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Electrical cardiometry to monitor hemodynamic alternations during pharmacological closure of hemodynamically significant patent ductus arteriosus in preterm neonates

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Abstract
Background: Children with a hemodynamically considerable patent ductus arteriosus (hsPDA) may physiologically modify through developing a higher-than-normal CO, which could serve as a substitute for an extensive PDA or as sign of a poor outcome following pharmacological PDA closure. Electrical cardiometry (EC) can continuously and non-invasively evaluate various hemodynamic parameters. This study aimed to use electrical cardiometry EC to monitor hemodynamic alternations during pharmaceutical termination of hemodynamically significant patent ductus arteriosus (hsPDA) in preterm neonates.
Methods: In this prospective observational study at Tanta University Hospitals, NICU department, 80 preterm neonates with GA between 28 and 35 weeks were enrolled, 40 of them with hsPDA received I.V paracetamol treatment course, and 40 hemodynamically stable preterm as control. 20 responders were matched with their GA and weight to 20 non-responders.
Results: baseline SV and CO were significantly higher in hsPDA 40 preterm than control while baseline SVR was significantly higher in control. Also, SV and CO were significantly higher in Non-Responders than Responders at baseline. In Responders, SV and CO were significantly decreased while SVR increased after treatment. In Non-Responders, SV and CO were significantly increased while SVR decreased after treatment. Baseline SVR showed weak significant positive correlation with LA/Ao ratio in responders.
Conclusion: Preterm neonates with hsPDA had higher baseline CO, SV, duct size and LA/Ao ratio compared to the control group, ln contrast with respondents, those who didn't exhibited greater baseline CO and SV.

Keywords: Electrical cardiometry, hemodynamically significant patent ductus arteriosus, preterm neonates

Introduction
In healthy term infants, a patent ductus arteriosus (PDA) is a typical physiologic residue throughout the first three days of life. Even so, a PDA in preterm newborns leads to major medical issues such as breathing difficulties, intraventricular hemorrhage, necrotizing enterocolitis, congestive heart failure, and failure to thrive as an outcome of left to right shunting [1].
Substantial ductal shunting and the severity of PDA have been strongly linked with a rise in left ventricular cardiac output (CO). The fundamental cause is that a PDA with pronounced left-to-right flow can end up in arise in CO as a means to preserve systemic blood flow. In fact, cardiac output returns to normal after ductus closure following medication or surgical ligation [2].
Serial evaluations are frequently required when employing echocardiography to get relevant hemodynamic data, which can be laborious and challenging. In clinical settings, electrical cardiometry (EC), a non-invasive, impedance-based monitor, offers estimations of absolute cardiac output. EC is simple to operate, continuous in its measurements, and operator independent, in contrast to echocardiography [3].

Electrical cardiometry can be beneficial in tracking hemodynamic changes in the clinical situation since COEC is favorably linked to gestational age (GA) and weight, and hemodynamic reference by EC for newborns without PDA and without invasive breathing assistance has been documented [4].

The aim of this work was to use Electrical Cardiometry EC to monitor hemodynamic alternations when hemodynamically considerable patent ductus arteriosus (hsPDA) in premature infants is pharmacologically closed.

Patients and Methods

80 preterm neonates with GA between 28 and 35 weeks who were admitted to the NICU during their first week of life were included in this prospective observational research. From October 2019 to April 2020, this study was carried out in the Tanta University Hospital's NICU department.

After receiving clearance from the Faculty of Medicine at Tanta University in Tanta, Egypt's ethical committee, the study was carried out. All research participants' parents provided signed, fully informed permission.

Neonatal with major cardiac abnormalities, aortic arch anomalies, right-to-left or bidirectional shunting PDA, needing hemodynamic support, requiring high frequency ventilation, persistent pulmonary hypertension, major complications like intraventricular hemorrhage (IVH) grade ≥3 or necrotizing enterocolitis (NEC), and neonates with poor renal function were excluded from the study.

