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Original Article

Effects of lung recruitment maneuvers using mechanical ventilator on preterm hemodynamics

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Abstract

Background Lung recruitment maneuvers (LRMs) are a strategy to gradually increase mean positive airway pressure (MAP) to expand the alveoli, leading to decreased pulmonary vascular resistance and increased cardiac output (CO). However, the hemodynamic impact of LRM using assist control volume guarantee (AC-VG) ventilator mode done in preterm infants born at 24 to 32 weeks' gestation, especially in the first 72 hours of life, remains unknown.

Objective To determine the effect of LRM on right- and left cardiac ventricular output (RVO and LVO), ductus arteriosus (DA) diameter and its pulmonary hypertension (PH) flow pattern, as well as superior mesenteric artery (SMA) flow.

Methods This randomized, controlled, single-blinded clinical trial was performed in 24-32-week preterm neonates with birth weights of >600 grams. Subjects were allocated by block randomization to the LRM and control groups, each containing 55 subjects. We measured RVO, LVO, DA diameter, PH flow pattern, and SMA resistive index (RI) at 1 and 72 hours after mechanical ventilation was applied. We analyzed for hemodynamic differences between the two groups.

Results During the initial 72 hours of mechanical ventilation, there were no significant differences between the control vs. LRM groups in mean changes of LVO [41.40 (SD 91.21) *vs.* 15.65 (SD 82.39) mL/kg/min, respectively; (P=0.138)] or mean changes of RVO [65.56 (SD 151.20) *vs.* 70.59 (SD 133.95) mL/kg/min, respectively; (P=0.859)]. Median DA diameter reduction was -0.08 [interquartile range (IQR) -0.55; 0.14] mm in the control group and -0.10 (IQR -0.17 to -0.01) mm in the LRM group (P=0.481). Median SMA resistive index was 0.02 (IQR -0.16 to 0.24) *vs.* 0.01(IQR -0.20 to 0.10) in the control *vs.* LRM group, respectively. There was no difference in proportion of pulmonary hypertension flow pattern at 72 hours (25.4% *vs.* 20% in the control *vs.* LRM group, respectively) (P=0.495).

Conclusion When preterm infants of 24-32 weeks gestational age are placed on mechanical ventilation, LRM gives neither additional hemodynamic benefit nor harm compared to standard ventilator settings. **[Paediatr Indones. 2023;63:173-80; DOI: https://doi.org/10.14238/pi63.3.2023.173-80**].

Keywords: *Henoch-Schönlein purpura; nephritis; childhood; risk factors*

Respiratory distress of the newborn (RDN) is the most common problem in preterm infants admitted to the neonatal intensive care unit (NICU),[1] with an incidence of around 6.7% of all live births. Infants with RDN need positive pressure ventilation support in 30% of premature, 20.9% of full term, and 4.2% of post-mature infants. Respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), neonatal pneumonia, and transient tachypnea of the newborn (TTN) are the most common etiologies of RDN.[2]

If infant lung compliance is very poor and non-invasive positive-pressure ventilation fails, the infant should be intubated and receive invasive mechanical ventilation. In our previous study at Dr. Cipto Mangunkusumo Hospital, Jakarta, among 100 infants with moderate respiratory distress (Downes scores 4 to 6) who received nasal continuous positive pressure (nCPAP), 26% experienced failure and subsequently needed invasive mechanical ventilation support.[3]

Surfactant deficiency leads to fluid-filled and collapsed alveoli, reducing oxygen uptake and CO_2

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removal from the alveoli. Hypoxemia and respiratory acidosis causes diminished decrease in pulmonary vascular resistance, further weakening cardiac contractility, in turn leading to cardiac failure. The ductus arteriosus (DA) tends to fail to close due to hypoxemia and increased levels of endogenous nitric oxide. Inside the DA, blood predominantly flows in a right to left pattern (> 30% total), further worsening hypoxemia.[4]

Lung recruitment maneuver (LRM) is a techniQRue to increase lung residual capacity (LRC) faster, using gradual increments of positive end-expiratory pressure (PEEP) in patients by way of mechanical ventilators.5 The more LRC increases, the better the arterial pulse oxygen saturation (SpO_2), and the lower the fraction of inspired oxygen (FiO_2) needed. Better arterial oxygenation and hemodynamic transition lead to greater cardiac output, reduced pulmonary vascular resistance, and improved splanchnic blood flow.

