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Research Article

Use of High Frequency Oscillatory Ventilation for Post Operative Pediatric Cardiac Patients - Single Center Retrospective Study

Bhavsar Keyoor[1], Tailor Kamlesh[1], Rao Suresh[2] and Kadam Shankar[2]*

[1]Department of Pediatrics, Kokilaben Dhirubhai Ambani Hospital, India

[2]Department of Surgery, Kokilaben Dhirubhai Ambani Hospital, India

Abstract

Objectives: Acute respiratory distress syndrome is a significant cause of morbidity and mortality in post operative pediatric cardiac patients. Aim of this study is to share our experience with high frequency oscillatory ventilation as a rescue therapy and its effect on morbidity and mortality parameters in post operative pediatric cardiac patients.

Methods: Single center retrospective data analysis was performed on all patients who received high frequency oscillatory ventilation for refractory hypoxemia or respiratory acidosis on conventional ventilation after pediatric cardiac surgeries from 2013 to 2020.

Results: Out of 6000 pediatric cardiac surgeries, 40 patients were put on high frequency ventilation. Nineteen patients were discharged, 24 patients were able to wean from high frequency ventilation and 21 patients died. Comparison of arterial blood gas and oxygen index value before putting on high frequency ventilation with two hours after putting on high frequency ventilation and after weaning from high frequency ventilation, were found statistically significant and comparison of same value between survivor and non survivor group were also found statistically significant. Average oxygen index value of non survivor group of patients was 40 ± 9 and of survivor group was 30 ± 8.

Conclusion: High frequency oscillatory ventilation improves ventilation and oxygen index which is not amenable to be managed by conventional mechanical ventilation. It improves survival if use before progression to significant lung damage in post operative pediatric cardiac patients.

Keywords: High frequency oscillatory ventilation; Acute respiratory distress syndrome (ARDS); Post operative pediatric Cardiac

Abbreviations

ARDS: Acute Respiratory Distress Syndrome; CPB: Cardio Pulmonary Bypass; LVEDP: Left Ventricular End Diastolic Pressure; HFOV: High Frequency Oscillatory Ventilation; MAP: Mean Airway Pressure; PVR: Pulmonary Vascular Resistance; ABG: Arterial Blood Gas; ECMO: Extracorpeal Membrane Oxygenation; POD: Post Operative Day; TAPVC: Total Anomalous Pulmonary Venous Connection; VSD: Ventricular Septal Defect; ICR: Intra Cardiac Repair; PDA: Patent Ductous Arterious; ICU: Intensive Care Unit; ET: Endo Tracheal Tube

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***Correspondence:** Keyoor Bipinbhai Bhavsar, Department of Pediatrics, Division of Pediatric Cardiac Anesthesia and Post Operative Critical Care, Kokilaben Dhirubhai Ambani Hospital, Rao Saheb, Achutrao Patwardhan Marg, Four Bugalows, Andheri West, Mumbai, Maharastra, 400053, India, Tel: +91-9769994994; E-mail: keyoorbhavsar1234@gmail.com; keyoor.bhavsar@kokilabenhospitals.com

Introduction

Acute Respiratory Distress Syndrome (ARDS) can occur after pediatric cardiac surgery. It is a significant cause of postoperative morbidity and mortality. Incidence of ARDS after pediatric cardiac surgery is around 0.75% [1]. Pre disposing factors can be neonatal age, low weight at the time of surgery, preoperative infection, preoperative lung congestion, long Cardiopulmonary Bypass Time (CPB), post operative multiple transfusions, postoperative infection and post operative high Left Ventricular End Diastolic Pressure (LVEDP) [2,3].

Mild ARDS can be managed with conventional ventilatory mode by optimizing Positive End Expiratory Pressure (PEEP). But moderate to severe ARDS is often difficult to manage with conventional ventilatory mode, which can further damage the injured lung due to end inspiratory over distension. Only few studies have supported the use of High Frequency Oscillatory Ventilation (HFOV) in post operative pediatric cardiac patients [1,4]. HFOV is a well-established practice in neonate with respiratory distress syndrome. HFOV is an ideal method of mechanical ventilation to minimize ventilator-associated lung injury. HFOV uses a constant distending pressure with pressure variations oscillating around the Mean Airway Pressure (MAP) at very high rate up to 600 to 900 cycles per minute. It delivers small tidal volumes, which is usually even less than the dead space. This avoids repetitive recruitment and de-recruitment of the damaged

lung alveoli, thus preventing end-expiratory collapse [5-8]. HFOV also reduces the Pulmonary Vascular Resistance (PVR) by improving ventilation and gas exchanges [4].