Patients were categorized into two main groups

Group I: included 40 preterm neonates with hemodynamically significant left-to-right PDA (hsPDA). They were further subdivided according to their response to the pharmacological treatment of (hsPDA) into 2 subgroups: Group IA included 20 responders and Group IB included 20 non-responders preterm neonates. I.V Paracetamol was given in a loading dose of 20 mg/kg, followed by 10 mg/kg every six hours for five days [5]. Within 24 hours following the end of the therapy, a responder was identified as the absence of ductal flow or a reduction in ductal diameter during echocardiography.

Group II: included 40 hemodynamically stable preterm neonates as a control group either completely free by routine echocardiography or with hemodynamically stable PDA, matched with patient group I as regard gestational age (GA), post-natal age and birth weight (BW).

Each patient had been revealed to: Full clinical examination, transthoracic echocardiography (TTE), laboratory investigations, chest X-Ray, and transcranial US.

Transthoracic echocardiography (TTE): The following commercially available ultrasound transducers and equipment were used for the echo cardiographic studies: Vivid 7, GE Healthcare, Hoten, Norway; Vivid 9, GE Healthcare, Horten, Norway; and ACUSON X300 machine, Siemens. Digital loops were sent to a workstation (Echo PAC, 112 and 113; GE, and Horten, Norway) for offline processing after being saved on the echocardiography device's hard drive. In respect to pharmacological therapy, serial echocardiogram was carried out within an hour of beginning of the treatment (baseline), 24 hours after the beginning of the course of therapy, and 24 hours after the end of the treatment regimen. This interval was chosen to provide for the greatest possible impact of the pharmaceutical therapy. Measures comprised left atrium to aortic root ratio (LA/Ao), left ventricular fractional shortening (FS), maximal flow velocity, pulsed-wave Doppler, ductal size and shunt direction, and left ventricular fractional shortening (FS).

Echocardiographic criteria for HsPDA: At least three of the circumstances that follow are necessitated to be true for a HsPDA diagnosis: In the left parasternal view, the PDA internal diameter was 1.4 mm/kg, which is the smallest colour flow diameter on the pulmonary side. [6] Pulsed Doppler imaging reveals a flow pattern across the PDA; "growing" and "pulsatile" patterns were assumed to be indicative of treatment-eligible HsPDA. [7, 8], maximum flow through PDA (measured by Doppler velocimetry in the left parasternal view), left atrium-to-aorta diameter ratio 1.4 (measured in the left parasternal long axis view), [9], and the existence of reverse flow in the descending aorta, calculated with the Doppler technique in the left parasternal short axis view, approximately below the ductal insertion [7].

Electrical cardiometry (EC)*:* The ICON® hemodynamic monitor (ICON Cardiotronics, Inc., La Jolla, CA 92307; Osypka Medical GmbH, Berlin and Germany, model C3, Serial no: 1817406) was applied to monitor hemodynamics. Infant demographic and anthropometric data (age, weight, and height) were input into the connected ICON EC device. In accordance with manufacturer guidelines, four skin electrodes (iElectrical Cardiometry Skin Sensors; Osypka Medical) were placed across the left side of the lateral aspect of the left thigh, the left mid-axillary line at the level of the xiphoid process, and the forehead. The EC electrodes were put as far away from the traditional NICU monitoring electrodes as feasible. The following elements were measured: stroke volume (SV), heart rate, cardiac output (CO), stroke volume variation (SVV), index of contractility (ICON), thorathic fluid content (TFC), and systemic vascular resistance (SVR). The original data were recorded 1 hour before treatment, 24 hours after therapy started out, and 24 hours after therapy ended.

Study outcomes: Electrical cardiometry provided a tool for continuous and non-invasive hemodynamic monitoring in preterm neonates and non-invasive monitoring of the hemodynamic changes that occurred during the pharmacological closure of hemodynamically significant PDA.

Sample Size Calculation: The total sample size was 80 preterm neonates (40 cases with hsPDA subdivides into 20 responders to treatment and 20 non-responders to treatment) and (40 control neonates).