In this study, we aimed to assess the effect of LRM on premature infants born at <32 weeks' gestation who received mechanical ventilation in assist control volume guarantee (AC-VG) mode on cardiac output, DA diameter-flow pattern, and splanchnic circulation measured by superior mesenteric artery resistive index (SMA-RI).

Methods

This study was a randomized, controlled, single-blinded clinical trial conducted in the NICU of Dr. Cipto Mangunkusumo Hospital, Jakarta, from March 2021 to April 2022. Inclusion criteria were preterm infants born in Dr. Cipto Mangunkusumo Hospital or Bunda Menteng Hospital, Jakarta at 24-32 weeks' gestation with birth weight of >600 grams who were intubated at <48 hours of age and used AC-VG mode mechanical ventilation with FiO_2 of >30%. Exclusion criteria were major congenital anomalies, inborn errors of metabolism, congenital heart defects, hypoxic-ischemic encephalopathy, or absence of parental consent to participate in the study. Before birth, potential subjects were assigned to the LRM or control group using block-of-four randomization. The randomization results were stored in a sealed envelope and was opened just before the infant was intubated.

We used the sample size estimation formula for hypothesis testing for two independent groups with continuous data with an alpha of 5% and power of 80%. We also calculated sample size for determination of differences in proportion for nominal data. The minimun required sample size was estimated to be 110 subjects. Subjects were recruited after parents provided written informed consent. This study was approved by the Universitas Indonesia Medical School and Dr. Cipto Mangunkusumo Hospital Ethics Committees.

All hemodynamic outcomes were measured using echocardiography by a pediatric cardiologist (AR) and two neonatologists (AK and AI). Kappa statistic for agreement between the three evaluators had been assessed prior to the study and was >80%. The outcomes of this study were RVO, LVO, DA diameter, type of flow pattern, left atrial to aortic root (La/Ao) ratio, and SMA-RI. RVO and LVO were measured in mL/Kg/minute and DA diameter was measured in milimeters. We also observed the proportion of infants with right-to-left shunt DA flow > 30% or pulmonary hypertension (PH) pattern. La/Ao ratio was defined as the diameter of the left atrium divided by the diameter of the aorta, while SMA-RI was defined as peak systolic velocity divided by end diastolic velocity of the SMA blood flow. For all measurements, we used a *Philips Affiniti 50* (*Philips*, Amsterdam) ultrasonography machine with a 12 Hz probe. RVO and LVO were measured from a high parasternal long axis and apical 5-chambers view. DA was measured from a high parasternal view; SMA flow was measured from a subcostal view. The measurements were performed twice, on the first hour and 72 hours after the baby was intubated. We then calculated increments or decrements between the first hour and 72 hours measurement outcomes.

All subjects were intubated preterm infants of 24-32 weeks' gestational age based on Ballard score assessment6 who required invasive mechanical ventilation. Mechanical ventilation was delivered using the *Dräger VN-500* (*Dräger*, Lübeck, Germany) in AC-VG mode with initial settings as follows: expiratory tidal volume (Vte) 5 mL/kg, PEEP 5 cm H2O, back-up rate 50x/minute, and inspiration time (IT) 0.35-0.4 seconds. FiO2 was given to target an SpO_2 90-95%. We administered 4 mL/kg of surfactant directly to infants' lungs as soon as they were intubated.

