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**Acknowledgement of Submission (#IJN-2102-2040)**

1 message

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Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Sunny Mariana Samosir, Martono Tri Utomo, Mahrus Abdul Rahman, Agus Harianto, Risa Etika, Dina Angelika, Kartika Darma Handayani, Mahendra Tri Arif Sampurna

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I wish to acknowledge receiving the of the above mentioned manuscript.

It should be noted that the manuscript will be reviewed for possible publication in the Scientific Journals Management System.

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I wish to take this opportunity to thank you for sharing your work with us.

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Executive managing Editor of **Iranian Journal of Neonatology IJN**



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**Manuscript Needs Major Revision (#IJN-2102-2040 (R2))**

2 messages

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Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Sunny Mariana Samosir, Martono Tri Utomo, Mahrus Abdul Rahman, Agus Harianto, Risa Etika, Dina Angelika, Kartika Darma Handayani, Mahendra Tri Arif Sampurna

Dear **Mr. Martono Tri Utomo**

Your manuscript has obtained major revisions. In this case we normally treat it as unacceptable for publication. However, as numerous editorial errors have pointed out by the reviewers, the **Iranian Journal of Neonatology IJN** editor believes that the manuscript could be rectified and prepare for possible publication.

Please let us know your views in this regard and in the case of positive response, reply us within 7 days time.

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Reviewers Recommendation:

**Reviewer 1:**

Reviewer Comment For Author:

Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

For each variable of interest, give sources of data and details of methods of assessment

Describe any efforts to address potential sources of bias

Discuss limitations of the study, taking into account sources of potential bias or imprecision.  
Discuss both direction and magnitude of any potential bias

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Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Sunny Mariana Samosir, Martono Tri Utomo, Mahrus Abdul Rahman, Agus Harianto, Risa Etika, Dina Angelika, Kartika Darma Handayani, Mahendra Tri Arif Sampurna

Date: 2021-02-16

Dear **Mr. Martono Tri Utomo**Thank you for submitting the revised file of your manuscript to the **Iranian Journal of Neonatology IJN**

The Editorial Office will proceed on your manuscript and inform you in the earliest time.

If there is anything else, please do not hesitate to contact us.

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Executive Managing Director of **Iranian Journal of Neonatology IJN**

1 **HEMODYNAMIC SIGNIFICANT PATENT DUCTUS ARTERIOSUS EFFECT ON**  
2 **TISSUE OXYGENATION IN PRETERM INFANT: A STUDY USING NEAR**  
3 **INFRARED SPECTROSCOPY**

4  
5 **ABSTRACT**

6 **Background:** Hemodynamic significant Patent Ductus Arteriosus (hsPDA) is one of the main  
7 complications of preterm birth. However, its management still needs further development. Ductal  
8 stealing, resulting in pulmonary hyperperfusion and systemic hypoperfusion, potentially causes  
9 oxygenation disorders that lead to target organ disruptions (i.e. cerebral, abdominal, and renal).  
10 Hence, monitoring tissue oxygenation is essential to detect organ disorders. Previous studies  
11 revealed that near infrared spectroscopy (NIRS) showed a promising result as a non-invasive  
12 method to monitor tissue oxygenation.

13 **Objective:** The study aimed to analyze the tissue oxygen saturation ( $rSO_2$ ) differences of  
14 premature babies with and without hsPDA.

15 **Patients and Methods:** A cross-sectional study was conducted on preterm infants aged 3-7 days  
16 with 24-33<sup>6/7</sup> weeks of gestation. hsPDA diagnosis was carried out by echocardiography; defined  
17 as >1.5mm diameter of ductus arteriosus and >1.4 left pulmonary artery and aorta (La/Ao) ratio.  
18 NIRS monitoring was carried out to measure tissue oxygen saturation of the cerebral ( $r_cSO_2$ ),  
19 abdomen ( $r_aSO_2$ ), and renal ( $r_rSO_2$ ). The statistical analysis was undertaken using SPSS 21.0.

20 **Results:** There were 11 out of 52 infants categorized as hsPDA. Mean birth weight was  
21 1213±293 gram; Mean gestational age was 30.72±2.01 weeks; and, Mean ductus diameter in  
22 hsPDA was 2.84±0.93 mm. There was no significant difference between the hsPDA and non-  
23 hsPDA groups in  $r_cSO_2$  (75.27±9.14% vs 79.03±9.11%;p=0.238),  $r_aSO_2$  (65.60±11.07% vs  
24 67.48±10.17%;p=0.594), and  $r_rSO_2$  (76.41±14.98% vs 82.61±10.41%;p=0.218).

25 **Conclusion:** The existence of hsPDA doesn't affect the oxygenation in cerebral, abdominal, and  
26 renal tissue in preterm babies. The decision regarding optimal time for ductal closure should be  
27 reconsidered.

28 **Keywords:**

29 *preterm infant, hemodynamic significant patent ductus arteriosus, near infrared spectroscopy*

30

31 **INTRODUCTION**

32

33 Ductus arteriosus (DA) will normally shrink after birth in term infant and be functionally  
34 closed at the age of 72 hours. The ductal closure is delayed until 4 days of age in 10% of preterm  
35 babies born in 30-37 weeks, 80% of those born in 25-28 weeks, and 90% of those born less than  
36 24 weeks of gestational age<sup>1,2</sup>. The persistent DA can cause hemodynamic significant Patent  
37 Ductus Arteriosus (hsPDA) where the systemic shunt to the pulmonary vessels results in  
38 pulmonary hyperperfusion and systemic hypoperfusion<sup>3</sup>. Therefore, understanding tissue  
39 perfusion and oxygenation is important as a consideration for the administration of ductal closure  
40 therapy in premature infants to avoid further morbidity and mortality<sup>4-6</sup>. The ductal shunting  
41 from systemic to pulmonary blood flow has an impact on the cerebral, abdominal, and renal  
42 circulation<sup>7</sup>. Uncorrected hsPDA can cause intra ventricular hemorrhage, necrotizing  
43 enterocolitis (NEC), and renal insufficiency<sup>6</sup>. The long-term impact of decreased cerebral  
44 oxygenation in infants less than a month includes brain damage and development disorders<sup>8</sup>.

45 Clinical assessment and echocardiography become reliable methods in diagnosing hsPDA.  
46 Near Infrared Spectroscopy (NIRS) has been validated as a non-invasive tool to measure tissue  
47 oxygen saturation (rSO<sub>2</sub>) that can detect early changes in organ perfusion and oxygenation, thus,  
48 it can help identify and monitor the hsPDA therapy<sup>9</sup>. A study by van der Laan showed that  
49 cerebral and renal oxygenation are not affected by hsPDA.<sup>6</sup> Lemmers et al., and Cohen et al.,  
50 proved the negative effects of hsPDA on cerebral oxygenation in premature infants<sup>8,10</sup>. There  
51 have been many studies on regional perfusion and oxygenation in premature infants with NIRS.<sup>8-</sup>  
52 <sup>10</sup> However, to the best of the researcher's knowledge, there have not been enough studies on  
53 regional oxygenation differences especially in preterm infants in our country, Indonesia, using  
54 NIRS.

55 The present study aimed to study regional tissue oxygenation differences in preterm infants  
56 with hemodynamic significant and non-hemodynamic significant Patent Ductus Arteriosus using  
57 NIRS in the early days of life of preterm babies.

58

59

## 60 **PATIENTS AND METHODS**

### 61 *Patients*

62 This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during

63 study times. The samples were determined using consecutive sampling technique. All preterm  
64 babies (with gestational age of 24-33 weeks) were born between November 2019 and May 2020  
65 at the tertiary level neonatal intensive care unit of Dr. Soetomo General Hospital whose oxygen  
66 support devices (i.e. high flow nasal canula, continuous positive airway pressure, invasive and  
67 non-invasive ventilator) were eligible for inclusion. Patients with multiple congenital anomaly,  
68 ductal dependent cyanotic heart defect, early onset of septicemia, and incomplete consent from  
69 parents were excluded. Demographic and clinical data were collected from medical records. The  
70 sample size is calculated using a formula for continuous data with the aim of hypothesizing two  
71 or more group. The ratio between the hsPDA and non hsPDA group was based on the previous  
72 study.<sup>11</sup>

**Commented [i-1]:** Setting and location: 3<sup>rd</sup> level NICU in Dr Soetomo General Hospital  
Period of recruitment = Nov 2019-May 2020

**Commented [i-2]:** eligibility criteria, sources, and participant selection methods

**Commented [i-3]:** the study size calculation

#### 74 *Echocardiography*

75 Echocardiography screening was performed between 3<sup>rd</sup> and 7<sup>th</sup> postnatal day by pediatric  
76 cardiology consultant using Sonoscape Portable Digital Color Doppler Ultrasound System Model  
77 S9 (SonoScape, Shenzhen). Echocardiography was performed by one pediatric cardiology  
78 consultant to minimize performance variability. The samples were categorized into two groups:  
79 hsPDA and non hsPDA. The hsPDA was considered existing if there were a ductus arteriosus  
80 with diameter > 1.5 mm on constriction phase, pulmonary perfusion seen in the left pulmonary  
81 artery diameter and aorta diameter ratio (LA/Ao) was > 1.4, and left to right shunt were present.  
82 While DA that was already closed and did not fulfill the requirement for hsPDA was considered  
83 non-hsPDA.

**Commented [i-4]:** Period of sample recruitment and time framing for data collection. Echocardiography data collection

#### 84 *NIRS Measurements*

85 INVOS 5100C near infrared spectrometer and neonatal sensors (Covidien, USA) were used  
86 to monitor the tissue oxygen saturation on the day of echocardiography was performed. Multisite  
87 sensors were placed on the frontoparietal side of the infant's head to evaluate the cerebral tissue  
88 oxygen saturation ( $r_cSO_2$ ), on the inferior side of umbilicus to evaluate the abdominal tissue  
89 oxygen saturation ( $r_aSO_2$ ), and on the lateral posterior flank to evaluate the renal oxygen  
90 saturation ( $r_rSO_2$ ). The evaluation was performed by different examiners without knowing the  
91 echocardiography result. The oxygen saturation changes were observed in 15 minutes  
92 continuously. Every 15 seconds, the machine records tissue oxygen saturation data. Mean  
93 regional rSO<sub>2</sub> were used for further analysis. A pulse oxymeter was also put on the baby's right

**Commented [i-5]:** exposure: babies with and without hsPDA

**Commented [i-6]:** effort to minimize bias

**Commented [i-7]:** NIRS data collection

94 hand to evaluate the peripheral oxygen saturation (spO<sub>2</sub>) for further calculation of fractional  
95 tissue oxygen extraction (FTOE) on each location using the following formula:  $FTOE = (spO_2 -$   
96  $rSO_2)/spO_2$ . A 15-minute measurement was simultaneously observed and the mean values were  
97 obtained.

