ARTICLE

Neonatal reference values and nomograms of systemic vascular resistances estimated with electrical cardiometry

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OBJECTIVE: Scanty data are available about neonatal systemic vascular resistances (SVR). We aim to provide reference values and nomograms for neonatal SVR.
DESIGN: Multicenter, cross-sectional,descriptive study performed in France and Italy. Neonates with complete hemodynamic stability were enrolled. Non-invasive measurements of SVR by electrical cardiometry performed once, after the first 72 h and before the 7th day of postnatal age.
RESULTS: We studied 1094 neonates: SVR was correlated with gestational age ($\rho = -0.55$, adj-$r = -0.46$, $p < 0.001$) and birth weight ($\rho = -0.59$, adj-$r = -0.45$, $p < 0.001$) irrespective of newborn sex. The relationships between SVR, gestational age and birth weight were represented by power equations and SVR was decreasing with increasing age and weight. Age- and weight-based SVR nomograms had optimal goodness-of-fit (non-linear $R^2 \geq 0.74$). Similar results were obtained for body surface indexed-SVR.
CONCLUSIONS: In hemodynamically stable neonates, SVR decrease with increasing gestational age and birth weight. Specific gestational age and birth weight-based nomograms are provided for the clinical interpretation.

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INTRODUCTION

Hemodynamic monitoring is crucial for the most critically ill patient as it helps optimizing vital support and reducing overtreatments [1]. Several monitoring techniques are available and can measure various advanced hemodynamic parameters such as, for instance, cardiac output (CO), extravascular lung water, oxygen delivery and consumption or systemic vascular resistances (SVR). Each of these parameters allows the intensivist to look at hemodynamics from a different point of view and increase the understanding of patient pathophysiology during acute illness [1]. Critically ill neonates also benefit advanced hemodynamic monitoring as several processes may alter their hemodynamics [2]. Unfortunately, in neonatal intensive care units (NICU), hemodynamic monitoring has been relatively limited so far, owing to difficulties related to the small patient size and the need of accurate and non-invasive technologies.

Nonetheless, certain techniques have recently spread allowing to have a closer insight at patient pathophysiology [3]. Point-of-care and targeted neonatal echocardiography are the commonest, but they do not provide a continuous monitoring and cannot directly measure some hemodynamic parameters [4, 5]. Other technologies have been more recently introduced and can overcome these problems [3]. An interesting example is represented by electrical cardiometry (EC). EC is based on thoracic electrical bioimpedance, and, with common electrodes, provides continuous, non-invasive and direct monitoring of some of the aforementioned advanced hemodynamic parameteres [6]. SVR is one of them and may be variously altered in shocked patients or influenced by several common NICU interventions such as inotropic support, analgesia or hypothermia [3, 7]. Echocardiography can only indirectly and intermittently calculate SVR. Scanty data are available about neonatal SVR and there are no reference nomograms based on gestational age and weight. They would be pivotal to interpret the measurements and tailor the hemodynamic support. We designed this study aiming to provide EC-derived reference values and nomograms for neonatal SVR.

METHODS

Setting and study design

This was a multicenter, observational, cross-sectional, descriptive study performed in two tertiary referral NICUs in France and Italy. The study was non-invasive as it used only data measured by EC and others collected during routine care, which was provided according to shared local protocols, essentially based on current international guidelines. In both centers, red blood cell transfusions were realized in the first week of life when hemoglobin dropped below 10–11 g/dL. EC is a part of routine care for NICU-admitted neonates in the two centers. Clinical management was not subjected to any change for study purposes. The study respected the Declaration of Helsinki, received local ethical approvals (n.14/13 and 149674) and parental informed consent was obtained before the enrollment. Data were recorded anonymously, and relevant privacy regulations were respected. The manuscript preparation followed appropriate guidelines [8].

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Table 1. Basic population details.

