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ADC-FNN Online First, published on October 20, 2005 as 10.1136/adc.2005.079079

Echocardiographic assessment of early circulatory status in preterm infants with suspected intrauterine infection

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Key words: prenatal infection, cardiac output, pulmonary hypertension, organ blood flow, chronic lung disease

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Abstract

Objective: To assess early circulatory status in very low birth weight (VLBW) infants with suspected intrauterine infections.

Patients: 13 VLBW infants who were diagnosed as infants with prenatal infections because of an elevation of serum immunoglobulin M (IgM) at birth (infectious group), and 39 gestational age-birth weight-matched infants (control group).

Methods: Echocardiographic assessments were performed consecutively from birth to days 28 in all VLBW infants. Left ventricular output (LVO) and left ventricular stroke volume (LVSV) were measured using Doppler echocardiography. Pulsed-Doppler assessment of pulmonary artery pressure (PAP) was performed by the corrected ratio of the pulmonary artery acceleration time to the right ventricular ejection time (AT:RVET(c)). Evaluation of blood flow in the superior mesenteric artery (SMA) was also performed by Doppler ultrasound.

Results: Both mean values of LVO and LVSV in infectious group were significantly higher than those in control group at 12h(LVO; 188 vs 154 ml/kg/min) and 72h of life(LVO; 216 vs 173ml/kg/min). Pulsed-Doppler assessment of PAP showed that mean values of AT:RVET(c) in infectious group were significantly lower than those in control group at 48h, 96h, on days 14, and days 28. In the analysis of SMA flow velocities, both peak systolic velocities (Vs) and time-averaged velocities (TAV) decreased significantly in infectious group compared to those in control group at 24h, 36h, 96h, and on days 28.

Conclusions: VLBW infants with suspected prenatal infections showed unique status of circulation, namely high cardiac output, latency of high PAP, and low organ flow.

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Introduction

Prenatal intrauterine infections are known to cause premature labor and postnatal life-threatening infections in both newborns and their mothers[1][2]. These infections include maternal chorioamnionitis (CAM), which may induce increased release of various cytokines[1][2][3][4] and may be a major risk factor for postnatal septicemia, acute[3][5][6] and chronic[3][5][6] respiratory insufficiency. In extremely premature babies, prenatal infections are often associated with intractable chronic lung disease (CLD)[5][6][7][8], which might affect the infant's quality of life both in the neonatal period and in the later growing years of life.

The premature cardiovascular system in preterm infants often seems unstable and fragile especially in the early neonatal period. The myocardium of preterm infants may be easily influenced by hypoxia and ischemia, resulting in systemic and pulmonary hypoperfusion. Actually in critically ill very low birth weight (VLBW) infants, reduced left ventricular function[9], decreased left ventricular output (LVO)[10], and persistency of pulmonary hypertension[11] had been reported by several researchers. But, no one had yet reported early, longitudinal changes of LVO, pulmonary hypertension and organ blood flow in unstable VLBW infants who were suspected congenital infections.

Immunoglobulin M (IgM) circulates in serum as a pentamer of disulfide-linked immunoglobulin molecules. Although IgM is generated early in the immune response to antigen stimulation, its large size means that it cannot cross the placenta. Accordingly, high serum concentrations of IgM in newborn infant at birth are regarded as evidence that the fetus can generate IgM prenatally when exposed to antigen stimulation in the womb [12]. In preterm infants, elevated concentrations of serum IgM have been shown to be significantly associated with both chorioamnionitis and chronic respiratory insufficiency [7][8]. The current study was planned to evaluate early circulatory status by echocardiography in VLBW infants who were suspected of contracting intrauterine infection because of a significant elevation of serum IgM at birth.