Statistical analysis: With the aid of the IBM SPSS software package version 20.0, data was input into the computer for analysis. Numbers and percentages were employed to describe the qualitative data. The normality of the distribution was examined through the Shapiro-Wilk test. The range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR) have been utilized to characterize quantitative data. To compare between several groups, use the chi-square test for categorical data. The Friedman test contrasted more than two periods or stages, the F-test (ANOVA) compared between more than two groups, the Kruskal Wallis test contrasted between more than two examined groups, and the

Post Hoc Test (Dunn's) for pairwise comparisons. It was statistically noteworthy at $p<0.05$.

Results

Between groups, the demographic information was comparable. With respect to group I, the diastolic blood pressure was considerably greater in the control group. Diastolic pressure did not differ between the groups of respondents and non-responders.

Table 1: Demographic, clinical data & anthropometric measurements in the studied groups

		Group IA (n = 20)	Group IB (n = 20)	Group II (n = 40)	P
Demographic data					
GA (weeks)		31.70±0.86	32.15±0.88	32.02±0.66	0.161
Gender %	Male	14 (70.0)	12 (60.0)	21 (52.5)	0.427
	Female	6 (30.0)	8 (40.0)	19 (47.5)	
Post-Natal Age (days)		3.55±0.51	3.60±0.50	3.55±0.50	0.929
Weight (kg)		1.64±0.17	1.69±0.17	1.72±0.13	0.173
Length (cm)		41.45±0.94	41.65±1.14	42.08±1.0	0.065
Body surface area (m^2)		0.14±0.01	0.15±0.01	0.14±0.01	0.093
Ponderal index (gm/cm^3)		2.20±0.08	2.22±0.08	2.24±0.08	0.169
Delivery No (%)	C.S	10 (50.0)	12 (60.0)	24 (60.0)	0.736
	NVD	10 (50.0)	8 (40.0)	16 (40.0)	
Clinical data					
Respiratory rate		56.25±1.65	57.15±1.84	52.73±2.62	
Sig. bet. grps.		$p_1=0.414$, $p_2<0.001^*$, $p_3<0.001^*$			
Blood pressure (mmHg)	Systolic	61.45±1.85	61.85±1.50	62.05±2.04	$<0.001^*$
	Diastolic	33.95±1.88	34.80±1.99	37.58±1.81	
Sig. bet. grps.		$p_1=0.328$, $p_2<0.001^*$, $p_3<0.001^*$			
Mottling		6 (30.0)	5 (25.0)	4 (10.0)	$^{MC}p=0.096$
Feeding intolerance		4 (20.0)	2 (10.0)	3 (7.5)	$^{MC}p=0.417$
Urine output (ml/kg/hr)		2.94±0.45	3.18±0.38	3.15±0.34	0.080

Data is displayed as a mean, standard deviation, or frequency (%). Gestational age, or GA. NVD stands for a natural vaginal delivery. p: The p-value used to compare the three groups under study. At $p \leq 0.05$, something is statistically significant. Monte Carlo, MC. Responders make up Group IA. Non-Responders are in Group IB. II: Control group. The p-values are as follows: p1: for comparing Group I and Group II; p2: for comparing Group I and Group III; and p3: for comparing Group II and Group III.

The ductal size an LA/Ao were highest in non-responders, followed by responders, and then control group, with substantial considerable between all groups. The max. flow velocity was highest in control, followed by responders, then non-responders group. substantial considerable existed between group I and control group. Regarding FS measurements, there were no substantial considerable among the studied groups. The SV and CO values were highest in non-responders group IB, followed by responders subgroup IA, then control group II. The SVR measurements were highest in control group II, followed by responders subgroup IA, then non-responders subgroup IB. The measurements of HR, SVV, ICON and TFC were comparable among the three groups.

