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ORIGINAL ARTICLE

A randomized controlled comparison of three modes of ventilation during cardiopulmonary bypass on oxygenation in pediatric patients with pulmonary hypertension undergoing congenital heart surgeries

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ABSTRACT

Background: Several studies have attempted to improve post bypass oxygenation, decrease extravascular total lung water volume, utilizing continuous positive airway pressure (CPAP) and high-frequency ventilation (HFV) during cardiopulmonary bypass (CPB).

Aims: To assess the influence of various ventilation modes during CPB on direct pulmonary artery systolic pressure and post bypass oxygenation in pediatric patients with moderate to severe pulmonary hypertension undergoing corrective cardiac surgeries.

Methods: Included in the study were 24 patients aged 4 months to 6 years, suffering from moderate to severe pulmonary hypertension, undergoing elective corrective cardiac surgeries for atrial septal defect (ASD) or ventricular septal defect (VSD) or atrioventricular canal defects (AVC) (ASA II and III). Group A patients (n = 8) received high-frequency positive pressure ventilation during cardiopulmonary bypass, Group B patients (n = 8) received continuous positive, while group C patients (n = 8) disconnected from the ventilation (passive deflation) (control group).

Results: There was no statistically significant difference regarding the pulmonary artery systolic pressure (PASP) and pulmonary artery systolic pressure to systemic systolic blood pressure (PASP/SSBP Ratio) at t1, t2, and t3 between the three groups.

Conclusion: After cadiopulmonary bypass, no significant changes in pulmonary artery pressure was observed in pediatric patients, regardless of the ventilation mode utilized during cardiopulmonary bypass. Conversely, the pulmonary outcomes; delivered Oxygen (DA-aO2), arterial oxygen tension (paO2) and paO2/FiO2 (p/f ratio) and lung ultrasound (LUS) were significantly improved when comparing continuous positive airway pressure (CPAP) with high frequency positive pressure ventilation (HFPPV) and passive deflation during cardiopulmonary bypass.

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KEYWORDS
Pulmonary hypertension; high-frequency positive pressure ventilation; pulmonary outcomes

1. Introduction

Congenital heart defects with intra-communications like atrial septal defect (ASD) and ventricular septal defect (VSD) allow for unrestricted pressure and volume overload on the pulmonary circulation resulting in pulmonary arterial hypertension (PAH) [1–3]. Pulmonary hypertension can be classified into three categories according to severity into mild 25–40 mmHg, moderate 41–55 mmHg, and severe >55 mmHg [4–7]

Cardiopulmonary bypass has a number of drawbacks like raised intrapulmonary shunt, increased extravascular lung water (EVLW), atelectasis [8].

One of the hazardous outcomes of cardiopulmonary bypass is reperfusion injury, where endothelial dysfunction of the pulmonary arterial system occurs with subsequent vasoconstriction and increased vascular permeability contributing to pulmonary hypertension, pulmonary edema, and hypoxia.[9] Several approaches have been tried to overcome the respiratory problems following cardiopulmonary bypass through using various modes of lung ventilation and oxygen concentrations to prevent post bypass lung injury.[10–13]. To increase post bypass oxygenation, decrease extravascular total lung water volume, and increase lung compliance, researchers used using continuous positive airway pressure (CPAP) [8,11], and high-frequency ventilation (HFV) [12] during cardiopulmonary bypass.

Lung ultrasound is used to assess the extravascular lung water (EVLW) postoperatively to evaluate and compare the impact of the three modes of ventilation, where the presence of "B-lines" indicates loss of lung aeration, which may be attributed to an increase in extravascular lung water. [13–15]

2. Materials and methods

The study is a single-center, prospective, randomized, controlled, double-blind conducted in the pediatric cardiothoracic operation rooms in Abu El Reesh

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Hospital in Cairo University starting from August 2019 to November 2020 on pediatric patients aged between 4 months and 6 years, after obtaining institutional ethics committee agreement and written informed consent from patients guardians. These children were partial or common atrioventricular canal. The study is also registered in clinicaltrials.gov (NCT04262037).

