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# Pulmonary arterial resistance and compliance in preterm infants☆

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ABSTRACT

*Background:* Preterm birth is known to be associated with an increased risk of pulmonary arterial hypertension, although how preterm birth influences pulmonary hemodynamics has not been fully understood. Pulmonary arterial resistance (Rp) and compliance (Cp) are important factors to assess the pulmonary circulation. The purpose of this study is to clarify the relationship between Rp and Cp in preterm infants.
*Methods:* We performed cardiac catheterization in 96 infants (50 males) with ventricular septal defect, and compared pulmonary hemodynamic parameters including Rp and Cp between preterm and full-term infants.
*Results:* Thirteen infants were preterm. There were no significant differences in sex, age, preoperative pulmonary arterial pressure, preoperative pulmonary-to-systemic flow ratio, and preoperative Rp between the 2 groups. However, preoperative Cp and resistor-capacitor (RC) time in preterm infants were significantly lower than those in full-term infants (2.1 vs 2.8 mL/mmHg/m$^2$ and 0.31 vs 0.36 s, respectively; $p < 0.05$ and $p < 0.01$, respectively). Postoperative systolic and mean pulmonary arterial pressures were higher in preterm infants than those in full-term infants (29 vs 25 mm Hg and 18 vs 14 mm Hg, respectively; both $p < 0.01$). It was also observed that postoperative Cp was lower in preterm infants, although postoperative Rp remained unchanged.
*Conclusions:* We demonstrated that preterm infants with pulmonary arterial hypertension had lower Cp than full-term infants, causing a modest increase in pulmonary arterial pressure. It is important to consider the unique pulmonary vasculature characterized by lower Cp, when managing preterm infants with congenital heart disease.



## 1. Introduction

The majority of infants who are born preterm (at <37 completed weeks of gestation) now survive to adulthood, because of significant advances in perinatal care. Epidemiological studies have particularly focused on the late adverse outcomes during adulthood among these populations [1–16]. Cardiovascular disease is one of the most serious complications, and individuals with preterm birth have a modestly high blood pressure throughout their lives [1,2,5,6,16]. Several authors have implied that prenatal programming of blood pressure was impaired by fetal growth retardation, poor maternal nutrition, maternal hypertensive disorders, and smoking during pregnancy [2,6]. This arterial dysfunction is hypothesized as "premature aging" theory, which is based on a decrease in capillary recruitment or an increase in extracellular matrix formation during the fetal and neonatal periods [16,17]. These changes can modify not only the condition of systemic arteries but also that of pulmonary arteries. Preterm birth is known to be linked to an increased risk of pulmonary arterial hypertension (PAH) [4,15], although how preterm birth influences pulmonary hemodynamics has not been fully understood.

In the pulmonary circuit, it is important to consider two parameters [18,19]: pulmonary arterial resistance (Rp), which refers to the resistance encountered by the blood as it flows through the pulmonary vasculature; and pulmonary arterial compliance (Cp), which refers to the elasticity and extensibility of vessels, representing the Windkessel model proposed by Otto Frank in 1899 [20]. There is an inverse relationship between Rp and Cp, and the Rp-Cp coupling reflects the state of pulmonary vasculature in patients with PAH [18,19]. The product of Rp and Cp, called the resistor-capacitor (RC) time, represents the exponential pressure decay in the pulmonary artery during diastole. This is potentially useful for the study of pulmonary circulation as an

*Abbreviations:* ASD, atrial septal defect; Cp, pulmonary arterial compliance; LAP, left atrial pressure; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; Pp/Ps, ratio of pulmonary arterial pressure and systemic arterial pressure; Qp, pulmonary blood flow; Qs, systemic blood flow; RC, resistor-capacitor; Rp, pulmonary arterial resistance; $SaO_2$, percentage of hemoglobin saturated with oxygen in arterial blood; SBP, systemic blood pressure; VEGF, vascular endothelial growth factor; VSD, ventricular septal defect.

