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RESEARCH

Positive end-expiratory pressure impact on cardiac output and cerebral hemodynamics in newborns

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Abstract

This study aimed to clarify the extrapulmonary effects of positive end-expiratory pressure (PEEP) in neonates using noninvasive monitoring techniques to monitor cardiac output (CO) and cerebral hemodynamics. This was a prospective, nonrandomized, consecutive enrollment, single-centre study. Newborns weighing ≥ 1,000 g admitted to the neonatal intensive care unit for invasive mechanical ventilation from April 2023 to December 2024 were included. PEEP levels increased sequentially to 5 cm H_2O, 7 cmH_2O, and 10 cm H_2O or peak inspiratory pressure not exceeding 25 cmH_2O (incremental phase) and then decreased to 5 cm H_2O by employing the reverse of the aforementioned procedure (decremental phase) while monitoring stroke volume (SV), CO, and cerebral hemodynamic indexes, including tissue haemoglobin oxygen saturation and total haemoglobin on term and preterm infants using the electrical cardiometry and near-infrared time-resolved spectroscopy. Throughout the procedure, fraction of inspired oxygen, inspiratory time, and tidal volume were maintained at baseline values determined before initiation. This study included 16 term infants (median gestational age: 38 [IQR, 38–39] weeks; median birth weight: 2,778 [IQR, 2,296–3,046] g) and 20 preterm infants (median gestational age: 31 [IQR, 30–33] weeks; median birth weight: 1,459 [IQR, 1,264–2,044] g). High PEEP significantly reduced SV and CO compared to mild PEEP in both term and preterm neonates. tNIRS-1 measurements remained stable throughout the procedure.

Conclusion PEEP levels used in this study reduced CO without affecting cerebral perfusion. Although clinically used PEEP levels have minimal impact on cerebral perfusion in newborns, high PEEP may decrease blood circulation to organs outside the brain.

What is Known:

- *Setting an appropriate positive end-expiratory pressure (PEEP) is a key component of ventilator management in newborns. PEEP influence extrapulmonary functions, including cardiac output (CO) and cerebral hemodynamics. However, limited research has explored these extrapulmonary effects of PEEP in neonates.*

What is New:

- *The PEEP levels used in this study reduced CO without affecting cerebral perfusion in newborns. Clinically used PEEP levels have minimal impact on cerebral perfusion in newborns. However, high PEEP may decrease blood circulation to organs outside the brain.*

Keywords Cardiac output · Neonatal intensive care units · Positive pressure respiration · Near-infrared spectroscopy · Stroke volume

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Abbreviations

CBV	Cerebral blood volume
CPP	Cerebral perfusion pressure
CO	Cardiac output
ELBWI	Extremely low birth weight infant
$ETCO_2$	End-tidal carbon oxide
F_IO_2	Fraction of inspired oxygen
HHb	Deoxygenated haemoglobin
HR	Heart rate
ICP	Intracranial pressure

NICU Neonatal intensive care unit
NIRS Near-infrared spectroscopy
TRS Near-infrared time-resolved spectroscopy
O_2Hb Oxygenated haemoglobin
PDA Patent ductus arteriosus
PEEP Positive end-expiratory pressure
SpO_2 Percutaneous oxygen saturation
StO_2 Tissue haemoglobin oxygen saturation
SV Stroke volume
tHb Total haemoglobin
V_T Tidal volume

Introduction

Many newborns admitted to the neonatal intensive care unit (NICU) require ventilator support. Setting an appropriate positive end-expiratory pressure (PEEP) is a key component of ventilator management [1, 2]. Low PEEP induces alveolar collapse, particularly in preterm infants prone to surfactant deficiency, while high PEEP can cause overinflation, increasing the risk of air leaks such as pneumothorax and pulmonary interstitial emphysema. The aim of mechanical ventilation is to maintain acceptable blood gas levels while minimising lung injury, which can result from excessively high or low pressure delivery. However, determining the optimal PEEP level is challenging due to the difficulty of quantifying lung volumes at the bedside [3]. In addition to its pulmonary effects, PEEP may also influence extrapulmonary functions, including cardiac output (CO) and cerebral hemodynamics [4, 5]. However, there is limited research on the extrapulmonary effects of PEEP in neonates, with a small number of cohorts and inconclusive results.