#### 98 *Statistical Analysis*

99 Differences in clinical characteristics of the two sample groups of hsPDA and non hsPDA  
100 were analyzed using Chi square test, Fisher exact test, and exact probability test. Statistical  
101 analyses for each regional oxygen saturation and fractional tissue oxygen extraction between  
102 both groups were performed using independent t-test and Mann Whitney test. IBM SPSS 21.0  
103 was used for all statistical analyses with significant value (*p*) at < .05.

#### 104 *Ethics*

105 The ethical clearance was issued by the Ethical Committee of Dr. Soetomo General Hospital  
106 (No.1766/105/XI/2019).

107

## 108 **RESULTS**

109 Our study shows that three babies had multiple congenital anomalies, four babies had  
110 early onset of septicemia, and the others were excluded due to incomplete data and consent.  
111 Eleven infants classified as hsPDA group based on echocardiography. There were 25 (48%) and  
112 27 (52%) preterm male and female babies, respectively. Majority of the subjects was in 28-<32  
113 weeks of gestational age (55.8%) with mean gestational age was 30.72±2 weeks for hsPDA and  
114 30.78±2 weeks for non hsPDA. Mean birth weight for hsPDA and non hsPDA were 1213±293  
115 and 1272±306 grams, respectively.

116 Table 1 shows the neonatal characteristics for both groups. There was no significant  
117 difference in all variables. Therefore, the samples considered as homogenous.

118 This study obtained that the smallest DA's diameter was 1.5 mm and the largest one was 4.8  
119 mm in the hsPDA group. From the eleven samples in hsPDA group, the duct diameter was  
120 obtained with an average of 2.84±0.93. The comparison between LA and Ao had an average  
121 score of 1.56±0.26. The ejection fraction of hsPDA and non hsPDA group were 71.55±5.72 and  
122 73.94±9.4%, respectively.

123 Linear regression was used to evaluate comorbidities on samples, namely perinatal asphyxia,  
124 respiratory distress syndrome, and persistent pulmonary hypertension of the newborn as

125 confounding factors of the regional oxygen saturation. All measurement was not significant.  
126 In accordance to Table 2, there were no significant differences in the tissue oxygen saturation  
127 ratio of cerebral ( $r_c\text{SO}_2$ ), abdominal ( $r_a\text{SO}_2$ ), or renal ( $r_r\text{SO}_2$ ) areas between hsPDA babies and  
128 non hsPDA ( $p = .238$ ,  $p = .598$ , and  $p = .218$  respectively). Fractional oxygen extraction in  
129 cerebral (cFTOE), abdominal (aFTOE), and renal (rFTOE) areas between the hsPDA and non  
130 hsPDA groups also revealed non-significant difference ( $p = .473$ ,  $p = .578$ , and  $p = .151$ ,  
131 respectively).

Commented [i-[8]: outcome of this study (tissue oxygen saturation & fractional oxygen extraction in tissue)

### 133 DISCUSSION

134 The present study obtained the characteristics of the two groups that were not significantly  
135 different so that it can be compared. Previous study showed that the incidence of hsPDA  
136 increased with lower oxygen saturation<sup>12</sup>. The mean SpO<sub>2</sub> in this study was around 97% with  
137 minimal setting of CPAP and mechanical ventilation. There were no significant differences in  
138  $r_c\text{SO}_2$  ( $p = .238$ ) between the hsPDA and non hsPDA groups in the study. These findings are in  
139 line with previous observational cohort designs by van der Laan et al. in Netherland, in which  
140 oxygen saturation and oxygen extraction in cerebral and renal of 49 preterm infants with  
141 gestational age <32 weeks evaluated using NIRS were not affected by hsPDA.<sup>6</sup> The  $r_c\text{SO}_2$  results  
142 in hsPDA group (69%) were lower than non hsPDA group (76%) and cFTOE in hsPDA group  
143 (0.22) were higher than non hsPDA group (0.33).

144 In contrast to the results of several previous research where a decrease in cerebral  
145 oxygenation was found in hsPDA, Lemmers et al. reported a lower  $r_c\text{SO}_2$  in infants with hsPDA  
146 compared to the asymptomatic PDA group (62±9% and 72±10%, sequentially). The difference  
147 might be caused by several factors affecting the patient's hemodynamics. In Lemmers' study, the  
148 patients in hsPDA group mostly used ventilator, morphine as sedatives that caused peripheral  
149 vasodilation, and more inotropic than control. Dopamine administration could increase cardiac  
150 output that affected an elevating perfusion. In addition, in the previous study, the sampling  
151 period was earlier (in the first 72 hours) compared to the present study (3-7 postnatal days)  
152 which could affect the results of oxygenation measurement. It is agreed that the cerebral oxygen  
153 supply increases as the baby age. Tissue oxygen extraction (FTOE) was also significantly higher  
154 in premature infants with hsPDA than those with non hsPDA<sup>13</sup>. The relationship between oxygen  
155 transport ( $\text{DO}_2$ ) and tissue oxygen consumption ( $\text{VO}_2$ ) is fractional tissue oxygen extraction



156 (FTOE= $VO_2/DO_2$ ). Negative correlation between  $r_cRSO_2$  and cFTOE indicated that if there was  
157 a decrease in the brain oxygen supply in sick premature babies, there was an increase in cerebral  
158 oxygen extraction aimed to maintain oxygen availability in the brain<sup>14</sup>.

159 A retrospective study by Chock et al. showed that a low  $r_cSO_2$  value of < 66% was associated  
160 with the presence of hsPDA in preterm infants<sup>9</sup>. Although the oxygenation value in cerebral  
161 tissue of hsPDA infant was lower than non hsPDA, the average value was still higher compared  
162 to the < 40% cerebral oxygen saturation limit associated with the appearance of symptoms, such  
163 as ischemic lesions and neuron damage. The normal value of  $r_cSO_2$  for preterm babies is 55-  
164 85%<sup>15</sup>. According to Dix et al., higher  $r_cSO_2$  values in neonatal sensors compared to adult NIRS  
165 sensors might be caused by differences in NIRS signal reception process where neonatal NIRS  
166 sensor algorithmic adjusted to thinner neonatal calvarium so that the light is easier to enter<sup>16</sup>.

167 Although the determination of "to treat or not to treat" is still a clinical question nowadays,  
168 Poon et al., reported an improvement in cFTOE after medical therapy and PDA ligation.<sup>17</sup>  
169 Observation using NIRS as an overview of PDA closure can help on evaluating the infants to  
170 reduce the burden of cerebral hypoxia. It is necessary to identify infants at high risk of long-term  
171 developmental disorders.

172 Although not statistically significant,  $r_aSO_2$  was lower in premature infants with hsPDA than  
173 non hsPDA ( $65.60\pm 11.07$  and  $67.48\pm 10.17$ , respectively) with  $p$  of .594. Similarly, abdominal  
174 fractional oxygen extraction in infants with and without hsPDA were  $0.33\pm 0.11$  and  $0.3\pm 0.1$ ,  
175 respectively ( $p= .578$ ). The findings are similar to the results of a study by Petrova et al., where  
176 no significant difference was found between tissue oxygen saturation in cerebral, abdominal, and  
177 renal in preterm infants aged < 32 weeks of gestational age with PDA diameter of  $\geq 3$  compared  
178 to < 3 mm<sup>18</sup>. Similarly, Gorman et al. found no statistical difference in hsPDA infants who were  
179 given ibuprofen therapy and who were not.<sup>19</sup> It was reported that NIRS facilitated benefits in  
180 terms of showing a downward trend of 20% of the base value before clinical manifestation of  
181 NEC appeared. In our study, we found 3 preterm babies with hsPDA and 7 non-hsPDA who  
182 experienced NEC based on Bell stage criteria.

183 Different results were reported by Ledo et al., where infants with hsPDA had significantly  
184 lower abdominal tissue oxygen saturation during observational prospective studies of 72  
185 premature infants.<sup>20</sup> Lower blood pressure and lower mesenteric oxygenation with increased  
186 extraction of oxygen by tissues were obtained. Continuous monitoring on abdominal

187 oxygenation needs to be done in newborns where a transition of gastrointestinal tract from a  
188 relatively dormant organ to a main area of nutrient absorption requiring sufficient supply of  
189 oxygen. Unlike cerebral circulation that has an autoregulation protection mechanism, mesenteric  
190 circulation in the abdomen does not have the ability to auto-regulate. Therefore, it is at risk of  
191 gastrointestinal hypoxia. Ledo et al. stated that hsPDA babies had lower blood pressure with  
192 lower abdominal oxygenation. Abdominal FTOE also reported an increase in the first five days  
193 and stabilized on day six. The stability of the aFTOE on the 6<sup>th</sup> day was along with the  
194 spontaneous closure of the DA. In the previous study, babies who got catecholamine were put in  
195 the exclusion group to minimize the confounding factors that affected oxygenation<sup>20,21</sup>. NIRS  
196 somatic sensors placed in the abdominal region were expected to detect oxygenation  
197 disturbances in abdomen. Abdominal oxygen saturation ( $r_aSO_2$ ) depicts blood flow in the  
198 mesenteric artery as it is the main vascular supplier of the gastrointestinal tract<sup>22</sup>.

199 In this study, there was no significant difference in  $r_rSO_2$  value between hsPDA compared to  
200 non hsPDA ( $76.41 \pm 14.98$  vs  $82.61 \pm 10.41$ ) ( $p = .218$ ). Normal value of  $r_rSO_2$  in premature babies  
201 is 80%. New born average  $r_rSO_2$  score is 40% that will increase in ten minutes to 80-90%, then  
202 decrease with improvements in renal blood flow and increase the utilization of oxygen in the  
203 kidneys<sup>18</sup>. In a cohort study of premature infants in the first week of life, it was found that  
204  $r_rSO_2 < 66\%$  was associated with the presence of hsPDA based on echocardiography criteria with  
205 a sensitivity of 81% and specificity of 77%. The difference could be due to the fact that the  
206 babies in the previous study who had  $r_rSO_2 < 66\%$  were  $< 1000$ grams of weight and used  
207 ventilators. Low  $r_rSO_2$  values can be caused by immature renal function or hemodynamic  
208 instability other than PDA<sup>9</sup>. Guzoglu et al. reported no significant difference in regional oxygen  
209 saturation of the kidneys with  $r_rSO_2$  value of 60% (ranged between 17-93%,  $p = .87$ ) and rFTOE  
210 .37 (ranged between .06-.83,  $p = .87$ ) in infants with hsPDA and control<sup>6,22,23</sup>. The  $r_rSO_2$  value  
211 obtained in the present study is relatively higher than other studies. This can be caused due to  
212 NIRS renal measurements conducted on post natal days 3 to 7 when perfusion and utilization of  
213 oxygen in the kidneys were still in the transition process.

214 This study provides information of oxygen saturation in three region simultaneously in both  
215 groups. However, there are several limitations of this study. First, the NIRS measurement of  
216 tissue oxygen saturation is only performed in short period. Longitudinal study is needed to study  
217 the oxygen saturation trends. Second, tissue oxygen saturation assessment is based on NIRS only

218 and not confirmed by other supporting examinations. And last, the small number of samples due  
219 to limitation of time.