Table 2: Echo data and EC in the studied groups

Echo (Baseline)	Group IA (n = 20)	Group IB (n = 20)	Group II (n = 40)	P
Ductal size (mm)	2.72±0.24	3.05±0.22	1.30±0.10	$<0.001^*$
Sig. bet. grps.	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
Maximum flow rate (m/seconds)	2.02±0.22	1.78±0.23	2.89±0.12	$<0.001^*$
Sig. bet. grps.	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
LA/Ao	1.56±0.07	1.59±0.09	1.20±0.06	$<0.001^*$
Sig. bet. grps.	$p_1=0.404$, $p_2<0.001^*$, $p_3<0.001^*$			
FS (%)	38.95±2.16	39.10±1.94	38.17±2.64	0.277
EC (baseline)				
SV (ml)	3.24±0.20	3.60±0.14	2.75±0.15	$<0.001^*$
Sig. bet. grps.	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
HR	141.65±3.12	140.50±3.66	140.83±3.33	0.530
CO (L/m)	0.46±0.03	0.50±0.02	0.40±0.02	$<0.001^*$
Sig. bet. grps.	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
SVV (%)	8.38±0.48	8.45±0.51	8.45±0.50	0.845
ICON	87.20±4.10	87.30±3.64	87.0±3.61	0.953
TFC	26.90±0.97	26.90±0.79	26.33±1.42	0.102
SVR (dyns/cm5)	5771.6±472.5	5398.0±302.1	6841.6±441.2	$<0.001^*$
Sig. bet. grps.	$p_1=0.017^*$, $p_2<0.001^*$, $p_3<0.001^*$			

Data presented as mean ± standared or frequency (%). FS: fractional shortening. SV: Stroke Volume, HR: heart rate, CO: cardiac output, SVV: stroke volume variation, TFC: thoracic fluid content, SVR: systemic vascular resistance. *: Statistically significant at p≤ 0.05. p1: p value for comparing between Group I and Group II, p2: p value for comparing between Group I and Group III, p3: p value for comparing between Group II and Group III.

The ductal size showed a progressive substantial drop from the baseline measurements in responders group IA but showed a progressive considerable rise in non-responders group IB. The max. flow velocity showed a progressive considerable rise during the follow-up period in responders group IA but showed a progressive considerable decline in non-responders group IB. There was a considerable difference between the follow-up measurements and the baseline, as well as between the two follow-up measurements. The LA/Ao measurements showed a reduction from the baseline values after starting treatment in responders group IA but showed a slight boost in non-responders group IB, there were no considerable differences among the three-time points. As regards the FS measurements, no important alterations from the baseline level were detected. The SV and CO measurements showed a significant decrease after starting treatment from the baseline values. After therapy started off, contrasted to the baseline values, the SVR measure confirmed a considerable rise. After completion of treatment, there was a significant decrease from the measurements after starting treatment. The measurements of HR, SVV, ICON, and TFC did not show significant changes from the baseline at the follow-up.

Table 3: Echo Follow-up data in responders group IA (n=20) and in non-responders group IB (n=20)