The first hemodynamic measurement was performed less than an hour after management was initiated. After that, subjects were randomized to either the treatment (LRM) or control (standard protocol) group. The treatment group received LRM as follows: PEEP was gradually increased by 0.2 cmH_2O every 3 minutes while SpO_2 of the right hand was observed. The FiO_2 would be reduced by 5% if SpO_2 was >95%. We stopped increasing PEEP when FiO_2 reached 21% (opening point), then gradually decreased PEEP by 0.2 cmH_2O every 3 minutes until desaturation (SpO_2 <90%) was observed (closing point), upon which the PEEP decrement was stopped. The PEEP was then rapidly increased to the level of the opening point for 3 minutes, then rapidly lowered to 0.2 cm H_2O above the closing point (optimal point). The control group received a constant PEEP of 5 cm H_2O during the first 48 hours. Other ventilator settings and adjustments (not including PEEP) were the same for both groups. Over the next 72 hours, we did not interfere with any decisions related to mechanical ventilator adjustment; these were at the discretion of the caring attending physician. On the fourth day, we performed a second hemodynamic measurement in all patients in both groups. Due to the nature of the intervention, subjects and parents were unaware of the subject's allocation, but blinding of outcome evaluators and attending physicians was not possible.

Cardiac outputs were measured with a Doppler ultrasound using apical, short, and long parasternal axis views,[6] and calculated by the following formula: (3.14 x ¼ x diameter of aorta or pulmonary artery) 2 x volume time integral x heart rate)/body weight. The DA and its flow pattern were measured from a high parasternal view using 2D and pulse wave (PW) Doppler, respectively. The SMA pulsatile index was obtained from a subcostal view using PW Doppler mode and spectral Doppler analysis.[7] Echocardiography examination was performed less than one hour after intubation and repeated after 72 hours.

Descriptive data were presented in tabular and textual forms. Numeric data with normal distribution were presented as mean and standard deviation (SD), while data with non-normal distribution were shown as median and interquartile range (IQR). The unpaired T-test or Mann-Whitney test were used for statistical analyses of numeric data. A P value of <0.05 was considered statistically significant. We incorporated 95% confidence intervals where appropriate. We employed per-protocol analysis aided by *SPSS for Mac version 20.0* (*IBM*, Armonk, New York).

Results

A total of 299 24-32-week preterm infants were born at Dr. Cipto Mangunkusumo Hospital and Bunda Menteng Hospital during the study period. Forty-six infants were stillborn, 15 were born with major congenital abnormalities, and 219 had birth weight of >600 grams. There were 166 infants with severe respiratory distress who required mechanical ventilation within <48 hours of life. In 56 infants, parents refused give consent for participation in the study and/or measurements were not available (instruments were not ready or investigators were not on site). Thus, a total of 110 subjects participated and underwent measurements according to the study protocol. Eight subjects died <72 hours after initiation of mechanical ventilation and were excluded from analysis.

Between the two groups, there were no notable differences in maternal characteristics that could affect RDN severity, such as hypertension, diabetes mellitus, chorioamnionitis, preterm premature rupture of the membranes (PPROM), mode of delivery, Apgar score, mode of resuscitation, or gender. The treatment group tended to receive more complete antenatal steroids, but had lower birth weight and older gestational age. The LRM group had a notably higher proportion of small-for-gestational-age (SGA). The clinical characteristics of study subjects are presented in **Table 1**.

The median FiO_2 in the control *vs.* treatment groups was 38.0 (IQR 35.0 to 40.0) *vs.* 36.0 (IQR 30.0 to 40.0)%, respectively (P=0.599) at the first hour and 21.00 (IQR 21.00 to 25.00) *vs.* 21.00 (IQR 21.00 to 22.00)%, respectively (P=0.151) at 72 hours. The mean opening, closing, and optimal PEEPs of the treatment group were 9.4 (SD 2.0), 4.6 (SD 0.6), and 5.4 (SD 0.6) cmH2O, respectively, while PEEP in the control group was 5 cm H_2O throughout the 72 hours.

