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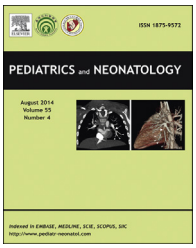

ORIGINAL ARTICLE

Novel Treatment Criteria for Persistent Ductus Arteriosus in Neonates

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Key Words
left ventricular end-diastolic dimension;
Qp/Qs;
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Background: The indications for ductus arteriosus ligation in very-low-birth-weight infants (VLBWIs) with persistent ductus arteriosus (PDA) are unclear. Increased left ventricular end-diastolic dimension (LVDd) is commonly found in patients with PDA. Here, the enlargement of LVDd in term and preterm neonates without congenital heart disease was estimated by two-dimensional echocardiography.
Methods: The value of the measured LVDd was divided by the normal LVDd as an index (LVDd ratio) to compare 30 patients who underwent PDA ligation with 30 patients treated with indomethacin and 30 patients who did not undergo radical therapy.
Results: An LVDd ratio between 122% and 197% (mean, 142%) was considered to be an indication for the ligation procedure. The proportion of patients exceeding 130% in the LVDd ratio was 87% (26/30) in those patients who underwent ligation. Catecholamines and/or vasodilators were required in 83% patients for the treatment of low ejection fraction or hypertension after operations, suggesting that patients had been in preload and/or afterload remodeling failure during the operation. The percentage of patients with less than 115% in the LVDd ratio was 90% in the non-radical-therapy patients. The LVDd ratios of 130% and 115% were regarded as cut-off values for surgical ligation and indomethacin treatment.
Conclusion: The LVDd ratio is a useful measure to determine the treatment of VLBWIs with PDA.

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1. Introduction

The treatment for very-low-birth-weight infants (VLBWIs) with persistent ductus arteriosus (PDA) is limited to indomethacin administration or surgical ligation of the ductus arteriosus (DA). Indications for treatment are based on several criteria applied singly or in combinations, including increased end-diastolic flow of the left pulmonary artery (LPA end), increased left atrium to ascending aorta diameter ratio (LA/Ao ratio) on echocardiography, increased cardiothoracic ratio on X-ray, increased heart rate, decreased diastolic blood pressure, decreased urinary output, and increased brain natriuretic peptide value. However, the indications for the treatment of VLBWIs with PDA have not been established.

Echocardiography has long been used to assess heart size in children. In this study, two-dimensional echocardiography with height as an index was used to examine left ventricular end-diastolic dimension (LVDd) and its rate of increase in neonates, including premature neonates.[1,2] In PDA patients, the flow through the DA increases mitral valve flow causing increased LVDd. We therefore compared the LVDd values in PDA patients to those of healthy patients and used the difference (LVDd ratio) as an index for PDA severity.

We had three objectives in this study: (1) to determine the usefulness of the LVDd ratio in patients with PDA compared to that of LPA-end and LA/Ao ratio; (2) to determine the cut-off value of the LVDd ratio for the selection of different treatment strategies; and (3) to propose a new treatment algorithm based on the LVDd ratio as an index in VLBWI with PDA.

2. Materials and methods

2.1. Study design

A retrospective case note review of the treatment of VLBWIs with PDA was performed. Patients included in the study were all born and/or treated at the Gifu Prefectural General Medical Center. The indications for treatment were analyzed in correlation with the LVDd ratio, LPA-end, and LA/Ao ratio.

The treatment choice did not depend on the LVDd ratio. We chose PDA ligation based on two criteria, bleeding in the head, lungs, or intestine, and the absence of an effective response to indomethacin treatment.

The patients receiving PDA ligation therapy were included in the Ligation Group. Patients who underwent indomethacin therapy were included in the Indomethacin Group. Patients who were not treated by PDA ligation and those who were not treated by PDA ligation or indomethacin therapy were included in the Control Group. These two groups matched the ligation group with respect to sex, gestational age, and birth body weight. Prophylactic indomethacin treatment was not regarded as a treatment for PDA. We investigated the relationship between the groups and LVDd ratio and calculated the mean and standard deviation (SD) of the LVDd ratio, LPA end, and LA/Ao ratio in each group.