Included in the study were 24 patients aged 4 months to 6 years, suffering from moderate to severe pulmonary hypertension, undergoing elective corrective cardiac surgeries for atrial sepatal defects (ASD) or ventricular septal defects (VSD) or atrio-ventricular canal defects.

Children with congenital anomalies of the lung like cystic fibrosis, congenital diaphragmatic hernia, having mild pulmonary hypertension, or required inotropes preoperatively were excluded from the study.

The patients were randomized in a double-blinded fashion to get enrolled into three equal groups: Group A patients (n = 8) received high-frequency positive pressure ventilation during cardiopulmonary bypass at tidal volume 2 ml/kg and respiratory rate 100, whereas group B patients (n = 8) received continuous positive airway pressure of 10 cm H_2O during cardiopulmonary bypass, while group C patients (n = 8) disconnected from the ventilation (passive deflation) (control group).

Pre-operative assessments were performed according to our institutional protocol. Given the variability in systemic artery pressure that exists among different age groups, we also calculated the ratio of pulmonary artery systolic pressure to systemic systolic blood pressure (SSBP).

In all groups, the patient was mechanically ventilated using pressure-controlled mode with FiO_2 50%, an inspiration to expiration time ratio of 1:2, peak inspiratory pressure (PIP) adjusted to deliver a tidal volume of 7–10 ml/kg, and a respiratory rate of 15 to 35 cycles/minute according to age to maintain a normal range of end-tidal carbon dioxide pressure at 35–45 mmHg. An assistant anesthetist performed a lung ultrasound after induction. Furosemide in a dose of 1 mg/kg was given to all patients.

Moreover, all patients received a milrinone loading dose of 50 mcg/kg/min, then a maintenance dose of 0.5–1.2 mcg/kg/min, and/or adrenaline 0.02–0.1 mcg/kg/min was utilized to facilitate weaning from cardiopulmonary bypass.

After sternotomy and exposure of the pulmonary artery, the pulmonary artery systolic pressure (PASP) was monitored by a direct arterial catheter 22 gauge inserted by the surgeon into the pulmonary artery and the ratio between pulmonary artery systolic pressure (PASP) and systemic systolic blood pressure (SSBP) was also calculated and recorded immediately after induction (t1) (baseline value), after aortic clamp removal (t2), and 10 min after the end of protamine infusion (t3).

During cardiopulmonary bypass, the patients enrolled in the study were randomly assigned to three groups using a computer-generated random sequence of numbers in Group A (n = 8). The lungs were allowed to inflate by delivery of O_2: air 3 liters/min with FiO_2 50% HFPPV with tidal volume 2 ml/kg, respiratory rate 100 per minute and I:E ratio 1:1, while Group B (n = 8) had their lungs inflated by delivery of oxygen: air 3 liters/min with FiO_2 50% and continuous airway pressure (CPAP) was maintained via a circle system with airway pressure maintained at 10 cm H_2O by adjustable pressure limiting valve (APL) valve. This was verified by a previously calibrated, in-circuit Bourdon gauge. Finally, in Group C (control group) (n = 8), their lungs were deflated by disconnecting the breathing circuit from the ventilator (passive deflation) [15].

Following cardiopulmonary bypass,all groups received intermittent positive pressure ventilation with FiO_2 0.5, VT 7–10 ml/kg, and ventilation frequency adjusted according to the age of the patients to maintain end-tidal carbon dioxide tension 35–45 mmHg. Positive end-expiratory pressure (PEEP) was not used, either before or after cardiopulmonary bypass.

Pulmonary function outcomes were recorded after induction and after weaning from cardiopulmonary bypass and before transferring to ICU as the following parameters: alveolar-arterial partial pressure oxygen difference (AaDO2) with each blood gas sampling according to the alveolar gas equation [16];

$$PAO2 = (Patm - PH_2O)FiO2 - PaCO2/RQ$$

Gases were measured at 1 atm (760 mmHg) barometric pressure (sea level). End-tidal carbon dioxide readings were used as alveolar carbon dioxide. The respiratory quotient was considered 0.8 [13]. Hypoxemia score (arterial partial pressure of oxygen/FiO_2) [17] and oxygenation (arterial partial pressure of oxygen). Clinical outcomes were recorded as ventilator-dependent time, length of stay in the intensive care unit, and length of hospital stay.