	Whole population (1094)	Preterm neonates (547)	Term neonates (547)
Gestational age (weeks)	35 (4.17)	32 (2.65)	39 (1.4)
Birth weight (g)	2385 (989)	1583 (571)	3188 (585)
C-section	470 (43.2%)	312 (57%)	159 (29%)
Male sex	546 (49.9%)	291 (53.2%)	255 (46.6%)
5′ Apgar score	10 [8–10]	9 [7–10]	10 [10-10]
SGA neonates	39 (3.6%)	21 (3.8%)	18 (3.3%)
SVR (dyn x s/cm^5)	8394 (5617)	10464 (6615)	6319 (3281)
SVRI (dyn x s x m^2/cm^5)	1377 (718)	1461 (796)	1292 (620)

Data are expressed as mean (standard deviation), number (%) or median [25th – 75th percentile]. Apgar score is a dimensionless variable.
SGA small for gestational age, *SVR* systemic vascular resistances, *SVRI* systemic vascular resistances indexed for body surface area.

Patients

Eligible patients were neonates of any gestational age with complete hemodynamic stability, defined when all the following were respected: (1) no need of volume resuscitation, inotropes, pulmonary vasodilators or any vasoactive drug, (2) normal heart rate and mean arterial pressure according to recent gestational age-based nomograms [9], and (3) normal peripheral hemoglobin saturation, temperature, skin refill time and urine output in the last 24 h. Beside the lack of fulfillment of these conditions, other exclusion criteria were the following: (1) major congenital malformation or chromosomal abnormalities, (2) congenital heart diseases (other than patent *foramen ovale* or *ductus arteriosus*), (3) viral myocarditis and other cardiomyopathies, (4) supra-ventricular tachycardia or other arrythmias, (5) perinatal asphyxia requiring therapeutic hypothermia [10], (6) any need for invasive ventilation [11], (7) surgery of any type, (8) acute kidney failure [12], (9) fetal hydrops of any origin, (10) cardiac tamponade. These conditions were screened within routine care and all patients underwent a screening echocardiography upon NICU admission. The neonates were enrolled after the first 72 h and before the 7th day of postnatal age. All these conditions were chosen as they might affect hemodynamics with the exception of *foramen ovale* or *ductus arteriosus* which may not significantly influence CO measurement by EC [13]. Patient sampling was systematic, including all neonates respecting the aforementioned criteria and admitted in the two recruiting centers from May 2021 to April 2024. Each neonate could have been enrolled only once (i.e. there was no repeated measurement on any patient).

Measurements and outcome

SVR represented the study outcome and they were measured with EC, whose principles of operation were described elsewhere [14]. A portable hand-held EC monitor, routinely applied in our clinical activity (ICON®, Osypka, San Diego-CA, USA) was used following the manufacturer's recommendations. Briefly, a high frequency and low amperage current is released through the thorax by two electrodes (placed on the forehead and the left thigh); two other electrodes were placed (on the left side of the neck and thorax) as far as possible from conventional electrocardiography (ECG) electrodes and received the signal modified by thoracic impedance [13]. Changes in the impedance are related to the ECG captured at the same time. EC measures CO and then estimates SVR using a calculation based on the following formula:

$$SVR = \frac{(Mean\ arterial\ pressure(MAP) - Central\ venous\ pressure(CVP))\ x\ 80}{CO}$$

MAP was obtained by oscillometry, right before EC measurements, with an appropriately sized cuff (cuff width-arm circumference ratio = 0.50) [15] on the right upper arm or, in case of contraindications (e.g. presence of vascular lines or lesions), on another limb, as per our routine care protocol; this is considered accurate in hemodynamically stable infants aged 6 months or less [16]. EC estimates CVP based on normative neonatal values [17]. All measurements were performed on quiet babies lying supine and patient position was not changed during measurements.

Data

SVR measurements were considered, after 1 minute from electrodes placement, when an optimal quality signal was achieved, as previously published (i.e. signal quality index at least 480 with simultaneous ECG free from any artifact) [18]. Since that moment, data were averaged with 10 seconds interval over 1′. SVR were also indexed to the body surface area (SVRI) using the Meban's formula [19]. Basic clinical and demographic data were recorded in real time from electronic patients' files. Newborn growth was evaluated using Fenton's curves [20].

Statistics

Ours was a descriptive, cross-sectional study describing reference data of a vital parameter (i.e. SVR) across different gestational age and birth weight classes. A formal sample size calculation was therefore unfeasible, but a large population was needed to be comprehensive. Thus, we decided a convenience sample size of at least 1000 neonates, which was approximately 4 times larger than the only pilot study published on this topic so far [21].