Both LVO and RVO increased on the fourth day of mechanical ventilation. The DA tended to close in both groups. There was reduction of pulmonary

Table 1. Characteristics of subjects

Characteristics	LRM (n=55)	Control (n=55)	P value
Hypertension in pregnancy, n (%)	11 (20.0)	13 (23.63)	0.760
Diabetes mellitus in pregnancy, n (%)	3 (5.45)	3 (5.45)	1.00
Clinical chorioamnionitis, n (%)	1 (1.81)	0 (0)	1.00
Premature rupture of membrane > 18 hours, n (%)	19 (34.54)	17 (30.90)	0.515
Mode of delivery, n (%)			
Normal delivery	12 (21.82)	17 (30.91)	0.279
Caesarean section	43 (78.218)	38 (69.109)	
Multiple pregnancy, n (%)	9 (16.436)	5 (9.109)	0.252
Antenatal steroid use, n (%)			
Never	20 (36.436)	19 (34.54)	0.202
Incomplete	14 (25.45)	22 (40.0)	
Complete	21 (38.218)	14 (25.45)	
Median (IQ)/mean (SD) birth weight, gram	1010 (890; 1325)	1120.7 (331.3)	0.729
Median gestational age (IQ), weeks	29 (28; 31)	28 (27; 30)	0.210
Extremely low birth weight, n (%)			
Gestational age <28 weeks	14 (25.45)	20 (36.436)	0.252
Gestational age ≥28-< 32 weeks	41 (74.54)	35 (63.63)	
SGA, n (%)			0.022*
No	44 (80.0)	52 (94.54)	
Yes	11 (20.0)	3 (5.45)	
Gender, n (%)			1.00
Male	31 (56.436)	31 (56.436)	
Female	24 (43.63)	24 (43.63)	
Median APGAR score (IQ)			
APGAR 1st minute	4 (2; 8)	4 (1; 8)	0.413
APGAR 5th minute	8 (4; 9)	8 (4; 9)	0.838
Resuscitation, n (%)			
VTP/chest compression/intubation	50 (90.90)	45 (81.81)	0.219
CPAP/NIPPV	5 (9.109)	10 (18.218)	
Radiologic diagnosis, n (%)			
RDS 1-2	36 (65.546)	39 (70.91)	0.081
RDS 3-4	7 (13.73)	5 (9.109)	
Pneumonia or other	12 (21.81)	11 (20.0)	

*Chi-square test; ^Fisher's test; >Mann-Whitney U test; IQ: interquartile; SGA: small for gestational age

Table 2. Hemodynamic parameters

Variables	At 1st hour			At 72 hours		
	LRM (n=55)	Control (n=55)	P value	LRM (n=52)	Control (n=50)	P value
Median DA diameter (range), mm	0.16 (0.11-0.21)	0.14 (0.096)	0.157	0.00 (0.0-0.067)	0.00 (0.00; 0.92)	0.876[a]
Median left cardiac output (range), mL/kg BW/min	193.01 (135.28-229.49)	171.96 (61.47)	0.155	215.91 (72.25)	186.12 (165.60-267.49)	0.733[a]
Median right cardiac output (range), mL/kg BW/min	232.67 (118.77)	200.06 (144.91-275.76)	0.365	308.51 (120.00)	285.94 (124.49)	0.353[b]
Median La/Ao ratio (IQ)	1.17 (0.50-2.20)	1.14 (0.60-2.67)	0.290	1.11 (0.09; 2.90)	1.13 (0.57; 2.33)	0.326[a]
Median SMA RI (IQ), mm	0.73 (0.075)	0.70 (0.69; 0.79)	0.340	0.735 (0.007)	0.721 (0.084)	0.379[a]
Mean proportion DA with PH pattern (SD), %	14 (25.45)	11 (20)	0.495	6 (10.90)	6 (10.90)	0.942[c]

[a]Mann-Whitney U test; [b]Independent T-test; [c]Chi-square test; IQ=interquartile

Table 3 . Hemodynamic parameter changes during 72 hours of mechanical ventilation

Variables	LRM (n=52)	Control (n=50)	95%CI	P value
Mean LVO (SD), mL/kg BW/min	15.65 (82.39)	41.40 (91.21)	-8.373 to 59.868	0.138
Mean RVO (SD), mL/kg BW/min	70.59 (133.95)	65.56 (151.20)	-61.089 to 51.037	0.859
Median DA (IQ), mm (IQ)	-0.10 (-0.17; -0.01)	-0.09 (0.10)	0.443 to 0.630	0.481
Median La/Ao ratio (IQ)	-0.094 (0.40)	0.00 (-0.20; 0.21)	0.018 to 0.109	0.059
Median SMA RI (IQ), mm (IQ)	0.010(-0.20; 0.10)	0.0356 (0.0949)	0.065 to 0.190	0.127

pressure in our preterm subjects. Meanwhile, the La/Ao ratio, a marker of pulmonary overcirculation, also tended to decrease in both groups. **Table 2** contains details on the hemodynamic parameters at the first and 72 hours after initiation of mechanical ventilation. We also calculated changes of hemodynamic parameters 72 hours after mechanical ventilation was initiated (**Table 3**).

