Left Atrial Volume Is Superior to the Ratio of the Left Atrium to Aorta Diameter for Assessment of the Severity of Patent Ductus Arteriosus in Extremely Low Birth Weight Infants

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Background: This study was undertaken to establish the appropriate correction of left atrial volume (LAV) to body surface area (BSA) to provide reference values and to assess the hypotheses that LAV is useful for assessing patent ductus arteriosus (PDA) severity in extremely low birth weight infants (ELBWIs) and could overcome the limitations of the LA-to-aortic dimension ratio (LA/Ao).

Methods and Results: Echocardiograms with 318 data points from 53 consecutive ELBWIs were assessed. PDA surgery was performed within the first 2 weeks in 6 patients. LAV was measured using the biplane (LAV) and single-plane (LAV4CV) area-length methods. The allometric model was used to correlate LAV to BSA. LAV4CV had a good correlation with LAV (R = 0.93). Although LAV/BSA1 had a residual relationship with BSA, LAV/BSA1.54 (23.5 ± 9.3 ml/m3.09) and LAV4CV/BSA1.52 (21.4 ± 9.4 ml/m3.54) did not. Receiver-operating characteristic analysis to detect hemodynamic status just before PDA surgery showed the superiority of LAV/BSA1.54 (area under the curve (AUC) 0.97) and LAV4CV/BSA1.52 (AUC 0.98) over LA/Ao (AUC 0.92). Moreover, LAV/BSA1.54 and LAV4CV/BSA1.52 were better correlated with left pulmonary arterial end-diastolic velocity than was LA/Ao.

Conclusions: This study provided appropriate BSA correction of LAV and its reference values in ELBWIs. LAV indices may be superior to LA/Ao for PDA severity assessment. Measurement of single-plane LAV is easy, with similar usefulness to biplane LAV. (Circ J 2014; 78: 1701–1709)

Key Words: Echocardiography; Left atrium volume; Left atrium-to-aortic dimension ratio; Patent ductus arteriosus; Preterm infants
BSA¹, is useful in both adults¹¹-¹³ and neonates.¹⁴ Khositseth et al measured LAV/BSA¹ in very LBWI using a prolate ellipse method.¹⁵ However, no study of LAV has specifically targeted ELBWIs, in whom PDA is considerably more clinically important than in any other birth weight group. In addition, indexing chamber volumes using BSA to the exponent of 1 may be physiologically incorrect,¹⁶ because an allometric model has been validated as the appropriate mathematical scaling for various cardiovascular structures to adjust for body size.¹⁷ Allometric model analysis revealed that not LAV/BSA¹ but rather LAV/BSA¹⁴ is an appropriate body size correction for LAV in children with BSA <1 m².¹⁶ Optimal BSA correction of LAV in ELBWIs may be achieved with this model because of an approximate 2-fold difference of BSA in ELBWIs.

Accordingly, this study was undertaken to (1) measure LAV by the biplane area-length method, a recommended ellipsoid method,¹² specifically in ELBWIs; (2) identify the appropriate BSA correction using an allometric model; (3) provide the reference value for BSA correction; and (4) determine the age-dependent changes in these variables and LA/Ao during the first 3 days after birth. Subsequently, we tested the usefulness of LAV determined by the single-plane method (LAV₄CV), which is more easily measured in the apical 4-chamber view. We tested our hypothesis that LAV may be useful for assessing PDA severity in ELBWIs and overcoming the limitations of LA/Ao.

### Methods

#### Patients

We enrolled 53 consecutive ELBWI patients (25 boys, 28 girls; mean gestational age 26.3±2.6 [23–31] weeks), birth weight 738±162 g) who were admitted to the neonatal intensive care unit (NICU) at Kanagawa Children’s Medical Center on day 0 between January 2010 and February 2011. The following were the indications for surgical closure of PDA: (1) further ventilatory support; (2) progressive congestive heart failure despite medical management; (3) large left-to-right shunt; (4) LA enlargement indicated by an LA/Ao ratio >1.3; and (5) peak left pulmonary artery end-diastolic velocity (LPA edv) >20 cm/s on echocardiography. All candidates for PDA surgery had undergone failed attempts at medical closure with indomethacin (n=6). The indication for PDA surgery was determined by neonotologists who were unaware of the study design and were blinded to the LAV data. We used indomethacin during the acute phase after 18 h of age in ELBWIs who showed no tendency for the PDA to close, who had a large left-to-right shunt, and who fulfilled some of the following criteria: (1) LA enlargement indicated by an LA/Ao ratio >1.3; (2) peak LPA edv >15 cm/s; (3) retrograde flow of renal arteries; and (4) LV end-diastolic dimension (LVDd) ≥120% of the normal estimated value.¹⁵ Physical and ultrasonographic measurements were performed as an integral part of the routine clinical practice for ELBWIs in the NICU. The latter included obtaining informed consent from the patient’s parents. This study was approved by the Institutional Review Board of Kanagawa Children’s Medical Center.