## 220 **CONCLUSION**

221 The results of our study suggest that hsPDA does not affect the oxygenation in cerebral,  
222 abdominal, and renal in preterm infants during the examination. The decision regarding optimal  
223 time for ductal closure should be reconsidered. However, further large scale studies needs to be  
224 conducted to reassess the present findings.

225

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229 following: Martono Tri Utomo, Sunny Mariana Samosir, and Mahrus A. Rahman designed and  
230 conducted the initial analysis. Risa Etika, Martono Tri Utomo, Dina Angelika, Kartika D.  
231 Handayani, and Mahendra T.A.S. worked together as the neonatologist in charge at NICU.  
232 Rahman performed the echocardiography examination in all patients. Samosir collected the  
233 NIRS data, conducted further analysis, and did the manuscript writing. Finally, all authors had  
234 read and approved the final version of this manuscript.

235

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310 **TABLES**

311

312 **Table 1.** Subject characteristics

313

	<b>hsPDA n (11)</b>	<b>non-hsPDA n (41)</b>	<b>Total n (52)</b>	<b>P</b>
Sex				1.000*
Male	5 (9.6)	20 (38.5)	25 (48.1)	
Female	6 (11.5)	21 (40.4)	27 (51.9)	
Gestational age				1.000**
<i>Extremely Preterm</i> (<28 weeks)	1 (1.9)	3 (5.8)	4 (7.7)	
<i>Very Preterm</i> (28 - <32 weeks)	6 (11.5)	23 (44.3)	29 (55.8)	
<i>Moderate Late Preterm</i> (32 - <37 weeks)	4 (7.7)	15 (28.8)	19 (36.5)	
Birth weight				0.902**
ELBW (<1000 g)	2 (3.9)	6 (11.5)	8 (15.4)	
VLBW (<1500 g)	7 (13.5)	24 (46.1)	31 (59.6)	
LBW (<2500 g)	2 (3.9)	11 (21.1)	13 (25)	
Singleton/multiple birth				0.322
Singleton	11 (21.1)	35 (67.4)	46 (78.5)	
Multiple birth	0 (0.0)	6 (11.5)	6 (11.5)	
Respiratory support				0.474**
<i>High flow nasal canule</i>	1 (1.9)	1 (1.9)	2 (3.8)	
CPAP	7 (13.5)	33 (63.5)	40 (77)	
Non invasive ventilator	1 (1.9)	1 (1.9)	2 (3.8)	
Invasive ventilator	2 (3.9)	6 (11.5)	8 (15.4)	
HR (x/minute), <i>mean</i> ± SD	165±14,4	148±10,5		
SpO <sub>2</sub> (%), <i>mean</i> ± SD	97.1±2,7	97.0±1,9		
Hb, <i>mean</i> ± SD	15.73±3.46	15.37±2.58		0.702
Inotropes				0.101
No	8 (15.4)	38 (73.1)	46 (88.5)	
Yes	3 (5.7)	3 (5.7)	6 (11.5)	
Age during recruitment				
3 day	3 (5.7)	21 (40.5)	24 (46.2)	0.118

4 day	6 (11.5)	10 (19.3)	16 (30.8)	
5 day	1 (1.9)	5 (9.6)	6 (11.5)	
6 day	1 (1.9)	4 (7.7)	5 (9.6)	
7 day	0 (0.0)	1 (1.9)	1 (1.9)	
Infant's comorbidity				0.086
Respiratory distress synd.	6 (11.5)	12 (23.1)	18 (34.6)	
Perinatal Asphyxia	2 (3.8)	11 (21.1)	13 (24.9)	
PPHN	3 (5.7)	3 (5.7)	6 (11.4)	
Hyperbilirubinemia	4 (7.7)	6 (11.5)	10 (19.2)	
Others	1 (1.9)	9 (17.3)	10 (19.2)	
APGAR score in 5 minutes				0.886*
≤5	6 (11.5)	19 (36.5)	25 (48)	
>5	5 (9.6)	22 (42.4)	27 (52)	
Mode of delivery				0.094**
SC with general anesthesia	6 (11.5)	7 (13.5)	13 (25)	
SC with regional anesthesia	3 (5.7)	19 (36.5)	22 (42.2)	
Spontaneous birth	2 (3.8)	14 (27.0)	16 (30.7)	
Assisted vaginal birth	0 (0.0)	1 (1.9)	1 (1.9)	
Amniotic fluid				0.134**
Clear	10 (19.3)	38 (73.1)	(92.4)	
Turbid	1 (1.9)	0 (0.0)	(1.9)	
Meconium	0 (0.0)	3 (5.7)	(5.7)	
Mother's comorbidity				0.357**
Healthy	1 (1.9)	2 (3.8)	3 (5.7)	
Hypertension	6 (11.5)	11 (21.1)	17 (32.7)	
Obesity	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal bleeding	1 (1.9)	1 (1.9)	2 (3.8)	
Combination of 2	1 (1.9)	14 (26.9)	15 (28.8)	
Combination of 3	2 (3.8)	9 (17.3)	11 (21.1)	
Others	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal corticosteroid				1.000
No	7 (13.5)	27 (52)	34 (65.5)	
Yes	4 (7.7)	14 (26.8)	18 (34.5)	

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316 **Table 2** Comparison of Regional Oxygen Saturation & Fractional Oxygen Extraction of hsPDA  
 317 and non hsPDA

	hsPDA		Non hs-PDA		p
	(n)	(mean±SD)	(n)	(mean±SD)	
r <sub>c</sub> SO <sub>2</sub>	11	75.27±9.14	41	79.03±9.11	0.238
r <sub>a</sub> SO <sub>2</sub>	11	65.60±11.07	41	67.48±10.17	0.594
r <sub>c</sub> SO <sub>2</sub>	11	76.41±14.98	41	82.61±10.41	0.218
cFTOE	11	0.22±0.09	41	0.19±0.08	0.473
aFTOE	11	0.33±0.11	41	0.30±0.10	0.578
rFTOE	11	0.26±0.19	41	0.16±0.12	0.151

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319

320 **FIGURES**

321 **Figure 1a.**Box plot diagram of regional FTOE values on hsPDA and non hsPDA group

322

323 **Figure 1b.**Box plot diagram of regional rSO<sub>2</sub> values on hsPDA and non hsPDA group

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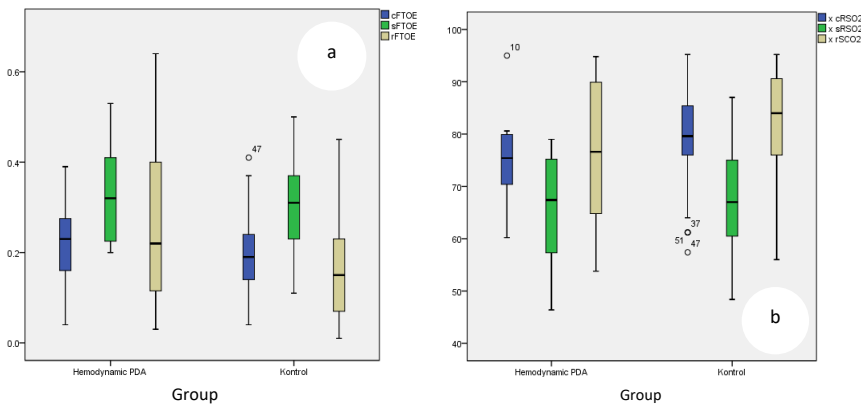
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## Acknowledgement of Revision (#IJN-2102-2040 (R3))

1 message

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To: mrmartono73@gmail.com

Manuscript ID: IJN-2102-2040 (R3)

Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Martono Tri Utomo, Risa Etika, Mahrus Abdul Rahman, Mahendra Tri Arif Sampurna, Sunny Mariana Samosir

Date: 2021-02-16

Dear **Mr. Martono Tri Utomo**

Thank you for submitting the revised file of your manuscript to the **Iranian Journal of Neonatology IJN**

The Editorial Office will proceed on your manuscript and inform you in the earliest time.

If there is anything else, please do not hesitate to contact us.

Truly yours,

Executive Managing Director of **Iranian Journal of Neonatology IJN**

1 **HEMODYNAMIC SIGNIFICANT PATENT DUCTUS ARTERIOSUS EFFECT ON**  
2 **TISSUE OXYGENATION IN PRETERM INFANT: A STUDY USING NEAR**  
3 **INFRARED SPECTROSCOPY**

4  
5 **ABSTRACT**

6 **Background:** Hemodynamic significant Patent Ductus Arteriosus (hsPDA) is one of the main  
7 complications of preterm birth. However, its management still needs further development. Ductal  
8 stealing, resulting in pulmonary hyperperfusion and systemic hypoperfusion, potentially causes  
9 oxygenation disorders that lead to target organ disruptions (i.e. cerebral, abdominal, and renal).  
10 Hence, monitoring tissue oxygenation is essential to detect organ disorders. Previous studies  
11 revealed that near infrared spectroscopy (NIRS) showed a promising result as a non-invasive  
12 method to monitor tissue oxygenation.

13 **Objective:** The study aimed to analyze the tissue oxygen saturation ( $rSO_2$ ) differences of  
14 premature babies with and without hsPDA.

15 **Patients and Methods:** A cross-sectional study was conducted on preterm infants aged 3-7 days  
16 with 24-33<sup>6/7</sup> weeks of gestation. hsPDA diagnosis was carried out by echocardiography; defined  
17 as >1.5mm diameter of ductus arteriosus and >1.4 left pulmonary artery and aorta (La/Ao) ratio.  
18 NIRS monitoring was carried out to measure tissue oxygen saturation of the cerebral ( $r_cSO_2$ ),  
19 abdomen ( $r_aSO_2$ ), and renal ( $r_rSO_2$ ). The statistical analysis was undertaken using SPSS 21.0.

20 **Results:** There were 11 out of 52 infants categorized as hsPDA. Mean birth weight was  
21 1213±293 gram; Mean gestational age was 30.72±2.01 weeks; and, Mean ductus diameter in  
22 hsPDA was 2.84±0.93 mm. There was no significant difference between the hsPDA and non-  
23 hsPDA groups in  $r_cSO_2$  (75.27±9.14% vs 79.03±9.11%;p=0.238),  $r_aSO_2$  (65.60±11.07% vs  
24 67.48±10.17%;p=0.594), and  $r_rSO_2$  (76.41±14.98% vs 82.61±10.41%;p=0.218).

25 **Conclusion:** The existence of hsPDA doesn't affect the oxygenation in cerebral, abdominal, and  
26 renal tissue in preterm babies. The decision regarding optimal time for ductal closure should be  
27 reconsidered.

