



# Assessing Patent Ductus Arteriosus (PDA) Significance on Cardiac Output by Whole-Body Bio-impedance

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## Abstract

We evaluated the effectiveness of a whole-body bioimpedance device (NICaS®, NI Medical, Petach Tikva, Israel) to predict the presence of a hemodynamically significant patent ductus arteriosus (PDA) in premature infants. A total of 36 infants less than 35 week's gestation age and birth weights of less than 1750 g were included in the study. Using the NICaS® device, we obtained whole-body bioimpedance measurements of stroke volume index (SI), cardiac output index (CI) and total peripheral resistance index. A total of 61 measurements were taken together with echocardiograph imaging. The study population was divided into three groups according to the echocardiograph results: group 1—small PDA, group 2—moderate PDA, and group 3—large PDA. Both SI and CI significantly increased from a median value of 22.6 ml/m<sup>2</sup> and 3.4 l/min/m<sup>2</sup> to 23.8 and 3.7, to 39.8 and 5.4 between groups 1, 2 and 3 respectively. The difference was statistically significant between groups 1 and 3 ( $P=0.005$  for SI and  $P=0.002$  for CI) and between groups 2 and 3 ( $P=0.037$  for SI and  $P=0.05$  for CI). We found statistically significant differences in SI and CI between infants with large PDAs and infants with no or small and medium PDAs. We suggest that these differences can be used in real time, in addition to echocardiography, in assessing the presence of significant PDAs.

**Keywords** Patent ductus arteriosus · Preterm infant · Whole-body bioimpedance · Stroke volume index (SI) · Cardiac output index (CI) · Total peripheral resistance index (TPRI)

## Introduction

Patent ductus arteriosus (PDA) is a prevalent condition affecting premature infants. The prevalence of PDAs is inversely related to gestational age. Approximately 75–80% of premature infants born less than 28 weeks gestation age will have a PDA [1–3]. PDAs increase the risk of intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), pulmonary hemorrhage and necrotizing enterocolitis (NEC) [2, 4, 5]. Most PDAs close by themselves but at a slower rate than in term infants. By the age of 6 months, 90–100% of the PDAs will spontaneously close [1–3, 6].

Current management options for PDAs include conservative and interventional approaches. The conservative

approach includes fluid restriction, diuretics, increasing systemic cardiac output and so forth. The interventional approach includes pharmacological and surgical treatments [1, 2, 5–7]. Historically, the pharmacological treatment was comprised of indomethacin treatment, but today, most centers use ibuprofen, paracetamol or indomethacin, which are currently known to be equal in potency [8–10]. When pharmacological treatments are unsuccessful or not feasible, surgical ligations are performed [2, 11].

Over the last 20 years, the pendulum has been slowly moving from treating all small preterm infants prophylactically, to treating all echocardiographically diagnosed PDAs regardless of symptoms, to treating only hemodynamically significant PDAs. Several studies compared long-term outcomes, including mortality, neurocognitive function and BPD between the years when treatment was more prevalent (up to 2008) and the years when treatment was reserved for patients with hemodynamically significant PDAs (after 2008), and found no significant differences [12, 13]. A recent large meta-analysis by Benitz concluded that there is no evidence of any long-term benefit in treating PDAs [1, 6]. The

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major limitation of these studies is that there was no real randomization of the patients, especially in the very early preterm group (23–27 weeks gestation), as there was a high percentage of open treatments in the control group according to clinical needs.

Therefore, there is great need to define the hemodynamically significant PDAs that should be treated [1, 5–7, 14, 15]. A study by Alagarsamy et al. concluded that there is no correlation between clinical symptoms and the presence and size of a PDA [16].

NiCaS® (NiCaS®, NI Medical, Petach Tikva, Israel) is a whole-body bioimpedance device. Bioimpedance monitoring has emerged in recent years as an easy non-invasive modality to monitor the patient's hemodynamic status [17, 18]. The basis behind the technology is that blood is more conductive than other body tissues [19]. The monitor sends a small electrical current through the body and measures the current's impedance (resistance). In every heartbeat, the blood vessels dilate, causing a decrease in the resistance. Using this change in resistance, together with the patient's other parameters influencing blood resistance (height, weight, sodium concentration, hematocrit, age and sex), we can calculate the patient's stroke volume by using the Frinerman and Tsoglin's algorithm [20].

Bioimpedance has been used in several medical situations, such as during surgeries and hemodialysis, to monitor the patient's hemodynamics. Mostly, it has been studied in adults, but there have been several studies done in children, affirming the accuracy of the device [18, 20–25]. Our hypothesis was that NiCaS can help in finding moderate and large PDA and thus in the future help in decision making in neonates with known PDAs who are deteriorating or safely monitor their improvement.