SVR, gestational age and birth weight correlations were studied with Spearman (ρ) coefficient. Differences between preterm and term neonates were studied with Student test. Sex differences were investigated in partial correlations adjusting for newborn sex and comparing SVR and SVRI in male and female neonates with Student test. The relationships between SVR and gestational age or birth weight was investigated with the curve estimation procedure of our statistical package [22], and the model with the highest R^2-value was chosen to fit the data [23].

SVR nomograms per class of gestational age or birth weight were then drawn regressing data with power equations, as these had the highest R^2 [23]. Gestational age-based SVRI nomogram was additionally drawn using models with the highest R^2-value [23]. Raw data described by each nomograms were also given for full transparency. Since weight is included in the body surface area calculation, it is mathematically related to SVRI and, to avoid any bias, a birth weight-based SVRI nomogram was not drawn. Analyses were performed with SPSS 28 (IBM, Armonk, NY-USA) and with Excel for Macintosh 16.8 (Microsoft, Redmond-WA, USA); $p < 0.05$ were considered statistically significant.

RESULTS

Table 1 reports basic population details: 1094 neonates, fairly divided between preterm and term infants, were enrolled. This was representing the hospital catchments and our usual distribution of NICU admissions. No problems were observed during SVR measurements. Both SVR ($p < 0.001$) and SVRI ($p < 0.001$) are significantly higher in preterm than in term neonates (Table 1). SVR significantly correlate with gestational age ($\rho = -0.55$, $p < 0.001$) and birth weight ($\rho = -0.59$, $p < 0.001$) and this is unchanged upon adjustment for newborn sex (adj-$r = -0.46$, $p < 0.001$; adj-$r = -0.45$, $p < 0.001$, for gestational age and birth weight, respectively). SVR are not significantly different between male (8475 (4261) dyn x s/cm^5) and female (8312 (6702) dyn x s/cm^5) neonates ($p = 0.632$). Similar results were observed for SVRI between male (1370 (585) dyn x s x m^2/cm^5) and female (1383 (830) dyn x s x m^2/cm^5) infants ($p = 0.766$).

The relationship between SVR, gestational age and birth weight are represented by power equations: SVR are decreasing with increasing age and weight (Fig. 1). Figures 2, 3 depict the