Echo	Baseline	24hr after treatment started	24hr after completion of treatment	P
Group IA (n = 20)				
Ductal size (mm)	2.72±0.24	2.27±0.22	1.74±0.20	<0.001*
Sig. bet. Periods	p_1<0.001*, p_2<0.001*, p_3<0.001*			
Max flow velocity (m/sec)	2.02±0.22	2.29±0.21	2.64±0.13	<0.001*
Relevance across Periods	p_1<0.001*, p_2<0.001*, p_3<0.001*			
LA/Ao	1.56±0.07	1.43±0.06	1.38±0.06	<0.001*
Relevance across Periods	p_1<0.001*, p_2<0.001*, p_3=0.003*			
FS (%)	38.95±2.16	38.25±1.71	38.05±2.48	0.148
Group IB (n = 20)				
Ductal size (mm)	3.05±0.22	3.20±0.19	3.38±0.21	<0.001*
Sig. bet. Periods	p_1<0.001*, p_2<0.001*, p_3<0.001*			
Max flow velocity (m/sec)	1.78±0.23	1.68±0.14	1.52±0.19	<0.001*
Sig. bet. periods	p_1=0.001*, p_2<0.001*, p_3<0.001*			
LA/Ao	1.59±0.09	1.60±0.12	1.68±0.07	0.135
FS (%)	39.10±1.94	39.15±1.53	38.95±1.47	
EC				
Group IA				
SV (ml)	3.24±0.20	2.89±0.18	3.06±0.19	<0.001*
Sig. bet. periods	p_1<0.001*, p_2<0.001*, p_3<0.001*			
HR	141.65±3.12	140.85±3.42	141.5±3.39	0.138
CO (L/m)	0.46±0.03	0.41±0.02	0.43±0.02	<0.001*
Sig. bet. periods	p_1<0.001*, p_2<0.001*, p_3<0.001*			
SVV (%)	8.38±0.48	8.40±0.50	8.40±0.50	0.330
ICON	87.20±4.10	87.20±3.49	85.95±3.98	0.247
TFC	26.90±0.97	26.35±1.42	26.45±1.32	0.099
SVR (dyns/cm5)	5771.6±472.5	6473.8±321.6	6105.9±400.1	<0.001*
Sig. bet. periods	p1<0.001*, p2<0.001*, p3<0.001*			
Group IB				
SV (ml)	3.60±0.14	3.56±0.15	3.68±0.12	<0.001*
Sig. bet. periods	p_1=0.148, p_2<0.001*, p_3<0.001*			
HR	140.5±3.66	140.0±3.06	140.25±2.69	0.550
CO (L/m)	0.50±0.02	0.50±0.02	0.52±0.02	<0.001*
Sig. bet. periods	p_1=0.028*, p_2=0.001*, p_3<0.001*			
SVV (%)	8.45±0.51	8.55±0.51	8.55±0.51	0.270
ICON	87.30±3.64	87.65±3.56	87.80±3.53	0.835
TFC	26.90±0.79	26.80±0.83	26.55±0.83	0.157
SVR (dyns/cm5)	5398.0±302.1	5454.9±313.1	5238.4±214.8	<0.001*
Sig. bet. periods	p_1=0.496, p_2=0.001*, p_3<0.001*			

Data presented as mean ± standared. Relevance across Periods were made via Post Hoc Test (Bonferroni). p_1: p value for comparing between Baseline and 24hr after treatment started, p_2: p value for comparing between Baseline and 24hr after completion of treatment, p_3: p value for comparing between 24hr after treatment started and 24hr

after completion of treatment.*: Statistically significant at p ≤ 0.05.

There were considerable negative associations between HR and weight, gestational age, length, and body surface area. As well, the SVR showed a significant positive weak association with LA/Ao. Otherwise, there were no observed significant associations.

Table 4: Correlations between EC data at baseline and (demographic, anthropometric and Echo data) in responders group IA (n= 20)

		EC (baseline)						
		SV	**HR**	**CO**	**SVV**	**ICON**	**TFC**	**SVR**
Weight	R	0.251	-0.671	-0.012	0.294	-0.282	-0.626	-0.039
	P	0.285	0.001*	0.960	0.208	0.228	0.003	0.871
GA (weeks)	R	0.411	-0.666	0.175	0.346	-0.220	-0.541	-0.173
	P	0.072	0.001*	0.461	0.135	0.352	0.014	0.466
Length	R	0.348	-0.677	0.155	0.187	-0.201	-0.639	-0.124
	P	0.132	0.001*	0.515	0.429	0.395	0.002	0.603
Body surface area	R	0.230	-0.572	0.000	0.296	-0.142	-0.512	-0.029
	P	0.328	0.008*	1.000	0.206	0.551	0.021	0.903
Ductal size	R	0.194	0.038	0.237	0.138	0.044	-0.037	-0.217
	P	0.412	0.872	0.314	0.563	0.853	0.878	0.359
Max flow velocity (m/sec)	R	-0.274	-0.113	-0.340	0.025	-0.122	-0.040	0.246
	P	0.243	0.637	0.142	0.917	0.609	0.868	0.297
LA/Ao	R	-0.402	0.070	-0.536	0.218	0.127	0.166	0.577
	P	0.079	0.769	0.015	0.355	0.593	0.483	0.008*
FS (%)	R	0.275	-0.167	0.286	0.296	-0.034	-0.078	-0.255
	P	0.241	0.483	0.221	0.206	0.885	0.744	0.279