#### Physical and Echocardiographic Measurements

Body weight (BW) and height (BH) were measured to calculate BSA.¹⁵ We used the initial BSA on admission during the first 3 days after birth because we did not measure BW or BH again during this period according to the institutional management protocol for ELBWIs. Echocardiography were performed using an ACUSON Sequoia 512 (Siemens, Mountain View, CA, USA) at 6, 12, 24, 36, 48, 60, and 72 h after birth. It was repeated just before and 24 h after surgery in the patients who underwent PDA surgery at the age of 2 weeks. We use sedatives to stabilize hemodynamics as routine clinical practice in our hospital and we performed echocardiography under such treatment.⁵ LAV was measured by the biplane area-length method¹² using only the 4-chamber view: LAV=0.85×(area 4-chamber)×(area 2-chamber)/shortest length (4-chamber or 2-chamber).

We also calculated LAV by the single-plane area-length method (LAV₄CV),¹²,¹⁸ using only the 4-chamber view:

\[
LAV_{4CV} = 0.85 \times \text{(area 4-chamber)}^2 / \text{(length 4-chamber)}
\]

LA/Ao¹⁵ and the LVDd were measured in the LV long-axis view. The ratio of maximal diastolic to systolic velocities and end-diastolic velocities in the LPA (LPA d/s, and LPA edv, cm/s, respectively) were measured as indices of the extent of left-to-right shunt via PDA.²²,²³

#### Data Analysis

LAV was divided by BSA (LAV/BSA¹). In addition, to determine the appropriate BSA correction, the allometric exponents (AEs) of indexed LAV were obtained by considering the equation y=m+bx. To determine the appropriate AE (b) by which BSA (x) should be raised, a logarithmic transformation of this equation was used: Ln y=Lm+Ln x. The AE was estimated using an ordinary least-squares linear regression method. The LAV was indexed using BSA to the power of the derived AE that was then regressed against BSA to assess for a residual relationship.¹⁶

LVDd% of normal (LVDd%N)²⁴ was calculated in percent as estimated LVDd, where estimated LVDd (in mm)=0.495×BH (in cm)–5.43.¹⁸

To seek an easier but accurate correction of LAV₄CV, we performed linear regression between LAV₄CV and BH, and obtained the estimated LAV₄CV by BH. Subsequently, we calculated LAV₄CV %N. We also tested LAV₄CV/BW.

#### Statistical Analysis

Data are summarized as mean±standard deviation. An un-
LAV vs. LA/Ao for PDA in ELBWIs

for all 318 data points. When we confined the analysis to the 149 data points in which the PDA was closed, LAV was 0.45 ± 0.18 ml, and LAV/BSA 1 was 5.74 ± 1.96 ml/m^2. There was no statistical difference in LAV or LAV/BSA 1 between ELBWIs with and without closure of the PDA. LA/Ao did not correlate with BSA (P=0.82, Figure 1A), but LAV (Figure 1B) and LAV/BSA 1 (P=0.0007, R=0.19, Figure 1C) were positively correlated with BSA. The relationship between LAV and BSA by the allometric model showed that (1) Ln LAV=3.08+1.54 * Ln BSA (P<0.0001, R=0.52) and (2) LAV divided by BSA 1.54 would be an appropriate correction for BSA, with 1.54, the slope of (1), providing the AE. In contrast, as shown in Figure 1D, LAV/BSA 1.54 (23.5 ± 9.3 ml/m^3.08) did not depend on BSA (P=0.72). This model met all the following validation criteria: (1) LAV/BSA 1.54 showed no significant residual relationship to BSA (Figure 1D); (2) the intercept of LAV with BSA 1.54 for this group was not significantly different from zero (0.0028 ml, P=0.95); and (3) minimal heteroscedasticity was observed by visual inspection. Similarly, AE was 1.52 for LAV/crv, LA/Ao (Figure 2A) and LAV/BSA 1.54 (Figure 2B) did not have overall dependency on the time after birth.