Discussion

The FiO_2 at the first hour ranged from 30% to 65% across both groups. This finding indicates that the infants' lungs had begun to expand and functional lung capacity had been established, even though it was not yet optimal. Post-intubation, infants were ventilated by T-piece resuscitator, with a peak inspiratory pressure (PIP) of 25-30 cm H_2O and PEEP of 5 cmH_2O. Using this technique, early positive airway pressure was established, causing the alveoli to gradually inflate with each breath.[8] Within 72 hours, infants in both groups were able to breathe with FiO_2 of 21%, which indicated that their lungs were optimally inflated.

In the AC-VG ventilator mode, the PIP would increase or decrease automatically to maintain expiratory tidal volume within the normal range.[9] Although not as effective as PEEP, increasing PIP would also increase mean airway pressure, which is needed to create optimal functional residual capacity (FRC). The more optimal the FRC, the lower the FiO_2 required.[10] This explains the lack of difference in FiO_2 requirements at 72 hours post-intubation between the two groups.

During the 72 hours of mechanical ventilation, we observed an RVO increment in both the treatment and control groups. This finding applied to LVO as well. At both 1 and 72 hours, RVO was always higher than LVO. In contrast, Evans et al., who studied preterm infants <1,500 g on mechanical ventilation, reported a median RVO of 202 (range 102 to 376) and median LVO of 233 (range 144 to 463) mL/kg/min at one day of age. The same study reported a median RVO of 240 (range 187-375) and median LVO of 239 (range 154-446) mL/kg/min on the third day.[11]

The right ventricular outflow tract (RVOT) is determined by systemic venous return, left-to-right shunting at the foramen ovale, pulmonary vascular resistance, and right ventricle contractility, while LVO is determined by pulmonary arterial blood flow, systemic vascular resistance, and left ventricle contractility.[12] After administration of surfactant and application of positive airway pressure, the median FiO_2 of the control and treatment groups were less than 40%, indicating that the alveoli had expanded quite well. Rapid lung expansion would be accompanied by a significant decrease in pulmonary vascular resistance.[13] On the other hand, the left ventricle had to overcome the SVR increase after the cord was clamped.[12] In fetal life, the right ventricle is relatively more hypertrophic than the left ventricle.[14] Hence, RVO can become higher than LVO at the 1st hour after intubation. On the 3rd day, the DAs of both groups had closed, but the foramen ovale remained open, which allowed bidirectional or left-to-right shunting through it. As a result, the preload of the right ventricle would be greater than that of the left ventricle.

Even though increments of RVO and LVO occurred in both groups, all measurements were generally in the normal range (150-300 mL/kg/min). However, a study which measured RVO and LVO in preterm infants using MV in volume control mode, reported that when PEEP was increased from 0.4 and 8 cm H_2O, there was a decrease in both RVO and LVO.[15] This difference might have been caused by different measurement timings. RVO was measured at

10 minutes before and after increasing PEEP from 5 cm H_20 to 8 cm H_20 in premature infants on mechanical ventilation [mean RVO 234 (SD 103) *vs.* 218 (SD 95) mL/kg/min, respectively].[15] The same study also found a reduction in RVO of 15 mL/kg/min in 28-week infants receiving high-frequency oscillatory ventilation (HFOV) and LRM treatment. When LRM was performed using either mechanical ventilation or HFOV, there was an increase in intrathoracic pressure, leading to an increase in left atrial pressure, an increase in right ventricular afterload, and a decrease in left cardiac output due to the interdependence of the two ventricles.[15] In our study, cardiac output was measured 30 minutes before and 72 hours after LRM, so none of the above effects occurred. A previous study showed that the use of a volume-targeted mechanical ventilator was associated with a more stable positive inspiratory airway pressure, which stabilized intra-alveolar pressure, as well as decreased the variability of vascular resistance (right ventricular afterload) and left heart preload.[16] This finding was consistent with our results of no significant differences in changes in right or left cardiac output.