The necessary number of neonates included in the study was determined according to Cohen's method,[3] and that showed 29 patients are needed to compare two groups with a Type 1 error of 0.05 in two-sided tests and a statistical power of 0.85, when the absolute difference divided by SD is presumed to be 0.80.

2.2. Study patients

The inclusion criteria were as follows: (1) birth weight of 1500 g or less; (2) gestational age less than 30 weeks; (3) patients with no congenital heart disease and no evidence of coronary artery lesions as determined by echocardiogram; and (4) patients who survived.

Only VLBWIs who were born from February 1999 to February 2012, at the Gifu Prefectural General Medical Center were included in the study.

The characteristics of the patients are shown in Table 1. The Ligation Group consisted of 30 neonates who underwent PDA ligation. The Indomethacin Group consisted of 30 neonates treated with indomethacin alone; and the Control Group consisted of 30 neonates who were treated with palliative therapies but did not receive radical treatments. All groups were matched by sex, gestational age, and birth weight.

Table 1 Characteristics of 90 patients.

Groups	Ligation	Indomethacin	Control
No. of patients	30	30	30
Sex (male/female)	11/19	11/19	12/18
Gestational age (wk)	26.6 ± 1.7	27.1 ± 1.8	27.0 ± 1.6
Birth weight (g)	891 ± 277	969 ± 243	958 ± 249
AGA/LGA	26/4	27/3	26/4
Birth height (cm)	33.9 ± 3.9	34.0 ± 3.1	33.9 ± 3.4
Age at ligation (d)	20 ± 11		
Age at exam (d)	15 ± 11*	6 ± 8	3 ± 4
Height at exam (cm)	34.8 ± 3.8	34.6 ± 3.3	34.2 ± 3.2
RDS	27	26	22
Surfactant administered	25**	20	13
Ventilation/CPAP at exam	28/2	24/6	26/4
Inotropes before treatment	17***	4	0
Prophylactic indomethacin	6	5	7
Bleeding tendency[a]	14****	5	4

*p = 0.0004, <0.0001 for Indomethacin Group and Control Group, respectively.
**p = 0.039 for Control Group.
***p = 0.013, <0.0001 for Indomethacin Group and Control Group, respectively.
****p = 0.038, 0.015 for Indomethacin Group and Control Group, respectively.
AGA = adequate for gestational age; CPAP = continuous positive airway pressure; LGA = light for gestational age; RDS = respiratory distress syndrome.
[a] Bleeding tendency means the patient is vulnerable to bleed in either the cranium, lung, and intestine.

2.3. Data acquisition

The two-dimensional echocardiographic studies were performed using the iE33 or Sonos 5500 apparatus (Philips Ultrasound, Bothell, WA, USA) in the left parasternal short-axis view at the chordae tendinae level immediately below the mitral valve with a 12–4 MHz transducer or a 7.5–5.5 MHz transducer, respectively, at rest. LVDd was measured as the distance between the endocardial surface of the intra-ventricular septum and the left ventricular posterior wall at the QRS complex onset on the electrocardiogram by M-mode recordings. We also measured PDA size. Each dimension was measured by the "center convention", i.e., using the middle bright contour excluding the inner and outer areas, with calibrated electronic calipers.[1]

All measurements were performed by two observers (HN, DT). The interobserver error was 4.5%, and the intraobserver errors were 3.2% and 4.1%, respectively, calculated on the basis of data from 30 participants. The final values were obtained from an average of more than three successive beats.

2.4. Statistical analyses

The F-test and Student *t* test were used to determine the differences in sample variance and means of two categories, respectively. Bonferroni correction was used to determine statistical equivalence of means in more than the three groups. The chi square analysis was used to ensure statistical equivalence of the occurrence rates of the two categories. A p *value* < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and treatments

The characteristics of the 90 patients are shown in Table 1.

The indication for ligation therapy was either no or minimal effectiveness of indomethacin in 25 of 30 patients in the Ligation Group. Indomethacin was not administered to the remaining five patients because of intracranial bleeding. The DA was closed by the end of the first consecutive indomethacin administration in 18 of 30 patients in the Indomethacin Group. Repeat indomethacin treatment was necessary for the other 12 patients, and the therapy was not fully effective for two of the 12 patients. Closed DA was confirmed in the 90 patients before discharge.