In this study, we used the NiCaS® device to monitor the hemodynamic status of premature infants with various degrees of PDA.

## Methods

This study was performed in the Neonatal Intensive Care Unit at Kaplan Medical Center, Israel and was approved by the Institutional Review Board of Kaplan Medical Center and the Israeli Ministry of Health.

Inclusion criteria were infants born at gestational age of less than 35 weeks with a birth weight of less than 1750 g. All infants had an echocardiography performed during the first days of their life for medical reasons.

Exclusion criteria were major heart malformations, or any severe health conditions (i.e., sepsis, necrotizing enterocolitis).

After parental consent, the neonates were non-invasively evaluated by NiCaS® (NiCaS®, NI Medical, Petach Tikva,

Israel). To collect patient signals, the NiCaS® electrodes were arranged in a wrist-to-ankle configuration. The other variables required for SV and CI calculation (age, gender, weight, height, hematocrit, and electrolytes) were taken from the patient's latest records and introduced into the algorithm at the start of monitoring, but were not necessarily measured the same day.

All hemodynamic measurements were taken by the NiCaS® device on the same day as the echocardiography, but not simultaneously. Stroke volume, cardiac output and total peripheral resistance were measured by the NiCaS® device. Stroke index (SI), cardiac index (CI), and total peripheral resistance index (TPRI) were calculated by dividing these parameters by body surface area (BSA) which was calculated using the Du Boise formula [26]. The study population was divided according to their PDA size as measured by the echocardiograms.

PDA size was estimated by cardiologists who compared the PDA to the left pulmonary artery and the aorta, by assessing retrograde aortic flow, and by measuring the pressure gradient across the PDA. The cardiologist was unaware of the NiCaS® results.

Small, moderate and large PDAs were defined in our unit as follows:

1. Small—diameter < 1 mm, LA/Ao (left pulmonary artery and the aorta) ration < 1.5, no retrograde flow in DecAo (descending aorta)
2. Moderate—diameter 1–2 mm, LA/Ao ration > 1.5, or some retrograde flow in DecAo
3. large—diameter > 2 mm, LA/Ao ration > 1.5, and retrograde flow in DecAo

## Statistical Analysis

Normal distribution of the hemodynamic parameters was assessed by Shapiro–Wilkinson and Kolmogorov–Smirnova tests. Most of the parameters were found to be non-normally distributed. Therefore, non-parametric tests were used for data analysis. For a two-parameter comparison, the Mann Whitney test was used, and for a three-parameter comparison, the Kruskal Wallis test was used. Correlations between PDA size and hemodynamic parameters were evaluated by calculating the Spearman correlation coefficient.

Statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) v. 20.0 for Windows.

## Results

A total of 36 patients met the inclusion criteria and parental consent was signed. Patient birth weeks ranged between 24 to 33 weeks gestation (mean of  $28 \pm 2.6$ ), and a birth weight between 608 and 1715 g. (mean  $1157 \pm 344$  g). For about two-two-thirds (67%), a PDA was seen in their first echocardiogram.

We classified the patients according to PDA size, and divided them into three groups: Group 1 had no or a small PDA, group 2 had a moderate PDA, and group 3 had a large PDA (Table 1).

A total of 61 NICaS® measurements were taken alongside echocardiograms, as several patients had more than one echocardiogram. Both SI and CI significantly increased from a median value of 22.6 ml/m<sup>2</sup> and 3.4 l/min/m<sup>2</sup> in group 1 to 23.8 and 3.7, and 39.8 and 5.4 in groups 2 and 3 respectively. The difference was statistically significant between groups 1 and 3 ( $P=0.005$  for SI and  $P=0.002$  for CI) and between groups 2 and 3 ( $P=0.037$  for SI and  $P=0.05$  for CI).

**Table 1** Birth weight and gestational age in the three groups

| First echo results |            |                 |                 |                  |
|--------------------|------------|-----------------|-----------------|------------------|
| Group              | PDA        | No. of patients | Gestational age | Birth weight     |
| 1                  | None-small | 17              | $29.2 \pm 2.4$  | $1.19 \pm 0.27$  |
| 2                  | Moderate   | 10              | $28.5 \pm 2.4$  | $1.19 \pm 0.37$  |
| 3                  | Large      | 9               | $27.1 \pm 2.6$  | $1.05 \pm 0.35$  |
| Total              |            | 36              | $28.8 \pm 2.6$  | $1.185 \pm 0.34$ |