In 48 hours, the DA would functionally close in postnatal term infants. The rate and degree of functional closure is highly dependent on the balance between promoting closure factors such as oxygen, endothelin, calcium channels, catecholamines, and Rho kinases and preventing factors such as intraluminal pressure, prostaglandins, nitric oxide, carbon monoxide, potassium channels, cyclic adenosine monophosphate, and cyclic guanosine monophosphate. Among all these factors, prostaglandin levels and partial pressure of arterial oxygen are considered the most important in the closing of the DA.[17,18]

A study noted no difference in the proportion of patent ductus arteriosus (PDA) of preterms <34 weeks and <2,000 grams who were born apneic and received LRM in the form of sustained inflation compared to regular VTP [18% *vs.* 13%, respectively; (P=0.37)].[19] Another study performed LRM on premature infants with RDS using the proportional assist ventilation mode. They also found no difference in the proportion of DA that was still open at 72 hours compared to controls (3/12 *vs.* 3/12, respectively).[20] A similar result was found in our study. We concluded that in both the treatment and control groups, the DA closing speed was equal. There was no difference in arterial oxygen pO_2 levels at the 1st and 72 hours after mechanical ventilation, which was the main factor for DA closing. In addition, the policy in our NICU is to administer paracetamol or ibuprofen as soon as there is echocardiographic evidence of a hemodynamically significant PDA (hs-PDA). Such practice leads to a significant decrease in prostaglandin levels, thus limiting patency of the DA in both groups.[21]

LRM is meant to open the alveoli so that optimal functional residual capacity can be achieved, followed by a rapid decrease in pulmonary vascular resistance. Along with the improvement of cardiac contractility due to increased arterial PO_2, right cardiac output and pulmonary blood flow will increase, which subsequently leads to an increase in left atrial preload.[22] We noted that the initial La/Ao ratio of the control group was smaller than LRM group. Nevertheless, at 72 hours, the control group La/Ao ratio was higher than that of the LRM group. This finding was consistent with the control group DA being relatively smaller than that of the treatment group at 1 hour of age. The larger the DA diameter, the greater the left-to-right shunt flow, thus, the greater the left atrium diameter. At 72 hours, although not statistically significant, there was a greater La/Ao ratio decrease in the treatment group compared to control, indicating that LRM might able to accelerate DA closure.

Right-to-left shunting will occur if pulmonary arterial pressure is > systemic arterial pressure. Both pulmonary and systemic pressure depends on vascular resistance [pulmonary vascular resistance (PVR) or systemic vascular resistance (SVR)].[23] The higher the resistance, the higher the pressure. At 1 hour, the proportion of PH flow pattern through the DA was higher in the treatment group. SGA babies have relatively higher pulmonary vascular resistance due to dysgenesis of the pulmonary vasculature. SGA babies with inadequate respiratory effort (apnea/no spontaneous breathing) at birth experience collapse of the alveoli and a relative persistence of the high pulmonary vascular resistance.[24] Due to the higher proportion of SGA in the LRM group, the PVR of the treatment group was relatively higher than that of the control group. However, this condition was not found at the age of 72 hours. We theorize that LRM was able to reduce PVR faster in the treatment group than in the control group. Although not as aggressive as LRM, the AC-VG mode in the control group also created

residual lung capacity due to an automatic increment of PIP when lung compliance was still poor. Therefore, at 72 hours, all subjects' lungs had already optimally expanded and pulmonary vascular resistance would have decreased in both groups as well, thus explaining our aforementioned findings.