2.1. Assessment of the lung using ultrasound

After induction of anesthesia and at the end of the operation, lung ultrasound was conducted. A well-trained physician investigated the patients in the supine position by recording 5 seconds videos. Lung ultrasound was assessed for the presence of B-lines.

The B-line which is a hydro aeric comet-tail artifact that arises from the pleural line is hyperechoic well-defined; spreads indefinitely; erases A-lines, reflecting the coexistence of fluid and air. Fluid at the subpleural interlobular septum surrounded by air-filled alveoli (i.e., septal edema) fulfills this condition [18].

The lung ultrasound score was obtained by scanning 12-rib interspaces with the probe longitudinally applied perpendicular to the wall. Each hemi-thorax was divided into six areas: two anterior areas, two lateral areas, and two posterior areas. The anterior chest wall (zone 1) was defined from the parasternal to the anterior axillary line. It was divided into upper and lower halves, from the clavicle to the third intercostal space and from the third intercostal space to the diaphragm. The lateral area (zone 2) was delineated from the anterior to the posterior axillary line and was divided into upper and basal halves. The posterior area (zone 3) was considered as the zone beyond the posterior axillary line. The sum of B-lines found on each scanning location (0: no B-lines; 1: multiple B- lines 7 mm apart; 2: multiple B lines 3 mm apart; 3: consolidation) yields a score from 0 to 36 [15,19,20]. Two ultrasound doctors examined all lung ultrasound images. Both doctors were unaware of the clinical data of the patients and to other doctor's ultrasound diagnoses.

2.2. Study outcomes and statistical analysis

Our main primary outcome was a direct measurement of pulmonary artery systolic pressure (PASP) during cardiopulmonary bypass and 10 minutes after protamine infusion, secondary outcomes measured were

- PASP/SSBP Ratio
- Lung ultrasound score.
- Alveolar-arterial oxygen difference (DA-aO2).
- The arterial partial pressure of oxygen (PaO2).
- Hypoxemia score (P/F ratio).
- Duration of postoperative mechanical ventilation (ventilator-dependent time).
- Length of ICU stay.
- Length of hospital stay.

Data were coded and entered using the statistical package for the social sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were executed using the non-parametric Kruskal-Wallis and Mann–Whitney tests. For comparing categorical data, Chi-square (χ^2) test was performed. The exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered statistically significant.

A one-way ANOVA test is used to compare the difference of the means of systolic pulmonary artery pressure (SPAP) during cardiopulmonary bypass in the three groups.

With an assumption that that high-frequency, low volume positive pressure ventilation will result in at least 20% reduction of SPAP reading after cardiopulmonary bypass and at a power of 0.9 and α error of 0.05, the sample size will be 21, and for possible drop-outs, the sample size will be increased by 10%. The sample size was calculated using the G*Power 3 analysis program.

3. Results

Twenty-four patients scheduled for corrective surgeries of intracardiac defects in Abu Elreesh hospital were enrolled in the current study and were randomly allocated into three equal groups [HFPPV Group A (n = 8) and CPAP Group B (n = 8) and CONTROL Group C (N = 8)] after approval of the local ethical committee (Figure 1).

- **The demographic characteristics** There was no statistically significant difference regarding the demographic characteristics between the three groups
- **PASP and PASP/SSBP Ratio**: (Table 1)
- **Pulmonary outcomes between the three groups**: Are demonstrated in Table 2

The alveolar-arterial oxygen difference displays significant difference after weaning from cardiopulmonary bypass in CPAP group in comparison to HFPPV group with P-value of **0.007**

As regards, DA-aO2 before transfer to ICU, CPAP group was lower than HFPPV group and control group, and this is considered statistically significant when comparing the CPAP group with the control group as P-value was **0.027**. Still, no significant results were compared to the CPAP group with the HFPPV group as P-value was 0.198, and when comparing the HFPPV group with the control group, as P-value was 1.