Recently, various monitoring devices suitable for neonates have been developed. An electrical cardiometry is a noninvasive, continuous CO monitoring system that utilizes electrical velocimetry. Previous research in adults has demonstrated a clinically acceptable correlation between CO measurements obtained from this device and those derived from transesophageal Doppler echocardiography and thermodilution methods [6–9]. Additionally, several studies have supported its effectiveness in assessing CO in infants [10–12]. Near-infrared spectroscopy (NIRS) enables continuous, noninvasive measurement of tissue haemoglobin oxygen saturation (StO_2) within a target tissue. More recently, near-infrared time-resolved spectroscopy (TRS) has been introduced as an advanced NIRS technique for clinical use. This method allows for the precise determination of absolute concentrations of oxygenated haemoglobin (O_2Hb), deoxygenated haemoglobin (HHb), and total haemoglobin (tHb) concurrently with StO_2. Furthermore, cerebral blood volume (CBV) can also be assessed using this approach [13]. Previous studies have been conducted utilizing TRS in neonates [14–16]. For example, Nakamura et al. reported that early postnatal elevations in CBV and cerebral StO_2 were predictive of poor outcomes in neonates with hypoxic-ischemic encephalopathy [14]. Another noninvasive method for assessing cerebral hemodynamics is measurement of superior vena cava flow; however, it presents certain limitations, including the challenge of continuous measurement and requirement for advanced technical expertise [17].

We hypothesised that elevated PEEP levels in neonates affect CO and cerebral perfusion. This study aimed to clarify the extrapulmonary effects of PEEP in neonates using noninvasive monitoring techniques.

Materials and methods

Study design and ethics

This is a prospective, nonrandomized, consecutive enrollment, single-centre study. This study was approved on March 22, 2023, by the Clinical Ethics Committee of the University Hospital Kyoto Prefectural University of Medicine, Kyoto, Japan (approval number: ERB-C-2794). Written informed consent was obtained from the legal guardians of each participant. The study was conducted in accordance with the Declaration of Helsinki and adhered to relevant guidelines and regulations.

Newborns admitted to the NICU from April 2023 to December 2024 were considered for inclusion (Fig. 1). The study focused on patients receiving invasive mechanical ventilation in synchronous intermittent mandatory ventilation mode. All participants were in stable condition, particularly regarding respiratory status, and were approved for inclusion by the attending medical staff. Exclusion criteria were extremely low birth weight infants (ELBWIs), congenital heart defects affecting systemic circulation (including symptomatic patent ductus arteriosus [PDA] and large patent foramen ovale [PFO]), cerebral anomalies such as hydrocephalus (including intraventricular haemorrhage), and infants who underwent therapeutic hypothermia.

Noninvasive monitoring techniques

The AESCULON mini® (OSYPKA MEDICAL and Heiwa Bussan, Tokyo, Japan) device was used to evaluate the neonates' stroke volume (SV) and CO fluctuations during PEEP changes. Four surface electrodes were attached to the patients, one on the forehead, one on the left side of the neck, one on the left lower thorax, and one on the left thigh. A portable three-wavelength TRS system (tNIRS-1; Hamamatsu Photonics K.K., Hamamatsu, Japan) was used, with the probe affixed to the forehead. Light emission and detection optodes were positioned on the parietal area, 30 mm apart. The TRS system utilises a time-correlated single-photon-counting method for detection, as previously described [15, 16, 18, 19]. The tHb, StO_2, and CBV were calculated as follows:

$$[tHb] = [O_2Hb] + [HHb]$$
$$StO_2(\%) = [O_2Hb]/[tHb] \times 100$$
$$CBV\ (ml/100g\ brain) = [tHb] \times MW_{Hb} \times 10 - 6/(Hb \times 10^{-2} \times D_t \times 10)$$

The square brackets denote the Hb concentration (μM). MW_{Hb} is the molecular weight of Hb (64,500), Hb is the blood Hb concentration (g/dl) and D_t is the brain tissue density (1.05 g/ml).

Study protocol

To clarify the extrapulmonary effects of PEEP in neonates, PEEP levels were modified according to the following protocol while monitoring CO, SV, heart rate (HR), StO_2, O_2Hb and HHb using the AESCULON mini® and tNIRS-1. Throughout the procedure, fraction of inspired oxygen (F_IO_2), inspiratory time, and respiratory rate were maintained at baseline values determined before initiation. Ventilator settings were adjusted to a fixed tidal volume (V_T) of 5–7 mL/kg based on predicted body weight, with a volume guarantee feature. End-tidal carbon dioxide ($ETCO_2$) and percutaneous oxygen saturation (SpO_2) were continuously monitored. In cases where FiO_2 is below 0.3 and the respiratory status is sufficiently stable to contemplate extubation and PDA and PFO flow did not affect circulation, PEEP was sustained at 5 cmH_2O (mild level) for 15–20 min. It was then incrementally increased every 10 min to 7 cmH_2O (moderate level) and 10 cm H_2O or peak inspiratory pressure not exceeding 25 cmH_2O (high level) (incremental phase). After a stabilisation period of 10 min, PEEP was sequentially decreased from high to moderate, then to mild levels (decremental phase). Mean values of measurements recorded each minute were calculated.

