

## ORIGINAL ARTICLE

## The perfusion index derived from a pulse oximeter for predicting low superior vena cava flow in very low birth weight infants

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**Objective:** Superior vena cava (SVC) flow is used as an index for evaluating systemic blood flow in neonates. Thus far, several reports have shown that low SVC flow is a risk factor for intraventricular hemorrhage (IVH) in the preterm infant. Therefore, it is likely to be a useful index in the management of the preterm infant. The perfusion index (PI) derived from a pulse oximeter is a marker that allows noninvasive and continuous monitoring of peripheral perfusion. The objective of this paper was to determine the accuracy of the PI for detecting low SVC flow in very low birth weight infants born before 32 weeks of gestation.

**Study Design:** We studied the correlation between PI and SVC flow 0 to 72 h after birth in very low birth weight infants born before 32 weeks of gestation. The best cut-off value for low SVC flow was calculated from the respective receiver-operating characteristic curves.

**Result:** A positive correlation was found between the PI and SVC flow ( $r = 0.509$ ,  $P < 0.001$ ). The best cut-off value for the PI to detect low SVC flow was 0.44 (sensitivity 87.5%, specificity 86.3%, positive predictive value 38.9%, negative predictive value 98.6%).

**Conclusion:** This study found that the PI was associated with SVC flow, and it was a useful index for detecting low SVC flow in very low birth weight infants born before 32 weeks of gestation. Therefore, use of the PI should be evaluated in the cardiovascular management of the preterm infant.

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**Keywords:** peripheral perfusion; preterm infant; intraventricular hemorrhage; systemic blood flow; noninvasive monitoring

## Introduction

Evaluation of systemic blood flow is useful in the cardiovascular management of neonates. Until date, several methods for

evaluating systemic blood flow in such infants have been published.<sup>1–4</sup> Measurement of systemic blood flow at the left and right ventricular outflow tracts is commonly used; however, in the early postnatal period, these methods of measurement may overestimate the systemic blood flow because of the presence of patent ductus arteriosus (PDA)<sup>3,5</sup> and patent foramen ovale in newborn infants.<sup>3</sup> On the other hand, superior vena cava (SVC) flow enables systemic blood flow to be evaluated even in infants with PDA and patent foramen ovale.<sup>6</sup> Several published reports have shown that low SVC flow is a risk factor for intraventricular hemorrhage (IVH) in preterm infants.<sup>7–9</sup> Although there is no evidence, suggesting that treating low SVC flow improves outcome, SVC flow can be a potentially useful index for the management of the preterm infant. However, the measurement is not easily performed. Kluckow and Evans<sup>6</sup> reported that interobserver variability was 14%, and this variability may increase among untrained observers. In addition, a general principle in the management of preterm infants is minimal handling; even echocardiography can prove stressful to such infants.

Osborn *et al.*<sup>10</sup> studied the correlation between SVC flow and several noninvasive and convenient bedside tests such as blood pressure, capillary refill time and central-peripheral temperature difference. They found that central-peripheral temperature difference did not correlate significantly with SVC flow, and that capillary refill time and blood pressure were imperfect bedside tests for detecting low SVC flow.

The perfusion index (PI) is derived from the photoelectric plethysmographic signal of a pulse oximeter and is calculated as the ratio of the pulsatile component (arterial compartment) and the nonpulsatile component (other tissues; venous blood, bone, connective tissue) of the light reaching the device's detector. PI has been used as a marker of peripheral perfusion. Lima *et al.*<sup>11</sup> reported that low PI was associated with low peripheral perfusion. De Felice *et al.*<sup>12</sup> reported that the PI was a useful predictor of high illness severity in neonates.

If PI is associated with SVC flow, PI can allow continuous and noninvasive monitoring of systemic blood flow. The objective of this paper was to determine the accuracy of the PI for detecting

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low SVC flow in very low birth weight infants born before 32 weeks of gestation.

## Methods

We conducted a prospective cohort observational study at a neonatal intensive care unit (National Center for Child Health and Development, Tokyo, Japan) between September 2006 and May 2007. We included very low birth weight infants born before 32 weeks of gestation at our hospital. The infants were excluded if parental consent was refused or if malformation syndrome, congenital heart disease (except PDA and patent foramen ovale), edema or excessive movements were present.