3.2. Distribution of the LVDd ratio in each group

The distribution of the LVDd ratio in each group is shown in Figure 1. The means and SDs of the LVDd ratio in the Ligation Group, Indomethacin Group, and Control Group were 142 ± 16% (range, 122–197%), 121 ± 9% (range, 106–142%), and 105 ± 8% (range, 86–122%), respectively. There were significant differences ($p < 0.0001$) between any two of the three groups. The ratios of patients exceeding 130% in the LVDd ratio were 87% (26/30) and 20% (6/30) in the Ligation Group and the Indomethacin Group, respectively. The ratios of patients with less than 115% in the LVDd ratio were 17% (5/30), and 90% (27/30) in the Indomethacin Group and the Control Group, respectively.

3.3. Comparison of LVDd ratio with end-diastolic left pulmonary artery flow and LA/Ao ratio

The distributions of LPA end and LA/Ao ratio in the three groups are shown in Figure 1. The means and SDs of LPA end in the Ligation Group, Indomethacin Group, and Control Group were 25 ± 12, 14 ± 12, and 5 ± 8, respectively. There was a significant difference ($p < 0.001$) between any two of the three groups.

The means and SDs of LA/Ao ratio in the Ligation Group, Indomethacin Group, and Control Group were 1.82 ± 0.31, 1.40 ± 0.31, and 1.20 ± 0.22, respectively. There was a significant difference ($p < 0.001$) between any two of the three groups. However, the distribution of values in the latter two categories was wider than that of the LVDd ratio, and overlapping data were observed in many patients.

3.4. Indications for PDA ligation

The inotropic treatments after PDA are shown in Table 2.

Catecholamine and/or vasodilator supplementation was needed by most patients (25/30) because of decreased EF or systemic hypertension after the operation. This indicates that approximately 83% of the patients in the Ligation Group were in preload and/or afterload remodeling failure after the operation. Moreover, because patients of the Ligation Group had a bleeding tendency or indomethacin ineffectiveness, our definitions for the selection of ligation therapy were almost always appropriate.

4. Discussion

Although the indications for the treatment of VLBWIs with PDA have been studied extensively, there are currently no clear guidelines for the treatment of these patients. This can be partly attributed to the difficulty of establishing criteria to decide disease severity. Several criteria are currently used to determine the optimal treatment of VLBWIs with PDA, including LPA end, LA/Ao ratio, LVO to superior vena cava flow (SVC) ratio (LVO/SVC), PDA size or its flow, PDA/LPA ratio, left ventricular output (LVO) to right ventricular output (RVO) ratio (LVO/RVO) determined by echocardiography, increased cardiothoracic ratio on the chest X-ray, increased heart rate, bounding pulse, decreased urinary output, and increased brain natriuretic peptide value. However, no previous study has reported a confirmed criterion for determining the management of VLBWIs with PDA as some of the criteria require special techniques or the data show very wide variance or are within the normal range in patients with significant PDA. Because of the ambiguous criteria involved in the treatment (mentioned above), deciding the appropriate treatment approach is difficult.

Clinical symptoms, electrocardiography, and chest X-ray are regarded as neither accurate nor specific.[4,5] Although echocardiography is commonly used to evaluate PDA