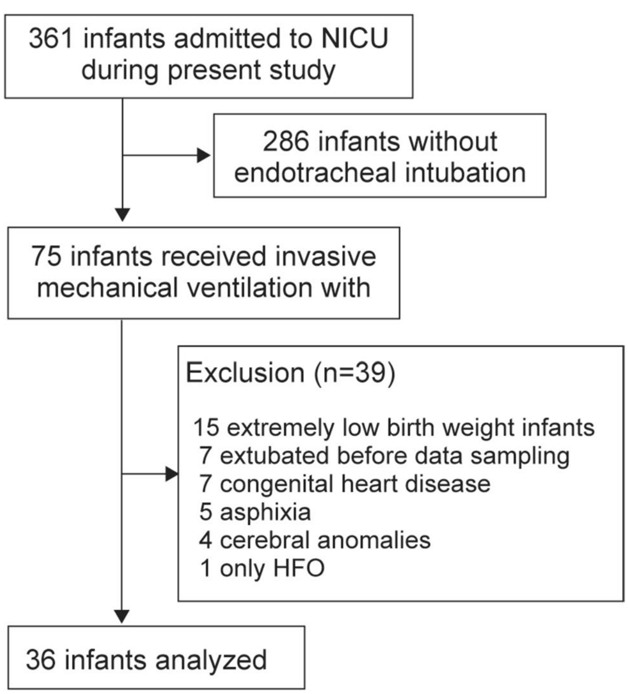

Fig. 1 Flow diagram showing the number of included infants

Statistical analyses

Ventilator settings, vital signs, and AESCULON mini® and tNIRS-1 measurements were compared among the three PEEP levels (mild, moderate, and high) using Friedman's analysis of variance, with Bonferroni correction for multiple comparisons. All statistical analyses were performed using EZR software (Saitama Medical Centre, Jichi Medical University, Saitama, Japan).

Results

This study included 16 term infants (median gestational age: 38 [IQR, 38–39] weeks; median birth weight: 2,778 [IQR, 2,296–3,046] g) and 20 preterm infants (median gestational age: 31 [IQR, 30–33] weeks; median birth weight: 1,459 [IQR, 1,264–2,044] g). The Apgar scores at 1 and 5 min were 5 [IQR, 3–7] and 7 [IQR, 6–8], respectively. The median number of days at measurement was 3 [IQR, 3–4] for term infants and 4 [IQR, 3–6] for preterm infants. The primary reasons for intubation were respiratory distress syndrome in 14 cases (39%), transient tachypnea of newborns in 9 cases (25%), meconium aspiration syndrome in 2 cases (6%), chylothorax in one case (3%) and surgery in 10 cases (28%) (Table 1). Furthermore, the number of patients who received catecholamines or sedatives is shown in Table 1.

Table 2 presents the measurement changes in term and preterm infants during the incremental phase. F_IO_2 and V_T remained stable, while SpO_2, $ETCO_2$ and HR showed no variation. Increasing PEEP from mild to high levels significantly reduced SV and CO in both term and preterm infants. Additionally, during the decremental phase, lowering PEEP facilitated the normalisation of SV and CO (Table 3). However, t-NIRS-1 measurements remained unchanged throughout the procedure (Tables 2 and 3).