With this retrospective study analysis, we like to share our experience with the use of HFOV as a rescue therapy and its effect on morbidity and mortality parameters in post operative pediatric cardiac patients.

Material and Methods

This single center retrospective data analysis was from January 2013 to December 2020. This study includes all operated pediatric cardiac patients which required use of HFOV. This study has been approved by ethics committee of our hospital. Primary outcome of our study was, child who successfully weaned from HFOV and discharged from hospital and secondary outcome studied were duration of HFOV and conventional ventilation, complication of HFOV, postoperative infection, duration of ICU stays, mortality and Extracorpeal Membrane Oxygenation (ECMO) support. All surgeries were performed through midline sternotomy with hypothermic CPB and intermittent anterograde cardioplegia except Patent Ductous Arterious ligation (PDA) and Potts shunt. Deep Hypothermic Circulatory Arrest (DHCA) was used in few cases. Sternum was kept open electively in cases with severe ventricular dysfunction, deranged coagulopathy and poor lung compliance. After received to Pediatric Cardiac Intensive Care Unit (PCICU), all patients were initially put on conventional ventilatory mode- Synchronized Intermittent Mandatory Ventilation+Pressure Regulatory Volume Control (SIMV+PRVC). We used following criteria to put on HFOV (three out of four)

1. Ph<7.25 and paco2>60 mmhg.
2. Pao2<60 mmhg (in biventricular correction) and pao2<30 mmhg (in single ventricle palliation) with fio2>80%.
3. Peak airway pressure >28 cm H_2O or mean airway pressure >17 cm H_2O.
4. Chest X ray showing bilateral lung congestion.

Out of above four criteria, three criteria had to be fulfilled in two different Arterial Blood Gases (ABG), one hour apart. Before applying above criteria; Endotracheal Tube (ET) position was checked, open tracheal suctioning and lung recruitment maneuver were performed and acute pneumothorax or pleural effusion was ruled out.

Exclusion criteria

Ventricular dysfunction on echocardiography and any other cardiac reasons for deteriorating clinical condition.

In above scenario we prefer veno arterial ECMO. Initial HFOV settings were applied as follow: Mean Airway Pressure (MAP) was kept 2 cm H_2O higher than MAP of conventional ventilation. ΔP was kept depending on chest wobbling up to midthigh. Fio2 was kept same as on conventional ventilation. Frequency kept at 8 Hz to 10 Hz. Inspiratory: Expiratory (I: E) ◊ 1:2.

ABG was performed after 30 minutes, after 2 hrs and then every 4^{th} hourly. Chest X ray was done after 2 hrs and then every day to see aeration and expansion of lung fields and to rule out pneumothorax. Aim was to maintained ph > 7.30, pco2 between 35 mmhg to 45 mmhg and po2 according to surgical correction. Sedation was provided with fentanyl and/or dexmedetomidine infusion and intermittent doses of muscle relaxant if required.

Hemodynamic stability was achieved with optimizing inotropic support like epinephrine, milrinone, dopamine and nor epinephrine infusion. Renal replacement therapy was provided with peritoneal dialysis in selected number of cases. Weaning from HFOV should be gradual and according to serial ABG, chest X-Rays and improvement of clinical condition. Change from HFOV to conventional mechanical ventilation (SIMV-PRVC) was attempted once we achieved Fio2 0.6, MAP 12 cm H_2O and ΔP 20 cm H_2O on HFOV. On conventional ventilation, first ABG was done after 30 minutes and then every 4^{th} hourly according to clinical condition. After extubation all patients were electively put non invasive Continuous Positive Pressure Support (CPAP). Enteral feeding was provided through Orogastric tube (OG). Child who intolerant to OG feeds, parenteral feeding was supplemented with amino acids and lipid infusion.

Other parameter studied were preoperative infection, preoperative ventilation, Post Operative Days (POD) on which HFOV started, delayed sternal closure, pulmonary artery pressure and use of inhaled Nitric Oxide (iNO) with HFOV. ABG and oxygen index value were studied before putting on HFOV, two hours after putting on HFOV and after putting on conventional ventilation from HFOV.

We divided the cohort of patients between survivor group and non survivor group. We calculated the oxygen index value by formula: MAP × 100 × Fio2 ÷ Pao2. Severity of ARDS according to oxygen index as follows: <15 mild, 16 to 25 moderate, 26 to 40 severe, >40 very severe [9].