28 **Keywords:**

29 *preterm infant, hemodynamic significant patent ductus arteriosus, near infrared spectroscopy*

30

31 **INTRODUCTION**

32

33 Ductus arteriosus (DA) will normally shrink after birth in term infant and be functionally  
34 closed at the age of 72 hours. The ductal closure is delayed until 4 days of age in 10% of preterm  
35 babies born in 30-37 weeks, 80% of those born in 25-28 weeks, and 90% of those born less than  
36 24 weeks of gestational age<sup>1,2</sup>. The persistent DA can cause hemodynamic significant Patent  
37 Ductus Arteriosus (hsPDA) where the systemic shunt to the pulmonary vessels results in  
38 pulmonary hyperperfusion and systemic hypoperfusion<sup>3</sup>. Therefore, understanding tissue  
39 perfusion and oxygenation is important as a consideration for the administration of ductal closure  
40 therapy in premature infants to avoid further morbidity and mortality<sup>4-6</sup>. The ductal shunting  
41 from systemic to pulmonary blood flow has an impact on the cerebral, abdominal, and renal  
42 circulation<sup>7</sup>. Uncorrected hsPDA can cause intra ventricular hemorrhage, necrotizing  
43 enterocolitis (NEC), and renal insufficiency<sup>6</sup>. The long-term impact of decreased cerebral  
44 oxygenation in infants less than a month includes brain damage and development disorders<sup>8</sup>.

45 Clinical assessment and echocardiography become reliable methods in diagnosing hsPDA.  
46 Near Infrared Spectroscopy (NIRS) has been validated as a non-invasive tool to measure tissue  
47 oxygen saturation (rSO<sub>2</sub>) that can detect early changes in organ perfusion and oxygenation, thus,  
48 it can help identify and monitor the hsPDA therapy<sup>9</sup>. A study by van der Laan showed that  
49 cerebral and renal oxygenation are not affected by hsPDA.<sup>6</sup> Lemmers et al., and Cohen et al.,  
50 proved the negative effects of hsPDA on cerebral oxygenation in premature infants<sup>8,10</sup>. There  
51 have been many studies on regional perfusion and oxygenation in premature infants with NIRS.<sup>8-</sup>  
52 <sup>10</sup> However, to the best of the researcher's knowledge, there have not been enough studies on  
53 regional oxygenation differences especially in preterm infants in our country, Indonesia, using  
54 NIRS.

55 The present study aimed to study regional tissue oxygenation differences in preterm infants  
56 with hemodynamic significant and non-hemodynamic significant Patent Ductus Arteriosus using  
57 NIRS in the early days of life of preterm babies.

58

59

## 60 **PATIENTS AND METHODS**

### 61 *Patients*

62 This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during

63 study times. The samples were determined using consecutive sampling technique. All preterm  
64 babies (with gestational age of 24-33 weeks) were born between November 2019 and May 2020  
65 at the tertiary level neonatal intensive care unit of Dr. Soetomo General Hospital whose oxygen  
66 support devices (i.e. high flow nasal canula, continuous positive airway pressure, invasive and  
67 non-invasive ventilator) were eligible for inclusion. Patients with multiple congenital anomaly,  
68 ductal dependent cyanotic heart defect, early onset of septicemia, and incomplete consent from  
69 parents were excluded. Demographic and clinical data were collected from medical records. The  
70 sample size is calculated using a formula for continuous data with the aim of hypothesizing two  
71 or more group. The ratio between the hsPDA and non hsPDA group was based on the previous  
72 study.<sup>11</sup>

73

#### 74 *Echocardiography*

75 Echocardiography screening was performed between 3<sup>rd</sup> and 7<sup>th</sup> postnatal day by pediatric  
76 cardiology consultant using Sonoscape Portable Digital Color Doppler Ultrasound System Model  
77 S9 (SonoScape, Shenzhen). Echocardiography was performed by one pediatric cardiology  
78 consultant to minimize performance variability. The samples were categorized into two groups:  
79 hsPDA and non hsPDA. The hsPDA was considered existing if there were a ductus arteriosus  
80 with diameter > 1.5 mm on constriction phase, pulmonary perfusion seen in the left pulmonary  
81 artery diameter and aorta diameter ratio (LA/Ao) was > 1.4, and left to right shunt were present.  
82 While DA that was already closed and did not fulfill the requirement for hsPDA was considered  
83 non-hsPDA.

#### 84 *NIRS Measurements*

85 INVOS 5100C near infrared spectrometer and neonatal sensors (Covidien, USA) were used  
86 to monitor the tissue oxygen saturation on the day of echocardiography was performed. Multisite  
87 sensors were placed on the frontoparietal side of the infant's head to evaluate the cerebral tissue  
88 oxygen saturation ( $r_c\text{SO}_2$ ), on the inferior side of umbilicus to evaluate the abdominal tissue  
89 oxygen saturation ( $r_a\text{SO}_2$ ), and on the lateral posterior flank to evaluate the renal oxygen  
90 saturation ( $r_r\text{SO}_2$ ). The evaluation was performed by different examiners without knowing the  
91 echocardiography result. The oxygen saturation changes were observed in 15 minutes  
92 continuously. Every 15 seconds, the machine records tissue oxygen saturation data. Mean  
93 regional rSO<sub>2</sub> were used for further analysis. A pulse oxymeter was also put on the baby's right

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94 hand to evaluate the peripheral oxygen saturation (spO<sub>2</sub>) for further calculation of fractional  
95 tissue oxygen extraction (FTOE) on each location using the following formula:  $FTOE = (spO_2 -$   
96  $rSO_2)/spO_2$ . A 15-minute measurement was simultaneously observed and the mean values were  
97 obtained.

#### 98 *Statistical Analysis*

99 Differences in clinical characteristics of the two sample groups of hsPDA and non hsPDA  
100 were analyzed using Chi square test, Fisher exact test, and exact probability test. Statistical  
101 analyses for each regional oxygen saturation and fractional tissue oxygen extraction between  
102 both groups were performed using independent t-test and Mann Whitney test. Analysis using  
103 logistic regression also performed which show no significant relationship between hsPDA and  
104 non hsPDA group. IBM SPSS 21.0 was used for all statistical analyses with significant value (*p*)  
105 at < .05.

#### 106 *Ethics*

107 The ethical clearance was issued by the Ethical Committee of Dr. Soetomo General Hospital  
108 (No.1766/105/XI/2019).

109

## 110 **RESULTS**

111 In this study, three babies had multiple congenital anomalies, four babies had early onset of  
112 septicemia, and the others were excluded due to incomplete data and consent. Eleven infants  
113 classified as hsPDA group based on echocardiography. There were 25 (48%) and 27 (52%)  
114 preterm male and female babies, respectively. Majority of the subjects was in 28-<32 weeks of  
115 gestational age (55.8%) with mean gestational age was 30.72±2 weeks for hsPDA and 30.78±2  
116 weeks for non hsPDA. Mean birth weight for hsPDA and non hsPDA were 1213±293 and  
117 1272±306 grams, respectively.

118 Table 1 depicts the neonatal characteristics for both groups. There was no significant  
119 difference in all variables. Therefore, the samples considered as homogenous.

120 This study obtained that the smallest DA's diameter was 1.5 mm and the largest one was 4.8  
121 mm in the hsPDA group. From the eleven samples in hsPDA group, the duct diameter was  
122 obtained with an average of 2.84±0.93. The comparison between LA and Ao had an average  
123 score of 1.56±0.26. The ejection fraction of hsPDA and non hsPDA group were 71.55±5.72 and  
124 73.94±9.4%, respectively.

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125 Linear regression was used to evaluate comorbidities on samples, namely perinatal asphyxia,  
126 respiratory distress syndrome, and persistent pulmonary hypertension of the newborn as  
127 confounding factors of the regional oxygen saturation. All measurement was not significant.  
128 In accordance to Table 2, there were no significant differences in the tissue oxygen saturation  
129 ratio of cerebral ( $r_c\text{SO}_2$ ), abdominal ( $r_a\text{SO}_2$ ), or renal ( $r_r\text{SO}_2$ ) areas between hsPDA and non  
130 hsPDA groups ( $p = .238$ ,  $p = .598$ , and  $p = .218$  respectively). Fractional oxygen extraction in  
131 cerebral (cFTOE), abdominal (aFTOE), and renal (rFTOE) areas between the hsPDA and non  
132 hsPDA groups also revealed non-significant difference ( $p = .473$ ,  $p = .578$ , and  $p = .151$ ,  
133 respectively).

134

## 135 **DISCUSSION**

136 The present study obtained the characteristics of the two groups that were not significantly  
137 different so that it can be compared. Previous study showed that the incidence of hsPDA  
138 increased with lower oxygen saturation<sup>12</sup>. The mean SpO<sub>2</sub> in this study was around 97% with  
139 minimal setting of CPAP and mechanical ventilation. There were no significant differences in  
140  $r_c\text{SO}_2$  ( $p = .238$ ) between the hsPDA and non hsPDA groups in the study. These findings are in  
141 line with previous observational cohort designs by van der Laan et al. in Netherland, in which  
142 oxygen saturation and oxygen extraction in cerebral and renal of 49 preterm infants with  
143 gestational age <32 weeks evaluated using NIRS were not affected by hsPDA.<sup>6</sup> The  $r_c\text{SO}_2$  results  
144 in hsPDA group (69%) were lower than non hsPDA group (76%) and cFTOE in hsPDA group  
145 (0.22) were higher than non hsPDA group (0.33).

146 In contrast to the results of several previous research where a decrease in cerebral  
147 oxygenation was found in hsPDA, Lemmers et al. reported a lower  $r_c\text{SO}_2$  in infants with hsPDA  
148 compared to the asymptomatic PDA group (62±9% and 72±10%, sequentially). The difference  
149 might be caused by several factors affecting the patient's hemodynamics. In Lemmers' study, the  
150 patients in hsPDA group mostly used ventilator, morphine as sedatives that caused peripheral  
151 vasodilation, and more inotropic than control. Dopamine administration could increase cardiac  
152 output that affected an elevating perfusion. In addition, in the previous study, the sampling  
153 period was earlier (in the first 72 hours) compared to the present study (3-7 postnatal days)  
154 which could affect the results of oxygenation measurement. It is agreed that the cerebral oxygen  
155 supply increases as the baby age. Tissue oxygen extraction (FTOE) was also significantly higher

156 in premature infants with hsPDA than those with non hsPDA<sup>13</sup>. The relationship between oxygen  
157 transport ( $DO_2$ ) and tissue oxygen consumption ( $VO_2$ ) is fractional tissue oxygen extraction  
158 ( $F_{TOE} = VO_2/DO_2$ ). Negative correlation between  $r_cRSO_2$  and cFTOE indicated that if there was  
159 a decrease in the brain oxygen supply in sick premature babies, there was an increase in cerebral  
160 oxygen extraction aimed to maintain oxygen availability in the brain<sup>14</sup>.