Patients and Methods

Two-hundred and six VLBW infants weighing less than 1500 g were admitted to the neonatal intensive care unit at Kakogawa Municipal Hospital between September 2000 and December 2003. Of these babies, 43 small for gestational age (SGA) infants, 5 infants with congenital abnormalities, 60 multiple births and 10 infants who died within 48 h of birth were excluded from the study; the remaining 104 VLBW infants were included in the analysis. According to the conventional description [12], a serum IgM concentration >20 mg/dl at birth was regarded as significant. Of the 104 VLBW infants, 13 had suspected intrauterine infection with significantly elevated serum IgM concentrations (infectious group, n=13). Three gestational age-birth weight-matched controls were selected for each infant in the infectious group, and 39 infants were included in the analysis (control group,

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n=39). Gestational age was calculated from the mother's last menstrual day and confirmed by ultrasonography during pregnancy by obstetricians. Neonatal data were collected from nursery records. Chronic lung disease (CLD) was diagnosed in an infant with respiratory distress who required oxygen at 36 weeks corrected age. Septicemia was suspected from clinical findings and proved by positive blood culture. The study was approved by the local ethics committee at Kakogawa Municipal Hospital.

All VLBW infants admitted to the intensive care unit were examined routinely by serial ultrasonographic assessment of the heart by one author (MM). Assessments of the heart were made using a Hewlett-Packard SONOS 2000 with a 5.5/7.5 MHz transducer. The 7.5 MHz transducer was used for two-dimensional studies, while the 5.5 MHz transducer was employed for color-Doppler flow recordings. These examinations commenced 3 h after birth, with subsequent measurements at 12, 24, 36, 48, 72 and 96 h of life, and on days 5, 6, 7, 14, 21 and 28. On initial physical and echocardiographic examination, none of the 52 infants were found to have any congenital abnormalities. Each echocardiographic estimate was expressed as the mean value of three to five measurements. Left ventricular function was assessed by M-mode echocardiograms taken from the parasternal long axis view according to the method of Sahn et al [13]. Doppler measurements of LVO were assessed by the method of Alverson et al [14]. Left ventricular stroke volume (LVSV) was derived by dividing the LVO by the heart rate measured on electrocardiograms that were recorded simultaneously.

Doppler assessment of pulmonary artery pressure (PAP) was performed using the corrected ratio of the pulmonary artery acceleration time to the right ventricular ejection time (AT:RVET(c))[15]. A two-dimensional image of the main pulmonary artery was visualized via the parasternal short axis view. The pulsed Doppler sample volume was then placed distal to the pulmonary valve and the systolic Doppler waveform was recorded from the centre of the artery. AT was measured as the time interval between the waveform leaving the baseline and reaching its peak velocity. RVET was the time interval between the waveform leaving and returning to the baseline. The AT:RVET(c) was subsequently calculated by dividing the ratio of AT to RVET by the square root of the R-R interval from a simultaneous electrocardiogram tracing. Pulsed-Doppler measurement of the peak systolic velocity (Vs), end-diastolic velocity (Ved) and time-averaged velocity (TAV) of the superior mesenteric artery (SMA) was performed using the method described by Deeg et al[16]. Patent ductus arteriosus (PDA) was diagnosed from clinical symptoms and serial echocardiography.

Statistical analysis was performed using the computer statistics package SPSS 6.1J for Macintosh (SPSS Japan, Tokyo). The Mann Whitney U test was used for continuous variables, and Fisher's exact test for discrete variables. Longitudinal comparisons of continuous variables were made by two-way repeated measures analysis of variance (ANOVA) and post-hoc analysis. Differences with p values <0.05 were considered statistically significant.

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Results

The clinical features of the two groups are shown in Table 1 and Table 2.