Statistics analyses were performed using SPSS software for windows (version 25, 2007, IBM Corporation, Armonk, New York). Normality of data was accessed using Shapiro Wilk Test. Independent Sample T test was used to analyze difference in parameters between survivors and non-survivors. Paired sample T test was used to analyze difference in parameters at different time points of HFOV intervention. $p<0.05$ was considered to be statistically significant. Data presented as Mean ± SD.

Results

Six thousand pediatric cardiac surgeries were performed between January 2013 to December 2020. Total 40 patients required HFOV during this period. Type of surgeries required HFOV are mentioned in (Table 1). Almost half of the patients (n-22, 55%) were of less than 1 month of age, 8 patients (20%) were less than 6 months of age and remaining 10 patients (25%) were more than 6 months of age (Table 1). Lowest weight of baby was 1.5 kg and maximum were 15 kg. Fourteen patients (35%) were on conventional mechanical ventilation pre procedure and five patients had pre procedure culture positive sepsis.

Twenty-eight patients had open sternum post surgical repair. Out of 28 patients, 17 (42.5%) required HFOV with open sternum and HFOV was weaned after closing the sternum. HFOV was initiated on POD 0 to POD 28. Initial HFOV settings was MAP 21.5 cm ± 4.6 cm H_2O (14 to 25), ΔP 32.7 ± 6.5 cm H_2O (18 to 47), Fio2 0.81 ± 0.14 (0.5 to 1). Inhaled Nitric Oxide (iNO) was started, when pulmonary arterial pressure remained systemic or supra systemic after initiation of HFOV. Eleven patients (27.5%) required iNO with HFOV to control pulmonary arterial pressure (Table 1).

Duration of HFOV was found statistically significant between survivor group and non survivor group of patients with p value

of 0.001 (Table 1). After weaning from HFOV, all patients were put on conventional mechanical ventilation. Average duration of conventional ventilation after HFOV was also found statistically significant with p value of 0.05 between survivor group and non survivor group (Table 1).

ABG and oxygen index value were compared before starting HFOV and two hours after HFOV. All values were statistically significant. Average oxygen index value before putting on HFOV was 35 ± 9 and two hours after HFOV was 23 ± 7.6 (Table 2).

ABG and oxygen index value were compared before starting HFOV and after weaning from HFOV. All values were statistically significant. Average oxygen index value before putting on HFOV was 35 ± 9 and after weaning from HFOV was 10 ± 4 (Table 3).

Veno venous ECMO was required in three patients after HFOV due to inability to maintain adequate gas exchanges with high HFOV settings. Three patients developed pneumothorax on HFOV and did not survive. Fifteen patients (39.4 %) in our cohort developed culture positive sepsis.

ABG and oxygen index value were compared between survivor group and non survivor group of patients before starting HFOV. All values were statistically significant. Average oxygen index value of non survivor group of patients was 40 ± 9 and of survivor group was 30 ± 8 (Table 4).

Out of 40 patients, 19(47.5%) patients were discharged and 21 (52.5%) patients did not survive. Twenty-four patients (60%) were successfully weaned from HFOV and extubated.

Table 1: Comparison of all parameters between survivor group and non survivor group of patients.

	Total patients (n =40)	Survivors (n = 19)	Non survivors (n = 21)
Age			
<1 Month	22	11	11
1 To 6 Months	8	2	6
>6 Months	10	6	4
Weight (kg)	4.2 ± 3.4	4.5 ± 3.1	3.8 ± 3.7
Preoperative Ventilation	14	9	5
Preoperative Infection	5	3	2
ECMO support veno venous	3	0	3
Sternum open	28	12	16
Post Operative Days (POD)	5.35 ± 6.2	3.2 ± 4.4	7.5 ± 7.1
Inhaled nitric oxide with HFOV	11	5	6
Duration of HFOV(hrs)	122 ± 50	81 ± 32	154 ± 65
Successful weaning of HFOV	24 (60%)	19	5
Duration of conventional ventilation after weaning from HFOV (hrs)	181 ± 75	113 ± 44	249 ± 113
Pneumothorax	3	0	3
Postoperative infection	15	3	12
Duration of ICU stay(hrs)	482 ± 200	446 ± 134	511 ± 269
Surgery			
Obstructed Total Anomalous Pulmonary Venous Connection (TAPVC) repair	17	10	7
Arch repair ± Ventricular Septal Defect closure(VSD)	6	2	4
VSD closure	4	2	2
Tetralogy of Fallot (TOF)	2	2	0
Patent Ductous Arterious ligation (PDA)	1	1	0
PDA ligation + airway repair surgery	1	1	0
Arterial switch + arch repair	2	0	2
Atrio ventricular septal defect repair	1	0	1
Anomalous origin of left coronary artery from pulmonary artery	1	1	0
Blalock-taussing shunt with unifocalisation	1	0	1
Norwood with sano shunt	1	0	1
Ross procedure	1	0	1
Potts shunt	1	0	1
VSD closure + conduit	1	0	1