Superior vena cava flow measurement was performed by echocardiography using the method described by Kluckow and Evans.<sup>6</sup> The data were obtained at 0 to 6, 6 to 24, 24 to 48 and 48 to 72 h of age. Low SVC flow was defined as  $<40 \text{ ml kg}^{-1} \text{ min}^{-1}$ , according to a previous report.<sup>7-9</sup> All echocardiographic measurements were performed by a neonatologist trained in pediatric echocardiography.

The PI derived from a pulse oximeter (Masimo SET Radical, Masimo, Irvine, CA, USA) was monitored continuously from the time the infant was admitted to the neonatal intensive care unit. The probe (LNOP NeoPt-L) was applied on one foot without a Posey wrap. PI values were obtained from a spot measurement just before the measurement of SVC velocity time integral; however, SVC flow measurements were not blinded to PI.

We measured maximum diastolic flow velocity of the left pulmonary artery using echocardiography to evaluate the degree of ductal shunting and examined ultrasonography to evaluate IVH (Papile classification). In addition, we measured skin temperature using an electronic thermometer placed on the back of the neck to evaluate the effect on the correlation between SVC flow and PI. We defined a large PDA as diastolic flow velocity of the left pulmonary artery  $>0.3 \text{ m s}^{-1}$ ,<sup>13</sup> higher skin temperature as  $\geq 37^\circ\text{C}$ , and lower skin temperature as  $<37^\circ\text{C}$ .

Correlations between the PI and the SVC flow were assessed using Pearson's correlation coefficient. The best cut-off value for low SVC flow was calculated from the respective receiver-operating characteristic curves. A good cut-off value is one that has small false-positive and false-negative rates across a range of cut-off values, and is represented by the point nearest to the upper left corner of the graph.

All data were analyzed using a statistical software program (Stat Flex for Windows Ver.6.0, Artec, Osaka, Japan). Statistical significance was defined as a *P*-value of  $<0.05$ .

## Results

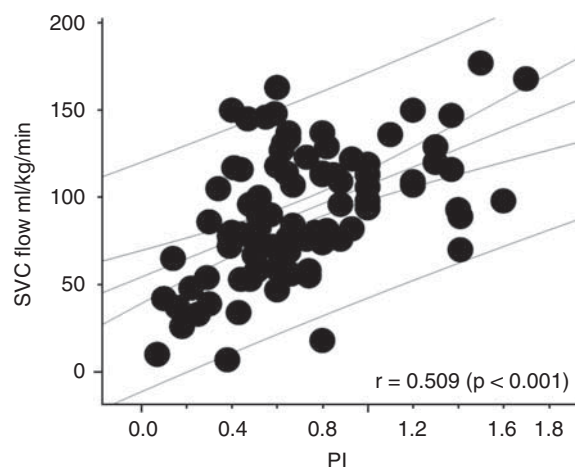
Between September 2006 and May 2007, 30 infants from 22 to 32 weeks of gestational age were admitted to the neonatal intensive

care unit. Informed consent was obtained for all the infants. Three infants were excluded because they met our exclusion criteria (two had excessive movement and one had hypoplastic left heart syndrome). The mean gestational age was  $28.6 \pm 2.2$  weeks (range, 23.4 to 31.9 weeks) and the mean birth weight was  $982 \pm 298 \text{ g}$  (range, 366 to 1462 g). The median Apgar score was 7 at 5 min after birth. As major complications, 22 infants had respiratory distress syndrome, 1 had necrotizing enterocolitis, 3 had IVH (grade 1, one infant; grade 4, two infants) and 1 had periventricular leukomalacia.

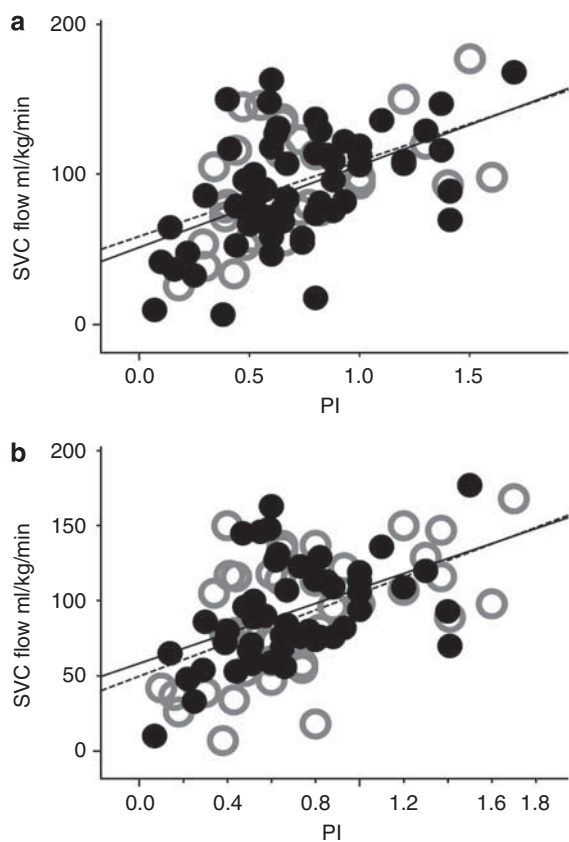
Superior vena cava flow and PI values were obtained from 24 infants at 0 to 6 h, 22 infants at 6 to 24 h, 22 infants at 24 to 48 h and 20 infants at 48 to 72 h. The total number of measurements was 88; and the median measuring time was 23 h of age (range, 1 to 71 h). The median measuring time in each period was 3 h (range, 1 to 5 h), 17.5 h (range, 7 to 23 h), 42 h (range, 26 to 47 h) and 67 h (range, 54 to 71 h), respectively.