Table 1 Comparisons of baseline characteristics between the two groups

	Infectious group (n=13)	Control group (n=39)	p Value
Gender (male/female)	**7/6**	**18/21**	**0.75**
Gestational age (weeks)	**29.7(2.2)**	**29.6(2.0)**	**0.86**
Birth weight (g)	**1232(194)**	**1221(191)**	**0.87**
1 minute Apgar	**7.2(1.7)**	**7.1(1.7)**	**0.80**
5 minute Apgar	**8.5(1.0)**	**8.5(0.8)**	**0.79**
Outborn patients	**3(23.1)**	**3(7.7)**	**0.32**
Cesarean section	**11(84.6)**	**37(94.9)**	**0.55**
Antenatal steroids	**4(44.4)**	**20(51.3)**	**0.34**
Clinical chorioamnionitis	**8(61.5)**	**9(23.1)**	**0.02***
Histological chorioamnionitis	**10(76.9)**	**6(15.4)**	**<0.0001*****

*p<0.05, ***P<0.001
Values are mean (SD) or numbers (percentages).

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Table 2 Comparisons of subsequent courses between the two groups

	Infectious group (n=13)	Control group (n=39)	p Value
Mechanical ventilation	**6(46.2)**	**24(61.5)**	**0.35**
Times of ventilation# (hours)	**31(49)**	**82(178)**	**0.11**
Days of oxygen treatment$ (days)	**45(34)**	**34(21)**	**0.37**
Surfactant	**6(46.2)**	**24(61.5)**	**0.35**
Home oxygen therapy	**2(15.4)**	**0(0)**	**0.10**
(Laboratory findings)			
Arterial pH	**7.28(0.10)**	**7.31(0.09)**	**0.61**
Arterial base deficit (mmol/l)	**4.1(3.6)**	**4.1(2.7)**	**0.86**
First CPK (IU/l)	**160(108)**	**195(145)**	**0.51**
First WBC ($x10^9$/l)	**24.5(13.1)**	**10.7(6.1)**	**<0.0001*** **
First hemoglobin (g/dl)	**14.9(1.4)**	**15.5(2.4)**	**0.43**
First IgM (mg/dl)	**77.5(51.2)**	**3.9(4.3)**	**<0.0001*** **
First CRP (mg/dl)	**0.28(0.51)**	**0.02(0.04)**	**0.002** **

**p<0.01, ***p<0.001
Values are mean (SD) or numbers (percentages).
#...mean length of time only in infants who were successfully extubated
$...mean length of day only in infants who were discharged without oxygen

There were no significant differences in clinical profiles between the two groups. Both rates of clinical and histological CAM in the infectious group were significantly higher than those in the control groups. Mothers of 12 infants in the infectious group showed clinical or histological CAM, except one mother who gave birth at home. Comparisons of laboratory findings showed that both mean whole white blood cell counts (WBC) and serum C-reactive protein (CRP) levels in the infectious group were significantly higher than those in the control group. Initiation of home oxygen therapy at hospital discharge was required for two infants in the infectious group.

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Table 3 Comparison of adverse clinical events between the two groups

	Infectious group (n=13)	Control group (n=39)	p Value
Pulmonary hemorrhage	**1(7.7)**	**2(5.1)**	**>0.99**
Pneumothorax	**0(0)**	**2(5.1)**	**>0.99**
Intraventricular hemorrhage	**1(7.7)**	**4(10.3)**	**>0.99**
Periventricular leukomalacia	**1(7.7)**	**1(2.6)**	**>0.99**
Septicemia	**5(38.5)**	**7(17.9)**	**0.15**
Retinopathy of prematurity requiring photocoagulation	**2(15.4)**	**3(7.7)**	**0.79**
Chronic lung disease	**4(30.8)**	**1(2.6)**	**0.01****

**p<0.01
Values are numbers (percentages).

The incidence of CLD in the infectious group was significantly higher than that in the control group (Table 3). All four infants with CLD in the infectious group showed radiological findings on chest radiographs characterized by diffuse small cystic translucencies, which indicated congenital infections. The occurrence of septicemia seemed to be higher in the infectious group, but the difference was not statistically significant. Figure 1 showed longitudinal comparisons of echocardiographically detected PDA. The rate of PDA by echocardiography was the same at all points of assessment between the two groups.

Serial echocardiographic assessment revealed no difference in the time-course of dimension of left ventricle, left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular ejection fraction, left and right ventricular systolic time intervals, and heart rate between the two groups (data not shown).

