/Ao [26]. Thus, at this stage, we cannot generally recommend the use of LAV/BBW to predict the need for PDA surgery.

The LVDD/BBW was an index representing the volume load on the left ventricle. Considering that the ventricle has a less compliant nature than the atrium, we expected the superiority of LA dilation indices (e.g. LAV/BBW, LA/Ao) over the LV dilation index (LVDD/BBW) for the evaluation of PDA severity. However, we determined that the AUC for LVDD/BBW was larger than that for LA/Ao, albeit without significant difference. The difficulty in LA/Ao measurement compared with that in LVDD/BBW measurement may partly contribute to the result. A perpendicular cut for both the left atrium and aortic root in LA/Ao measurement by M-mode is sometimes difficult in preterm infants [13] with poor echocardiographic window due to mechanical ventilation/hyperinflation of the lung or with difficulty to move them into ideal left decubitus position suitable for echocardiography.

An indication for PDA surgical closure needs to be carefully determined with all merit/demerit and an expectation of natural course taken into consideration. There are considerable variations in heart and vessel characteristics such as LV stiffness [35,36] or changes in pulmonary vascular resistance after birth, respiratory function, inflammatory status, and bleeding tendency in early preterm infants. Although we showed that only the PDAd/BBW had significantly higher predictive ability than LA/Ao, the LPAedv and LAV/BBW also had good predictive ability, and their 95% confidence intervals for AUCs overlapped well with that of PDAd/BBW. Thus, we do not recommend the use of a single index (e.g. PDAd/BBW) alone for the assessment of PDA severity. Instead, we recommend that multiple echocardiographic indices and all clinical information be used for clinical decision-making as to whether and how to treat PDA in each patient. This topic merits a future study aimed at constructing a model formula to predict surgical closure of the PDA using echocardiographic indices.

Limitations

The present study has potential limitations inherent in the heterogeneity of 34 institutes and multiple echocardiographers (>200). Because interobserver or intraobserver variance assessment was difficult to perform for all echocardiographers in this observational study, they have been evaluated and met the predefined criteria for accurate echocardiographic measurements before data acquisition [26]. Of 34 institutes, 5 (15%) needed to transfer patients, 6 (18%) needed to invite surgeons for PDA surgical closure, and only the remaining 23 (68%) can perform PDA surgical closure without such preparations. These environmental differences in PDA surgical closure may affect management and decision-making for PDA surgical closure. The use of surfactant may affect the association between echocardiographic indices and PDA ligation. However, we did not collect the data regarding the use of surfactant and were not able to separately analyze the data of infants with and without the use of surfactant.

Furthermore, echocardiographic data were not completely blinded to decision-making owing to the nature of the observational study. However, the decision for the PDA surgical closure

was clinically made on the basis of careful assessments of respiratory, renal, intestinal, and nutritional conditions as well as the tendency for the general condition to deteriorate. Further, when we excluded the 16 surgically treated patients without circulatory instability (Table 1), the overall result showing the usefulness of PDA diameter and LPAedv was preserved (Online Table 2). Although the variance of the decision-making process for PDA surgery potentially tends to hamper determining the significance, we obtained similar significant results in the original (Table 3) and added (Online Table 2) analysis. Thus, despite such possible concerns of variance and unblinded nature of study design, current results indicating the usefulness of simple but robust indices of PDAd and LPAedv in predicting the need for PDA surgical closure should still be valid.

Conclusion

Each echocardiographic index is useful in predicting the need for PDA surgical closure. Among those, PDAd/BBW showed the best predictive ability, whereas LAV/BBW and LPAedv had good predictive ability. To construct an evidence-based therapeutic stratification in early preterm infants with significant PDA, further development needs to be pursued in light of international standardization of echocardiographic measurements to optimally stratify patients by hemodynamic significance.

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Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

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Appendix A. PLASE study group investigators

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.05.004.

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