r: Pearson coefficient. *: mathematically considerable at p ≤ 0.05

There were substantial negative associations between HR and weight, gestational age, length, and body surface area. Otherwise, there were no observed significant associations.

Table 5: Correlations between EC data 24hr after treatment completed and (demographic, anthropometric and Echo data) in responders group IA (n= 20)

		EC (24hr after completion of treatment)						
		SV	**HR**	**CO**	**SVV**	**ICON**	**TFC**	**SVR**
Weight	r	0.252	-0.731	-0.047	0.239	0.059	0.010	-0.012
	p	0.283	<0.001*	0.845	0.311	0.806	0.968	0.961
GA (weeks)	r	0.371	-0.669	0.138	0.291	0.072	0.032	-0.154
	p	0.107	0.001*	0.561	0.214	0.763	0.892	0.516
Length	r	0.369	-0.707	0.094	0.155	0.202	-0.087	-0.081
	p	0.109	<0.001*	0.693	0.513	0.392	0.716	0.734
Body surface area	r	0.260	-0.648	-0.053	0.246	-0.242	0.101	0.029
	p	0.268	0.002*	0.825	0.295	0.304	0.671	0.904
Ductal size	r	0.176	-0.148	0.060	0.219	-0.202	-0.142	0.117
	p	0.457	0.534	0.801	0.353	0.393	0.549	0.623
Max flow velocity (m/sec)	r	-0.406	0.330	-0.262	-0.144	-0.067	0.270	-0.034
	p	0.076	0.155	0.265	0.545	0.778	0.249	0.886
LA/Ao	r	-0.297	0.222	-0.253	0.272	-0.370	-0.273	0.338
	p	0.204	0.348	0.281	0.246	0.109	0.245	0.145
FS (%)	r	-0.230	-0.022	-0.365	0.279	0.022	0.234	0.313
	p	0.330	0.928	0.113	0.234	0.928	0.320	0.180

r: Pearson coefficient. GA: gestational age, FS: fractional shortening. *: Statistically significant at p≤ 0.05

There were significant negative associations between SVV and weight, gestational age, length, body surface area, and Max flow velocity. Alternatively, SVR and FS% had a very strong positive correlation. In addition, there was a strong positive correlation between CO and LA/Ao. Otherwise, no statistically significant relationships were found.

Table 6: Correlations between EC data at baseline and (demographic, anthropometric and Echo data) in non-responders group IB (n= 20)

		EC (baseline)						
		SV	**HR**	**CO**	**SVV**	**ICON**	**TFC**	**SVR**
Weight	r	0.183	-0.068	0.149	-0.584	-0.063	-0.449	-0.154
	p	0.439	0.775	0.530	0.007*	0.792	0.047	0.517
GA (weeks)	r	0.136	-0.008	0.153	-0.630	-0.064	-0.435	-0.165
	p	0.568	0.973	0.521	0.003*	0.787	0.055	0.486
Length	r	0.121	-0.107	0.088	-0.531	-0.253	-0.511	-0.090
	p	0.611	0.652	0.713	0.016*	0.282	0.021	0.706
Body surface area	r	0.247	-0.063	0.205	-0.494	-0.264	-0.466	0.010
	p	0.294	0.793	0.385	0.027*	0.260	0.038	0.968

