Decreased Variability and Low Values of Perfusion Index on Day One Are Associated with Adverse Outcome in Extremely Preterm Infants

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Objective To develop new quantitative features for the Perfusion Index signal recorded continuously over the first 24 hours of life in a cohort of extremely low gestational age newborns and to assess the association of these features with normal and adverse short-term outcome.

Study design A cohort study of extremely low gestational age newborns. Adverse outcome was defined as early mortality before 72 hours of life, acquired severe periventricular-intraventricular hemorrhage, or severe cystic leukomalacia. Perfusion Index values were obtained from the plethysmographic signal of a pulse oximeter. Perfusion Index signals were separated into low-frequency (trend) and high-frequency (detrend) components. Three features were extracted during four 6-hour epochs: mean of the trend component (mean-trend), SD of the trend component (SD-trend), and SD of the detrend component (SD-detrend). The SD features represent long-term variability (SD-trend) and short-term variability (SD-detrend) of the Perfusion Index. A mixed-effects model was fitted to each feature.

Results Ninety-nine infants were included in the analysis. Quadratic-time mixed-effects models provided the best fit for all 3 features. The mean-trend component was lower for the adverse outcome compared with the normal outcome group with a difference of 0.142 Perfusion Index ($P = .001$). SD-detrend component was also lower for the adverse compared with the normal outcome group, although this difference of 0.031 Perfusion Index/days^2 was dependent on time ($P < .001$).

Conclusion Low values and reduced short-term variability of Perfusion Index on day 1 are associated with adverse outcome *(J Pediatr 2016;178:119-24).*

Hemodynamic transition at birth is a challenging process for extremely low gestational age newborns (ELGANs). Periventricular-intraventricular hemorrhage (IVH) occurs in about one-third of ELGANs and is a risk factor for death, hydrocephalus, and poor neurodevelopmental outcome.[1-3]

With a structurally immature myocardium, the ELGAN has limited capacity to respond to changes in pre- and afterload accompanied at birth.[4-7] This transient phenomenon may lead to reduced systemic and cerebral blood flow. Numerous studies have highlighted the important role of perfusion in the etiology of preterm brain injury.[6,8-12] Recently, functional echocardiography and near-infrared spectroscopy have added more insight in the pathophysiology of acquired brain injury in the neonate.[10,13-15]

Further evaluation of the role of perfusion is feasible by use of the Perfusion Index, which is derived from the plethysmographic signal of a pulse oximeter. The Perfusion Index represents the ratio of the amount of light absorbed by pulsatile and nonpulsatile absorbers[16] and it is an indirect, noninvasive, readily available, and highly reproducible measure of peripheral perfusion.[17] Point measurements of Perfusion Index are found to be predictive for low cardiac output[18] in preterm babies and indicative of disease severity in newborns.[19] Reference values for continuous Perfusion Index measurements during the first 3 days of life have been published.[20]

The aim of this study was to assess whether quantitative features of the Perfusion Index signal, recorded in the first 24 hours of life, could highlight a vulnerable phase in the peripheral perfusion of ELGANs during neonatal adaptation. Signal analysis methods were used to develop quantitative features to capture short-term and long-term variability of Perfusion Index in addition to long-term average Perfusion Index values.

Methods

Patients included in the study were ELGANs born before 28 weeks' gestation and admitted to the neonatal intensive care unit of the University Hospital of Antwerp,

ELGAN	Extremely low gestational age newborn
GA	Gestational age
IVH	Intraventricular hemorrhage
PVL	Periventricular leukomalacia

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Edegem, Belgium, between January 1, 2012, and December 31, 2014. Infants were excluded from the study if they were transferred in after a postnatal age of 24 hours, had congenital heart disease, or were considered nonviable. The study was approved by the institutional ethical review board.

Antenatal characteristics (gestational age [GA], reason for delivery, timing and exposure to antenatal steroids) and postnatal characteristics (sex, mode of delivery, birth weight, Apgar score, lactate level at admission, ventilatory support, administration of surfactant, presence and size of a patent ductus arteriosus) were obtained from the medical record.

