Non-invasive cardiac output measurement in low and very low birth weight infants: a method comparison

Oswin Grollmuss¹* and Patricia Gonzalez²

¹ Centre Chirurgical Marie Lannelongue, INSERM 999, Université Paris XI Sud, Orsay, France
² Institut de Puériculture et de Péri-natalogie, Université Paris V Descartes, Clamart, France

INTRODUCTION

Information about cardiac output (CO) in newborn and especially in pre-term, low birth weight (LBW), and very low birth weight (VLBW) infants is difficult to obtain. However, this information is particularly important in such patients with their numerous circulatory features [heart–lung interaction (1, 2), sepsis (3), changes in circulatory volume, need for catecholamine treatment, hemorrhage].

Clinical observation does not deliver sufficient information (4). Invasive (potentially traumatic) and non-invasive blood pressure measurement (5), influenced by vascular resistances, reflects CO only partially. Electrocardiogram (ECG) and heart rate (HR) variability only give indirect information. NIRS indicates compromised regional circulation possibly related to an underlying general low flow (6) but can deliver no evidence on its cause.

In LBW infants, conventional invasive CO measurement methods, often considered as “gold standards” like the Swan – Ganz catheter, are too traumatic in these patients, therefore research for non-invasive alternatives is necessary. Transthoracic cardiac ultrasound (TTE) with trans-aortic Doppler (7) is used in daily clinical practice, but is technically highly demanding and can only be applied sporadically. Another possible technique, bioimpedance, referring to thoracic impedance changes by CO-dependent intrathoracic blood flow, has been developed in the 60s by Kubicek (8). One of its most recent modifications is electrical velocimetry (EV) based on the mathematical algorithms formulated by Bernstein and Lemmens (9) in 2005.

Electrical velocimetry and trans-aortic Doppler have been validated against invasive CO measurement reference techniques [thermodilution (10, 11), Fick (12)]. EV has been evaluated against the Fick and the thermodilution method as gold standards, but data are scarce, the cohorts enrolled in the studies heterogeneous, and the results remain controversial concerning the measurement of “true” CO. On the other hand, with special regard to clinical purposes, EV has been found interchangeable with Doppler ultrasound in adults (13) and, recently, evidence was given for the interchangeability of the two methods in newborns with and without underlying congenital heart disease (14–16).

The aim of this method comparison study was to investigate if EV and TTE are even interchangeable in LBW and VLBW infants in order to create a rationale for further clinical validation studies of EV.

Background: Cardiac output (CO) measurement in low (LBW) and very low (VLBW) birth weight infants is difficult. Hitherto, sporadical transthoracic echocardiography (TTE) is the only non-invasive measurement method. Electrical velocimetry (EV) has been evaluated as a promising regional circulation possibly related to an underlying low flow (6) but can deliver no evidence on its cause.

Objectives: The study was designed to evaluate if EV could be interchangeable with TTE even in LBW and VLBW infants.

Methods: In 28 (17 LBW, 11 VLBW) pre-mature newborns, n = 228 simultaneous TTE (trans-aortic Doppler), and EV measurements (134 LBW, 94 VLBW) of stroke volume (SV) and heart rate (HR) were performed, thereof calculating body weight indexed SV (=SV*) and CO (=CO*) for all patients and the subgroups. Method comparison was performed by Bland–Altman plot, method precision expressed by calculation of the coefficient of variation (CV).

Results: Mean CO* in all patients was 256.4 ± 44.8 (TTE) and 265.3 ± 48.8 (EV) ml/kg/min. Bias and precision were acceptable, limits of agreement within the 30% criterion for method interchangeability (17). According to their different anatomic dimensions and pathophysiology, there were significant differences of SV(*), HR, and CO* for LBW and VLBW infants as well for inotropic treatment and ventilation mode.

Conclusion: Extending recent publications on EV/TTE comparison in newborns, this study suggests that EV is also applicable in LBW/VLBW infants as a safe and easy to handle method for continuous CO monitoring in the NICU and PCICU.

Keywords: low birth weight infants, very low birth weight infants, neonatal intensive care unit, pediatric cardiac intensive care unit, stroke volume, cardiac output, electrical velocimetry, transthoracic echocardiograph
METHODS

In this prospective, observational study, we performed 228 CO measurements in 28 pre-term newborns (subgroups: 17 LBW, 11 VLBW). Detailed epidemiological data are given in Table 1.