Table 2: Comparison of ABG and oxygen index value before starting HFOV and two hours after putting on HFOV.

	Before starting HFOV on conventional ventilation	Two hours after putting on HFOV	t value	p value
Ph	7.1 ± 0.1	7.3 ± 0.1	-10.486	0.001
Pco2	69 ± 10	50.3 ± 4.6	18.045	0.001
Po2	60 ± 14	73.4 ± 18.2	-15.152	0.001
Oxygen index	35 ± 9	23 ± 7.6	21.627	0.001

Data presented as Mean ± SD. Significant at p value 0.001. Paired sample t test was used to analyze

Table 3: Comparison of ABG and oxygen index value before starting HFOV and after weaning from HFOV on conventional ventilation.

	Before starting HFOV on conventional ventilation	After weaning from HFOV On conventional ventilation	t value	p value
Ph	7.1 ± 0.1	7.4 ± 0.1	-9.363	0.001
Pco2	69 ± 10	41 ± 6	12.388	0.001
Po2	60 ± 14	106 ± 35	-8.253	0.001
Oxygen index	35 ± 9	10 ± 4	12.798	0.001

Data presented as Mean ± SD. Significant at p value 0.001. Paired sample t test was used to analyze.

Table 4: Comparison of ABG and oxygen Index value between survivor group and non survivor group of patients before starting HFOV.

	Survivors (n=19)	**Non survivors** (n=21)	**t value**	**p value**
Ph	7.23 ± 0.1	7.10 ± 0.1	3.093	0.004
Pco2	66 ± 10	79 ± 8	-4.437	0.001
Po2	60 ± 11	48 ± 15	3.038	0.004
Oxygen index	30 ± 8	40 ± 9	-3.59	0.001

Data presented as Mean ± SD. Significant at p value <0.05. Independent sample t test was used to analyze.

Discussion

Our study is a single centre retrospective study. Mortality after ARDS is 40% in general population and 80% after cardiac surgery [10]. Mild ARDS can be managed with conventional ventilation. Moderate to severe ARDS required use of HFOV [9]. Out of 6000 pediatric cardiac surgeries, 40 (0.6%) patients were required HFOV. ARDS in post operative pediatric cardiac patients is a significant cause of morbidity and mortality. Large pressure changes and volumes associated with conventional ventilation contribute to the pathogenesis of ventilator induced lung injury [8]. Prolonged hypoxemia and respiratory acidosis might not be tolerated by heart after open heart surgery and may lead to unusual cardio pulmonary events.

Only few studies have supported the use of HFOV in post operative pediatric cardiac patients. Mirela Bojan and Simone Gioanni in their article concluded that HFOV was a better mode of ventilation as compared to conventional ventilation in neonates and infants after respiratory distress after open heart surgery [4]. In 2013 by Li et al. [1] published a study of HFOV in severe ARDS after pediatric cardiac surgery when conventional ventilation failed.

Our study demonstrated HFOV as a rescue therapy when ARDS occurs after pediatric cardiac surgery which could not be managed by conventional ventilation and its effect on morbidity and mortality parameters. In our study we found that HFOV improved ventilation and oxygenation when hypoxemia, respiratory acidosis and lung opacifications developed after pediatrics cardiac surgery.

We compared the ph, pco2, and po2 and oxygen index value before putting on HFOV and two hours after putting on HFOV. We found all values were statistically significant at p value 0.001 (Table 2). Comparison of ph, pco2, po2 and oxygen index value before putting on HFOV and after weaning from HFOV on conventional ventilation were significant at p value (Table 3). We can conclude that HFOV improves ventilation and oxygen index.