Results

PDA surgery was performed within 2 weeks in 6 patients (11%) on days 1, 7, 10, 14, and 15. The demographic data of the 53 patients are shown in Table 1. There were no statistically significant differences in body size or Apgar score between the 2 groups with or without PDA surgery in this period. All patients had a patent foramen ovale (PFO). We administered indomethacin during this study period to 25 patients (47%). Neonatal death, intraventricular hemorrhage with grade III/VI, and pulmonary hemorrhage did not occur in this series.

Reference Value and Body Size Correction of LAV in ELBWIs

LAV was 0.48±0.22 ml and LAV/BSA 1 was 5.96±2.38 ml/m^2 for all 318 data points. When we confined the analysis to the 149 data points in which the PDA was closed, LAV was 0.45±0.18 ml, and LAV/BSA 1 was 5.74±1.96 ml/m^2. There was no statistical difference in LAV or LAV/BSA 1 between ELBWIs with and without closure of the PDA. LA/Ao did not correlate with BSA (P=0.82, Figure 1A), but LAV (Figure 1B) and LAV/BSA 1 (P=0.0007, R=0.19, Figure 1C) were positively correlated with BSA. The relationship between LAV and BSA by the allometric model showed that (1) Ln LAV=3.08+1.54 * Ln BSA (P<0.0001, R=0.52) and (2) LAV divided by BSA 1.54 would be an appropriate correction for BSA, with 1.54, the slope of (1), providing the AE. In contrast, as shown in Figure 1D, LAV/BSA 1.54 (23.5±9.3 ml/m^3.08) did not depend on BSA (P=0.72). This model met all the following validation criteria: (1) LAV/BSA 1.54 showed no significant residual relationship to BSA (Figure 1D); (2) the intercept of LAV with BSA 1.54 for this group was not significantly different from zero (0.0028 ml, P=0.95); and (3) minimal heteroscedasticity was observed by visual inspection. Similarly, AE was 1.52 for LAV/crv, LA/Ao (Figure 2A) and LAV/BSA 1.54 (Figure 2B) did not have overall dependency on the time after birth.

paired t-test was used for 2-group comparisons. A paired t-test was used to analyze changes before and after surgery. The correlation between 2 variables was assessed using Pearson’s correlation coefficient. The effect of time after birth on the change in LAV indices and LA/Ao was assessed by repeated measures ANOVA. Receiver-operating characteristic (ROC) curve analysis was performed for the sensitivity/specificity analysis to determine the status just before PDA surgery.

Figure 1. Effect of body surface area (BSA) on left atrial to aortic dimension ratio (LA/Ao) and LA volume (LAV). (A) No relationship between BSA and LA/Ao can be seen (P=0.82). (B) There is a significant dependency of LAV on BSA (P<0.0001, R=0.50). (C) Despite correction for BSA, a significant dependency of LAV/BSA 1 on BSA remains (P=0.0007, R=0.19). (D) After correcting LAV by BSA 1.54, based on an allometric model, no significant relationship was found between BSA and LAV/BSA 1.54 (P=0.72).
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**Figure 2.** Effect of early age on left atrial to aortic dimension ratio (LA/Ao) and body surface area (BSA)-corrected left atrial volume (LAV). (A) LA/Ao and (B) LAV/BSA$^{1.54}$ were measured at 6, 12, 24, 36, 48, 60, and 72 h after birth. There were no significant changes related to age (in hours) in either LA/Ao or LAV/BSA$^{1.54}$.