The study was designed as an observational method comparison study for the interchangeability of TTE and EV and not as a clinical validation study. Nevertheless, clinical observations will be communicated for correlation of SV and CO measurements with body weight, and observations for SV and CO under inotropic treatment (epinephrine 0.05 µg/kg/min and milrinone 0.375 µg/kg/min) and under different respiration conditions that may illustrate the utility of EV (and TTE) in daily clinical practice.

The local ethical committee’s permission and informed parental consent were obtained in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

| Parameter | Total |
|-----------|-------|
| Number of patients (measurements) | 28 (228) |
| Number of LBW infants (measurements) | 17 (134) |
| Number of VLBW infants (measurements) | 11 (94) |
| Male (patients) | 18 |
| Female (patients) | 10 |
| Mean gestational age (weeks), all patients | 31.7 ± 3.1 |
| Mean gestational age (weeks), VLBW | 29.2 ± 2.8 |
| Median age at exam (days) | 15 (1 – 48) |
| Mean weight at exam (kg), all patients | 1.618 ± 0.346 |
| Mean weight at exam (kg), LBW | 1.866 ± 0.145 |
| Mean weight at exam (kg), VLBW | 1.236 ± 0.161 |
| Patients ventilated (number) | 19 |
| Inotropic support (patients) | 10 |

ELECTRICAL VELOCIMETRY

Stroke volume (SV) was measured by EV as \( SV_{EV} \) using the ICON® bioimpedance monitor (Osypka Medical, La Jolla, CA, USA). The principles of EV and the method itself have been discussed elsewhere in detail (9, 16). \( CO_{EV} \) was measured as:

\[
CO_{EV} = SV_{EV} \times HR \text{ (ml/min)}
\]

and indexed to body weight as \( CO^*_{EV} \) (ml/kg/min), \( SV_{EV} \) indexed to body weight as \( SV^*_{EV} \) (ml/kg).

Utmost attention was paid to the best signal quality and ECG and \( dZ/dt \) curve on the ICON® monitor (Figure 1). Conventional pediatric electrodes were placed according to the recommendations for the use of the ICON® in small children (Figure 1). EV (\( SV_{EV} \)) and trans-aortic Doppler measurements of SV (\( SV_{TTE} \)) were performed simultaneously.

TRANS-AORTIC DOPPLER ULTRASOUND

\( SV_{TTE} \) measurements were performed as described in detail by Grollmuss et al. (16). For the measurement of the velocity time integral (VTI), utmost attention was paid to the ultrasound sample being placed directly behind the aortic valve, in line with the blood stream ejected from the left ventricle into the aorta. \( CO_{TTE} \) and the body weight indexed \( CO^*_{TTE} \) (ml/kg/min) were then calculated in analogy to the EV measurements. \( SV_{TTE} \) was indexed to body weight as \( SV^*_{TTE} \) (ml/kg).

In order to minimize artifacts and errors of the EV and TTE measurements that have been described in the literature, in particular referring to the exact measurement of the diameter of the aortic annulus five subsequent measurements were made under optimal measurement and signal conditions and then averaged.

FIGURE 1 | EV – electrode placement in the small infant and EV signals.

It is important that the electrode placing keeps sufficient distance between the electrodes to avoid interferences and signal disturbances which may be difficult in very small infants. ECG and EV signals must be clearly identified on the monitor as they correlate with the intra-aortic blood flow changes. Further explanations are given in the text. (With kind permission of Osypka Medical, Berlin, Germany and La Jolla, CA, USA, modified for scientific publication by the authors).
### Results

#### Patients' data

Mean gestational age of all patients was 31.7 ± 2.8 weeks (VLBW 29.2 ± 2.8 weeks), 27/28 (=96.4%) being pre-term born infants with 24/28 (=85.7%) being under 35 weeks of gestation. Mean weight of all patients at the time of CO measurement was 2.88 ± 0.90 kg, mean weight of the VLBW patients 2.23 ± 0.16 kg, the smallest infant enrolled in the study weighing 0.860 kg. Ten out of 28 patients (35.7%) had low dose inotropic support, 19/28 patients (=67.9%) were artificially ventilated.

#### Method comparison

Bland–Altman method comparison for CO* TTE and CO* EV and precision calculation are given in Table 2 and Figure 2. Bias was consistently positive for all patients and the subgroups with consistently higher CO* EV than CO* TTE values and clinically acceptable with values <10% of the mean of both methods. Limits of agreement for both methods in all patients and the subgroups were below the 30% limits stipulated by Critchley and Critchley (17) for method interchangeability (Figure 2). There was practically no difference of EV and TTE interchangeability for CO measurement between ventilated and non-ventilated infants with bias of 4.0% of mean in ventilated patients and 2.5% in non-ventilated patients and limits of agreement of 23.6 and 25.2% for ventilated and non-ventilated infants, respectively.