Table 1 Descriptive characteristics of the enrolled patients

parameter	terminfants(n = 16)	preterm infants (n = 20)
Gestationalage,weeks	38(38–39)	31(30–33)
Birthweight,g	2,778 (2,296–3,046)	1,459(1,264–2,044)
Male/Female,n	7/9	8/10
Cesareansection,n(%)	4(25)	18(90)
Twinbirth,n(%)	0(0)	7(35)
Apgarscoreat1min	5(4–7)	5(3–6)
Apgarscoreat5min	6(5–9)	7(7–8)
Surfactant administration,n (%)	0(0)	14(70)
Daysofmeasurements,days	3(3–4)	4(3–6)
Catecholamines use, n (%)	9 (56)	15 (75)
Administration of sedatives, n (%)	4 (25)	3 (15)
Reasonsofintubation		
Respiratory distress syndrome,n(%)	0 (0)	14(70)
Transient tachypnea of newborns, n (%)	7 (44)	2 (10)
Meconium aspiration syndrome, n (%)	2 (13)	0 (0)
Chylothorax, n (%)	0 (0)	1 (5)
Surgery, n(%)	7(44)	3(15)

Values are represented as median (interquartile range) unless specified otherwise

Table 2 The influence of PEEP on incremental phase

parameter	term infants(n = 16)			preterminfants(n = 20)		
	mild	moderate	high	mild	moderate	high
PEEP,cmH_2O	5.0 ± 0	7.0 ± 0††	9.9 ± 0.4††	5.0 ± 0	7.0 ± 0††	9.6 ± 0.7††
PIP,cmH_2O	15.6 ± 2.1	18.8 ± 2.0††	23.2 ± 1.5††	15.2 ± 3.1	19.6 ± 3.3††	23.6 ± 2.7††
MAP,cmH_2O	7.1 ± 0.6	9.3 ± 0.6††	12.4 ± 1.1††	7.4 ± 0.7	9.9 ± 1.1††	12.9 ± 0.8††
F_IO_2	0.21(0.21–0.25)	0.21 (0.21–0.25)	0.21 (0.21–0.25)	0.21(0.21–0.27)	0.21(0.21–0.27)	0.21(0.21–0.27)
V_T/kg,ml/kg	5.2(5.0–6.2)	5.4 (5.0–6.4)	5.2(5.0–6.5)	5.4(5.1–5.6)	5.2(5.0–5.4)	5.3(5.0–5.6)
S_pO_2,%	97.3 ± 2.4	97.6 ± 2.4	98.6 ± 1.6	96.4 ± 3.0	96.4 ± 3.0	96.9 ± 3.3
$ETCO_2$,mmHg	40.0 ± 3.9	39.9 ± 3.9	39.7 ± 4.3	40.0 ± 7.4	39.5 ± 7.5	37.5 ± 5.9
HR,/min	123 ± 11	123 ± 11	125 ± 11	141 ± 13	143 ± 13	144 ± 14
SV,ml/kg	1.99(1.82–2.16)	1.96 (1.82–2.17)	1.85(1.63–2.01)††	1.64(1.56–2.04)	1.57(1.51–1.97)†	1.50(1.44–1.77)†
CO,ml/kg/min	238(209–283)	237(204–273)	224(198–264)††	242(233–278)	234(229–259)††	222(212–256)††
StO_2,%	64(60–66)	63(60–65)	63(61–65)	65(64–67)	66(63–67)	67(63–69)
tHb,µmmol/L	47(41–58)	47(42–58)	48(42–58)	51(48–55)	51(48–55)	51(47–54)
CBV,ml/100g brain	2.1(1.7–2.7)	2.2(1.8–2.7)	2.1(1.8–2.7)	2.3(2.1–2.5)	2.3(2.1–2.5)	2.3(2.0–2.5)

Values are represented as mean ± standard deviation or median (interquartile range) unless specified otherwise. *CBV*, cerebral blood volume; *CO*, cardiac output; $ETCO_2$, end-tidal carbon oxide; FIO_2, fraction of inspired oxygen; *HR*, heart rate; *MAP*, mean airway pressure; PEEP, positive end-expiratory pressure;*PIP*, positive inspiratory pressure; *SV*, stroke volume; SpO_2, percutaneous oxygen saturation; StO_2, tissue hemoglobin oxygen saturation; tHB, total hemoglobin; V_T, tidal volume. The difference among the groups was tested for significance with Friedman's analysis of variance after bonferoni adjusted.† <.05 versus mild; ††<.01 versus mild