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Table 4 Longitudinal comparisons of mean (SD) values of left ventricular output between the two groups

	Infectious group (n=13)	Control group (n=39)	p Value
Postnatal age			
3h	**222.5(55.6)**	**231.6(70.6)**	**0.73**
12h	**187.8(50.9)**	**153.7(56.5)**	**0.02***
24h	**197.2(52.4)**	**164.3(57.9)**	**0.06**
36h	**192.3(43.6)**	**177.1(50.8)**	**0.21**
48h	**178.2(47.1)**	**178.5(46.7)**	**0.86**
72h	**216.1(69.3)**	**173.2(57.9)**	**0.03***
96h	**184.4(94.5)**	**178.8(60.7)**	**0.68**
Days 5	**205.5(50.9)**	**179.6(53.7)**	**0.07**
Days 6	**203.9(48.6)**	**181.7(43.8)**	**0.17**
Days 7	**189.5(52.5)**	**171.4(43.6)**	**0.30**
Days14	**191.9(62.0)**	**168.2(49.8)**	**0.24**
Days21	**199.8(58.7)**	**171.2(45.1)**	**0.13**
Days28	**182.0(58.6)**	**169.9(51.1)**	**0.62**

*$p<0.05$ (ml/kg/min)

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Table 5 Longitudinal comparisons of mean (SD) values of left ventricular stroke volume between the two groups

	Infectious group (n=13)	Control group (n=39)	p Value
Postnatal age			
3h	**1.50(0.47)**	**1.47(0.46)**	**0.95**
12h	**1.37(0.39)**	**1.10(0.43)**	**0.02***
24h	**1.50(0.45)**	**1.18(0.45)**	**0.03***
36h	**1.41(0.33)**	**1.26(0.37)**	**0.17**
48h	**1.28(0.30)**	**1.24(0.36)**	**0.71**
72h	**1.54(0.44)**	**1.20(0.38)**	**0.02***
96h	**1.31(0.65)**	**1.26(0.44)**	**0.95**
Days 5	**1.50(0.39)**	**1.31(0.39)**	**0.08**
Days 6	**1.51(0.34)**	**1.31(0.35)**	**0.07**
Days 7	**1.41(0.33)**	**1.27(0.35)**	**0.13**
Days14	**1.29(0.35)**	**1.19(0.40)**	**0.30**
Days21	**1.37(0.41)**	**1.14(0.31)**	**0.06**
Days28	**1.28(0.57)**	**1.13(0.32)**	**0.68**

*$p<0.05$ (ml/kg)

Both mean values of LVO and LVSV in the infectious group were significantly higher than those in the control group within 28 days of life (Table 3 and Table 4). There were no differences in the course of arterial blood pressure between the two groups (data not shown).

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Table 6 Longitudinal comparisons of mean (SD) values of corrected ratio of the pulmonary artery acceleration time to the right ventricular ejection time [AT:RVET©] between the two groups

	Infectious group (n=13)	Control group (n=39)	p Value
Postnatal age			
3h	**0.44(0.12)**	**0.40(0.11)**	**0.31**
12h	**0.38(0.09)**	**0.41(0.10)**	**0.51**
24h	**0.40(0.07)**	**0.43(0.09)**	**0.27**
36h	**0.38(0.08)**	**0.44(0.08)**	**0.10**
48h	**0.38(0.06)**	**0.46(0.10)**	**0.01***
72h	**0.39(0.06)**	**0.43(0.09)**	**0.21**
96h	**0.39(0.08)**	**0.45(0.08)**	**0.04***
Days 5	**0.40(0.10)**	**0.43(0.07)**	**0.50**
Days 6	**0.40(0.12)**	**0.43(0.10)**	**0.14**
Days 7	**0.42(0.10)**	**0.42(0.09)**	**0.97**
Days14	**0.41(0.08)**	**0.48(0.10)**	**0.04***
Days21	**0.44(0.07)**	**0.49(0.09)**	**0.12**
Days28	**0.42(0.12)**	**0.48(0.09)**	**0.04***

*$p<0.05$

Table 5 shows the longitudinal comparison of AT:RVET(c) between the two groups. Mean values of AT:RVET(c) in the infectious group were significantly lower than those in the control group. Comparisons of the time-course of SMA flow velocities are shown in Fig. 2. Both mean values of Vs and TAV in the infectious group were significantly lower than those in the control group within 28 days of life, while there was no difference in values for Ved and resistance index (RI) between the two groups.