The arterial partial pressure of oxygen (PaO_2) after weaning from cardiopulmonary bypass was higher in CPAP group than HFPPV group and control group, which is considered statistically significant between CPAP group and HFV group as P-value was **0.007** but no significance when comparing CPAP group and control group as P-value was 0.077 and no significance when comparing HFV group and control group as P-value was 1.

(PaO_2) before transfer to ICU was higher in CPAP group than HFPPV group and control group, and this is considered statistically significant when comparing CPAP group with the control group as P-value was **0.027**. Still, no significant difference was detected when comparing the HFPPV group with the CPAP group with a P-value 0.198.

P/F ratio after weaning from CPB was higher in CPAP group than HFPPV group and control group, and there was a statistically significant difference when comparing the CPAP group with HFPPV group as P-value 0.007. However, the results show no significance neither when

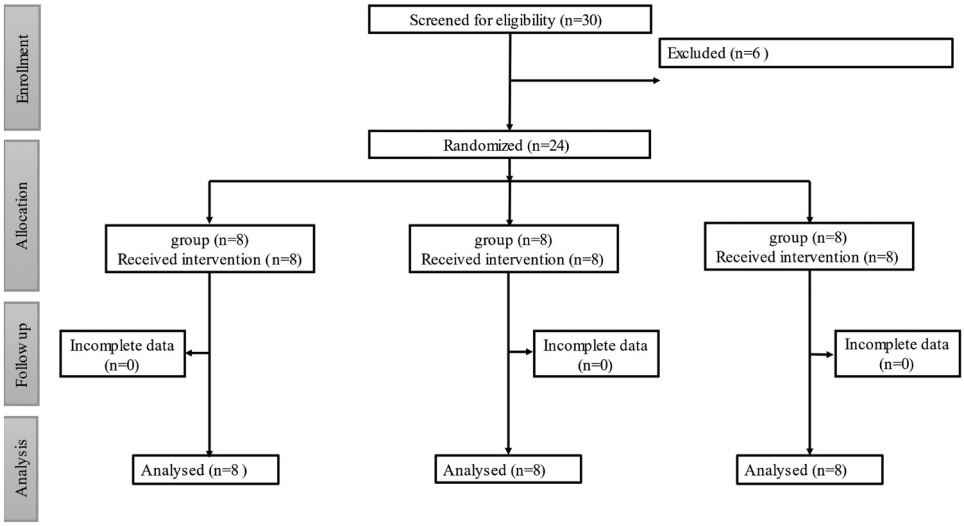

Figure 1. CONSORT flow diagram showing the number of patients at each phase of the study.

Table 1. PASP and PASP/SSBP ratio: There was no statistically significant difference regarding the **(PASP)** and **(PASP/SSBP ratio)** at **t1, t2, and t3** between the three groups when the groups were compared together.

	HPPV		CPAP		Control		
	Mean	SD	Mean	SD	Mean	SD	P value
SPBP after induction T1	51.00	15.31	41.00	15.57	45.88	11.76	0.346
SPBP after aortic cross clamp removal T2	34.50	11.35	25.00	11.82	29.88	11.51	0.212
SPBP 10 min after protamine infusion T3	31.75	9.72	28.75	11.13	29.50	5.10	0.833
SPBP/SSBP after induction T1	0.79	0.18	0.68	0.34	0.75	0.19	0.269
SPBP/SSBP after aortic cross clamp removal T2	0.55	0.20	0.41	0.21	0.49	0.15	0.235
SPBP/SSBP 10 min after protamine T3	0.44	0.12	0.41	0.15	0.42	0.08	0.553

Table 2. Pulmonary outcomes of three groups (* = statistically significant).