The median SVC flow values were  $76.5 \text{ ml kg}^{-1} \text{ min}^{-1}$  (range, 6.9 to 150) at 0 to 6 h after birth,  $70.5 \text{ ml kg}^{-1} \text{ min}^{-1}$  (range, 10 to 177) at 6 to 24 h,  $95 \text{ ml kg}^{-1} \text{ min}^{-1}$  (range, 53 to 168) at 24 to 48 h and  $111 \text{ ml kg}^{-1} \text{ min}^{-1}$  (range, 65 to 148) at 48 to 72 h. The median PI values were 0.60 (range, 0.10 to 1.60) at 0 to 6 h after birth, 0.51 (range, 0.07 to 1.50) at 6 to 24 h, 0.70 (range, 0.40 to 1.70) at 24 to 48 h and 0.80 (range, 0.14 to 1.41) at 48 to 72 h.

Seventy-three of the 88 measurements were obtained from infants with PDA. The median diastolic flow velocity of the left pulmonary artery of infants with PDA was  $0.28 \text{ m s}^{-1}$  (range, 0 to  $0.72 \text{ m s}^{-1}$ ). The median skin temperature was  $36.9^\circ\text{C}$  (range,  $35.1$  to  $38.2^\circ\text{C}$ ). Eight of the 88 measurements were obtained from infants undergoing nasal continuous positive airway pressure treatment, and the remaining measurements were obtained from infants receiving intermittent mandatory ventilation or high-frequency oscillation ventilation.



**Figure 1** A scatter plot of superior vena cava (SVC) flow against the perfusion index (PI) for all observations, with regression line ( $y = 54.32 + 52.51x$ ), confidence limits (95%) for the regression line, and 95% limits for estimating the PI for a given SVC flow value.



**Figure 2** (a) A scatter plot of superior vena cava (SVC) flow against the perfusion index (PI) for infants with (open circles) or without (closed circles) large patent ductus arteriosus (PDA). The dotted line represents the regression line of infants with large PDA ( $y = 58.99 + 49.82x$ ,  $r = 0.499$ , 95% confidence interval (0.170 to 0.729)). The solid line represents infants without large PDA ( $y = 51.64 + 54.23x$ ,  $r = 0.517$ , 95% confidence interval (0.298 to 0.683)). (b) A scatter plot of SVC flow against the PI for infants with higher skin temperature (open circles) or lower skin temperature (closed circles). The dotted line represents the regression line of infants with higher skin temperature ( $y = 49.73 + 55.09x$ ,  $r = 0.5412$ , 95% confidence interval (0.273 to 0.732)). The solid line represents infants with lower skin temperature ( $y = 58.30 + 49.91x$ ,  $r = 0.4755$ , 95% confidence interval (0.224 to 0.668)).