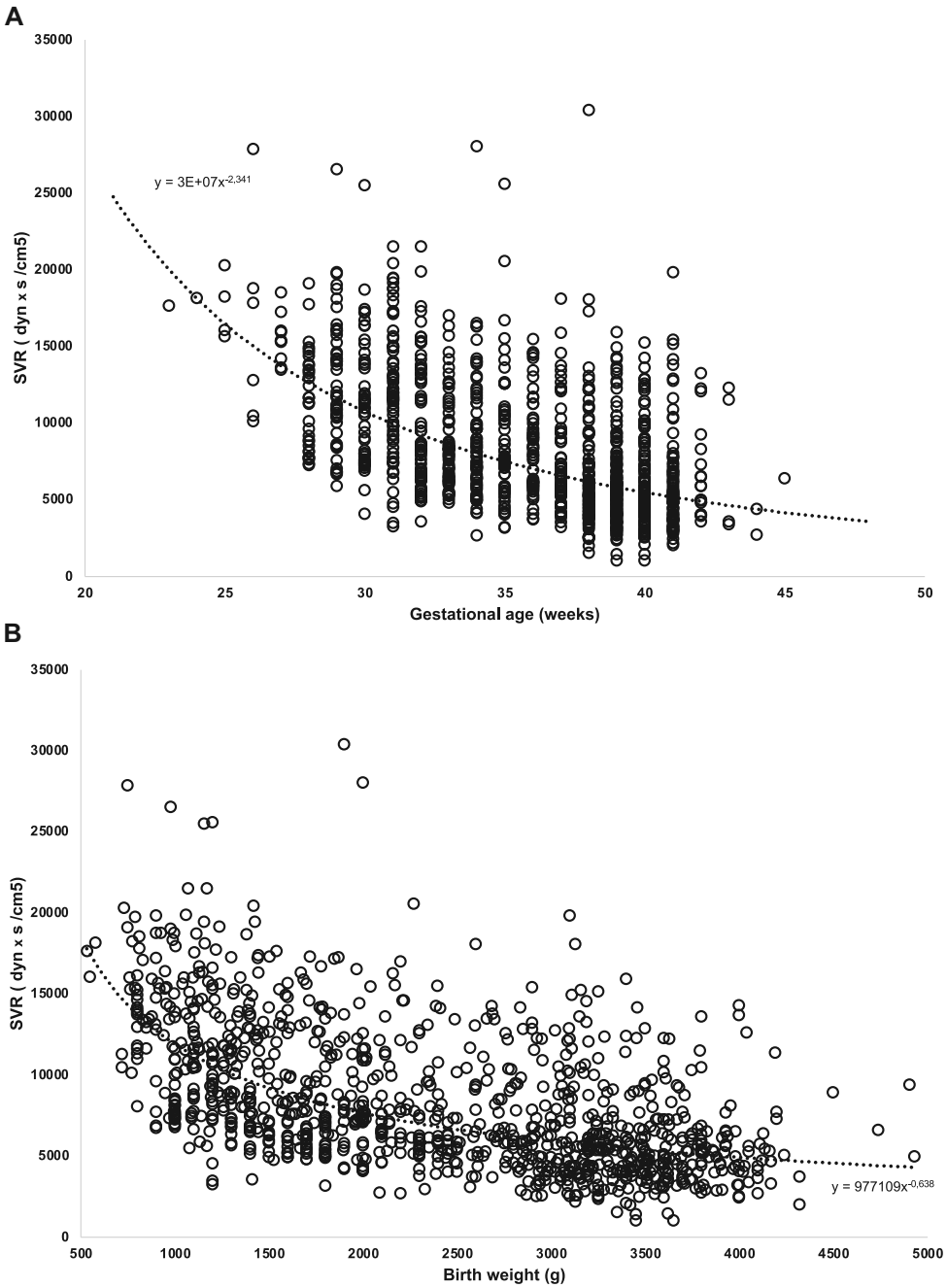

Fig. 1 Relationship between systemic vascular resistances and gestational age or birth weight. A, **B** depict the relationship with gestational age and birth weight, respectively. The dotted curve is the best fitting data one generated with the curve estimation procedure and represents a power equation, whose formula is shown. SVR systemic vascular resistances.

gestational age- and birth weight-based SVR nomograms for preterm and term neonates, respectively. Goodness-of-fit is optimal for each nomogram (non-linear R^2 always ≥0.74). Raw data on which nomograms are based are shown in Supplementary Tables 1, 2, respectively. Figure 4 and Supplementary Table 3 shows the SVRI nomogram according to gestational age and the associated raw data, respectively.

DISCUSSION

We provide neonatal reference values and nomograms of SVR, after the first 72 h and within the first week of life, to be used for clinical monitoring at the bedside. We found that SVR: (1) are higher in preterm than in term neonates; (2) are not influenced by newborn sex; (3) are decreasing with increasing gestational age and birth weight following a peculiar trend which is visible in all nomograms.

These are novel information since only one pilot study previously reported (in a smaller population of 280 neonates) the mean values of SVR without any nomogram or detailed normative data [21]. In order to provide these, a large and well selected population as well as a multicenter design were needed. Our study had these characteristics, allowed to draw reliable nomograms and found absolute numbers and correlations that are fully consistent with those reported in that preliminary study [21].