	HPPV		CPAP		Control		
	Mean	SD	Mean	SD	Mean	SD	P value
DA-aO2 after induction	102.88	30.53	122.88	41.91	106.25	25.30	0.497
DA-aO2 after weaning from CPB	184.75	47.17	114.25	40.86	166.13	39.21	0.007
DA-aO2 before transfer to ICU	135.75	43.87	91.50	37.52	155.63	42.07	0.027
PaO2 after induction	198.38	29.88	184.13	42.87	195.12	29.21	0.637
PaO2 after weaning from CPB	130.75	47.17	201.25	40.86	149.38	39.21	0.007
PaO2 before transfer to ICU	179.75	43.87	224.00	37.52	159.88	42.07	0.027
P/F Ratio after induction	368.75	94.17	368.25	85.74	390.25	58.41	**0.850**
P/F Ratio after weaning from CPB	261.50	94.35	402.50	81.72	298.75	78.43	0.007
P/F Ratio before transfer to ICU	342.75	96.09	448.00	75.04	319.25	84.23	0.028

comparing the CPAP group with control group with a P-value of 0.077 nor when comparing the HFPPV Group with control group with a P-value of 1 (Figure 2).

P/F ratio before transfer to ICU was higher in CPAP group than HFPPV group and control group, and there was a statistically significant difference when comparing the CPAP group with the control group as P-value was 0.028.

- There was no statistically significant difference in Alveolar-arterial oxygen difference (DA-Ao2), after induction when comparing the CPAP group with the other two groups, While, after weaning from cardiopulmonary bypass and before transferring to ICU, there was a statistically significant difference when comparing the CPAP group with the other two groups as the P-value was <0.05 (statistically significant) (Table 3).

3.1. Lung US score between groups

As regarding the lung US before transfer to ICU, there was a statistically significant difference in CPAP group with HFPPV group with P-value 0.026 and when compared with control group as P-value was 0.004 (statistically significant). (Figures 3 and 4)

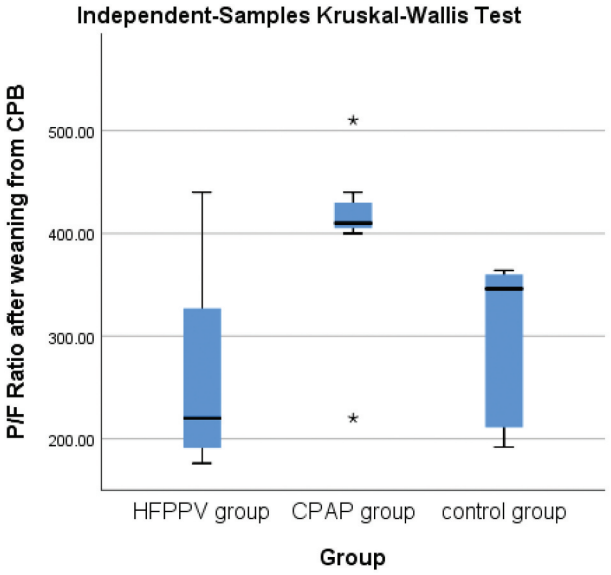

Figure 2. P/F ratio after weaning from CPB; P/F ratio after weaning from CPB was higher in CPAP group than HFPPV group and the control group.

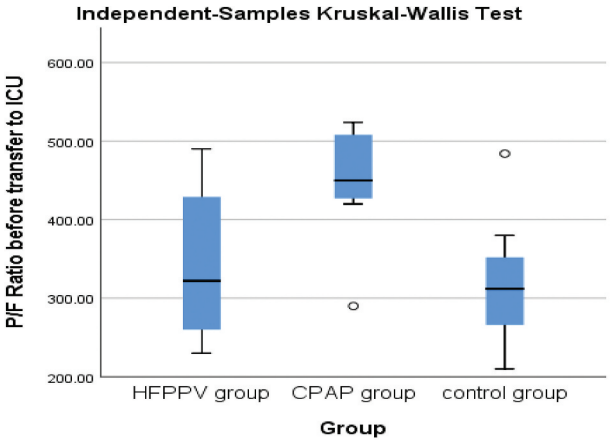

Figure 3. Lung ultrasound before transfer to ICU: statistically significant difference in CPAP group with HFPPV group with P-value 0.026 and when compared with control group as P-value was 0.004.

However, no significance was detected when comparing the HFPPV Group with the control Group with P-value 1.