Ductal size	r	-0.161	0.125	-0.122	0.367	0.564	0.117	0.089
	p	0.497	0.599	0.609	0.112	0.010*	0.625	0.708
Max flow velocity (m/sec)	r	0.112	-0.168	0.067	-0.489	-0.595	-0.309	-0.052
	p	0.637	0.479	0.780	0.029*	0.006*	0.185	0.827
LA/Ao	r	-0.006	0.115	0.097	0.149	0.184	0.050	-0.011
	p	0.980	0.628	0.683	0.530	0.437	0.834	0.963
FS (%)	r	0.216	-0.148	0.038	0.005	-0.034	0.247	-0.169
	p	0.362	0.534	0.873	0.982	0.886	0.293	0.477

r: Pearson coefficient. GA: gestational age, FS: fractional shortening. *: substantial noteworthy at $p \leq 0.05$

There were significant negative associations between SVV and weight, gestational age, length, body surface area and Max flow velocity. Otherwise, there were no observed significant associations.

Table 7: Correlations between EC data 24hr after treatment completed and (demographic, anthropometric and Echo data) in non-responders group IB (n= 20)

		EC (24hr after completion of treatment)						
		SV	**HR**	**CO**	**SVV**	**ICON**	**TFC**	**SVR**
Weight	R	0.152	-0.328	-0.012	-0.575	0.311	-0.043	0.084
	P	0.523	0.158	0.959	0.008*	0.182	0.857	0.726
GA (weeks)	R	0.223	-0.262	0.076	-0.666	0.368	-0.193	0.014
	P	0.344	0.264	0.750	0.001*	0.111	0.415	0.952
Length	R	0.134	-0.245	0.005	-0.649	0.375	-0.064	0.120
	P	0.572	0.298	0.982	0.002*	0.103	0.787	0.616
Body surface area	R	0.370	-0.094	0.264	-0.494	0.221	-0.195	0.070
	P	0.108	0.694	0.261	0.027*	0.350	0.411	0.768
Ductal size	R	-0.200	-0.016	-0.265	0.376	0.119	-0.068	0.069
	P	0.398	0.946	0.259	0.102	0.617	0.777	0.772
Max flow velocity (m/sec)	R	0.150	-0.039	0.178	-0.587	0.013	-0.090	-0.023
	P	0.529	0.870	0.453	0.007*	0.958	0.705	0.924
LA/Ao	R	-0.059	-0.102	0.059	0.108	0.021	-0.200	0.134
	P	0.804	0.668	0.804	0.651	0.931	0.397	0.574
FS (%)	R	-0.150	0.030	-0.004	0.179	0.059	0.284	0.078
	P	0.527	0.900	0.986	0.450	0.805	0.224	0.743

r: Pearson coefficient. GA: gestational age, FS: fractional shortening. *: Statistically significant at $p \leq 0.05$

Discussion

Baseline measurements obtained by echocardiography showed that ductal size and LA/Ao were highest in non-responders group, followed by responders group IA, and then substantial differences between all groups in the control group II ($p<0.001$). The max. flow velocity was highest in (control group II), followed by (responders group IA), then (non-responders group IB) with substantial important between all the groups ($p<0.001$). This disagreed from Hsu *et al*., [10] who enrolled 18 preterm neonates received three days' course of ibuprofen for hsPDA and 18 infants without PDA, There was no discernible difference between responders along with non-responders in terms of baseline ductal size, maximum flow velocity, or LA/Ao ratio when 9 responders were contrasted with 9 non-responders of 18 PDA neonates.

With agreement with the results, Pees *et al*., [11] who screened 29 preterm neonates < 28 week GA for hsPDA at 24–72 h of life in observational longitudinal study of which The ibuprofen therapy group comprised 15 newborns with a hsPDA, 9 infants constituted control group, despite the fact that it tended to be smaller in the responder group when linked to birth weight (p=0.073), it came to light that baseline ductal diameter was comparable across responders and non-responders.