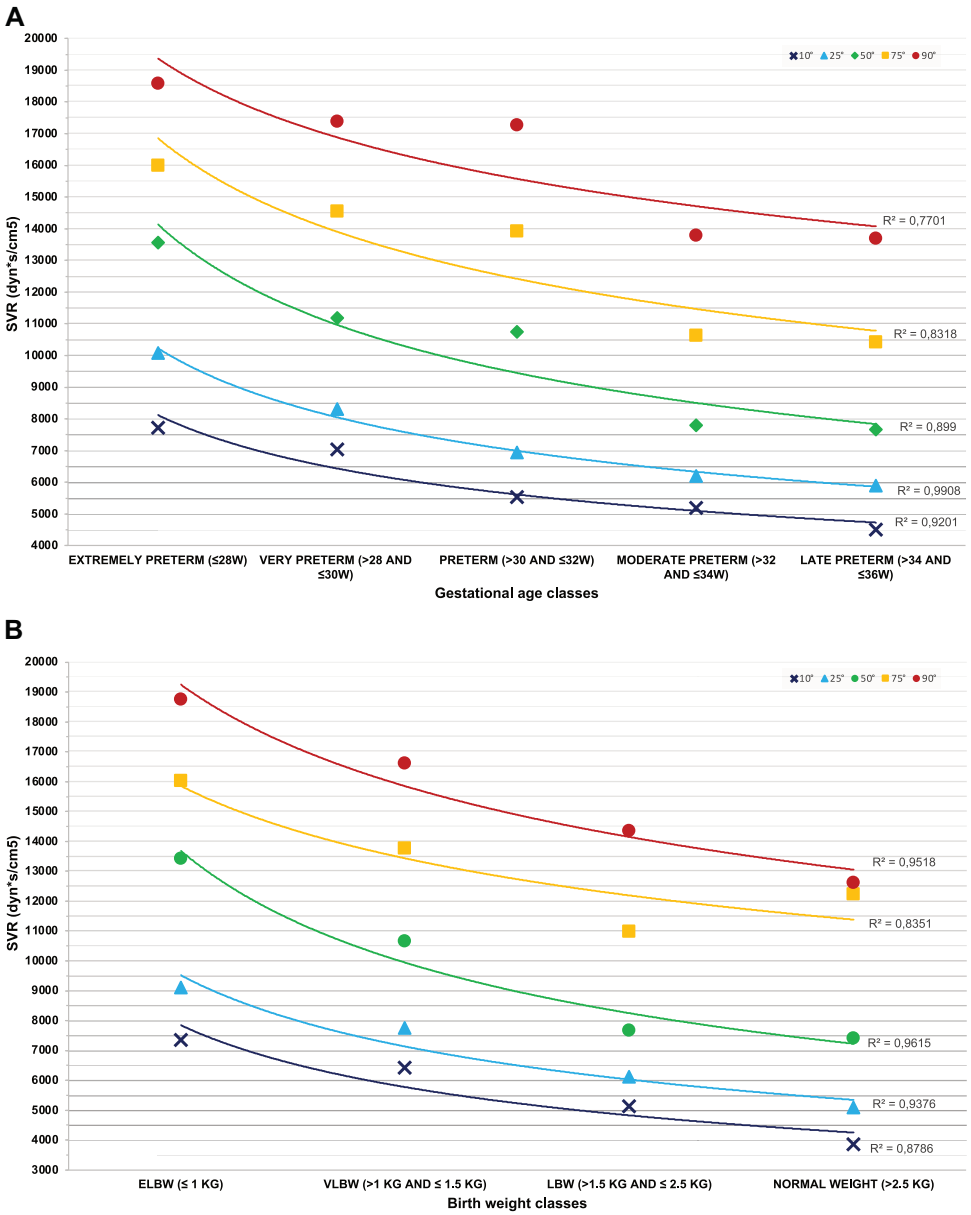

Fig. 2 Systemic vascular resistance nomograms for preterm neonates based on gestational age or birth weight. A, **B** depict the relationship with gestational age and birth weight, respectively. Blue crosses, light blue triangles, green diamonds, yellow squares and red circles represent the 10th, 25th, 50th,75th and 90th percentile, respectively. Lines represent the best fitting data curves corresponding to power equations as this was the model with the highest R^2. Respective R^2-value is shown for each line. ELBW extremely low birth weight, LBW low birth weight, SVR systemic vascular resistances, VLBW very low birth weight.

The higher SVR observed in preterm neonates, and their reduction with increasing maturity may be due to two processes. First, SVR strongly depend on vessels' diameter, and smaller neonates have narrower vessels and obviously greater SVR [21]. Second, CO becomes greater with increasing gestational age and weight [13]. The CO increment (e.g. the denominator in the SVR formula) may be relatively greater than the MAP increment (e.g. the numerator in the formula) and since CVP does not significantly change in stable neonates [17], this would eventually cause a reduction in SVR. This is consistent with the well-known increment of CO [24], and the reduction of SVR observed in children after the neonatal age [25]. The lack of sex influence over SVR is also fully consistent with data previously reported in older patients using various techniques [24, 26], and helpful as it allows a simpler interpretation of SVR in clinical practice.