SMA blood flow is a marker of splanchnic organ blood flow, which always decreases when systemic circulation is compromised. Resistive index (RI) is the ratio of systemic organ velocity divided by diastolic organ blood flow. The higher the index, the worse the splanchnic blood flow. McCurnin et al. found that hs-PDA reduced post-prandial mesenteric blood flow.[25] A previous study found no significant difference in SMA-RI at the first hour or 72 hours after infants were ventilated using HFOV.[26] We found no significant differences in SMA-RI between the control and treatment groups at 1 hour and 72 hours after subjects were ventilated. Nevertheless, RI tended to increase more in the control than the LRM group, meaning that splanchnic blood flow was better in the LRM than in the control group. These results were consistent with our findings on DA diameter, which closed faster in the LRM than in the control group. The sooner the DA closed, the sooner left-to-right ductal shunting ceased, leading to improvement in splanchnic circulation.

Limitations of our study included the lack of blinding of the evaluators of the outcome parameters. As such, there was a possibility of subjectivity bias, even though it was small, as the investigators did not intervene in clinical decisions and measurements were objective. In addition, early targeted therapy by administering paracetamol or ibuprofen could have affected the speed of DA closure in both groups. In addition, eight subjects died before the age of 72 hours; neither cardiac output nor DA could be measured in these patients.

In conclusion, there was no significant difference in hemodynamic macrocirculatory parameters (RVO, LVO, DA closure rate, and proportion of PH flow pattern) between preterm infants born at 23-32 weeks' gestation ventilated using LRM and standard protocol mechanical ventilation.

Conflict of interest

None declared.

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References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, *et al.* National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379:2162-72. DOI: https://doi.org/ 10.1016/S0140-6736(12)60820-4.
2. Kumar A, Vishnu BB. Epidemiology of respiratory distress of newborns. Indian J Pediatr. 1996;63:93-8. DOI: https://doi.org/10.1007/BF02823875.
3. Iskandar ATP, Kaban R, Djer MM. Heated, humidified high-flow nasal cannula vs. nasal CPAP in infants with moderate respiratory distress. Paediatr Indones. 2019;59:331-2. DOI: https://doi.org/10.14238/pi59.6.2019.331-9.
4. Wu TW, Azhibekov T, Seri I. Transitional hemodynamics in preterm neonates: clinical relevance. Pediatr Neonatol. 2016;57:7-18. DOI: https://doi.org/10.1016/j.pedneo.2015.07.002.
5. Castoldi F, Daniele I, Fontana P, Cavigioli F, Lupo E, Lista G. Lung recruitment maneuver during volume guarantee ventilation of preterm infants with acute respiratory distress syndrome. Am J Perinatol. 2011;28:521-8. DOI: https://doi.org/ 10.1055/s-0031-1272970.
6. Singhal R, Jain S, Chawla D, Guglani V. Accuracy of New Ballard Score in small-for-gestational age neonates. J. Trop. Pediatr. 2017;63:489-94. DOI: https://doi.org/ 10.1093/tropej/fmx055.
7. Nestaas E, Fugelseth D, Eriksen BH. Assessment of systemic blood flow and myocardial function in the neonatal period using ultrasound. In: Kleinman CS, Seri I, Polin RA, editors. Hemodynamics and cardiology. 3rd ed. Philadelphia: Elsevier; 2019. p. 191-5. ISBN: 9780323533669.
8. Bjorland PA, Ersdal HE, Haynes J, Ushakova A, Oymar K, Rettedal SI. Tidal volume and pressure delivered by NeoPuff T-piece resuscitator during resuscitation of term newborns. Resuscitation. 2022;170:222-9. DOI: https://doi.