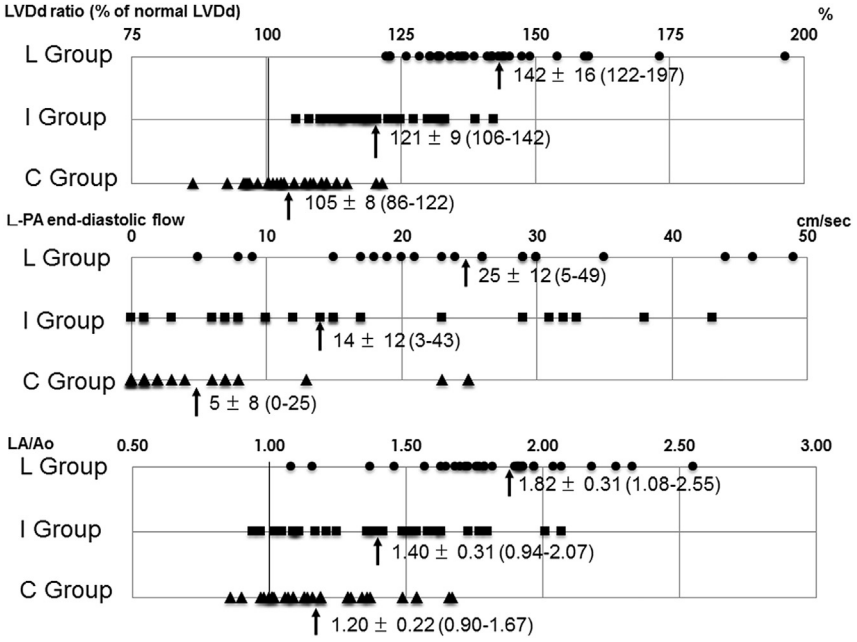

Figure 1 Distribution of the LVDd ratio, the end-diastolic flow of left pulmonary artery, and the LA/Ao ratio. The LVDd ratio is the measured LVDd divided by the normal LVDd derived from the equation. LA/Ao = the ratio of left atrium diameter divided by ascending aorta diameter; LVDd = left ventricular end-diastolic dimension.

severity, other methods have been proposed in different studies.

Hojjar et al[6] reported that LVO/SVC was the most appropriate criterion and that LA/Ao, DA diameter, mean, and LPA end were accurate and easy to measure compared with left ventricular output divided by superior vena cava flow (LVO/SVC) in 23 neonates. However, LVO/SVC measurement requires a special technique, and LA/Ao is considerably influenced by the three-dimensional shape of the LA, which varies significantly between patients. The LPA end also has wide variance as shown in the present study. Condò et al[7] reported that the size of the DA and the flow through it were both appropriate for evaluating PDA severity in 97 extremely low birth weight infants (ELBWI). The DA size estimation is often difficult because it is not a simple straight vessel but has a complex shape. There was no apparent relation between the DA size and LVDd ratio (Figure 2). Importantly, flow volume through the DA depends on two parameters, the diameter of the DA at the narrowest point and the pressure gradient between the aorta and the pulmonary artery. The blood flow through the DA is variable, as the flow is influenced not only by the pressure gradient, but also the angle between the Doppler echocardiography echo beam and blood flow. Ramos et al[8] assessed 115 ELBWIs and reported that a moderate to large PDA determined from the PDA/LPA ratio at or before days after birth can identify neonates <27 weeks' gestation who subsequently require PDA closure. However, this study assessed the criteria for treatment only in neonates <27 weeks' gestation. Phillipos et al[9] reported that LVO/RVO was an appropriate measure of PDA severity. These authors determined that the value of the LVO minus the RVO equals the flow through the DA. However, because the flow through the oval foramen influences RVO in premature neonates, the formula is not always applicable.[4] Furthermore, previous reports have not included a sufficient number of patients for an accurate evaluation.

Although the evaluation of neonates using the criteria mentioned above can detect statistically significant

Table 2 Characteristics of patients after treatment.

Groups	Ligation	Indomethacin	Control
Catecholamines	22	4	0
Vasodilators	6	0	0
At least one therapy	25*	4	0

*$p < 0.0001$ for Indomethacin Group and Control Group.

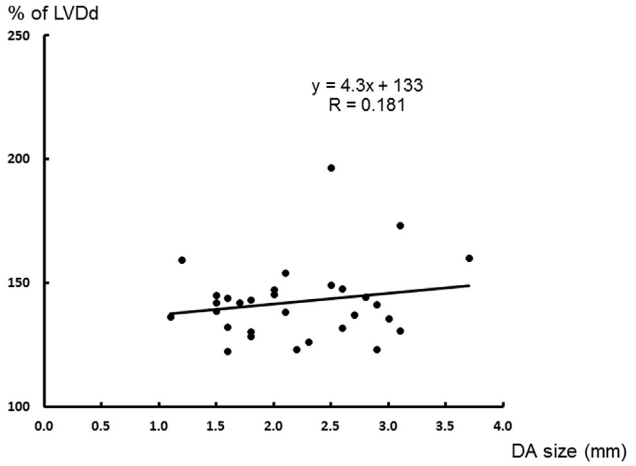

Figure 2 Relationship between the DA size and the LVDd ratio. No proportional relationship was observed between the DA size and the LVDd ratio.