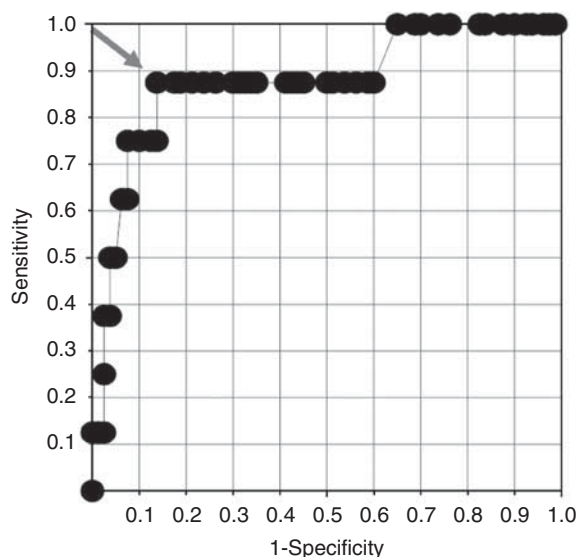
A positive correlation was found between the PI and SVC flow for all measurements ( $r = 0.509$ , 95% confidence interval: 0.335 to 0.649,  $P < 0.001$ ) (Figure 1). A positive correlation was found between PI and SVC flow both in infants with and in those without a large PDA (Figure 2a). A positive correlation was also found between PI and SVC flow at both lower and higher skin temperature (Figure 2b). No significant difference was seen in the regression lines between infants with and without a large PDA and those with lower and higher skin temperature. Eight infants in the study had low SVC flow (Table 1). The best cut-off value for detection of low SVC flow in the PI was 0.44 (sensitivity 87.5%, 95% confidence interval: 47.4 to 99.7%; specificity 86.3%, 95% confidence interval: 76.7 to 92.9%; positive predictive value 38.9%, 95% confidence interval: 17.3 to 64.5%; negative predictive value

**Table 1** Two-way contingency table

	Low SVC flow <sup>a</sup>		Total
	Positive	Negative	
PI < 0.44	7	11	18
PI ≥ 0.44	1	69	70
Total	8	80	88

Abbreviations: PI, perfusion index; SVC, superior vena cava.

<sup>a</sup>Low SVC flow is defined as  $< 40 \text{ ml kg}^{-1} \text{ min}^{-1}$ .



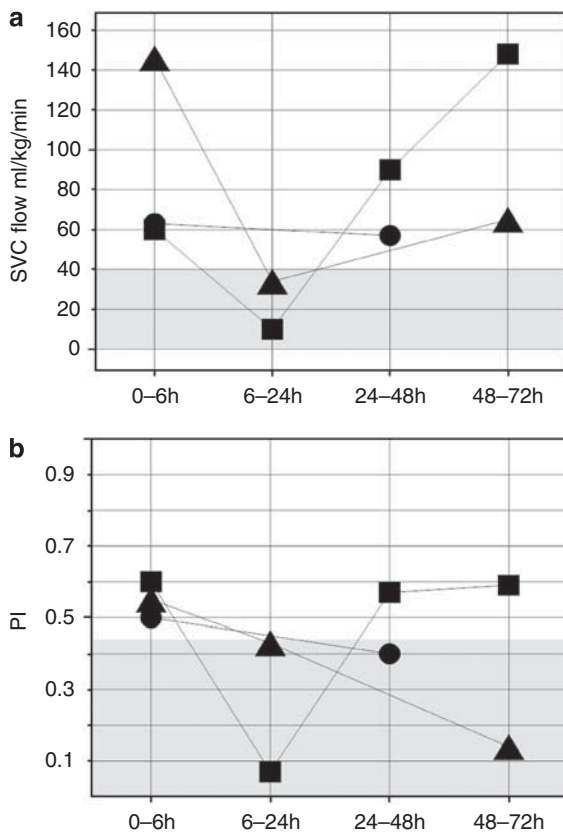
**Figure 3** The receiver-operating characteristic (ROC) curves for the PI. The best cut-off value (arrow) for detecting low superior vena cava (SVC) flow in the perfusion index (PI) was 0.44 (sensitivity 87.5%, specificity 86.3%, positive predictive value 38.9%, negative predictive value 98.6%). The area under the ROC was 0.877 (95% confidence interval: 0.701 to 1.000)

98.6%, 95% confidence interval: 92.3 to 99.9%; likelihood ratio positive 6.36, 95% confidence interval: 3.46 to 11.69; likelihood ratio negative 0.145, 95% confidence interval: 0.02 to 0.91). The area under the receiver-operating characteristic was 0.877 (95% confidence interval: 0.701 to 1.000) (Figure 3).

In our study population, three infants developed IVH. One infant had grade 1 IVH at 50 h of age, and two infants had grade 4 IVH at 29 and 34 h of age, respectively. Although the infant with grade 1 IVH did not have low SVC flow, PI was  $< 0.44$ ; however, both infants with grade 4 IVH had low SVC flow and PI  $< 0.44$  before developing IVH (Figures 4a and b).