org/10.1016/j.resuscitation.2021.12.006

9. Carlo WA, Ambavalan N. Assisted ventilation. In: Fanaroff J, Fanaroff A, editors. Care of the high-risk neonate. 6th ed. Philadelphia: Saunders; 2013. p. 270-5. ISBN: 9781416040019.
10. Keszler M, Abubakar K. Physiologic principle. In: Goldsmith JP, Karotkin E, editors. Assisted ventilation of the neonate. 6th ed. Philadelphia: Saunders; 2017. p. 8-30. ISBN: 9780323392150.
11. Evans N, Kluckow M. Early determinants of right and left ventricular output in ventilated preterm infants. Arch Dis Child Fetal Neonatal Ed. 1996;74:F88-94. DOI: https://doi.org/ 10.1136/fn.74.2.f88.
12. Vrancken SL, van Heijst AF, de Boode WP. Neonatal hemodynamics: from developmental physiology to comprehensive monitoring. Front Pediatr. 2018;6:87. DOI: https://doi.org/ 10.3389/fped.2018.00087.
13. Lakshminrusimha S. The pulmonary circulation in neonatal respiratory failure. Clin Perinatal. 2012;39:655-83. DOI: https://doi.org/ 10.1016/j.clp.2012.06.006.
14. Hilman N, Kallapur SG, Jobe A. Physiology of transition from intrauterine to extrauterine life. Clin Perinatol. 2012;39:769-83. DOI: https://doi.org/ 10.1016/j.clp.2012.09.009..
15. De Waal K, Evans N, van der Lee J, van Kaam A. Effect of lung recruitment on pulmonary, systemic, and ductal blood flow in preterm infants. J Pediatr. 2009;154:651-5. DOI: https://doi.org/ 10.1016/j.jpeds.2009.01.012. .
16. Sehgal A, Ruoss JL, Stanford AH, Lakshminrusimha S, McNamara PJ. Hemodynamic consequences of respiratory interventions in preterm infants. J Perinatol. 2022;42:1153-60. DOI: https://doi.org/10.1038/s41372-022-01422-5.
17. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. J Perinatol. 2006;26:14-8. DOI: https://doi.org/ 10.1038/sj.jp.7211465.
18. Clyman RI. Mechanisms regulating the ductus arteriosus. Biol Neonate. 2006;89:330-5. DOI: https://doi.org/ 10.1159/000092870.
19. Grasso C, Sciacca P, Giacchi V, Carpinato C, Mattia C, Palano GM, *et al.* Effects of sustained lung inflation, a lung recruitment maneuver in primary acute respiratory distress syndrome, in respiratory and cerebral outcomes in preterm infants. Early Hum Dev. 2015;91:71-5. DOI: https://doi.org/ 10.1016/j.earlhumdev.2014.12.002.
20. Wu R, Li S, Tian Z, Li N, Zheng G, Zhao Y, *et al.* Lung recruitment manoeuvre during proportional assist ventilation of preterm infants with acute respiratory distress syndrome. J Perinatol. 2014;34:524-7. DOI: https://doi.org/ 10.1038/jp.2014.53.
21. Stefano JL, Abbasi S, Pearlman SA, Spear ML, Esterly KL, Bhutani VK. Closure of the ductus arteriosus with indomethacin in ventilated neonates with respiratory distress syndrome. Effects on pulmonary compliance and ventilation. Am Rev Respir Dis. 1991;143:236-9. DOI: https://doi.org/ 10.1164/ajrccm/143.2.236.
22. Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Pediatr. 1994;125:270-7. DOI: https://doi.org/10.1016/s0022-3476(94)70210-1.
23. Martinho S, Adao R, Leite-Moreira AF, Bras-Silva C. Persistent pulmonary hypertension of the newborn: pathophysiological mechanisms and novel therapeutic approaches. Front Pediatr. 2020;8:342. DOI: https://doi.org/ 10.3389/fped.2020.00342.
24. Delaney C, Cornfield DN. Risk factors for persistent pulmonary hypertension of the newborn. Pulm Circ. 2012;2:15-20. DOI: https://doi.org/ 10.4103/2045-8932.94818.
25. McCurnin D, Clyman RI. Effects of patent ductus arteriosus on postprandial mesenteric perfusion in premature baboons. Pediatrics. 2008;122:1262-7. DOI: https://doi.org/ 10.1542/peds.2008-2045.
26. Ayoub D, Elmashad A, Rowisha M, Eltomey M, El Amrousy D. Hemodynamic effects of high-frequency oscillatory ventilation in preterm neonates with respiratory distress syndrome. Pediatr Pulm. 2021;56:424-32. DOI: https://doi.org/ 10.1002/ppul.25195.