**Figure 3.** Relationship between fundamental left atrial (LA) and left ventricular (LV) echocardiographic measurements. (A) LA/Ao and LVd (mm) ($P<0.0001$, $R=0.32$), (B) LAV (ml) and LVd (mm) ($P<0.0001$, $R=0.70$), (C) LAV (ml) and LA/Ao ($P<0.0001$, $R=0.53$), (D) LA/Ao and LVd$^{n}$ (P<0.0001, R=0.38), (E) LAV/BSA$^{1.54}$ and LVd$^{n}$ (P<0.0001, R=0.53) and (F) LAV/BSA$^{1.54}$ and LA/Ao (P<0.0001, R=0.60). All these correlations are significantly positive. (Red square) Points just before PDA surgery, which are located predominantly higher in this plot in (B), (C), (E) and (F), indicating that LAV and LAV/BSA$^{1.54}$ reflect a markedly enlarged LA more sensitively in patients with a PDA than does LA/Ao, LVd, or LVd$^{n}$. BSA, body surface area; LA/Ao, left atrial to aortic dimension ratio; LAV, left atrial volume; LVd, left ventricular end-diastolic dimension; LVd$^{n}$, LVd corrected by body size; PDA, patent ductus arteriosus.

**LAV Indices and LA/Ao for the Evaluation of PDA in ELBWIs**

Figure 3 shows the relationships between LA/Ao, LVd, and LAV, with and without body size correction for the latter 2 values. All these correlations were significantly positive. In the graphs, the points just before PDA surgery were predominantly located higher, and LAV and LAV/BSA$^{1.54}$ tended to be larger than expected by linear regression (Figures 3B,C,E,F). These findings suggested that LAV/BSA$^{1.54}$ may reflect an
LAV vs. LA/Ao for PDA in ELBWIs

The evaluation of the severity of PDA (Figure 4). ROC curve analysis revealed the superiority of LAV/BSA\textsuperscript{1.54} (cutoff 32.1, sensitivity 100%, specificity 87%, area under the curve (AUC) 0.97) and LAV\textsubscript{4CV}/BSA\textsuperscript{1.52} (AUC=0.98) provided a better determination of state just before PDA surgery than did LA/Ao (AUC=0.92). AUC, area under the curve; BSA, body surface area.

Table 2. Summary of Results of Receiver-Operator Curve Analysis to Detect Status Before Patent Ductus Ligation

<table>
<thead>
<tr>
<th>Index</th>
<th>AUC</th>
<th>Cutoff point</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAV/BSA\textsuperscript{1.54} (ml/m\textsuperscript{3.08})</td>
<td>0.970</td>
<td>32.1</td>
<td>100</td>
<td>87.0</td>
</tr>
<tr>
<td>LAV/BSA\textsuperscript{1} (ml/m\textsuperscript{2})</td>
<td>0.975</td>
<td>8.15</td>
<td>100</td>
<td>87.3</td>
</tr>
<tr>
<td>LAV\textsubscript{4CV}/BSA\textsuperscript{1.52} (ml/m\textsuperscript{3.04})</td>
<td>0.979</td>
<td>32.5</td>
<td>100</td>
<td>91.6</td>
</tr>
<tr>
<td>LAV\textsubscript{4CV}/BSA\textsuperscript{1} (ml/m\textsuperscript{2})</td>
<td>0.982</td>
<td>8.69</td>
<td>100</td>
<td>91.2</td>
</tr>
<tr>
<td>LVDD%N (%)</td>
<td>0.912</td>
<td>117.9</td>
<td>100</td>
<td>71.0</td>
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<tr>
<td>LA/Ao</td>
<td>0.919</td>
<td>1.32</td>
<td>100</td>
<td>79.7</td>
</tr>
<tr>
<td>LPA d/s</td>
<td>0.965</td>
<td>0.26</td>
<td>100</td>
<td>90.0</td>
</tr>
<tr>
<td>LPA edv (cm/s)</td>
<td>0.976</td>
<td>20.9</td>
<td>100</td>
<td>95.6</td>
</tr>
<tr>
<td>LAV\textsubscript{4CV} %N(%)</td>
<td>0.972</td>
<td>151</td>
<td>100</td>
<td>90.1</td>
</tr>
<tr>
<td>LAV\textsubscript{4CV}/BW</td>
<td>0.980</td>
<td>0.948</td>
<td>100</td>
<td>92.2</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.