differences between neonates with and without significant PDA, this is only one of the requirements for determining treatment. The important criterion used should have good sensitivity and specificity in practical use, in other words, the ideal criterion is associated with few exceptions and can be measured at any institution. We assessed two representative conventional criteria that have been used to determine the severity of PDA, LPA end and LA/Ao ratio. Although these criteria showed statistical significance for determining the therapy for PDA, the data obtained using these methods as indexes were associated with several exceptions.

4.1. The superiority of the LVDd ratio as a criterion

Nagasawa[1] reported novel regression equations for the determination of LVDd in premature neonates. The LVDd in PDA patients is commonly increased because of its extended pulmonary flow, as a consequence of the flow volume through the DA. Therefore, LVDd measurement should be a useful criterion for determining treatment in VLBWIs with PDA, which are characterized by increased left ventricular end-diastolic volume. We estimated that the measured LVDd divided by the normal LVDd (LVDd ratio) might be the most appropriate index, which can be measured at most institutions without the need for expert personnel or special techniques.

The LVDd ratio was assessed in VLBWIs with PDA retrospectively. We selected 30 patients who had undergone DA ligation, and the number of patients necessary for an accurate assessment was determined according to Cohen.[3] We also selected VLBWIs treated using indomethacin and patients who had not received radical therapy for PDA. Our results showed that the LVDd ratio has good sensitivity (86%) and specificity (84%) for disease staging to determine the need for PDA ligation in VLBWIs.

4.2. Calculation of cut-off index for decision-making

The cut-off index to evaluate the indications for ligation operation and indomethacin therapy in PDA patients was investigated.

Qp/Qs >2.0 is the standard indication volume ratio to operate patients with ventricular septal defect.[10] An LVO/RVO ratio close to 2 was reported to be associated with increased intraventricular hemorrhage and periventricular leucomalacia.[9] The increase in LVDd when the LV is enlarged to twice its volume has not been determined. We measured the conventional fractional shortening (FS) and the FS of the long dimension (Lg-FS) in the LV in 155 normal full-term neonates. The mean Lg-FS/FS ratio was 0.69, when the increased LVDd value is defined as "x", the equation is as follows: $(1+x)^2 \times (1+0.69\times x) = 2$; $x = 0.29$. We calculated that the cut-off value of the LVDd ratio for DA ligation was 130% of the normal ratio.

The criterion value to administrate indomethacin was calculated in two ways. When Qp/Qs = 1.5 and the LVDd ratio was defined as "y", the equation was $(1 + y)^2 \times (1+0.69 \times y) = 1.5$; $y = 0.16$. The mean LVDd ratio in the Indomethacin Group minus its SD was 112% and that of the Control Group plus its SD was 113%. The cut-off value of the LVDd ratio for indomethacin treatment was 115% of the normal value.

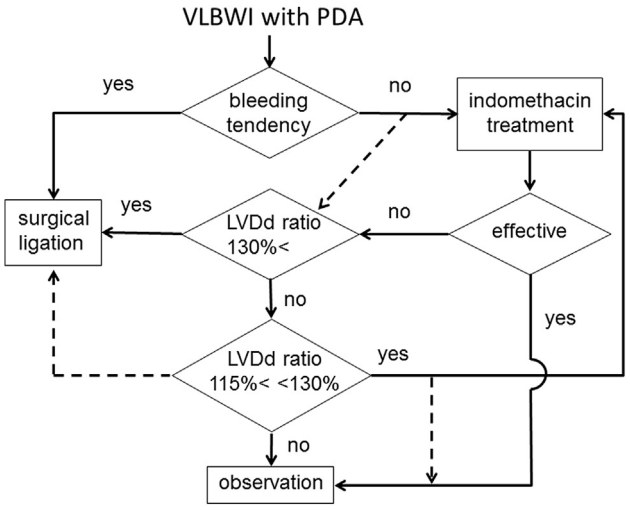

Figure 3 Treatment algorithm for VLBWIs with PDA. Dotted lines show alternative ways to the primary choices. ICH = intra-cranial hemorrhage.