A cranial ultrasound study was performed as soon as possible after birth with an 8-MHz convex neonatal transducer probe (Vivid S6, GE Healthcare, Little Chalfont, United Kingdom). Follow-up ultrasound studies were performed daily until 72 hours of life and weekly thereafter. IVH was graded according to the Papile classification.[21] Acquired severe IVH was defined as grade 3 or greater not present on the initial scan. Cystic periventricular leukomalacia (PVL) was defined according to the DeVries classification of PVL.[22] Severe PVL was defined as grade 3 or greater. An adverse outcome was defined as patients who died within 72 hours after birth or were diagnosed with a severe acquired IVH or severe PVL on a brain ultrasound study at day 28 or earlier where applicable.

Data Capturing and Processing

Perfusion Index was monitored continuously with a pulse oximeter probe (Nelcor; Covidien, Mansfield, Massachusetts) placed on a limb at the discretion of the nurse, preferably on the side without peripheral cannulation. Perfusion Index values were recorded with an Intellivue MP 70 patient monitor (Philips Medical Systems, Best, The Netherlands) at a sample rate of 0.016 Hz (1 Perfusion Index value per minute) and digitally stored in a patient data management system (PDMS Metavision; iMDsoft, Dusseldorf, Germany). Data used in this study were collected as per routine clinical care.

High-amplitude spikes, known to be associated with movement of the probe, were identified and removed before further analysis. Spikes were defined as segments with amplitude jumps (difference in amplitude from one Perfusion Index to the next) greater than 1. (This equates to defining the derivative as greater than 1 by use of the forward-finite difference as the derivative estimate.) The identified spike, in addition to a 2-minute collar on either side of the spike, was removed. These missing values were then replaced by cubic-spline interpolation. The Perfusion Index signal was separated into a low-frequency (trend) and a high-frequency (detrend) component (**Figure 1**). The trend was calculated by applying a 20-minute moving-average filter to the Perfusion Index signal. The detrend component was calculated by subtracting the trend from the Perfusion Index signal. Quantitative features were calculated for both the trend and detrend components over 4 time periods: 0-6 hours, >6-12 hours, >12-18 hours, and >18-24 hours. Three quantitative features were used to summarize the temporal evolution of the Perfusion Index: mean and SD of the trend component and SD of the detrend component. The mean of the

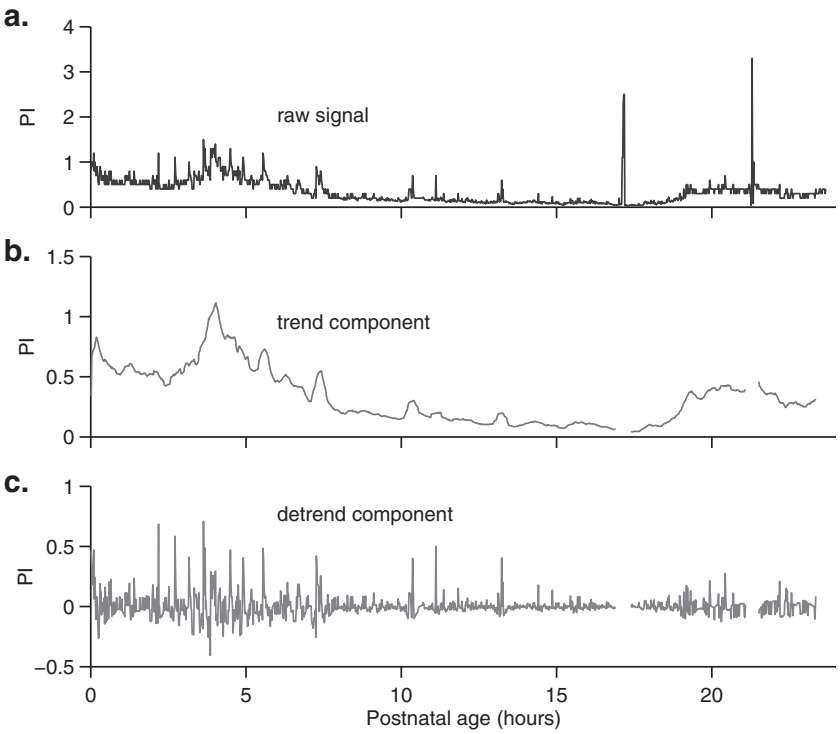

Figure 1. Example of the decomposition of the **A,** Perfusion Index signal into **B,** trend and **C,** detrend components. The artifact-removal algorithm identifies and removes large-amplitude spikes at 18 and 22 hours from the trend and detrend components. *PI*, Perfusion Index.