Table 3 The influence of PEEP on incremental phase

parameter	term infants (n=16)			preterm infants (n=20)		
	High	moderate	mild	High	moderate	mild
PEEP, cmH_2O	9.9 ± 0.4	7.0 ± 0††	5.0 ± 0††	9.6 ± 0.7	7.0±0††	5.0 ± 0††
PIP, cmH_2O	23.2±1.5	16.6 ±2.2††	16.0 ± 1.8††	23.6 ± 2.7	18.2 ± 3.6††	14.2 ± 2.8††
MAP, cmH_2O	12.5±1.0	9.0 ± 1.0††	7.1 ± 0.5††	12.9 ± 0.8	9.8 ± 1.4††	7.2 ± 0.7††
FIO_2	0.21 (0.21–0.25.21.25)	0.21 (0.21–0.25.21.25)	0.21 (0.21 - 0.25)	0.21 (0.21 - 0.27)	0.21 (0.21 - 0.27)	0.21 (0.21 - 0.27)
V_T/kg, ml/kg	5.2 (5.0–6.5.0.5)	5.2 (5.0–6.4.0.4)	5.2 (5.0 - 6.3)	5.3 (5.0 - 5.6)	5.3 (5.0 - 5.7)	5.3 (5.1 –5.6)
SpO_2, %	98.6±1.6	98.2 ± 2.3	97.3 ± 2.3	96.9 ± 3.3	97.6 ± 2.6	97.4±2.3
$ETCO_2$, mmHg	39.1±3.7	39.9 ± 3.9	40.7±6.3	38.6 ±7.2	39.1± 7.4	37.8±5.2
HR,/min	125 ± 11	123 ± 12	123 ±11	144 ± 14	141 ± 13	139 ±14
SV, ml/kg	1.84 (1.55–1.97.55.97)	1.96 (1.76 –2.10)†	1.99 (1.82- 2.16)††	1.53 (1.40 - 1.74)	1.58(1.53 –1.87)††	1.63 (1.58 –1.97)††
CO, ml/kg/min	223 (193 –259)	232 (192 –274)†	238 (209- 283)††	214 (207 - 249)	228 (218 –259)†	233 (223–259)†
StO_2, %	64 (60–65)	62 (59–65)	64 (60 - 66)	66 (62 - 70)	67 (63 - 71)	68 (63–70)
tHb, μmmol/L	50 (45–59)	47 (42- 58)	47 (41 - 58)	51 (46 - 54)	51 (46 –53)	50 (47–53)
CBV, ml/100g brain	2.3 (1.8–2.7.8.7)	2.2(1.8 –2.7)	2.1 (1.7 - 2.7)	2.3 (2.1- 2.4)	2.4 (2.1- 2.4)	2.3 (2.1–2.5.1.5)

Values are represented as mean ± standard deviation or median (interquartile range) unless specified otherwise. *CBV*, cerebral blood volume;*CO*, cardiac output; $ETCO_2$, end-tidal carbon oxide; FIO_2, fraction of inspired oxygen; *HR*, heart rate; *MAP*, mean airway pressure; *PEEP*, positive end-expiratory pressure; *PIP*, positive inspiratory pressure; SV, stroke volume; SpO_2, percutaneous oxygen saturation; StO_2, tissue hemoglobin oxygen saturation; *tHB*, total hemoglobin; V_T, tidal volume. The difference among the groups was tested for significance with Friedman's analysis of variance after bonferoni adjusted. † <.05 versus mild; ††<.01 versus high

Discussion

This study demonstrated that high PEEP in ventilated neonates reduces SV and CO, while the PEEP levels used in this study did not affect cerebral perfusion. In patients receiving mechanical ventilation, PEEP exerts a dual influence on circulation [20]. It can elevate pulmonary vascular resistance and right ventricular afterload due to increased transpulmonary pressure. Conversely, by increasing intrathoracic pressure, it may reduce cardiac preload [21, 22]. However, few studies have examined the impact of PEEP on systemic circulation in neonatal and pediatric populations. Recently, Karlsson et al. reported that increasing PEEP to 10 cmH_2O in anesthetized children resulted in an 18% relative decrease in CO [23]. Similarly, Junqueira et al. found that high PEEP improved oxygen saturation but significantly reduced cardiac index in pediatric patients with acute respiratory distress syndrome [24]. Earlier studies on mechanically ventilated newborns with respiratory distress syndrome also showed that stepwise PEEP increases depressed CO [25]. Using a noninvasive approach, we confirmed that elevating PEEP from 5 cmH_2O to 10 cmH_2O reduced SV and CO in ventilated newborns, consistent with previous reports.