We compared the ph, pco2, and po2 and oxygen index value between survivor group and non survivor group of patients before putting on HFOV (Table 4). All values were statistically significant at p value <0.05. We found that early shift to HFOV from conventional ventilation improved survival. When significant lung damage had occurred then HFOV did not improve survival. Non survivor group of patient's average oxygen index was 40 ± 9. When oxygen index >40, HFOV improved ventilation and oxygenation but did not improve survival.

Average duration of HFOV between survivor group and non survivor group of patients was statistically significant with p value 0.001 (Table 1). Average duration of conventional ventilation after weaning from HFOV was statistically significant with p value 0.05 between survivor group and non survivor group of patients (Table 1). Survivor group of patient's average duration of ICU stay was 446 ± 134 hrs as compared to 511 ± 269 hrs for non survivor group of patients (Table 1). In our study we found that HFOV maintained oxygenation and ventilation in all non survivor group of patients except three patients who required veno venous ECMO. But in non survivor group, all patients were difficult to wean from HFOV. It could be possible that all these patients were put on HFOV late when oxygen index >40.

Both neonatal and pediatrics patients were included in our study. In neonatal age groups Total Anomalous Pulmonary Venous Connection (TAPVC) and Ventricular Septal Defect (VSD) ± arch repair were common substrates that required HFOV. Neonatal age and low weight caused more capillary leaking, low urine output and high pulmonary arterial pressure post open heart surgery. Finally, chest wall edema increased and lungs became congested becoming difficult to manage with conventional ventilation. HFOV by providing tidal volume less than the dead space, higher rate and continuous positive pressure improved oxygenation, ventilation and ensured hemodynamic stability. Improvement of oxygenation and ventilation reduced the pulmonary vascular resistance and improved right ventricular function that reduced the requirement of inhaled nitric oxide [4]. If child was put on HFOV when sternum was open then HFOV continued until sternum was closed. As child started passing good amount of urine, chest wall edema reduced and lung became decongested.

HFOV was gradually weaned commensurate to improvement of blood gases. Inotropic support requirement increased in HFOV patients [4]. Because HFOV gives higher mean positive pressure as compared to conventional ventilation that leads to decrease venous return. Muscle relaxants and sedatives cause vasodilatation that further increased the fluids and inotropic requirement. If oxygenation and ventilation improve and hemodynamic become better after putting on HFOV then inotropic support requirement decreased.

In pediatrics age groups, two patients of Tetralogy of Fallot (TOF) after Intracardiac Repair (ICR) required HFOV. TOF child were very cyanotic with high preoperative hematocrit and had collateral bleed into lungs post repair. Most common is bronchial collateral bleed that led to pulmonary hemorrhage. This caused hypoxia, respiratory acidosis and high mean airway pressure which was difficult to manage with conventional ventilation. HFOV proved to be a better mode of ventilation until bleeding was controlled and lung condition improved. HFOV by giving high pressure decreased the transudation of hemorrhagic edema and reduced the collateral bleeding by increasing intrathoracic pressure and decreasing the blood flow to ruptured arterioles. It improved the ventilation and oxygen index. Child was taken to the cardiac catheterization laboratory; angiography was done and embolization of the bleeding bronchial collateral was carried out. After that HFOV was gradually weaned. Elisabeth Duval and Dick G. Markhorst from Netherlands concluded in their study that HFOV can be life saving in massive lung hemorrhage in children [11]. Ko et al. [12] demonstrated successful use of HFOV in massive pulmonary hemorrhage in neonate. Both above studies were in non cardiac patients.

Four patients of VSD required HFOV. Out of these four patients, two patients were of low weight (<2.5 kg), pre mature birth history and indication of surgery was failure to gain weight. These two VSD patients were able to wean from HFOV and managed to extubate but one child had prolonged ICU stay and over the period became septic and died and another child died due to pulmonary hemorrhage after extubation. Another two VSD patients after extubation trial developed

ARDS like features due to high LVEDP but managed to discharge.

It is said that HFOV should not be used with the airway problem [5,6]. In our study, we successfully used HFOV for one patient after airway repair surgery with rising pco2. This child presented to us with complaint of respiratory distress. Child was on conventional ventilation before surgery. Computerized tomography scan showed severe left bronchial stenosis. For which 'slide tracheoplasty' was performed. Post surgery; child had high pco2 with respiratory acidosis on full conventional ventilation. This was initially managed with HFOV. After doing bronchoscopy, found that residual airway narrowing was still present. Child was again taken to the operation theatre and surgery was revised. After that we were able to wean HFOV. We feel that for child with airway problem we can use HFOV, but with low MAP.