### Discussion

We studied the association between the PI, which allows noninvasive and continuous monitoring, and SVC flow. Both the PI and SVC flow in very low birth weight infants born before 32 weeks of gestation had the lowest value at 6 to 24 h after birth, after



**Figure 4** Individual change in superior vena cava (SVC) flow (a) and perfusion index (PI) (b) in three infants with intraventricular hemorrhage (IVH). The shaded area represents low SVC flow ( $<40 \text{ ml kg}^{-1} \text{ min}^{-1}$ ) and  $\text{PI} < 0.44$ , respectively. The infant represented by the circle (●) developed grade 1 IVH at 50 h of age, and infants represented by the square (■) and the triangle (▲) developed grade 4 IVH at 29 and 34 h of age, respectively.

which their values started to increase. Our study showed that the PI correlated significantly with SVC flow, and it was also a useful index for detecting low SVC flow.

De Felice *et al.*<sup>12</sup> reported that the PI was a useful predictor for high illness severity in neonates (with a mean gestational age of 34.7 weeks and a mean birth weight of 2310 g). The mean PI value in the study was 1.54. Zaramella *et al.*<sup>14</sup> reported that the mean PI in healthy infants (with a mean gestational age of 39.1 weeks and a mean birth weight of 3474 g) was 1.26, and that the PI correlated with calf muscle perfusion measured by near-infrared spectroscopy. Furthermore, Granelli *et al.*<sup>15</sup> reported that a  $\text{PI} < 0.70$  might indicate illness, and it might be a useful addition in the early detection of left heart obstruction. The PI in our study population was lower in comparison with that reported by De Felice *et al.*, Zaramella *et al.* and Granelli *et al.* This may be attributable to the fact that our study population included only very low birth weight infants born before 32 weeks of gestation. The myocardium of a preterm infant is immature and the cardiovascular system of this infant is adapted to the low-resistance intrauterine environment.<sup>16</sup> Therefore, a preterm infant in the early postnatal period may have

a poorer circulation in comparison with a term infant. Alternatively, the PI can be defined as the ratio of the pulsatile to the nonpulsatile components; therefore, when the venous blood, bone and connective tissue representing the nonpulsatile components are relatively greater than the arterial components, the PI drops to a lower value. This suggests that very low birth weight infants may have more of the nonpulsatile components in comparison with term infants.

Most very low birth weight infants have PDA in the early postnatal period. In our study, 73 of 88 measurements (83%) were evaluated in infants with PDA. It is important to consider PDA when evaluating the correlation between SVC flow and PI in this population, because infants with hemodynamically significant PDA can have a bounding pulse, which can increase PI more than true perfusion by increasing the pulsatile component. However, our study suggests that the PI is associated with SVC flow regardless of the degree of PDA.

Changes in PI can occur as a result of local vasoconstriction (decrease in PI) or vasodilation (increase in PI) in the skin at the monitoring site.<sup>17</sup> Therefore, PI can be affected by skin temperature; however, our study suggests that skin temperature of infants in an incubator has no influence on the correlation between SVC flow and PI.

Superior vena cava flow represents the flow that returns from the upper body. In our study, the sensors for measuring the PI were applied on one foot rather than on an arm. This placement was necessary because most infants in our neonatal intensive care unit had peripherally inserted central catheters, peripheral catheters or arterial catheters inserted in the arm, making it difficult to affix the sensors to the arm. The study by Granelli *et al.*<sup>15</sup> found that the PI measured on the right hand is similar to that measured on one foot; however, the problem of sensor placement is a limitation of our study.

The PI values were recorded just before SVC flow was measured in this study. The PI value fluctuates widely because of changes in the venous pulse caused by movement. Therefore, the mean PI value obtained over a 30- or 60-min period may be more reliable than the value obtained at a single time point.

A PI of  $< 0.44$  had good sensitivity, good specificity and negative predictive value for detecting low SVC flow; however, the positive predictive value was 38.9%. This indicates that nearly half the infants with a  $\text{PI} < 0.44$  did not have low SVC flow. In preterm infants, excess water intake is a risk factor for necrotizing enterocolitis, PDA, bronchopulmonary dysplasia and death.<sup>18,19</sup> If volume expansion is performed to improve circulation in all preterm infants with a PI of  $< 0.44$ , then the incidence of the preceding complications may increase.