161 A retrospective study by Chock et al. showed that a low  $r_cSO_2$  value of  $< 66\%$  was associated  
162 with the presence of hsPDA in preterm infants<sup>9</sup>. Although the oxygenation value in cerebral  
163 tissue of hsPDA infant was lower than non hsPDA, the average value was still higher compared  
164 to the  $< 40\%$  cerebral oxygen saturation limit associated with the appearance of symptoms, such  
165 as ischemic lesions and neuron damage. The normal value of  $r_cSO_2$  for preterm babies is 55-  
166 85%<sup>15</sup>. According to Dix et al., higher  $r_cSO_2$  values in neonatal sensors compared to adult NIRS  
167 sensors might be caused by differences in NIRS signal reception process where neonatal NIRS  
168 sensor algorithmic adjusted to thinner neonatal calvarium so that the light is easier to enter<sup>16</sup>.

169 Although the determination of "to treat or not to treat" is still a clinical question nowadays,  
170 Poon et al., reported an improvement in cFTOE after medical therapy and PDA ligation.<sup>17</sup>  
171 Observation using NIRS as an overview of PDA closure can help on evaluating the infants to  
172 reduce the burden of cerebral hypoxia. It is necessary to identify infants at high risk of long-term  
173 developmental disorders.

174 Although not statistically significant,  $r_aSO_2$  was lower in premature infants with hsPDA than  
175 non hsPDA ( $65.60 \pm 11.07$  and  $67.48 \pm 10.17$ , respectively) with  $p$  of .594. Similarly, abdominal  
176 fractional oxygen extraction in infants with and without hsPDA were  $0.33 \pm 0.11$  and  $0.3 \pm 0.1$ ,  
177 respectively ( $p = .578$ ). The findings are similar to the results of a study by Petrova et al., where  
178 no significant difference was found between tissue oxygen saturation in cerebral, abdominal, and  
179 renal in preterm infants aged  $< 32$  weeks of gestational age with PDA diameter of  $\geq 3$  compared  
180 to  $< 3$  mm<sup>18</sup>. Similarly, Gorman et al. found no statistical difference in hsPDA infants who were  
181 given ibuprofen therapy and who were not.<sup>19</sup> It was reported that NIRS facilitated benefits in  
182 terms of showing a downward trend of 20% of the base value before clinical manifestation of  
183 NEC appeared. In our study, we found 3 preterm babies with hsPDA and 7 non-hsPDA who  
184 experienced NEC based on Bell stage criteria.

185 Different results were reported by Ledo et al., where infants with hsPDA had significantly  
186 lower abdominal tissue oxygen saturation during observational prospective studies of 72

187 premature infants.<sup>20</sup> Lower blood pressure and lower mesenteric oxygenation with increased  
188 extraction of oxygen by tissues were obtained. Continuous monitoring on abdominal  
189 oxygenation needs to be done in newborns where a transition of gastrointestinal tract from a  
190 relatively dormant organ to a main area of nutrient absorption requiring sufficient supply of  
191 oxygen. Unlike cerebral circulation that has an autoregulation protection mechanism, mesenteric  
192 circulation in the abdomen does not have the ability to auto-regulate. Therefore, it is at risk of  
193 gastrointestinal hypoxia. Ledo et al. stated that hsPDA babies had lower blood pressure with  
194 lower abdominal oxygenation. Abdominal FTOE also reported an increase in the first five days  
195 and stabilized on day six. The stability of the aFTOE on the 6<sup>th</sup> day was along with the  
196 spontaneous closure of the DA. In the previous study, babies who got catecholamine were put in  
197 the exclusion group to minimize the confounding factors that affected oxygenation<sup>20,21</sup>. NIRS  
198 somatic sensors placed in the abdominal region were expected to detect oxygenation  
199 disturbances in abdomen. Abdominal oxygen saturation ( $r_aSO_2$ ) depicts blood flow in the  
200 mesenteric artery as it is the main vascular supplier of the gastrointestinal tract<sup>22</sup>.

201 In this study, there was no significant difference in  $r_rSO_2$  value between hsPDA compared to  
202 non hsPDA ( $76.41 \pm 14.98$  vs  $82.61 \pm 10.41$ ) ( $p = .218$ ). Normal value of  $r_rSO_2$  in premature babies  
203 is 80%. New born average  $r_rSO_2$  score is 40% that will increase in ten minutes to 80-90%, then  
204 decrease with improvements in renal blood flow and increase the utilization of oxygen in the  
205 kidneys<sup>18</sup>. In a cohort study of premature infants in the first week of life, it was found that  
206  $r_rSO_2 < 66\%$  was associated with the presence of hsPDA based on echocardiography criteria with  
207 a sensitivity of 81% and specificity of 77%. The difference could be due to the fact that the  
208 babies in the previous study who had  $r_rSO_2 < 66\%$  were  $< 1000$  grams of weight and used  
209 ventilators. Low  $r_rSO_2$  values can be caused by immature renal function or hemodynamic  
210 instability other than PDA<sup>9</sup>. Guzoglu et al. reported no significant difference in regional oxygen  
211 saturation of the kidneys with  $r_rSO_2$  value of 60% (ranged between 17-93%,  $p = .87$ ) and rFTOE  
212 .37 (ranged between .06-.83,  $p = .87$ ) in infants with hsPDA and control<sup>16,22,23</sup>. The  $r_rSO_2$  value  
213 obtained in the present study is relatively higher than other studies. This can be caused due to  
214 NIRS renal measurements conducted on post natal days 3 to 7 when perfusion and utilization of  
215 oxygen in the kidneys were still in the transition process.

216 This study provides information of oxygen saturation in three region simultaneously in both  
217 groups. However, there are several limitations of this study. First, the NIRS measurement of



218 tissue oxygen saturation is only performed in short period. Longitudinal study is needed to study  
219 the oxygen saturation trends. Second, tissue oxygen saturation assessment is based on NIRS only  
220 and not confirmed by other supporting examinations. And last, the small number of samples due  
221 to limitation of time.

## 222 **CONCLUSION**

223 The results of our study suggest that hsPDA does not affect the oxygenation in cerebral,  
224 abdominal, and renal in preterm infants during the examination. The decision regarding optimal  
225 time for ductal closure should be reconsidered. However, further large scale studies needs to be  
226 conducted to reassess the present findings.

227

## 228 **ACKNOWLEDGMENT**

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230 ethical approval and endless supports. The author's contributions were described as the  
231 following: Martono Tri Utomo, Sunny Mariana Samosir, and Mahrus A. Rahman designed and  
232 conducted the initial analysis. Risa Etika, Martono Tri Utomo, Dina Angelika, Kartika D.  
233 Handayani, and Mahendra T.A.S. worked together as the neonatologist in charge at NICU.  
234 Rahman performed the echocardiography examination in all patients. Samosir collected the  
235 NIRS data, conducted further analysis, and did the manuscript writing. Finally, all authors had  
236 read and approved the final version of this manuscript.

237

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310 **TABLES**

311

312 **Table 1.** Subject characteristic

313

	<b>hsPDA n (11)</b>	<b>non-hsPDA n (41)</b>	<b>Total n (52)</b>	<b>P</b>
Sex				1.000*
Male	5 (9.6)	20 (38.5)	25 (48.1)	
Female	6 (11.5)	21 (40.4)	27 (51.9)	
Gestational age				1.000**
<i>Extremely Preterm</i> (<28 weeks)	1 (1.9)	3 (5.8)	4 (7.7)	
<i>Very Preterm</i> (28 - <32 weeks)	6 (11.5)	23 (44.3)	29 (55.8)	
<i>Moderate Late Preterm</i> (32 - <37 weeks)	4 (7.7)	15 (28.8)	19 (36.5)	
Birth weight				0.902**
ELBW (<1000 g)	2 (3.9)	6 (11.5)	8 (15.4)	
VLBW (<1500 g)	7 (13.5)	24 (46.1)	31 (59.6)	
LBW (<2500 g)	2 (3.9)	11 (21.1)	13 (25)	
Singleton/multiple birth				0.322
Singleton	11 (21.1)	35 (67.4)	46 (78.5)	
Multiple birth	0 (0.0)	6 (11.5)	6 (11.5)	
Respiratory support				0.474**
<i>High flow nasal canule</i>	1 (1.9)	1 (1.9)	2 (3.8)	
CPAP	7 (13.5)	33 (63.5)	40 (77)	
Non invasive ventilator	1 (1.9)	1 (1.9)	2 (3.8)	
Invasive ventilator	2 (3.9)	6 (11.5)	8 (15.4)	
HR (x/minute), <i>mean</i> ± SD	165±14,4	148±10,5		
SpO <sub>2</sub> (%), <i>mean</i> ± SD	97.1±2,7	97.0±1,9		
Hb, <i>mean</i> ± SD	15.73±3.46	15.37±2.58		0.702
Inotropes				0.101
No	8 (15.4)	38 (73.1)	46 (88.5)	
Yes	3 (5.7)	3 (5.7)	6 (11.5)	
Age during recruitment				
3 day	3 (5.7)	21 (40.5)	24 (46.2)	0.118

4 day	6 (11.5)	10 (19.3)	16 (30.8)	
5 day	1 (1.9)	5 (9.6)	6 (11.5)	
6 day	1 (1.9)	4 (7.7)	5 (9.6)	
7 day	0 (0.0)	1 (1.9)	1 (1.9)	
Infant's comorbidity				0.086
Respiratory distress synd.	6 (11.5)	12 (23.1)	18 (34.6)	
Perinatal Asphyxia	2 (3.8)	11 (21.1)	13 (24.9)	
PPHN	3 (5.7)	3 (5.7)	6 (11.4)	
Hyperbilirubinemia	4 (7.7)	6 (11.5)	10 (19.2)	
Others	1 (1.9)	9 (17.3)	10 (19.2)	
APGAR score in 5 minutes				0.886*
≤5	6 (11.5)	19 (36.5)	25 (48)	
>5	5 (9.6)	22 (42.4)	27 (52)	
Mode of delivery				0.094**
SC with general anesthesia	6 (11.5)	7 (13.5)	13 (25)	
SC with regional anesthesia	3 (5.7)	19 (36.5)	22 (42.2)	
Spontaneous birth	2 (3.8)	14 (27.0)	16 (30.7)	
Assisted vaginal birth	0 (0.0)	1 (1.9)	1 (1.9)	
Amniotic fluid				0.134**
Clear	10 (19.3)	38 (73.1)	(92.4)	
Turbid	1 (1.9)	0 (0.0)	(1.9)	
Meconium	0 (0.0)	3 (5.7)	(5.7)	
Mother's comorbidity				0.357**
Healthy	1 (1.9)	2 (3.8)	3 (5.7)	
Hypertension	6 (11.5)	11 (21.1)	17 (32.7)	
Obesity	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal bleeding	1 (1.9)	1 (1.9)	2 (3.8)	
Combination of 2	1 (1.9)	14 (26.9)	15 (28.8)	
Combination of 3	2 (3.8)	9 (17.3)	11 (21.1)	
Others	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal corticosteroid				1.000
No	7 (13.5)	27 (52)	34 (65.5)	
Yes	4 (7.7)	14 (26.8)	18 (34.5)	