The effect of PEEP on cerebral hemodynamics remains inconclusive. Excessively elevated PEEP may reduce CPP due to decreased CO. Although few data exist describing the influence of PEEP on cerebral perfusion in patients without intracranial pathology, because ICP is not ordinarily monitored, if cerebral autoregulation functions normally, CBF is preserved. The use of noninvasive methods to assess ICP, such as TCD and optic nerve sheath diameter measurement, indicates that a PEEP of 8 cm H_2O exerts minimal impact on ICP [26, 27]. In addition, the influence of PEEP on cerebral perfusion and oxygenation has been investigated using TCD and NIRS in patients without brain injury undergoing elective surgical procedures. While opinions diverge on the impact of airway pressure on CBF [28, 29], it is generally accepted that local oxygenation is preserved during airway pressure application in healthy volunteers [30]. Conversely, in patients with brain injuries, elevated PEEP may increase ICP and reduce CPP due to diminished autoregulatory capacity [31, 32]. Our results indicate that changes in PEEP did not reduce cerebral StO_2 or CBV, suggesting that clinically used PEEP levels have little impact on cerebral perfusion in preterm and term newborns without brain injuries, because their effect on cardiac output remains within the limits of the autoregulatory capacity. Consequently, in newborns with limited autoregulatory capacity, such as ELBWIs, hypoxic ischemic encephalopathy and hydrocephalus, it remains uncertain whether high PEEP does not impact cerebral perfusion [33–35].

This study has some clinical implications. Various strategies for determining bedside PEEP settings in adults include volumetric capnography, transpulmonary pressure measurements, and imaging techniques such as computed tomography or electrical impedance tomography [36]. However, research on PEEP titration in neonates remains limited. We propose that combining conventional respiratory monitoring, such as pulse oximetry, with the AESCULON mini® may help optimise PEEP settings in neonates.

Additionally, our findings suggest that while increasing PEEP reduces CO, cerebral perfusion is preserved. In this study, we observed an approximate 9% reduction in CO and SV, which was attributable to the elevated PEEP. Nevertheless, these values remained within the 25th to 75th percentile range of the gestational age-specific reference values previously documented [37]. Further investigation is warranted to ascertain their clinical significance in this regard. However, several previous studies have indicated that high PEEP induced a reduction in intestinal blood flow or renal failure [38–40]. Therefore, it may be advisable to avoid the use of high PEEP, particularly in instances of circulatory failure or conditions that impair organ perfusion, such as necrotising enterocolitis and prerenal failure. In situations requiring high PEEP, careful monitoring of gastrointestinal symptoms and urinary output is essential.

This study has several limitations. First, the reduction in CO may be caused not only by PEEP but also by mean airway pressure or peak inspiratory pressure. In the future, it will be necessary to change only PEEP while maintaining minute ventilation, to clarify the isolated effect of PEEP. Second, the median days at measurement were 3 days for term infants and 4 days for preterm infants, closely aligning with the transitional period. Considering the intricate hemodynamic changes that occur in newborns after birth, these findings may not be applicable beyond this timeframe. Third, the penetration depth of the NIRS signal is limited to the cerebral cortex, thereby excluding information on deeper cerebral structures. Beyond the use of NIRS, it is imperative to evaluate cerebral perfusion using a more extensive and comprehensive multimodal hemodynamic assessment. Finally, this study was conducted at a single centre with a relatively small and heterogeneous sample, including both term and preterm infants who underwent intubation for various reasons. In addition, we assessed the impact of PEEP only for 10 min in neonates with respiratory stability, and did not account for factors such as sedative or vasopressor use, and blood glucose or haemoglobin levels which may influence cerebral perfusion [41, 42]. Future research should involve larger, more homogeneous cohorts to refine PEEP recommendations for mechanically ventilated infants.

Conclusion

This pilot study demonstrated that PEEP used in this study reduced CO without affecting cerebral perfusion in preterm and term newborns. Although clinically used PEEP levels have little impact on cerebral perfusion without brain injurious, high PEEP may reduce blood circulation to organs outside the brain. Future research is warranted to refine PEEP recommendations for mechanically ventilated infants.

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Author's contributions M.Z. designed and performed the experiments and wrote the initial draft of the manuscript. All other authors contributed to the interpretation and critically reviewed the manuscript. All the authors approved the final version of the manuscript and shared accountability for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Data availability Data is provided within the manuscript.

Declarations

Ethics approval The study protocol was reviewed and approved by the Clinical Ethics Committee of the University Hospital, Kyoto Prefectural University of Medicine (approval number: ERB-C-2426). Research was carried out in line with the principles of the Declaration of Helsinki.

Consent to participate This study was designed and received ethical approval to written informed consent obtained from the legal guardians of each participant.

STROBE statement The authors have read the STROBE statement checklist of items, and the manuscript was prepared in accordance with this statement and checklist.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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