☆ Each author listed on the manuscript takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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independent factor of right ventricular afterload and better explains the changes in cardiac index than other parameters [18,19,21]. Thus, to determine the characteristics of pulmonary circulation in preterm infants, we compared hemodynamic parameters including pulmonary arterial pressure (PAP), Rp, and Cp, between full-term and preterm infants with ventricular septal defect (VSD), which is a congenital heart disease that causes PAH.

## 2. Methods

### 2.1. Patients

A total of 96 infants [50 males and 46 females; median age 2 months (0–11 months)] with VSD were enrolled in this study (Fig. 1). They were admitted at our institute between January 2000 and June 2016. All patients had symptoms indicative of cardiac failure and/or PAH. Accentuated pulmonic second heart sound was noted in addition to right ventricular hypertrophy on electrocardiography and echocardiography in patients with suspected PAH. As is the standard clinical practice at our institute, cardiac catheterization was indicated before and after corrective surgery to confirm the improvement in heart function or PAH in infants with left-to-right congenital heart disease [18]. We retrospectively obtained right heart catheter measurements from clinical records before and after corrective surgery. We excluded patients with other cardiac lesions, such as patent ductus arteriosus, moderate to large atrial septal defect (ASD), moderate or severe valve regurgitation, right or left ventricular outflow obstruction, arch anomaly, and left ventricular dysfunction (ejection fraction <0.6) because the study aimed to determine the relationship between Rp and Cp in PAH relevant to the increase in pulmonary blood flow (Qp). Patients with cytogenetic abnormalities such as trisomy 13, 18, or 21 were excluded. We also excluded patients with partial cardiac catheterization data. Informed consent was obtained from the parents of patients included in this study, and the study protocol was approved by the Institutional Review Board of our institute (approval number 463).

### 2.2. Cardiac catheterization and data collection

Cardiac catheter examinations were performed before and after corrective surgery to evaluate pulmonary hemodynamics, as described in a previous study [18]. All catheterization measurements were performed in the supine position under sedation with thiamylal sodium using fluoroscopic guidance with standard techniques. Pressures were measured using a Berman angiographic catheter or a Swan-Ganz catheter (Gadelius Medical K.K., Tokyo, Japan) at end of exhalation. If feasible, left atrial pressure (LAP) was measured through the foramen ovale, else, pulmonary capillary wedge pressure (PCWP) was measured to calculate transpulmonary pressure. PAH was confirmed if the mean PAP was >25 mm Hg or the ratio of mean PAP and systemic arterial pressure (Pp/Ps) is >0.3 [18]. Qp was calculated using the Fick principle [22]. Rp was calculated either as the difference between mean PAP and LAP, or PCWP divided by Qp. Pulmonary stroke volume was calculated as Qp divided by the heart rate during examination. Cp was calculated as pulmonary stroke volume divided by pulmonary arterial pulse pressure (the difference between systolic and diastolic PAPs). The RC time was the product of Rp and Cp as described in the previous reports [19,21]. Since the measurement unit for Rp differed from that in the previous report, we calculated RC time according to the following equation: RC time = Rp × Cp × 60/1000 [21]. Birth earlier than 37 completed weeks of gestation was defined as preterm.