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315

316 **Table 2** Comparison of Regional Oxygen Saturation & Fractional Oxygen Extraction of hsPDA  
 317 and non hsPDA

	hsPDA		Non hs-PDA		p
	(n)	(mean±SD)	(n)	(mean±SD)	
r <sub>c</sub> SO <sub>2</sub>	11	75.27±9.14	41	79.03±9.11	0.238
r <sub>a</sub> SO <sub>2</sub>	11	65.60±11.07	41	67.48±10.17	0.594
r <sub>c</sub> SO <sub>2</sub>	11	76.41±14.98	41	82.61±10.41	0.218
cFTOE	11	0.22±0.09	41	0.19±0.08	0.473
aFTOE	11	0.33±0.11	41	0.30±0.10	0.578
rFTOE	11	0.26±0.19	41	0.16±0.12	0.151

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319

320 **FIGURES**

321 **Figure 1a.**Box plot diagram of regional FTOE values on hsPDA and non hsPDA group

322

323 **Figure 1b.**Box plot diagram of regional rSO<sub>2</sub> values on hsPDA and non hsPDA group

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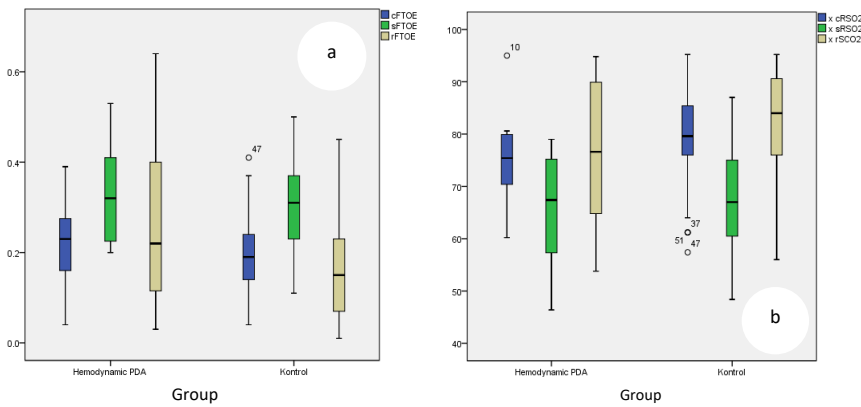
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**Manuscript Needs Revision (#IJN-2102-2040 (R3))**

2 messages

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Sat, Oct 9, 2021 at 3:30 PM

To: mrmartono73@gmail.com

Manuscript ID: IJN-2102-2040 (R2)

Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Sunny Mariana Samosir, Martono Tri Utomo, Mahrus Abdul Rahman, Agus Harianto, Risa Etika, Dina Angelika, Kartika Darma Handayani, Mahendra Tri Arif Sampurna

Dear **Mr. Martono Tri Utomo**

Your Manuscript #IJN-2102-2040 (R2), is not acceptable for publication in the presented form. Numerous Literary grammatical errors have made this article totally unprofessional. You should be advised to partner with highly proficient individuals especially from academia to review the article and change it drastically.

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Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

Give the eligibility criteria, and the sources and methods of selection of participants

Describe any efforts to address potential sources of bias

Explain how the study size was arrived at

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1 **HEMODYNAMIC SIGNIFICANT PATENT DUCTUS ARTERIOSUS EFFECT ON**  
2 **TISSUE OXYGENATION IN PRETERM INFANT: A STUDY USING NEAR**  
3 **INFRARED SPECTROSCOPY**

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15

16 **ABSTRACT**

17 **Background:** Hemodynamic significant Patent Ductus Arteriosus (hsPDA) is one of the main  
18 complications of preterm birth. However, its management still needs further development. Ductal  
19 stealing, resulting in pulmonary hyperperfusion and systemic hypoperfusion, potentially causes  
20 oxygenation disorders that lead to target organ disruptions (i.e. cerebral, abdominal, and renal).  
21 Hence, monitoring tissue oxygenation is essential to detect organ disorders. Previous studies  
22 revealed that near infrared spectroscopy (NIRS) showed a promising result as a non-invasive  
23 method to monitor tissue oxygenation.

24 **Objective:** The study aimed to analyze the tissue oxygen saturation (rSO<sub>2</sub>) differences of  
25 premature babies with and without hsPDA.

26 **Patients and Methods:** A cross-sectional study was conducted on preterm infants aged 3-7 days  
27 with 24-33<sup>6/7</sup> weeks of gestation. hsPDA diagnosis was carried out by echocardiography; defined  
28 as >1.5mm diameter of ductus arteriosus and >1.4 left pulmonal artery and aorta (La/Ao) ratio.  
29 NIRS monitoring was carried out to measure tissue oxygen saturation of the cerebral (r<sub>c</sub>SO<sub>2</sub>),  
30 abdomen (r<sub>a</sub>SO<sub>2</sub>), and renal (r<sub>r</sub>SO<sub>2</sub>). The statistical analysis was undertaken using SPSS 21.0.



31 **Results:** There were 11 out of 52 infants categorized as hsPDA. Mean birth weight was  
32 1213±293 gram; Mean gestational age was 30.72±2.01 weeks; and, Mean ductus diameter in  
33 hsPDA was 2.84±0.93 mm. There was no significant difference between the hsPDA and non-  
34 hsPDA groups in  $r_c\text{SO}_2$  (75.27±9.14% vs 79.03±9.11%; $p=0.238$ ),  $r_a\text{SO}_2$  (65.60±11.07% vs  
35 67.48±10.17%; $p=0.594$ ), and  $r_i\text{SO}_2$  (76.41±14.98% vs 82.61±10.41%; $p=0.218$ ).

36 **Conclusion:** The existence of hsPDA doesn't affect the oxygenation in cerebral, abdominal, and  
37 renal tissue in preterm babies. The decision regarding optimal time for ductal closure should be  
38 reconsidered.

39 **Keywords:**

40 *preterm infant, hemodynamic significant patent ductus arteriosus, near infrared spectroscopy*

41

42 **INTRODUCTION**

43

44 Ductus arteriosus (DA) will normally shrink after birth in term infant and be functionally  
45 closed at the age of 72 hours. The ductal closure is delayed until 4 days of age in 10% of preterm  
46 babies born in 30-37 weeks, 80% of those born in 25-28 weeks, and 90% of those born less than  
47 24 weeks of gestational age<sup>1,2</sup>. The persistent DA can cause hemodynamic significant Patent  
48 Ductus Arteriosus (hsPDA) where the systemic shunt to the pulmonary vessels results in  
49 pulmonary hyperperfusion and systemic hypoperfusion<sup>3</sup>. Therefore, understanding tissue  
50 perfusion and oxygenation is important as a consideration for the administration of ductal closure  
51 therapy in premature infants to avoid further morbidity and mortality<sup>4-6</sup>. The ductal shunting  
52 from systemic to pulmonary blood flow has an impact on the cerebral, abdominal, and renal  
53 circulation<sup>7</sup>. Uncorrected hsPDA can cause intra ventricular hemorrhage, necrotizing  
54 enterocolitis (NEC), and renal insufficiency<sup>6</sup>. The long-term impact of decreased cerebral  
55 oxygenation in infants less than a month includes brain damage and development disorders<sup>8</sup>.

56 Clinical assessment and echocardiography become reliable methods in diagnosing hsPDA.  
57 Near Infrared Spectroscopy (NIRS) has been validated as a non-invasive tool to measure tissue  
58 oxygen saturation ( $r\text{SO}_2$ ) that can detect early changes in organ perfusion and oxygenation, thus,  
59 it can help identify and monitor the hsPDA therapy<sup>9</sup>. A study by van der Laan showed that  
60 cerebral and renal oxygenation are not affected by hsPDA.<sup>6</sup> Lemmers et al., and Cohen et al.,  
61 proved the negative effects of hsPDA on cerebral oxygenation in premature infants<sup>8,10</sup>. There

62 have been many studies on regional perfusion and oxygenation in premature infants with NIRS.<sup>8-</sup>  
63 <sup>10</sup> However, to the best of the researcher's knowledge, there have not been enough studies on  
64 regional oxygenation differences especially in preterm infants in our country, Indonesia, using  
65 NIRS.

66 The present study aimed to study regional tissue oxygenation differences in preterm infants  
67 with hemodynamic significant and non-hemodynamic significant Patent Ductus Arteriosus using  
68 NIRS in the early days of life of preterm babies.

69  
70

## 71 PATIENTS AND METHODS

### 72 *Patients*

73 This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during  
74 study times. The samples were determined using consecutive sampling technique. All preterm  
75 babies (with gestational age of 24-33 weeks) were born between November 2019 and May 2020  
76 at the tertiary level neonatal intensive care unit of Dr. Soetomo General Hospital whose oxygen  
77 support devices (i.e. high flow nasal canula, continuous positive airway pressure, invasive and  
78 non-invasive ventilator) were eligible for inclusion. Patients with multiple congenital anomaly,  
79 ductal dependent cyanotic heart defect, early onset of septicemia, and incomplete consent from  
80 parents were excluded. Demographic and clinical data were collected from medical records. The  
81 sample size is calculated using a formula for continuous data with the aim of hypothesizing two  
82 or more group. The ratio between the hsPDA and non hsPDA group was based on the previous  
83 study.<sup>11</sup>

84

### 85 *Echocardiography*

86 Echocardiography screening was performed between 3<sup>rd</sup> and 7<sup>th</sup> postnatal day by pediatric  
87 cardiology consultant using Sonoscape Portable Digital Color Doppler Ultrasound System Model  
88 S9 (SonoScape, Shenzhen). Echocardiography was performed by one pediatric cardiology  
89 consultant to minimize performance variability. The samples were categorized into two groups:  
90 hsPDA and non hsPDA. The hsPDA was considered existing if there were a ductus arteriosus  
91 with diameter > 1.5 mm on constriction phase, pulmonal perfusion seen in the left pulmonal  
92 artery diameter and aorta diameter ratio (LA/Ao) was > 1.4, and left to right shunt were present.

Commented [i-1]: these sentences were moved from the result section.

93 While DA that was already closed and did not fulfill the requirement for hsPDA was considered  
94 non-hsPDA.

#### 95 *NIRS Measurements*

96 INVOS 5100C near infrared spectrometer and neonatal sensors (Covidien, USA) were used  
97 to monitor the tissue oxygen saturation on the day of echocardiography was performed. Multisite  
98 sensors were placed on the frontoparietal side of the infant's head to evaluate the cerebral tissue  
99 oxygen saturation ( $r_c\text{SO}_2$ ), on the inferior side of umbilicus to evaluate the abdominal tissue  
100 oxygen saturation ( $r_a\text{SO}_2$ ), and on the lateral posterior flank to evaluate the renal oxygen  
101 saturation ( $r_r\text{SO}_2$ ). The evaluation was performed by different examiners without knowing the  
102 echocardiography result. The oxygen saturation changes were observed in 15 minutes  
103 continuously. Every 15 seconds, the machine records tissue oxygen saturation data. Mean  
104 regional rSO<sub>2</sub> were used for further analysis. A pulse oxymeter was also put on the baby's right  
105 hand to evaluate the peripheral oxygen saturation ( $\text{spO}_2$ ) for further calculation of fractional  
106 tissue oxygen extraction (FTOE) on each location using the following formula:  $\text{FTOE} = (\text{spO}_2 -$   
107  $r\text{SO}_2)/\text{spO}_2$ . A 15-minute measurement was simultaneously observed and the mean values were  
108 obtained.