AUC, area under curve; d/s, the ratio of diastolic to systolic velocity; edv, end-diastolic velocity; 4CV, 4-chamber view; LA/Ao, the ratio of left atrial to aortic diameter; LPA, left pulmonary artery. Other abbreviations as in Table 1. LAV\textsubscript{4CV} %N(%) was calculated as a percentage of normal to the estimated values of LAV\textsubscript{4CV} by body height, estimated LAV\textsubscript{4CV}=–0.567+3.285×body height (P<0.0001, R=0.40).

enlarged LA more sensitively than LA/Ao. LAV\textsubscript{4CV}, a simpler measurement of LAV, correlated well with LAV measured by the biplane method (LAV\textsubscript{4CV}=–0.0025+0.96 × LAV, P<0.0001, R=0.93; Figure 4A). LAV\textsubscript{4CV}/BSA\textsuperscript{1.52} was 21.4±9.4 ml/m\textsuperscript{3.04}, which closely correlated with LAV/BSA\textsuperscript{1.54} (R=0.92). When we confined the analysis to the 149 data points in which the PDA was closed, LAV/BSA\textsuperscript{1.54} was 22.7±7.8 ml/m\textsuperscript{3.08} and LAV\textsubscript{4CV}/BSA\textsuperscript{1.52} was 20.8±7.8 ml/m\textsuperscript{3.04}.

Table 2 summarizes the results of ROC curve analysis to detect 6 data points just before PDA surgery from all data points using the LAV indices, as well as other indices used for the evaluation of the severity of PDA (Figure 4). ROC curve analysis revealed the superiority of LAV/BSA\textsuperscript{1.54} (cutoff 32.1, sensitivity 100%, specificity 87%, area under the curve (AUC) 0.97) and LAV\textsubscript{4CV}/BSA\textsuperscript{1.52} (cutoff 32.5, sensitivity 100%, specificity 92%, AUC 0.98) compared with LA/Ao (cutoff 1.32, sensitivity 100%, specificity 80%, AUC 0.92). Regardless of whether the LAV measurements were biplane (LAV/BSA\textsuperscript{1.54}) or single-plane (LAV\textsubscript{4CV}/BSA\textsuperscript{1.52}), the LAV indices provided improved specificity and AUC compared with those of LA/Ao. To seek an easier but accurate correction of LAV\textsubscript{4CV}, we corrected LAV\textsubscript{4CV} using BH or BW. LAV\textsubscript{4CV} positively...
rates of reduction were 33\(\pm\)12\% for LA/Ao, 56\(\pm\)19\% for LAV/BSA\(^{1.54}\), and 59\(\pm\)21\% for LAV\(^{4CV}/BSA^{1.52}\) (P<0.05 by ANOVA). These results indicated that the LAV indices are more sensitive to changes in LA size than is LA/Ao.

**Discussion**

To our knowledge, this is the first study to assess LAV specifically targeted for ELBWIs. This study provides: (1) reference values of LAV in ELBWIs; (2) LAV/BSA\(^{1.54}\) as an appropriate body size correction by an allometric model; and (3) no overall dependency of LAV/BSA\(^{1.54}\) on the time after birth up to 3 days (\(\text{Figure 2B}\)). LAV\(^{4CV}\), which can be measured only by a 4-chamber view, closely correlated with LAV/BSA\(^{1.54}\) and LAV\(^{4CV}/BSA^{1.52}\) detected marked enlargement of the LA just before PDA surgery. BSA, body surface area; LA/Ao, left atrial to aortic dimension ratio; LAV, left atrial volume; PDA, patent ductus arteriosus.

**Table 2.**

<table>
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<th>Index</th>
<th>AUC</th>
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</thead>
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<tr>
<td>LAV(^{4CV}/)BW</td>
<td>0.980</td>
</tr>
<tr>
<td>LAV/BSA(^{1.54})</td>
<td>0.972</td>
</tr>
<tr>
<td>LAV(^{4CV}/BSA^{1.52})</td>
<td>0.972</td>
</tr>
<tr>
<td>LA/Ao</td>
<td>0.965</td>
</tr>
</tbody>
</table>

**Figure 5.** Correlation between left pulmonary arterial end-diastolic velocity (LPA edv) and (A) LA/Ao, (B) LAV/BSA\(^{1.54}\), and (C) LAV\(^{4CV}/BSA^{1.52}\). Correlations with (B) LAV/BSA\(^{1.54}\) and (C) LAV\(^{4CV}/BSA^{1.52}\) were better than with (A) LA/Ao (all P<0.0001, R=0.40 in (B) and 0.35 in (C), vs. R=0.32 in (A)). (Red square) Points just before PDA surgery, which are predominantly located the right in plots (B) and (C), indicating that the LAV indices reflect a markedly enlarged LA more sensitively in patients with a PDA than does LA/Ao or LPA edv. BSA, body surface area; LA/Ao, left atrial to aortic dimension ratio; LAV, left atrial volume; PDA, patent ductus arteriosus.