3.2. Inotropic support requirements between groups

There was no statistically significant difference regarding the inotropic support between the three groups as P-value > 0.05.

3.3. Discussion

We investigated the effect of different ventilation modes during cardiopulmonary bypass for patients undergoing corrective surgeries for intra-cardiac defects. There were no significant differences between the three groups regarding PASP, PASP/SSBP, the demographic characteristics, the clinical outcomes (Hospital stay, ICU stay, ventilator-dependent time), and the need for isotopes.

Table 3. Posthoc pairwise comparison as regard A-aDO2 (dO2) after weaning from CPB (** = statistically significant).

Alveolar-Arterial difference Oxygen difference	P-value
CPAP group-control group	0.077**
CPAP group-HFPPV group	0.007**
control group-HFPPV group	1.000

The pulmonary outcomes as alveolar-arterial oxygen difference (DA-aO2) arterial partial pressure of oxygen (PaO2), hypoxic score (P/F ratio), and lung ultrasound (LUS) showed significant results when comparing the CPAP group with other groups.

Apostolakis et al. evaluated the various inflammation pathways during cardiopulmonary bypass that leads to pulmonary injury. They came to the conclusion that potential protection from this inflammatory process is by maintaining mechanical ventilation during cardiopulmonary bypass [21,22].

Continuous ventilation with a low tidal volume during the entire duration of extracorporeal circulation would minimize the cardiopulmonary bypass-related inflammatory response and resultant tissue damage [17,23], and may reduce extravascular lung water as well as certain anti-inflammatory mediators [24].

A systematic review conducted by **Yi-Chia Wang, et al** concluded that when compared to apnea, CPAP improved oxygenation and gas exchange during cardiopulmonary bypass while mechanical ventilation did not. Neither CPAP nor ventilation during cardiopulmonary bypass shortened the ventilator-dependent time or the length of hospital stay. [25]

We anticipated that by lowering the total lung water (TLW), enhancing lung compliance, and lowering the shunt fraction, high-frequency positive pressure ventilation (HFPPV) could improve post-bypass oxygenation. In the current research, however, high-frequency ventilation had no effect on DA-aO2 or total lung water.

In brief, the explanation of why CPAP is better than other ventilation modes during cardiopulmonary bypass is that pulmonary perfusion during cardiopulmonary bypass is limited, and thus oxygenation is mainly determined using Fick's law of diffusion, which states that flow is proportional to the surface area, diffusibility, and partial pressure gradient but inversely proportional to membrane thickness [26]. According to Fick's law; the pulmonary oxygen uptake (UpVO2) is expressed as

UpVO2 = QCa02 – Qcvo2, where the oxygen flow from the lung to the peripheral tissues is the product of cardiac output (Q) and oxygen content of arterial blood (Ca02), and the oxygen flow from the peripheral tissues to the lung is the product of cardiac output (Q) and oxygen content of venous