Nomograms are visual tools commonly used in neonatology and pediatrics, thus clinicians are used to apply them for the interpretation of clinical parameters at the bedside. The shapes of our nomograms, both for SVR and SVRI, is consistent with those reported in older children beyond the first month of life [25]. Our findings bring the possibility to monitor the effect of vasopressors (e.g. norepinephrine, vasopressin) in critically ill neonates with hemodynamic impairment, as it is currently suggested for adults and children [27, 28]. The consideration of SVR together with parameters issued from other monitoring tools (e.g. echocardiography, near-infrared spectroscopy) gives a more precise picture of patient pathophysiology by capturing several factors influencing hemodynamics, oxygen delivery and consumption. A more accurate understanding of patient pathophysiology would, in its turn, allow a personalized therapy with potential benefits on clinical outcomes.

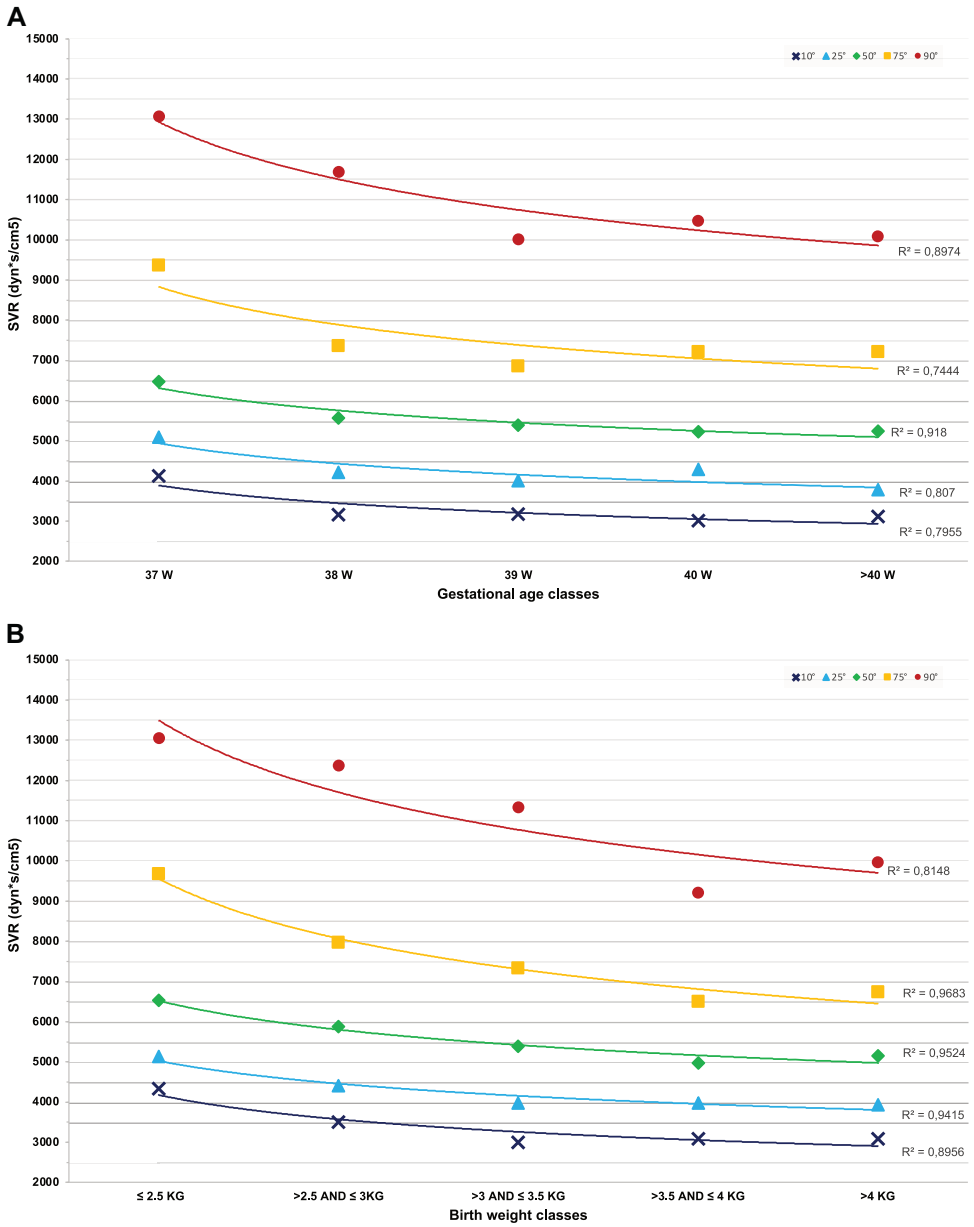

Fig. 3 Systemic vascular resistance nomograms for term neonates based on gestational age or birth weight. A, B depict the relationship with gestational age and birth weight, respectively. Blue crosses, light blue triangles, green diamonds, yellow squares and red circles represent the 10th, 25th, 50th,75th and 90th percentile, respectively. Lines represent the best fitting data curves corresponding to power equations as this was the model with the highest R^2. Respective R^2-value is shown for each line. SVR systemic vascular resistances.

This can be particularly helpful in critically ill neonates whose SVR may drastically change (e.g. septic shock) or in those undergoing interventions influencing SVR (e.g. therapeutic hypothermia, anesthesia).