**Figure 6.** Changes in LAV indices and LA/Ao before and after PDA surgery. Significant reductions were observed in all 3 indices (P<0.01). Reduction rates in (B) LAV/BSA\(^{1.54}\) (56\%\pm19\%), and (C) LAV\(^{4CV}/BSA^{1.52}\) (59\%\pm21\%) tended to be greater than in (A) LA/Ao (33\%\pm12\%) (P<0.05). BSA, body surface area; LA/Ao, left atrial to aortic dimension ratio; LAV, left atrial volume; Op, ligation of patent ductus arteriosus (PDA).
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2.0 ml/m² in non-hemodynamically significant PDA and a higher incidence of cerebrovascular disease or mortality was reported that (1) LAV/BSA 1 depends on BSA; (2) LAV/BSA 1 reduces as BSA reduces; and (3) LAV/BSA 1 was approxi-

mately 10 ml/m² in patients with BSA=0.2 m², which is signiﬁcantly smaller than that in adults. Similarly, Juutinen et al reported 11.7±4.2 ml/m² in normal neonates with a mean BSA of 0.19 m². Khostis ethal et al used the prolate ellipse method, in which 3-dimensional diameters are multiplied, to calculate LAV, and assessed the relationship between LAV/BSA 1 and PDA in preterm infants with gestational age <33 weeks. Although caution should be exercised because the prolate el-

lipse method routinely yields smaller values than either the area-length or Simpson method, the mean LAV/BSA 1 was 9.1±4.2 ml/m² in hemodynamically signiﬁcant PDA (mean gestational age 29.4 weeks, mean birth weight 1,237 g) and BSA 0.055–0.098 m²), in whom PDA is more clin-

ical than LA/Ao. LA/Ao must be considered as a good indicator, because it is independent of BSA and does not re-

quire body size correction (Figure 1C), comparison or follow-up of LA size is limited to the AP dimension, but the LA does not dilate equally in 3 dimensions. The LA is located behind the sternum and in the AP dimension could be restricted compared with the other 2 dimensions. Therefore, the LA/Ao could be underesti-

mated when the LA dilates predominantly in the superior-in-

ferior and medial-lateral directions rather than in the AP di-

rection. Furthermore, (3) the LA cross-sectional area in a markedly dilated LA may become a rounded rectangle rather than a similarly extended ellipse. In such a situation, the ellipse

Figure 1C shows the positive correlation between LAV/BSA 1 and LA/Ao. In this plot, the data points just before PDA surgery were located higher, indicating that LAV/BSA 1 may reﬂect LA dilation more sensitively than LA/Ao. ROC curve analysis to detect the status just before PDA surgery revealed the superiority of LAV indices to LA/Ao (Table 2, Figure 4C). Furthermore, as shown in Figure 5, the LAV indices were better correlated with LPA edv, a reliable index of PDA severity, than was LA/Ao. Data points just before PDA surgery (Figures 5B,C) were located to the right, again indicating that LA dilation may be better reﬂected by the LAV indices than by LA/Ao and LPA edv. Although we cannot simply compare the advantages by comparing the reduction rates, the reduction rate for LAV indices on PDA surgery tended to be greater than that for LA/Ao (Figure 6). These results indicate that the LAV indices may be more sensitive and specific to LA dilation induced by PDA than is LA/Ao; however, a future larger-scale validation study will be needed to conﬁrm this.

LA/Ao has contributed to neonatal medicine as a simple marker of LA dilation. LA/Ao must be considered as a good indicator, because it is independent of BSA and does not re-

quire body size correction (Figure 1). However, this study indicates that LA indices may be better markers of PDA severity than is LA/Ao. The following are the advantages of LAV indices over LA/Ao: (1) smaller likelihood of measurement error; (2) limitations of LA/Ao inherent to only measuring in the AP dimension; and (3) the greater importance of measuring area rather than diameters alone, even with 3 dimensions. In detail: (1) potentially larger inter- and intra-observer variance of LA/Ao may result from variations in the position and angle used to measure aortic and LA dimensions; (2) LA/Ao applies only to the AP dimension, but the LA does not dilate equally in 3 dimensions. The LA is located behind the sternum and in front of the descending aorta and the vertebrae; thus, dilation in the AP dimension could be restricted compared with the other 2 dimensions. Accordingly, LA/Ao could be underesti-

mated when the LA dilates predominantly in the superior-in-

ferior and medial-lateral directions rather than in the AP di-

rection. Furthermore, (3) the LA cross-sectional area in a markedly dilated LA may become a rounded rectangle rather than a similarly extended ellipse. In such a situation, the ellipse