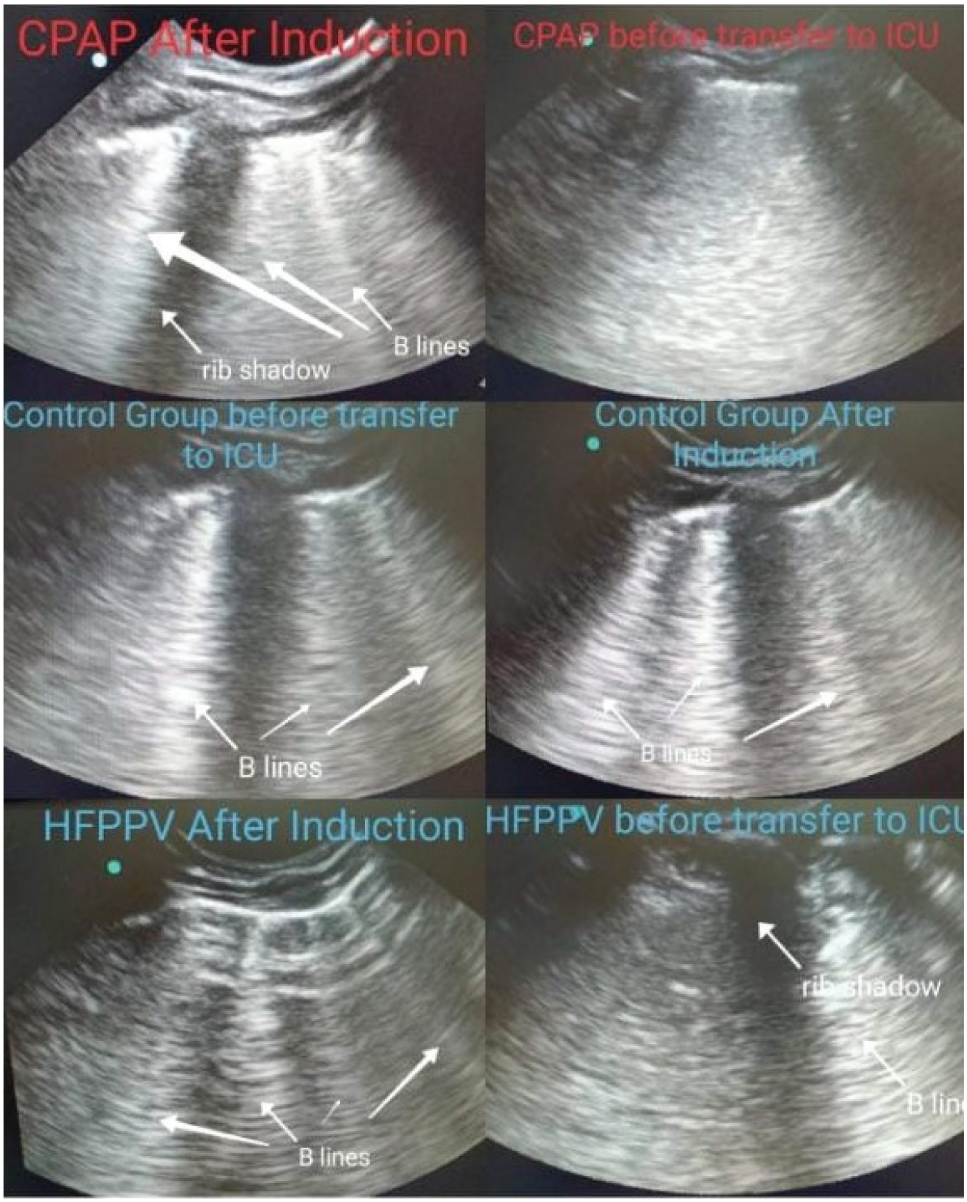

Figure 4. Comparative views of apical lung zones in the three groups illustrating difference in lung congestion before and after cardiopulmonary bypass.

blood (Cv02). Because CPAP reduces the thickness of the alveolar septum, it may be possible to abolish the oxygen transfer barrier [27]. Low tidal volume ventilation may not result in alveolar recruitment because of low pressure, and alveolar collapse or atelectasis still may occur [28].

Recruitment of collapsed lungs by using 10 cm H2O CPAP during the bypass could explain the improvement in lung ultrasound at the end of the operations compared to the beginning. congenital heart disease repair and the elimination of pulmonary circulation overload and lung congestion may be another factor for the improvement of lung ultrasound. Use of diuretics after bypass may have also decreased EVLW, thereby increasing pulmonary compliance and improving gas exchange at the end of operation compared to those at baseline.

4. Conclusion

When comparing CPAP with HFPPV and passive deflation during cardiopulmonary bypass, there was no difference in direct pulmonary artery pressure and its relationship to systemic blood pressure following cardiopulmonary bypass in pediatric patients, but the pulmonary outcomes (dO2, paO2, p/f ratio) and Lung ultrasound were much improved.

4.1. Limitations of the study

Although ultrafiltration was not used during bypass in all our patients but we think it contributed to improvement of oxygenation after bypass, also the use of positive end pressure ventilation (PEEP) after weaning

from bypass improves lung function. Future studies including these two variables will add to the significance of the results.

Disclosure statement

No conflict of interest

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