EC has the advantage to be non-invasive, continuous, easy and applicable to neonates of any size and age. Compared to echocardiography, EC has a relatively poor precision and a small bias in measuring CO, in neonates including during transportation [29]. A comparative meta-analysis suggests that EC is an accurate continuous monitoring tool for children [30]. Conversely, other monitoring techniques may be unsuitable for smallest neonates.

Thus, SVR monitoring can be added to the list of NICU monitoring tools for the sickest patients and neonatologists can integrate its findings within the clinical and pathophysiology reasoning. Anecdotical experience supports this, as SVR measurement allowed an early detection of hemodynamic impairment and was helpful in clinical decision making [31]. Less sick neonates often does not need this level of vital function monitoring, but with increasing clinical severity, a better understanding of patients' pathophysiology becomes crucial, although for relatively few patients [32].

It is important to note that our findings have been produced in a population of hemodynamically stable neonates sampled within the first week but after the first 72 h of life. This has been purposely decided to exclude most of the adaptative phenomena typical of the perinatal period [33]. Previous studies have enrolled neonates in the transitional period but have not produced SVR reference values or nomograms [18, 34–36]. Therefore, our findings cannot be immediately generalized, and a dedicated study is ongoing in our centers to describe normal SVR values in early life. Similarly, it is conceivable that SVR would decrease with increasing postnatal age due to raising CO [24, 25], and caution should be exercised to apply these data later in the first month of life.