#### 109 *Statistical Analysis*

110 Differences in clinical characteristics of the two sample groups of hsPDA and non hsPDA  
111 were analyzed using Chi square test, Fisher exact test, and exact probability test. Statistical  
112 analyses for each regional oxygen saturation and fractional tissue oxygen extraction between  
113 both groups were performed using independent t-test and Mann Whitney test. IBM SPSS 21.0 was  
114 used for all statistical analyses with significant value ( $p$ ) at  $< .05$ .

#### 115 *Ethics*

116 The ethical clearance was issued by the Ethical Committee of Dr. Soetomo General Hospital  
117 (No.1766/105/XI/2019).

118

## 119 **RESULTS**

120 In this study, three babies had multiple congenital anomalies, four babies had early onset of  
121 septicemia, and the others were excluded due to incomplete data and consent. Eleven infants  
122 classified as hsPDA group based on echocardiography. There were 25 (48%) and 27 (52%)  
123 preterm male and female babies, respectively. Majority of the subjects was in 28-32 weeks of

124 gestational age (55.8%) with mean gestational age was  $30.72 \pm 2$  weeks for hsPDA and  $30.78 \pm 2$   
125 weeks for non hsPDA. Mean birth weight for hsPDA and non hsPDA were  $1213 \pm 293$  and  
126  $1272 \pm 306$  grams, respectively.

127 Table 1 depicts the neonatal characteristics for both groups. There was no significant  
128 difference in all variables. Therefore, the samples considered as homogenous.

129 This study obtained that the smallest DA's diameter was 1.5 mm and the largest one was 4.8  
130 mm in the hsPDA group. From the eleven samples in hsPDA group, the duct diameter was  
131 obtained with an average of  $2.84 \pm 0.93$ . The comparison between LA and Ao had an average  
132 score of  $1.56 \pm 0.26$ . The ejection fraction of hsPDA and non hsPDA group were  $71.55 \pm 5.72$  and  
133  $73.94 \pm 9.4\%$ , respectively.

134 Linear regression was used to evaluate comorbidities on samples, namely perinatal asphyxia,  
135 respiratory distress syndrome, and persistent pulmonary hypertension of the newborn as  
136 confounding factors of the regional oxygen saturation. All measurement was not significant.  
137 In accordance to Table 2, there were no significant differences in the tissue oxygen saturation  
138 ratio of cerebral ( $r_cSO_2$ ), abdominal ( $r_aSO_2$ ), or renal ( $r_rSO_2$ ) areas between hsPDA and non  
139 hsPDA groups ( $p = .238$ ,  $p = .598$ , and  $p = .218$  respectively). Fractional oxygen extraction in  
140 cerebral (cFTOE), abdominal (aFTOE), and renal (rFTOE) areas between the hsPDA and non  
141 hsPDA groups also revealed non-significant difference ( $p = .473$ ,  $p = .578$ , and  $p = .151$ ,  
142 respectively).

143

## 144 **DISCUSSION**

145 The present study obtained the characteristics of the two groups that were not significantly  
146 different so that it can be compared. Previous study showed that the incidence of hsPDA  
147 increased with lower oxygen saturation<sup>12</sup>. The mean SpO<sub>2</sub> in this study was around 97% with  
148 minimal setting of CPAP and mechanical ventilation. There were no significant differences in  
149  $r_cSO_2$  ( $p = .238$ ) between the hsPDA and non hsPDA groups in the study. These findings are in  
150 line with previous observational cohort designs by van der Laan et al. in Netherland, in which  
151 oxygen saturation and oxygen extraction in cerebral and renal of 49 preterm infants with  
152 gestational age <32 weeks evaluated using NIRS were not affected by hsPDA.<sup>6</sup> The  $r_cSO_2$  results  
153 in hsPDA group (69%) were lower than non hsPDA group (76%) and cFTOE in hsPDA group  
154 (0.22) were higher than non hsPDA group (0.33).

155 In contrast to the results of several previous research where a decrease in cerebral  
156 oxygenation was found in hsPDA, Lemmers et al. reported a lower  $r_cSO_2$  in infants with hsPDA  
157 compared to the asymptomatic PDA group ( $62\pm 9\%$  and  $72\pm 10\%$ , sequentially). The difference  
158 might be caused by several factors affecting the patient's hemodynamics. In Lemmers' study, the  
159 patients in hsPDA group mostly used ventilator, morphine as sedatives that caused peripheral  
160 vasodilation, and more inotropic than control. Dopamine administration could increase cardiac  
161 output that affected an elevating perfusion. In addition, in the previous study, the sampling  
162 period was earlier (in the first 72 hours) compared to the present study (3-7 postnatal days)  
163 which could affect the results of oxygenation measurement. It is agreed that the cerebral oxygen  
164 supply increases as the baby age. Tissue oxygen extraction (FTOE) was also significantly higher  
165 in premature infants with hsPDA than those with non hsPDA<sup>13</sup>. The relationship between oxygen  
166 transport ( $DO_2$ ) and tissue oxygen consumption ( $VO_2$ ) is fractional tissue oxygen extraction  
167 ( $FTOE=VO_2/DO_2$ ). Negative correlation between  $r_cRSO_2$  and cFTOE indicated that if there was  
168 a decrease in the brain oxygen supply in sick premature babies, there was an increase in cerebral  
169 oxygen extraction aimed to maintain oxygen availability in the brain<sup>14</sup>.

170 A retrospective study by Chock et al. showed that a low  $r_cSO_2$  value of  $< 66\%$  was associated  
171 with the presence of hsPDA in preterm infants<sup>9</sup>. Although the oxygenation value in cerebral  
172 tissue of hsPDA infant was lower than non hsPDA, the average value was still higher compared  
173 to the  $< 40\%$  cerebral oxygen saturation limit associated with the appearance of symptoms, such  
174 as ischemic lesions and neuron damage. The normal value of  $r_cSO_2$  for preterm babies is 55-  
175 85%<sup>15</sup>. According to Dix et al., higher  $r_cSO_2$  values in neonatal sensors compared to adult NIRS  
176 sensors might be caused by differences in NIRS signal reception process where neonatal NIRS  
177 sensor algorithmic adjusted to thinner neonatal calvarium so that the light is easier to enter<sup>16</sup>.

178 Although the determination of "to treat or not to treat" is still a clinical question nowadays,  
179 Poon et al., reported an improvement in cFTOE after medical therapy and PDA ligation.<sup>17</sup>  
180 Observation using NIRS as an overview of PDA closure can help on evaluating the infants to  
181 reduce the burden of cerebral hypoxia. It is necessary to identify infants at high risk of long-term  
182 developmental disorders.

183 Although not statistically significant,  $r_aSO_2$  was lower in premature infants with hsPDA than  
184 non hsPDA ( $65.60\pm 11.07$  and  $67.48\pm 10.17$ , respectively) with  $p$  of .594. Similarly, abdominal  
185 fractional oxygen extraction in infants with and without hsPDA were  $0.33\pm 0.11$  and  $0.3\pm 0.1$ ,

186 respectively ( $p = .578$ ). The findings are similar to the results of a study by Petrova et al., where  
187 no significant difference was found between tissue oxygen saturation in cerebral, abdominal, and  
188 renal in preterm infants aged < 32 weeks of gestational age with PDA diameter of  $\geq 3$  compared  
189 to < 3 mm<sup>18</sup>. Similarly, Gorman et al. found no statistical difference in hsPDA infants who were  
190 given ibuprofen therapy and who were not.<sup>19</sup> It was reported that NIRS facilitated benefits in  
191 terms of showing a downward trend of 20% of the base value before clinical manifestation of  
192 NEC appeared. In our study, we found 3 preterm babies with hsPDA and 7 non-hsPDA who  
193 experienced NEC based on Bell stage criteria.

194 Different results were reported by Ledo et al., where infants with hsPDA had significantly  
195 lower abdominal tissue oxygen saturation during observational prospective studies of 72  
196 premature infants.<sup>20</sup> Lower blood pressure and lower mesenteric oxygenation with increased  
197 extraction of oxygen by tissues were obtained. Continuous monitoring on abdominal  
198 oxygenation needs to be done in newborns where a transition of gastrointestinal tract from a  
199 relatively dormant organ to a main area of nutrient absorption requiring sufficient supply of  
200 oxygen. Unlike cerebral circulation that has an autoregulation protection mechanism, mesenteric  
201 circulation in the abdomen does not have the ability to auto-regulate. Therefore, it is at risk of  
202 gastrointestinal hypoxia. Ledo et al. stated that hsPDA babies had lower blood pressure with  
203 lower abdominal oxygenation. Abdominal FTOE also reported an increase in the first five days  
204 and stabilized on day six. The stability of the aFTOE on the 6<sup>th</sup> day was along with the  
205 spontaneous closure of the DA. In the previous study, babies who got catecholamine were put in  
206 the exclusion group to minimize the confounding factors that affected oxygenation<sup>20,21</sup>. NIRS  
207 somatic sensors placed in the abdominal region were expected to detect oxygenation  
208 disturbances in abdomen. Abdominal oxygen saturation ( $r_aSO_2$ ) depicts blood flow in the  
209 mesenteric artery as it is the main vascular supplier of the gastrointestinal tract<sup>22</sup>.

210 In this study, there was no significant difference in  $r_rSO_2$  value between hsPDA compared to  
211 non hsPDA ( $76.41 \pm 14.98$  vs  $82.61 \pm 10.41$ ) ( $p = .218$ ). Normal value of  $r_rSO_2$  in premature babies  
212 is 80%. New born average  $r_rSO_2$  score is 40% that will increase in ten minutes to 80-90%, then  
213 decrease with improvements in renal blood flow and increase the utilization of oxygen in the  
214 kidneys<sup>18</sup>. In a cohort study of premature infants in the first week of life, it was found that  
215  $r_rSO_2 < 66\%$  was associated with the presence of hsPDA based on echocardiography criteria with  
216 a sensitivity of 81% and specificity of 77%. The difference could be due to the fact that the

217 babies in the previous study who had  $r_t\text{SO}_2 < 66\%$  were  $< 1000$  grams of weight and used  
218 ventilators. Low  $r_t\text{SO}_2$  values can be caused by immature renal function or hemodynamic  
219 instability other than PDA<sup>9</sup>. Guzoglu et al. reported no significant difference in regional oxygen  
220 saturation of the kidneys with  $r_t\text{SO}_2$  value of 60% (ranged between 17-93%,  $p = .87$ ) and rFTOE  
221 .37 (ranged between .06-.83,  $p = .87$ ) in infants with hsPDA and control<sup>16,22,23</sup>. The  $r_t\text{SO}_2$  value  
222 obtained in the present study is relatively higher than other studies. This can be caused due to  
223 NIRS renal measurements conducted on post natal days 3 to 7 when perfusion and utilization of  
224 oxygen in the kidneys were still in the transition process.