Discussion

The present study showed that values of LVO and LVSV in infants who had suspected congenital infections due to elevated concentrations of serum IgM at birth remained high throughout the early neonatal period. Although the true cause of this high-output status in the early neonatal period remains unclear, a significant elevation of both WBC and CRP in infants in the infectious group suggests that they had already suffered from systemic inflammation at birth. Many investigators have reported that intrauterine, amniotic fluid

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infection results in increased release of various inflammatory cytokines[11][12][13][14]. Some of these cytokines may induce a significant increase in cardiac output directly, or by stimulating other mediators such as cortisol or prostaglandins[3][4]. From the current study, it is suggested that the high value of LVO in VLBW infants with intrauterine infection in the early neonatal period might result from a continuation of the fetal systemic inflammatory response.

The type of prenatal infections that lead to acute respiratory disease in premature infants is still controversial[1][4][5][17][18], but it is now widely established that intrauterine infection is a major risk factor for chronic lung instability in later life[3][5][6]. Fujimura et al. reported that many preterm infants with maternal CAM who showed elevated IgM concentrations at birth developed Wilson-Mikity syndrome, which is known to be a unique and intractable form of CLD[7][8]. The incidence of CLD in infants in the infectious group in the current study was significantly high, and all these CLD infants might have similar clinical and radiological findings to those described by Fujimura et al[7][8]. Oxygen and high airway pressure due to long-term mechanical ventilation is known to injure and alter the pulmonary vasculature in premature infants with CLD[19][20]. It is generally established that these acquired pulmonary vascular lesions may lead to an elevation in pulmonary vascular resistance through narrowing of the vessel diameter and decreased vascular compliance, and the development of pulmonary hypertension in CLD infants[19][20].

Direct assessment of PAP by cardiac catheterization is difficult in premature infants, but Doppler echocardiography has provided physicians with a noninvasive method by which PAP can be measured. AT:RVET, which can be estimated noninvasively from Doppler pulmonary artery waveforms, has been shown to correlate negatively with PAP in adults[21], children, older infants, and recently, premature infants[15][23][24][25][26]. Some investigators have encountered several methodological problems in the clinical assessment of AT:RVET. Skinner et al. suggested that AT:RVET values in newborn infants with persistent pulmonary hypertension bear little relation to PAP assessed by other methods, and might be of little value because of poor reproducibility[23]. In our previous studies[24], it was also reported that AT:RVET values in VLBW infants depended significantly upon gestational age, and did not correlate well with PAP assessed by tricuspid regurgitation in the early neonatal period.

However, the importance of AT:RVET values in the management of premature CLD infants is supported by many authors[25][26][27]. Several studies have shown that early pulmonary hypertension in premature infants, as assessed by AT:RVET, is a good predictor of late onset CLD[26][27]. In this report, it was found that AT:RVET(c) values in infants with prenatal infections were lower than those in controls during the first month of life, and these changes might resemble the previously reported course of AT:RVET in CLD infants[25][27]. Although it remains to be investigated whether AT:RVET(c) values really reflect PAP in premature infants, it is suggested that the low values of AT:RVET(c) within 28 days of life in VLBW infants with prenatal infections represent latency of pulmonary

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hypertension. In the infectious group, four of 13 infants went on to develop CLD, but the remaining nine infants had no dependency on oxygen in the later neonatal period. If AT:RVET(c) correlated inversely with PAP in premature infants, the infants with prenatal infections might have pulmonary hypertension for several weeks after birth irrespective of their dependency on oxygen, which could be detected only by assessment of AT:RVET(c) using serial Doppler echocardiography.