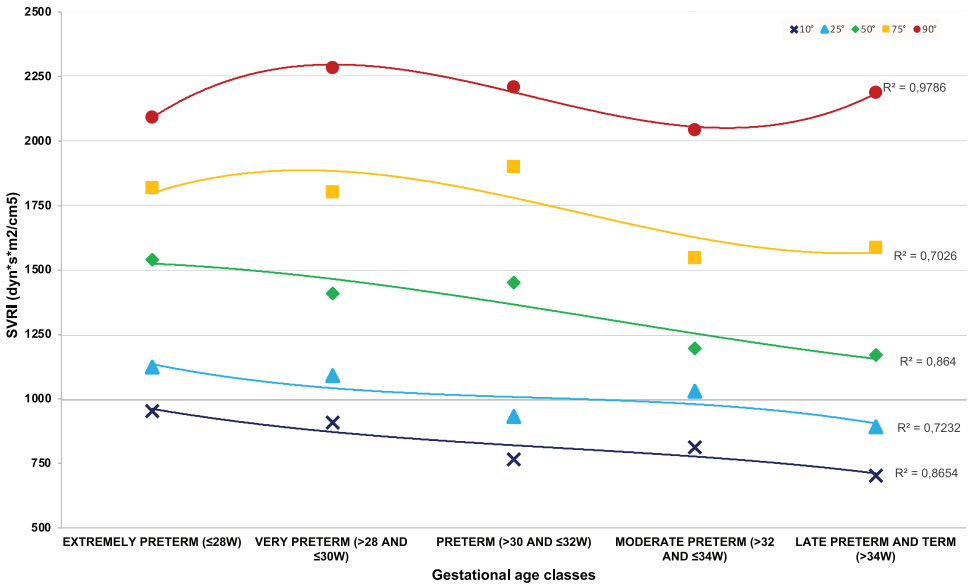

Fig. 4 Body surface indexed—systemic vascular resistance (SVRI): gestational age-based nomogram. Blue crosses, light blue triangles, green diamonds, yellow squares and red circles represent the 10th, 25th, 50th,75th and 90th percentile, respectively. Lines represent the best fitting data curves corresponding to polynomial equations, as this was the model with the highest R^2. Respective R^2-value is shown for each line. SVRI systemic vascular resistances indexed for body surface area.

The study has some limitations. Our nomograms are produced with EC and should not be directly extrapolated to SVR assessed with other techniques. SVR estimations are performed with calculations based on CO and CVP which are not measured with the gold standard technique (i.e. cardiac catheterization). Nonetheless, this latter is not available in NICUs, EC is sufficiently accurate to estimate CO [6], and CVP does not significantly change in hemodynamically stable neonates [17]. Furthermore, EC might be useful to assess the SVR trend within individual patients as a "point-of-care" technique, even if the measurements do not provide the true absolute values. As for many other measurements in neonatal critical care, we believe that assessing an individual trend can be better than being completely blinded towards an important variable. We excluded mechanically ventilated infants, since the application of high mean airway pressures is known to have an impact on hemodynamics [37]. This needs to be more accurately investigated with dedicated studies on neonates of different weight, supported with various levels of pressures and ventilatory modes and is particularly important for critically ill neonates with simultaneous respiratory failure and cardiovascular impairment. We have very few small for gestational age neonates, thus our findings cannot be directly extrapolated to that type of patient. We cannot provide any insight about the SVR change in relation to postnatal age, as our design was cross-sectional, we focused on the whole first week and did not enroll enough patient per each day of the first week. Therefore, further work has to be done to clarify these issues related to patient selection, as not all questions can be answered with one study. We did not exclude neonates with patent *ductus arteriosus* as this did not influence EC accuracy in our previous study [13]. However, several other studies have reported otherwise and two case series suggested a possible SVR increment upon *ductus arteriosus* closure [36, 38]. Therefore, our nomograms should be used with caution in babies with patent *ductus arteriosus*. Finally, a future study should verify the accuracy and resolution of EC in capturing SVR changes due to therapeutic interventions: this study can now be based on our reference values.

CONCLUSIONS

In hemodynamically stable neonates, after the first 72 h and within the first week of life, SVR decrease with increasing gestational age and birth weight without sex differences. Specific gestational age and birth weight-based nomograms are provided for the clinical interpretation and use of EC as bedside point-of-care tool.

SUMMARY

What is already known on this topic

- Electrical cardiometry can estimate systemic vascular resistances (SVR) non-invasively and continuously but scanty data are available about their normal values in neonates.

What this study adds

- We clarified that SVR decrease with increasing gestational age and birth weight, irrespective of newborn sex. We provided reference values and nomograms for neonatal SVR and for body surface area-indexed SVR.

How this study might affect research, practice or policy

- These findings are helpful to monitor cardiovascular function at the bedside and tailor the hemodynamic support in most critically ill neonates.

DATA AVAILABILITY

Deidentified study dataset is available upon reasonable request to researchers who provide a methodologically sound proposal. Data requestors will need to sign a data transfer agreement and respect all relevant regulations.

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AUTHOR CONTRIBUTIONS

VB and BL collected and interpreted the data, performed the statistical analysis and wrote the original draft of the manuscript. OV, AP, MEF, LV helped to collect and interpret the data and critically revised the manuscript. MDN and SM helped in data design and data interpretation and critically revised the manuscript. DDL conceived the study and designed it, performed the statistical analysis and prepared the figures and provide the study general supervision. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

French Critical Care Ethical Commission n.14/13 and Niguarda Hospital Institutional Ethical Board n.149674. The study respected the Helsinki Declaration.

ADDITIONAL INFORMATION

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