LAV/BSA 1.48 may be worth routinely evaluating and may contribute to the circulatory management of ELBWIs. However, this study included only 6 patients undergoing PDA surgery. Prospective testing of the usefulness of these 2 LAV indices in a multicenter trial with a larger number of patients, including more patients undergoing PDA surgery, is needed.

Reference Value and Body Size Correction of LAV in ELBWIs

Soon after the birth of the ELBWIs in this study, LAV/BSA 1 was 5.96±2.38 ml/m² for all data points and 5.72±1.98 ml/m² for the data points with closure of the PDA. In healthy adults, regardless of age, LAV/BSA 1 is approximately 22±6 ml/m², and a higher incidence of cerebrovascular disease or mortality is reported in patients with LAV/BSA 1 >32 ml/m². Thus, the value reported here for LAV/BSA 1 in ELBWIs is much smaller than that reported in adults. Recently, Bhatla et al re-

ported that LAV/BSA 1.54 is appropriate for ELBWIs. This AE=1.54 is almost consistent with AE=1.48 (LAV/ BSA 1.48) in a previous report in children; however, the LAV/BSA 1.48 values differ greatly between that study and the present study. When we used body size correction by BSA 1.48 for our study patients, LAV/BSA 1.48 was 20.2±8.0 ml/m² for all data points and 19.5±6.7 ml/m² for the data points with PDA closure. In contrast, LAV/BSA 1.48 for healthy children is 31.5±5.5 ml/m². Our observation that LAV/BSA 1.48 in ELBWIs was much smaller than in children may be partly explained by differences in the volume of water in the body. Because the proportion of water in the body of an ELWI is much higher than that in a child, and the BSA is much smaller in ELBWIs than in children, the same BSA correction may result in a smaller LAV/BSA 1.48 in ELBWIs. Future studies combining data from children and infants with BW >1,000 g with current data in ELBWIs are need-

ed to assess whether 1 allometric model can be applied to the whole pediatric population from ELBWIs to children, by plot-

ting all data in a double logarithmic chart.

Unexpectedly, this study did not show a statistically signiﬁcant difference between LAV with and without PDA closure. Among ELBWIs, there is great patient-by-patient variation in cardiopulmonary adaptation. Besides PDA opening/closure, pulmonary resistance, loading conditions, and LV stiffness may greatly affect LAV. In addition, many patients had a hemodynamically insignificant PDA. Moreover, circulatory management, with diuretics or indomethacin, was applied to minimize the effect of PDA opening. These factors may contribute to the lack of a significant difference in LAV be-

tween the patients with and without PDA closure. We discuss the potential for evaluating hemodynamically signiﬁcant PDA using LAV and other indices in the next section.
area calculated by diameters would be smaller than the directly measured area of a dilated LA. Hence, LA size assessed only by linear measurements may be underestimated and direct area measurement seems critical for the accurate determination of LAV. This possibility is supported by the observations that the prolate ellipse method of calculating LAV by 3-directional dimensions produced a smaller LAV than that obtained by the biplane area-length and biplane modified Simpson’s methods, and the differences increased with increased LAV. 28

Notably, this study highlighted the clinical usefulness of LAV 4CV, which is derived solely from a single-plane (apical 4-chamber view) area-length method in ELBWIs. This method is not recommended in adult guidelines, because it is based on possibly inaccurate geometric assumptions. 32 However, this study revealed that single-plane-derived LAV 4CV closely correlated with LAV calculated by the biplane area-length method (R=0.93) in ELBWIs. Other results (Figures 4–6, Table 2) showed the almost equivalent clinical usefulness of LAV 4CV in ELBWIs. Although the apical 2-chamber view, which is required for the biplane area-length method, is sometimes difficult to obtain in ELBWIs who have lung disease or are under mechanical ventilation, the 4-chamber view, which is the only one needed for the single-plane area-length method (LAV 4CV), can be readily obtained in ELBWIs without needing additional echocardiographic time. Given the similar usefulness of these 2 LAV indices, the easy and less invasive approach of LAV 4CV may be of great clinical importance in the daily circulatory management of ELBWIs. BW or BH correction for LAV 4CV in this population may provide an easy and sufficiently accurate body size correction (Table 2); this warrants future detailed assessment.