Previous reports have shown that low SVC flow in the first days of life is associated with IVH.<sup>7-9</sup> Two infants had grade 4 IVH in our study, and both had low SVC flow and  $\text{PI} < 0.44$  within 24 h of life and before developing IVH. Our results are similar to those



reported by other investigators. Furthermore, all three infants with IVH, including grade 1, had  $PI < 0.44$  within 24 h of life and before developing IVH. This finding may suggest an association between PI and IVH. However, our study was not designed to investigate correlations between PI and IVH. To date, the association between PI and IVH is not well understood. Therefore, we propose that the PI should be used only as a screening test for low SVC flow.

There were some limitations to our study. We studied 88 measurements; however, the number of infants was small. The reference value of PI in very low birth weight infants has not been reported, and the repeatability and reliability of PI in the population is likewise unclear. We also did not evaluate the problem of PI in our study. Furthermore, as noted above, another limitation of our study relates to whether the probe placement for pulse oximetry was appropriate.

In conclusion, we found that the PI correlated with SVC flow, and it was a useful index for detecting low SVC flow in very low birth weight infants born before 32 weeks of gestation. However, additional studies are required to provide further validation of this method in another sample and investigate the use of PI in detecting low systemic blood flow without a prespecified intervention protocol.

### Conflict of interest

We used the pulse oximeter (Masimo SET<sup>®</sup>; Radical, Masimo) and the probe (LNOP<sup>®</sup>; NeoPt-L); however, none of the authors have a financial relationship with Masimo.

### References

- 1 Alverson DC, Eldridge M, Dillon T, Yabek SM, Berman Jr W. Noninvasive pulsed Doppler determination of cardiac output in neonates and children. *J Pediatr* 1982; **101**: 46–50.
- 2 Tsai-Goodman B, Martin RP, Marlow N, Skinner JR. The repeatability of echocardiographic determination of right ventricular output in the newborn. *Cardiol Young* 2001; **11**: 188–194.
- 3 Evans N, Kluckow M. Early determinants of right and left ventricular output in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1996; **74**: F88–F94.
- 4 Walther FJ, Siassi B, Ramadan NA, Ananda AK, Wu PY. Pulsed Doppler determinations of cardiac output in neonates: normal standards for clinical use. *Pediatrics* 1985; **76**: 829–833.
- 5 Alverson DC, Eldridge MW, Johnson JD, Burstein R, Papile L, Dillon T *et al*. Effect of patent ductus arteriosus on left ventricular output in premature infants. *J Pediatr* 1983; **102**: 754–757.
- 6 Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed* 2000; **82**: F182–F187.
- 7 Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2000; **82**: F188–F194.
- 8 Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. *Pediatrics* 2003; **112**: 33–39.
- 9 Miletin J, Dempsey EM. Low superior vena cava flow on day 1 and adverse outcome in the very low birthweight infant. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**: F368–F371.
- 10 Osborn DA, Evans N, Kluckow M. Clinical detection of low upper body blood flow in very premature infants using blood pressure, capillary refill time, and central-peripheral temperature difference. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F168–F173.
- 11 Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. *Crit Care Med* 2002; **30**: 1210–1213.
- 12 De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. *Eur J Pediatr* 2002; **161**: 561–562.
- 13 Suzumura H, Nitta A, Tanaka G, Arisaka O. Diastolic flow velocity of the left pulmonary artery of patent ductus arteriosus in preterm infants. *Pediatr Int* 2001; **43**: 146–151.
- 14 Zaramella P, Freato F, Quaresima V, Ferrari M, Vianello A, Giongo D *et al*. Foot pulse oximeter perfusion index correlates with calf muscle perfusion measured by near-infrared spectroscopy in healthy neonates. *J Perinatol* 2005; **25**: 417–422.
- 15 Granelli AW, Ostman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. *Acta Paediatr* 2007; **96**: 1455–1459.
- 16 Evans N, Seri I. Cardiovascular compromise in the Newborn infant. In: Taeusch HW, Ballard RA, Gleason CA (eds). *Avery's Disease of the Newborn*, 8th edn. Elsevier: Philadelphia, 2004, pp 398–409.
- 17 Hales JR, Stephens FR, Fawcett AA, Daniel K, Sheahan J, Westerman RA *et al*. Observations on a new non-invasive monitor of skin blood flow. *Clin Exp Pharmacol Physiol* 1989; **16**: 403–415.
- 18 Bell EF, Warburton D, Stonestreet BS, Oh W. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *N Engl J Med* 1980; **302**: 598–604.
- 19 Tammela OK, Koivisto ME. Fluid restriction for preventing bronchopulmonary dysplasia? Reduced fluid intake during the first weeks of life improves the outcome of low-birth-weight infants. *Acta Paediatr* 1992; **81**: 207–212.



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