In this study, a significant decrease in SMA flow velocity was demonstrated in infants with suspected prenatal infections within 28 days of life[16][27][28][29]. Several authors have described how gastrointestinal blood flow velocity in full-term and preterm neonates, as assessed by ultrasound, might be influenced by asphyxia[27], intrauterine growth retardation (IUGR), congenital heart disease, necrotizing enterocolitis[16][28], and cystic periventricular leukomalacia. Recently, Kempley et al. showed that in preterm neonates with perinatal sepsis, the flow velocity in the celiac artery (CA) increased while the pulsatility index of both the CA and SMA decreased, suggesting the possibility of splanchnic hemodynamic disturbance caused by inflammation resulting from the early infectious event[29]. In the current analysis, the flow velocity of SMA decreased in infants with prenatal infections, and the RI values of SMA seemed to be similar to those in controls. These findings may appear to be inconsistent with the report of Kempley et al[29]. Their assessment of Doppler flow velocities, however, appeared to be made at only single point within 24 h of birth, and to differ significantly from our longitudinal assessment from birth to 28 days. Akinbi et al. reported a significant reduction in SMA flow velocities in proportion to the severity of infant's asphyxia[27]. It is likely that the significant decrease in SMA flow velocity in our infants with suspected prenatal infections might be associated with intrauterine fetal exposure to ischemia and hypoxia caused by the fetal inflammatory response.

In summary, left ventricular output in infants with suspected intrauterine infections because of an elevation of serum IgM at birth proved to be significantly higher in the early neonatal period, while both AT:RVET values and SMA flow velocities in the infectious infants were decreased significantly compared to those in controls. It is suggested that this unique status of the systemic/pulmonary circulation, namely high output, high PAP and low organ flow, might be caused by a continuation of the fetal inflammatory response-derivedincrease in release of cytokines. These findings in premature infants with suspected intrauterine infection may be of value in the management of early cardiopulmonary circulation.

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Competing Interests

Some investigators previously reported early cardiac output in preterm infants. Otherwise, studies in pulmonary hypertension of preterm infants using AT:RVET might have increased. Several investigators also reported assessment of visceral flow velocities in preterm infants using Doppler ultrasound. In this present study, we add three new points of findings as follows: high output status, continuation of pulmonary hypertension, and low organ blood flow in preterm infants with suspected intrauterine infection. The last finding may be somewhat inconsistent with the result reported by Dr. Kempley.

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What is already known on this topic

There was no report that investigated both early values of LVO and AT: RVET in infants with intrauterine infections.

Recently, it had been shown that in preterm neonates with perinatal sepsis, the flow velocity in the celiac artery.

What this study adds

Early values of LVO in infants with suspected intrauterine infections appeared to be significantly higher than those in controls.

Mean values of AT: RVET(c) in infants with intrauterine infections were significantly lower than those in controls.

In the analysis of SMA flow velocities, both peak systolic velocities and time-averaged velocities decreased significantly in infants with intrauterine infections compared to those in controls.

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Figure legends

Figure 1
Longitudinal comparisons of echocardiographically detectable PDA between thetwo groups in the early neonatal period.

Figure 2
Longitudinal comparisons of mean (SE) values of peak systolic velocity (Vs) and time-averaged velocity (TAV) in superior mesenteric artery (SMA) between the two groups in the early neonatal period. *$p<0.05$, **$p<0.01$