#### Precision of the methods

Overall CV was <10%, expressing clinically acceptable precision of TTE and EV. There was a significantly higher CV for CO* TTE in spontaneously breathing (mean 11.2 ± 8.5%) than in ventilated infants (mean 8.2 ± 9.4%, p = 0.025), thus less precision for EV in extubated patients.

### Table 2 | Bland–Altman test for method agreement and coefficient of variations (CV) for precision calculation in all patients, LBW and VLBW infants.

| Population  | Method | Mean        | CV (%) | Agreement (Bland–Altman) |
|-------------|--------|-------------|--------|--------------------------|
|             |        |             | Upper limit | Lower limit | % of mean | Bias  | % of mean |
| All patients| TTE    | 256.4 ± 44.8 | 8.0     | 71.6 | −53.8 | 24.0 | 8.9 | 3.4 |
|             | EV     | 265.3 ± 48.8 | 6.3     |        |       |      |     |     |
| LBW infants | TTE    | 248.3 ± 39.9 | 8.7     | 70.9 | −50.2 | 23.9 | 10.4 | 4.1 |
|             | EV     | 268.7 ± 44.7 | 7.1     |        |       |      |     |     |
| VLBW infants| TTE    | 274.2 ± 53.8 | 10.5    | 69.1 | −48.4 | 23.5 | 5.3 | 1.9 |
|             | EV     | 268.8 ± 49.0 | 7.0     |        |       |      |     |     |

Means, bias, and limits are expressed as absolute values (ml/kg/min), bias and limits also as % of means.
**DISCUSSION**

This study was a pure observational method comparison of EV and TTE in LBW and VLBW infants with supplementary clinical observations indicating a possible use of EV in daily neonatological and cardiological practice. It was not designed to evaluate a “true” CO comparing EV to a convenved gold standard like Fick’s method or thermodilution, which is not possible in very small infants, but to explore the utility of EV as an easily feasible alternative to the technically demanding trans-aortic Doppler for the measurement of CO in these patients.

Method comparison of the two non-invasive CO measurement methods, TTE and EV, shows that they are interchangeable, fulfilling the criteria of Critchley and Critchley (17), with narrow limits of agreement, low and constant bias, and, finally, good precision of either method with EV being somewhat more precise than TTE.

Method interchangeability was not altered by the respiratory mode (ventilation or spontaneous respiration) whereas CO* measurements were significantly less precise in extubated than in ventilated infants suggesting a particularly careful interpretation of EV in these patients as movements of the awake-patients might interfere with the EV signal.

Stroke volume correlated well with the patients’ body weight and was therefore higher in LBW than in VLBW patients, thus reflecting correctly the patients’ differences of weight and age. As the body weight related SV* was not different in the two groups, the paradoxically higher CO* in the VLBW group was obviously due to a higher HR in these patients.

The higher SV and CO in ventilated patients may be due to positive effects of positive intrathoracic pressure on left ventricular (LV) afterload reduction as has been previously reported (1, 2). Extending the previous studies in normal weight newborns (15, 16), the present study shows that EV and TTE are also interchangeable even in LBW and VLBW infants, fulfilling the criteria of Critchley and Critchley (17) for method comparison of two
non-reference methods, with clinically acceptable precision of CO measurement by EV (16).

As a conclusion, EV may represent a valuable tool for CO monitoring in LBW and VLBW infants, particularly helpful in detecting imminent risks of low CO (16) associated to the pathology of very small and pre-term newborns like circulatory degradation in the case of sepsis or bleeding, and it may help to conduct volume substitution treatment. These aspects of a possible role of EV in the critical care management of very small NICU or PCICU patients should be evaluated by further, clinical studies.

Compared to TTE, the advantage of EV may be a continuous and relatively easy manageable CO monitoring completing the “traditional” circulatory monitoring in neonatal, pediatric, and pediatric cardiological intensive care units. Its clinical utility still needs to be confirmed, but evidence is growing (15, 16). In fact, the clinical observations of the present study with regard to variations of SV\textsubscript{EV}, SV\textsubscript{TT}, and CO\textsubscript{EV} related to weight, ventilation, and inotropic treatment support a potential role of EV in the clinical practice of CO monitoring even in very small infants.

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