225 This study provides information of oxygen saturation in three region simultaneously in both  
226 groups. However, there are several limitations of this study. First, the NIRS measurement of  
227 tissue oxygen saturation is only performed in short period. Longitudinal study is needed to study  
228 the oxygen saturation trends. Second, tissue oxygen saturation assessment is based on NIRS only  
229 and not confirmed by other supporting examinations. And last, the small number of samples due  
230 to limitation of time.

## 231 **CONCLUSION**

232 The results of our study suggest that hsPDA does not affect the oxygenation in cerebral,  
233 abdominal, and renal in preterm infants during the examination. The decision regarding optimal  
234 time for ductal closure should be reconsidered. However, further large scale studies needs to be  
235 conducted to reassess the present findings.

236

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241 conducted the initial analysis. Risa Etika, Martono Tri Utomo, Dina Angelika, Kartika D.  
242 Handayani, and Mahendra T.A.S. worked together as the neonatologist in charge at NICU.  
243 Rahman performed the echocardiography examination in all patients. Samosir collected the  
244 NIRS data, conducted further analysis, and did the manuscript writing. Finally, all authors had  
245 read and approved the final version of this manuscript.

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340 **TABLES**

341

342 **Table 1.** Subject characteristic

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	<b>hsPDA n (11)</b>	<b>non-hsPDA n (41)</b>	<b>Total n (52)</b>	<b>P</b>
Sex				1.000*
Male	5 (9.6)	20 (38.5)	25 (48.1)	
Female	6 (11.5)	21 (40.4)	27 (51.9)	
Gestational age				1.000**
<i>Extremely Preterm</i> (<28 weeks)	1 (1.9)	3 (5.8)	4 (7.7)	
<i>Very Preterm</i> (28 - <32 weeks)	6 (11.5)	23 (44.3)	29 (55.8)	
<i>Moderate Late Preterm</i> (32 - <37 weeks)	4 (7.7)	15 (28.8)	19 (36.5)	
Birth weight				0.902**
ELBW (<1000 g)	2 (3.9)	6 (11.5)	8 (15.4)	
VLBW (<1500 g)	7 (13.5)	24 (46.1)	31 (59.6)	
LBW (<2500 g)	2 (3.9)	11 (21.1)	13 (25)	
Singleton/multiple birth				0.322
Singleton	11 (21.1)	35 (67.4)	46 (78.5)	
Multiple birth	0 (0.0)	6 (11.5)	6 (11.5)	
Respiratory support				0.474**
<i>High flow nasal canule</i>	1 (1.9)	1 (1.9)	2 (3.8)	
CPAP	7 (13.5)	33 (63.5)	40 (77)	
Non invasive ventilator	1 (1.9)	1 (1.9)	2 (3.8)	
Invasive ventilator	2 (3.9)	6 (11.5)	8 (15.4)	
HR (x/minute), <i>mean</i> ± SD	165±14,4	148±10,5		
SpO <sub>2</sub> (%), <i>mean</i> ± SD	97.1±2,7	97.0±1,9		
Hb, <i>mean</i> ± SD	15.73±3.46	15.37±2.58		0.702
Inotropes				0.101
No	8 (15.4)	38 (73.1)	46 (88.5)	
Yes	3 (5.7)	3 (5.7)	6 (11.5)	
Age during recruitment				
3 day	3 (5.7)	21 (40.5)	24 (46.2)	0.118

4 day	6 (11.5)	10 (19.3)	16 (30.8)	
5 day	1 (1.9)	5 (9.6)	6 (11.5)	
6 day	1 (1.9)	4 (7.7)	5 (9.6)	
7 day	0 (0.0)	1 (1.9)	1 (1.9)	
Infant's comorbidity				0.086
Respiratory distress synd.	6 (11.5)	12 (23.1)	18 (34.6)	
Perinatal Asphyxia	2 (3.8)	11 (21.1)	13 (24.9)	
PPHN	3 (5.7)	3 (5.7)	6 (11.4)	
Hyperbilirubinemia	4 (7.7)	6 (11.5)	10 (19.2)	
Others	1 (1.9)	9 (17.3)	10 (19.2)	
APGAR score in 5 minutes				0.886*
≤5	6 (11.5)	19 (36.5)	25 (48)	
>5	5 (9.6)	22 (42.4)	27 (52)	
Mode of delivery				0.094**
SC with general anesthesia	6 (11.5)	7 (13.5)	13 (25)	
SC with regional anesthesia	3 (5.7)	19 (36.5)	22 (42.2)	
Spontaneous birth	2 (3.8)	14 (27.0)	16 (30.7)	
Assisted vaginal birth	0 (0.0)	1 (1.9)	1 (1.9)	
Amniotic fluid				0.134**
Clear	10 (19.3)	38 (73.1)	(92.4)	
Turbid	1 (1.9)	0 (0.0)	(1.9)	
Meconium	0 (0.0)	3 (5.7)	(5.7)	
Mother's comorbidity				0.357**
Healthy	1 (1.9)	2 (3.8)	3 (5.7)	
Hypertension	6 (11.5)	11 (21.1)	17 (32.7)	
Obesity	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal bleeding	1 (1.9)	1 (1.9)	2 (3.8)	
Combination of 2	1 (1.9)	14 (26.9)	15 (28.8)	
Combination of 3	2 (3.8)	9 (17.3)	11 (21.1)	
Others	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal corticosteroid				1.000
No	7 (13.5)	27 (52)	34 (65.5)	
Yes	4 (7.7)	14 (26.8)	18 (34.5)	

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346 **Table 2** Comparison of Regional Oxygen Saturation & Fractional Oxygen Extraction of hsPDA  
 347 and non hsPDA

	hsPDA		Non hs-PDA		p
	(n)	(mean±SD)	(n)	(mean±SD)	
r <sub>c</sub> SO <sub>2</sub>	11	75.27±9.14	41	79.03±9.11	0.238
r <sub>a</sub> SO <sub>2</sub>	11	65.60±11.07	41	67.48±10.17	0.594
r <sub>c</sub> SO <sub>2</sub>	11	76.41±14.98	41	82.61±10.41	0.218
cFTOE	11	0.22±0.09	41	0.19±0.08	0.473
aFTOE	11	0.33±0.11	41	0.30±0.10	0.578
rFTOE	11	0.26±0.19	41	0.16±0.12	0.151

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353 **FIGURES**

354 **Figure 1a.**Box plot diagram of regional FTOE values on hsPDA and non hsPDA group

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356 **Figure 1b.**Box plot diagram of regional rSO<sub>2</sub> values on hsPDA and non hsPDA group

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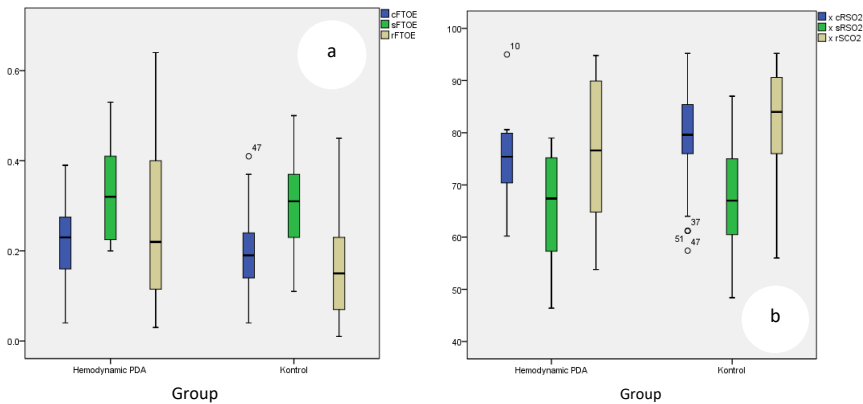
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**Manuscript Needs Major Revision (#IJN-2102-2040 (R4))**

2 messages

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**Iranian Journal of Neonatology IJN** <ijn@mums.ac.ir>

Mon, Nov 1, 2021 at 12:37 PM

To: mrmartono73@gmail.com

Manuscript ID: IJN-2102-2040 (R3)

Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Martono Tri Utomo, Risa Etika, Mahrus Abdul Rahman, Mahendra Tri Arif Sampurna, Sunny Mariana Samosir

Dear **Mr. Martono Tri Utomo**

Your manuscript has obtained major revisions. In this case we normally treat it as unacceptable for publication. However, as numerous editorial errors have pointed out by the reviewers, the **Iranian Journal of Neonatology IJN** editor believes that the manuscript could be rectified and prepare for possible publication.

Please let us know your views in this regard and in the case of positive response, reply us within 7 days time.

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Reviewers Recommendation:

**Reviewer 1:**

Reviewer Comment For Author:

Dear author, please check the following:

- The authors stated, " This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during study times. The samples were determined using consecutive sampling technique". These sentences should be moved to the patient section.
- The authors stated, "The study aimed to analyze the tissue oxygen saturation (rSO<sub>2</sub>) differences of premature babies with and without hsPDA". To this end, the logistic regression could be suitable. Therefore, add the odds ratio in the results section.
- In Figure 1, concerning the outliers, the analysis is re-examined.



Martono Utomo &lt;mrmartono73@gmail.com&gt;

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**Acknowledgement of Revision (#IJN-2102-2040 (R4))**

1 message

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**Iranian Journal of Neonatology IJN** <ijn@mums.ac.ir>

Sun, Nov 7, 2021 at 9:35 PM

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Authors: Martono Tri Utomo, Risa Etika, Mahrus Abdul Rahman, Mahendra Tri Arif Sampurna, Sunny Mariana Samosir

Date: 2021-02-16

Dear **Mr. Martono Tri Utomo**Thank you for submitting the revised file of your manuscript to the **Iranian Journal of Neonatology IJN**

The Editorial Office will proceed on your manuscript and inform you in the earliest time.

If there is anything else, please do not hesitate to contact us.

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Executive Managing Director of **Iranian Journal of Neonatology IJN**



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## Acceptance of Manuscript (#IJN-2102-2040 (R4))

1 message

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Fri, Jan 14, 2022 at 7:19 PM

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Manuscript ID: IJN-2102-2040 (R4)

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Authors: Martono Tri Utomo, Risa Etika, Mahrus Abdul Rahman, Mahendra Tri Arif Sampurna, Sunny Mariana Samosir

Dear **Mr. Martono Tri Utomo**

This is to confirm that after technical and in-house evaluation, the above mentioned manuscript has been finalized and accepted for publication in the journal.

A copy of the Journal issue with 5 reprints will be sent to the corresponding author after publication.

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