One patient of Blalock-Taussing (B.T.) shunt with unifocalisation developed ARDS due to lung hyper perfusion with superimposed infection. This child was weaned from HFOV and extubated. On CPAP child developed endotracheal bleed which proved to be massive pulmonary hemorrhage and died. One PDA child already presented to hospital with lung congestion. After ligating PDA lungs became more congested and difficult to manage by conventional ventilation. Hence with the use of HFOV we were able to send the child home.

Another option of acute lung injury is to put patient on ECMO support. Veno arterial ECMO can be considered if ARDS like feature developed with hemodynamic instability after open heart surgery. But ECMO support is much more invasive as compared to HFOV. ECMO support have some drawback like bleeding complication, transfusion of blood and blood products, proper cannula placement, expertise in ECMO support, some time sternum is to be opened to achieve a good support and financial issue. HFOV is less invasive as compared to ECMO. HFOV is just one step ahead of routine conventional ventilation. In a series 122 infants meeting the criteria for ECMO, Lamos et al. [13] demonstrated that the use of HFOV with an appropriate strategy decreased the need for ECMO in 53% of cases. Another study by Carter et al. [14] demonstrated that HFOV can be considering as a one-step prior to ECMO. Both above studies were in non cardiac patients.

Almost all HFOV patients were required use of higher antibiotics. Factors like lung injury, prolonged mechanical ventilation, prolonged ICU stay and positive culture report required use of higher antibiotics. Sepsis was the leading cause of death in all patients who failed HFOV weaning and died. Total 15 patients developed culture positive sepsis post procedure. Out of 15 patients 12 patients died. Oxygenation and ventilation were maintained with HFOV in all the patients who died except three patients who required veno venous ECMO. Prevention and control of infection with good nursing care and proper use of antibiotics were the key factor in getting favorable outcome of HFOV.

Pneumothorax was the only complication with HFOV [1,5]. In our study three patients developed pneumothorax and all three patients died in spite of putting early intercostals drainage tube. May be due to pneumothorax had aggravated the lung injury in already damaged lung. Gradual and incremental use of MAP and with frequent chest X rays could perhaps avoid this complication. MAP was >24 H_2O in all three patients [15].

Only three patients failed to maintain oxygenation and ventilation with HFOV and required veno venous ECMO. These all three patients died due to inability to wean from veno venous ECMO. One patient was redo vsd closure+conduit replacement. This child developed ARDS due to residual vsd with superimposed lung infection. This child was put on HFOV on POD 16 when oxygen index was 44. After 24 hrs of HFOV, we had to initiate veno-venous ECMO for 320 hrs. We feel we should have initiated HFOV earlier before development of severe ARDS changes and high oxygen index. Another patient had a desperate Ross procedure for severe persisting aortic stenos is with left ventricle failure after unsuccessful balloon aortic valvotomy. This child died due to pre operative renal shut down, high LVEDP with lung infection. In this child we initiated HFOV on POD 12 when oxygen index was 45. In this child we could have initiated HFOV or ECMO support earlier before end organ affliction. Third patient Potts shunt died due to relatively large size of shunt with flooding the lung field. This was our first child with severe idiopathic pulmonary hypertension. This child operated early before doing catheterization study as the catheterization study was found to be fraught with risk due to severe pulmonary hypertension.

Out of 40 patients; 19 patients were discharged; 24 patients were able to wean from HFOV and 21 patients died. HFOV instituted at an early stage after pediatrics cardiac surgery with moderate elevation of oxygen index, good repair and absence of sepsis could ensure a good outcome. It could possibly avoid institution of ECMO support if use early and cardiac function and hemodynamic parameter are satisfactory [16-18].

Limitation

This single centre study is a retrospective non randomized controlled study. There was no control group. Sample size of the study is not large enough. There was always some bias regarding decision by team of intensivist to start HFOV and wean from HFOV. Presence of individual biases to begin and weaning from HFOV was encountered.

Conclusion

Acute respiratory distress syndrome is a fairly significant cause of morbidity and mortality in post operative pediatric cardiac patients after complex repairs associated with cardiopulmonary bypass and aortic cross clamp. HFOV is an effective method of ventilation being one step ahead of routine conventional ventilation when severe ARDS changes begin to be seen. It improves ventilation and oxygen index which is not amenable to be managed by conventional ventilation. It improves survival if use before progression to significant lung damage.

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