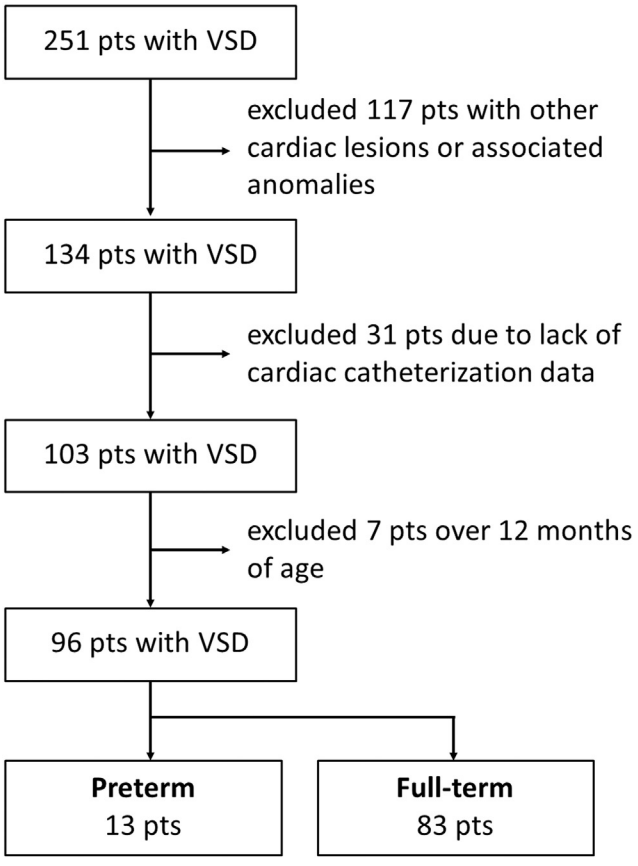


**Fig. 1.** Flowchart of the clinical study on patients with pulmonary artery hypertension associated with ventricular septal defect. Birth before 37 completed weeks of gestation is defined as preterm. pts, patients; VSD, ventricular septal defect.

### 2.3. Statistical analysis

Differences in the results were analyzed using the Mann-Whitney *U* test, Wilcoxon rank sum test, 2 × 2 Chi-square test, or covariance analysis, as appropriate. *P* values of <0.05 were considered significant. Correlation coefficients (r) were used for the association study. Analyses and calculations were performed using ystat2008.xls (Igakutosho-shuppan Ltd., Tokyo, Japan) or the analysis toolpack in Microsoft Office Excel add-in software.

## 3. Results

### 3.1. Total study population

The demographic data of patients is shown in Table 1; preterm infants ($n = 13$) accounted for 14% of the patients enrolled in the study. The preterm infants were delivered at median gestational age of 35 (26–36) weeks. Median birth weights in preterm and full-term infants were 2030 (470–2532) g and 2890 (2000–4358) g, respectively. Eight infants were below 2500 g and one was over 4000 g birth weight among full-term infants. Three infants were on oxygen supplement therapy before corrective surgery owing to upper airway obstruction or bronchopulmonary dysplasia (one infant in each group). No infant was treated or tested with pulmonary vasodilators such as a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist. Cardiac morphology findings revealed perimembranous VSD in 76 infants and subarterial VSD in 18 infants. There was no significant difference in maximum size of VSD between the two groups. Nine infants had a coexisting small ASD. In the full-term group, two patients underwent pulmonary artery banding before corrective surgery. Infants underwent corrective surgery at a median corrected gestational age of 13 (1–65) weeks. The catheterizations before and after corrective surgery were performed at a median corrected gestational of 11 (-1–47) weeks and 15 (4–67) weeks, respectively. The first and second catheterizations were performed 11 (1–343) days before and 14 (10–71) days after the corrective surgery, respectively. Three and 7 infants underwent pre- and postoperative catheter examination with pure oxygen supplementation, respectively. After surgery, 9 infants received nitric oxide inhalation in the intensive care unit. Oxygen supplement therapy at home was administered after discharge to 7 infants who had postoperative hypoxia (arterial saturation < 95%) or systolic PAP above 45 mm Hg (Table S1). All infants discontinued oxygen therapy within 6 months after corrective surgery, as electrocardiography and echocardiography showed improvement in PAH during the follow-up period. There was no in-hospital death but one death occurred among the full-term infants during the follow-up period as a result of acquired pulmonary venous obstruction. There were significant differences between the preterm and full-term infants with respect to gestational age (35 vs. 39 wk.; $p < 0.001$), birth weight (2030 vs. 2890 g; $p < 0.001$), proportion of the postoperative nitric oxide inhalation (31 vs. 6%; $p = 0.020$), and need for oxygen supplement therapy (23 vs. 5%; $p = 0.049$). Other demographic parameters had no significant differences between the two groups.

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