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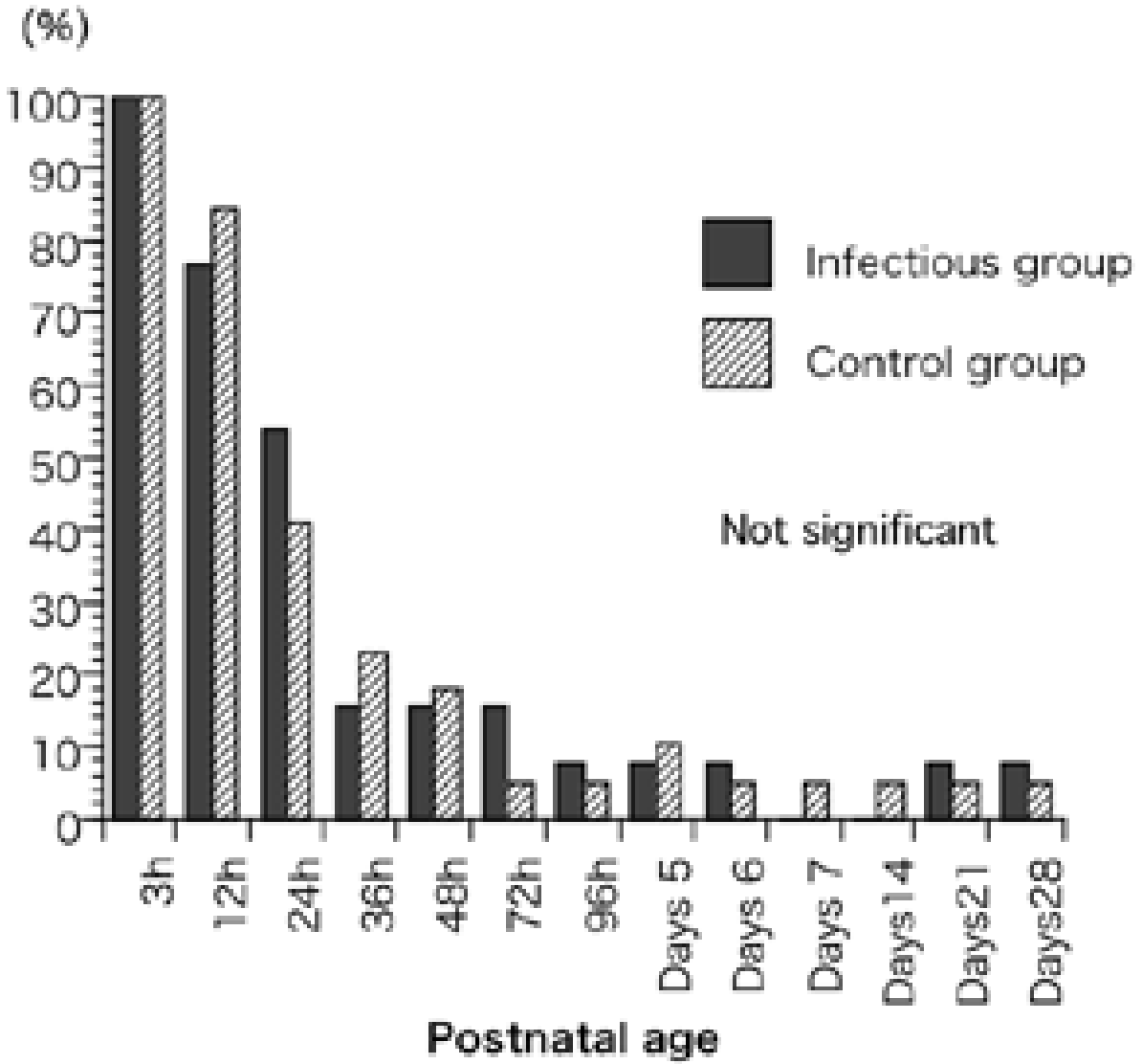