Our Echo follow-up data in responders group IA showed that ductal size showed a progressive significant decrease, while there were significant variations between each follow-up, the maximum flow velocity rose gradually over the course of the follow-up period (p 0.001). This was in agreement with Pees *et al*. [11], who noted that 3 children (20%) had already closed ducts 24 hours after receiving the first dosage of ibuprofen, while 11 of the 12 remaining newborns had reduced ductal diameters. All infants who responded needed a second round of therapy because their ducts were closed or had a dropped width after the procedure was finished. Additionally, they reported that all responder infants' maximum flow velocity enhanced 24 hours after the first ibuprofen therapy (three of the kids already had a closed PDA).

According to our Echo follow-up data in non-responders group IB in which ductal size showed a progressive significant increase from the baseline measurements, while max. flow velocity showed a progressive significant decrease during the follow-up period from baseline. Matching to our results, Pees *et al*., [11] reported that the 8 of non-responders showed a lower PDA max. Flow velocity after completing 1st course of ibuprofen compared to baseline measurements and After the second cycle of ibuprofen, 5 non-responders who underwent surgical ligation had a wider ductal diameter.

The baseline data extracted from EC in our studied groups showed that SV and CO values were highest in non-responders group IB, followed by responders group IA, then control group II with mathematically noteworthy among all the groups ($p<0.001$). This agreed with Hsu *et al*. [12] found that CO_{EC} was significantly highest in PDA infants, non-responders, followed by responders, then infants with no PDA with significant differences among all the groups. But in contrast to our results, They discovered that there was only an important distinction between responders and non-responders in the baseline COEC but not the SVEC.

In (responders group IA), SV and CO measurements showed a significant decrease after starting treatment from the baseline values, then significant increase after completion of treatment. Meanwhile, the levels after completing treatment were still significantly lower than the baseline measurements (p<0.001). SVR measurement displayed important distinction after starting treatment from the baseline values, then significant decrease from the measurements after completion of treatment. Meanwhile, the levels after completing treatment were still significantly higher than the baseline measurements (p<0.001). de la Blanca *et al*. [12] who conducted similar prospective observational study that included 18 preterm infants (12 received ibuprofen for hsPDA, matched to our results regarding responders, 72 hours after the start of therapy, they discovered a substantial reduction in systolic volume (SVI 1.88 vs 1.62 ml/kg) as well as a statistically significant decline in median COEC from 0.29 to 0.24L/kg/min (17%). In contrast to our babies, who demonstrated that SVR levels after completing therapy were considerably higher than the baseline measures, they also reported a non-significant rise in SVR (8940 vs 10,637 dyn/cm2; P 0.14), 72 hours after the first dosage of ibuprofen.

Hsu *et al*. [10] agreed with our results that COEC was reduced by 25 ml/kg/min, which implied an important but small-scale decline or ten percent when comparing baseline CO_{EC} to initial ductal closure signs visualized by echocardiography in responders.

In (non-responders group IB), CO measurements showed a significant decrease after starting treatment, then significant increase after completion of treatment which were significantly higher than the baseline measurements also. Hsu *et al*. [10] study agreed with our results which discovered that 4/9 (44%) of non-responders also had COEC reductions of more than 10% at various time periods.

In contrast to our outcomes, de la Blanca *et al*. [12] reported that the COEC maintained steady and no alterations at any stage of the therapy were identified in the non-responding patients in the pharmaceutical group.

In responders group IA, we found no observed significant associations between CO data at baseline and Ductal size or LA/Ao. Hsu *et al*. [10] noted that baseline COEC has a positive relationship to PDA diameter and LA/Ao in contrary to our outcomes Owing to the positive link, babies with higher COEC are more probable to have more substantial ductal shunting.

Also in responders group IA in that research, the SVR revealed weak association to LA/Ao (coefficient 0.577, p=0.008). Otherwise, there were no observed significant associations.

Conclusions

Preterm neonates with hsPDA had higher baseline CO, SV and lower SVR compared to control group, and non-responders had higher baseline CO, SV and lower SVR compared to responders. Both SV and CO were significantly decreased while SVR increased after treatment in Responders group, while both SV and CO were significantly increased while SVR decreased after treatment in Non-Responders.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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