This study indicates that LAV indices improve the assessment of PDA-induced LA dilation in ELBWIs, overcome the limitations of LA/Ao, and may contribute to the circulatory management of ELBWIs.

The hemodynamic problem in PDA patients comes mainly from a large amount of left-right shunting, and the LV volume should indicate the severity of PDA. Because we did not measure the LV volume, we cannot fairly compare the volume enlargement between the LA and LV in the assessment of PDA in this population. These results and the aforementioned AUC analysis indicate that LAV and LAV/BSA 1.54 reflect a markedly enlarged LA more sensitively in PDA patients than LA/Ao, LVDd or LVDd%NL (Figure 3). Given the superiority of volume assessment to dimension assessment in the LA, future study is warranted to test the combined LA and LV volume assessments for evaluation of PDA severity.

Study Limitations

We could not assess the inter- and intra-observer differences in the LAV indices because echocardiography in ELBWIs is invasive to a certain degree and echocardiographic examination time is limited. Instead, to minimize the bias, only 1 experienced sonographer, who did not participate in the decision-making for PDA surgery, performed all echocardiographic examinations, and the neonatologists who decided on the indication for PDA surgery were not informed of the LAV data, but only of LA/Ao and other indices of PDA severity. There is currently no fully validated formula to calculate BSA by BW and BH in ELBWIs, and BSA calculated by the Mosteller formula 19 may be slightly underestimated in children and infants. 30 Using the initial BSA during the first 3 days may have caused some inconsistencies in the data. If we assume the ELBWIs had group mean values of 747 g for BW, 30.9 cm for BH, and 0.48 ml for LAV, a 10% change in BW with the same BH would change the LAV/BSA 1.54 from 93% to 108%. This level of variance in the LAV/BSA 1.54 would occur as a result of using the initial BSA during the acute phase in ELBWIs, and our data should be viewed in that light. Despite such limitations, given that the cutoff value for the status just before PDA operation was 137%, the effects of this potential variance may not be large enough to prevent us using the initial BSA in the LAV body size correction for the assessment of PDA severity. We could not perform echocardiography for all data points over the first 3 days in all patients because of the individual clinical circumstances of the ELBWIs. A PFO may influence the LAV. Left-to-right shunt via a PFO may depress the LA, but the same volume of blood in turn returns to the LA. Thus, it is uncertain how left-to-right shunt via a PFO affects LAV in this situation. MRI is the gold standard modality for measuring cardiac chamber volume in adults and children. However, we did not validate the echocardiographic LAV using MRI because such evaluations are not clinically practical in the acute phase in ELBWIs. Instead, we used the biplane area-length method, which is a recommended standard measurement in adults. 12, 32, 35 to validate the single-plane area-length method. We compared the clinical usefulness of the LAV indices with that of LA/Ao for the detection of a severely enlarged LA just before PDA surgery, and their correlation with LPA edv, a reliable index of PDA severity. 22, 33 However, this study included only 6 patients undergoing PDA surgery. Some other points were the status necessitating indomethacin. The results of ROC analysis under these circumstances may not be robust. Thus, further prospective examination of the usefulness of the LAV indices with greater consideration of the infants’ precise growth in a much larger number of patients, including a comparison of surgical outcomes between surgical decision-making based on LA/Ao or LA volume, is essential to assess the robustness and clinical merits of these markers for the detection of LA dilation necessitating PDA surgery.

Conclusions

Although the long-term contribution of LA/Ao to neonatal medicine should be noted, area-length LAV measurements provide a more useful evaluation of PDA severity. This study set the reference values of LAV/BSA 1.54 and LAV 4CV/BSA 1.52. Because single-plane LAV measurement is relatively easy and as useful as biplane LAV, it may deserve more widespread use. The validity and usefulness of these indices should be further tested in a larger cohort of ELBWIs.

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References