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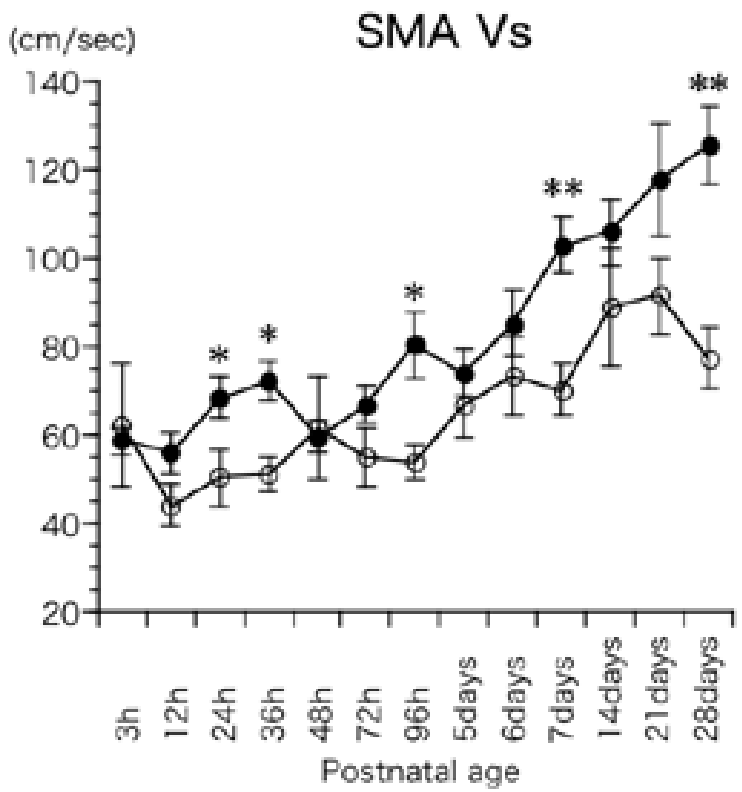

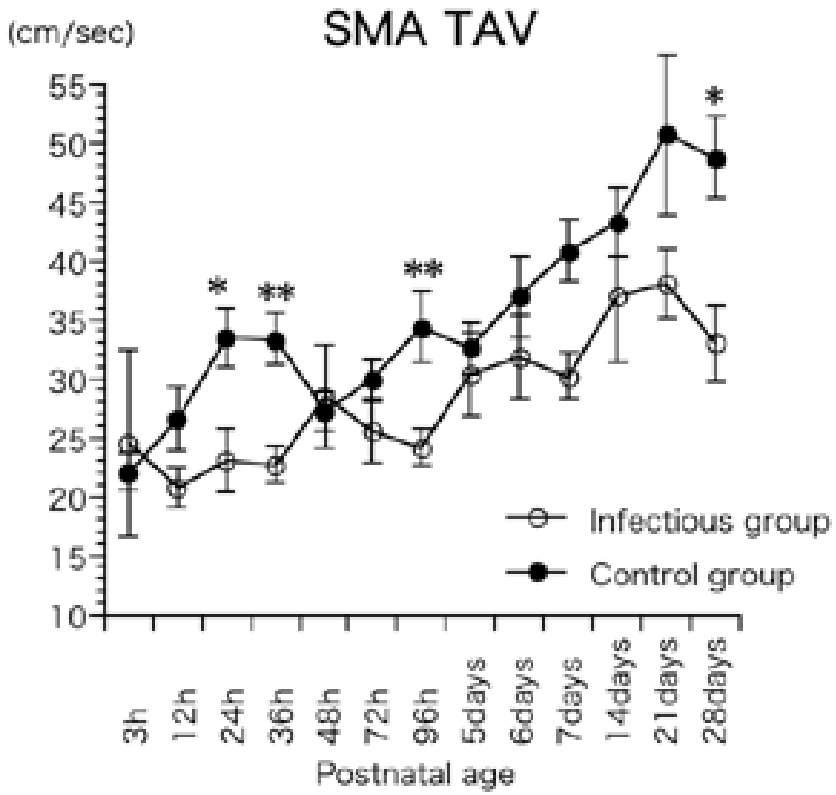

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Echocardiographic assessment of early circulatory status in preterm infants with suspected intrauterine infection

Masanori Murase and Akihito Ishida

Arch Dis Child Fetal Neonatal Ed published online October 20, 2005

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