**Table 2** PDA size and hemodynamic parameters

|   | PDA size (group number) |                |               | Comparison between groups ( $P$ value) |       |       |
|---|-------------------------|----------------|---------------|--|-------|-------|
|   | Small 1                 | Moderate 2     | Large 3       | "1-2"                                  | "2-3" | "1-3" |
| SI ml/m <sup>2</sup>  |                         |                |               |  |       |       |
| Mean $\pm$ std  | $24 \pm 8.3$            | $26 \pm 11$    | $36 \pm 12.2$ | 0.537                                  | 0.037 | 0.005 |
| Median  | 22.6                    | 23.8           | 39.8          |  |       |       |
| Range   | 13–50.4                 | 8.2–51.4       | 12.6–56.2     |  |       |       |
| CI ml/m <sup>2</sup>  |                         |                |               |  |       |       |
| Mean $\pm$ std  | $3.7 \pm 1.3$           | $4.1 \pm 1.8$  | $5.4 \pm 1.8$ | 0.327                                  | 0.05  | 0.002 |
| Median  | 3.4                     | 3.7            | 5.4           |  |       |       |
| Range   | 1.75–7.8                | 1.2–8.7        | 1.9–8.3       |  |       |       |
| TPRI dyn $\times$ sec/cm <sup>5</sup> $\times$ m <sup>2</sup> |                         |                |               |  |       |       |
| Mean $\pm$ std  | $1099 \pm 404$          | $1031 \pm 687$ | $730 \pm 334$ | 0.131                                  | 0.207 | 0.003 |
| Median  | 989.5                   | 784            | 655           |  |       |       |
| Range   | 390–1881                | 368–3119       | 394–1562      |  |       |       |

Significant differences were demonstrated in all hemodynamic parameters between the three groups. The largest difference was seen between the small and large PDA groups

SI stroke index, CI cardiac index, and TPRI total peripheral resistance index

TPRI decreased from 989 dyn  $\times$  s/cm<sup>5</sup>  $\times$  m<sup>2</sup> in group 1 to 783 and 655 in groups 2 and 3 respectively. The difference was statistically significant only between groups 1 and 3 ( $P=0.003$ ), but not between group 2 and 3 (Table 2).

A Spearman correlation analysis revealed a positive linear correlation between PDA size and the SI and CI ( $R=0.36$ ; 0.4 respectively), and a negative correlation between PDA size and TPRI ( $R=0.4$ ).

## Discussion

In this study, we found statistically significant differences in SI, CI and TPRI between infants with no or small PDAs, and infants with large PDAs. Both SI and CI increased and the TPRI decreased as the PDA size increased. When comparing only the closed or small PDA group with the large PDA group, the differences are even more significant. A positive correlation was found between PDA size and CI and SI and a negative correlation was found between the PDA size and TPRI.

These results reflect the hemodynamic changes that occur in the presence of a PDA. When a PDA is present, a portion of the cardiac output is diverted through the PDA to the lungs, resulting in a decreased effective cardiac output to the lower part of the body. To preserve adequate peripheral cardiac output, contractility increases and peripheral resistance decreases, allowing the heart to increase its overall stroke volume and cardiac output to overcome the “ductal steal”. In small to moderate PDAs, the flow through the PDA is insignificant, thus no significant change is seen in the cardiac output. However, in the large PDA group, the CI was 61%

higher than in patients with no PDA, reflecting a large flow through the PDA.

A recent study by de la Blanca et al. used a similar method called electrical velocimetry, with similar findings, showing a decrease in CO and an increase in peripheral resistance after PDA closure [27]. The NICaS® device used in our study was shown in multiple studies to be in good correlation with cardiac output, as measured by other, previously validated methods [22–25]. Most recently, in the study of Beck et al. in the pediatric population, a good correlation was found between NICaS® and the CardioQ® transesophageal Doppler, a minimally invasive cardiac output monitor [21].

Our study has several limitations. First, the small sample size, resulting from being a single center pilot study, prevented us from performing multiple analyses with stratification according to gestational age and birth weight. Second, PDA sizing was estimated according to echocardiographic criteria as detailed above and was somewhat subjective and operator dependent. Moreover, the NICaS® electrodes need to be placed above the radial artery in the wrist and the tibialis posterior artery in the ankle for accurate measurements. Small body proportions and IV lines may cause poor electrode placement. Lastly, the echocardiograph and NICaS® measurements were performed on the same day but not simultaneously, sometimes several hours apart, resulting in possible PDA size changes between the two tests, thus hampering the correlation.

In conclusion, we found significant differences in hemodynamic parameters between premature infants with and without significant PDAs. We believe these changes can aid in the diagnosis of large PDAs and in the decision to start treatment. The NICaS® device can provide a quick and simple bedside assessment, and together with an echocardiogram, can improve our treatment. Larger studies are needed to confirm our findings.

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## Compliance with Ethical Standards

**Conflict of interest** The authors of the article have no conflict of interest.

**Informed Consent** Before inclusion there we received maternal consent.

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