4.3. Algorithm for the assessment and treatment of VLBWIs with PDA

An algorithm for the assessment and treatment of VLBWIs with PDA was proposed and is shown in Figure 3.

An LVDd ratio of 130% of the normal value or higher indicates the need for PDA ligation. If the LVDd ratio is between 115% and 130%, indomethacin treatment should be initiated. In cases in which indomethacin treatment is not effective or contraindicated in patients with intracranial hemorrhage, DA ligation should be performed. If the ratio is less than 115%, the patient should be treated with conventional therapy.

Koch et al reported that at least one-third of neonates with a birth weight of 1000 g or less had spontaneous DA closure and did not need medical treatment.[11] Previous reports have shown that the prognosis of patients with indomethacin treatment is not necessarily affirmative,[12–15] and adverse effects have been reported in association with its use, which suggests that indomethacin administration should be avoided whenever possible. The indication of indomethacin treatment should be based on both different indexes and physiological symptoms.

LVDd ratio as a criterion for treatment has some limitations. Differences in the measurement of the LVDd ratio according to sex, race, institution, and equipment have not been determined. The ratio should be applied carefully within 24 hours after birth owing to its elliptic shape in the short axis view of the LV.

A prospective study analyzing the LVDd ratio will be performed in the future.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

1. Nagasawa H. Novel regression equations of left ventricular dimensions in infants less than 1 year of age and premature neonates obtained from echocardiographic examination. *Cardiol Young* 2010;**20**:526—31.
2. Mertens L, Seri I, Marek J, Arlettaz R, Barker P, McNamara P, et al. Targeted neonatal echocardiography in the neonatal intensive care unit: practice guidelines and recommendations for training. Writing Group of the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC). *J Am Soc Echocardiogr* 2011;**24**:1057—78.
3. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988. pp. 19—74.
4. Evans N. Diagnosis of patent ductus arteriosus in the preterm newborn. *Arch Dis Child* 1993;**68**:58—61.
5. Kupferschmid C, Lang D, Pohlandt F. Sensitivity, specificity and predictive value of clinical findings, m-mode echocardiography and continuous wave Doppler sonography in the diagnosis of symptomatic patent ductus arteriosus in preterm infants. *Eur J Pediatr* 1988;**147**:279—82.
6. El Hajjar M, Vaksmann G, Rakza T, Kongolo G, Storme L. Severity of the ductal shunt: a comparison of different markers. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F419—22.
7. Condò M, Evans N, Bellù R, Kluckow M. Echocardiographic assessment of ductal significance: retrospective comparison of two methods. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:35—8.
8. Ramos FG, Rosenfeld CR, Roy L, Koch J, Ramaciotti C. Echocardiographic predictors of symptomatic patent ductus arteriosus in extremely-low-birth-weight preterm neonates. *J Perinatol* 2010;**30**:535—9.
9. Phillipos EZ, Robertson MA, Byrne PJ. Serial assessment of ductus arteriosus hemodynamics in hyaline membrane disease. *Pediatrics* 1996;**98**:1149—53.
10. Bernstein Daniel. *Nelson textbook of pediatrics*. 16th ed. London: WB Saunders Co. Ltd; 2000. pp. 1369—71.
11. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arterisosus in neonates at a birth weight of 1000 grams or less. *Pediatrics* 2006;**117**:1113—21.
12. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001;**344**:1966—72.
13. Laughon MM, Simmons MA, Bose CL. Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated? *Curr Opin Pediatr* 2004;**16**:146—51.
14. Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM, Nwaesei C, et al. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the trial of indomethacin prophylaxis in preterms (TIPP). *J Pediatr* 2006;**148**:730—4.
15. Carmo KB, Evans N, Paradisis M. Duration of indomethacin treatment of the preterm patent ductus arteriosus as directed by echocardiography. *J Pediatr* 2009;**155**:819—22.