

Review

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Mechanical ventilation and cardiopulmonary bypass: a narrative review of the mechanistic lung protective measures

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Abstract

Postoperative pulmonary dysfunction is a multifactorial complication in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Numerous risk factors including individual, surgery- and anesthesia-related have been identified. Exacerbated systemic and pulmonary inflammatory response to CPB is one of the most studied mechanisms of lung injury in this patient setting. However, current literature lacks specific intraoperative mechanical ventilation (MV) strategies associated with a significant improvement in patients' outcomes. We reviewed the randomized clinical trials and other reports published within the last 5 years involving patients undergoing cardiac surgery with CPB in order to summarize the existing MV strategies used in these patients and their associated outcomes. Moreover, we described the pathophysiological mechanisms involved in post-CPB lung injury and the mechanistic effects of protective ventilation.

Keywords: Cardiopulmonary bypass, mechanical ventilation, postoperative pulmonary complications, protective mechanical ventilation

INTRODUCTION

Impaired postoperative pulmonary function is a common and multifactorial complication after cardiac surgery^[1,2]. Exacerbated cellular and humoral activation is a widely-known response ensuing from cardiopulmonary bypass (CPB), being the major cause of postoperative lung injury^[3,4]. Protective



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mechanical ventilation (PMV) strategies such as the use of continuous positive airway pressure (CPAP) have shown benefits in non-cardiac surgeries^[2]. Likewise, CPAP, low tidal volume (V_T) and recruitment maneuvers have been used in patients undergoing cardiac surgeries under CPB aiming to ameliorate lung mechanics and to decrease postoperative pulmonary complications (PPCs)^[5,6].

Mild respiratory dysfunction is commonly reported after cardiac surgery under CPB with a small percentage of patients developing severe lung dysfunction^[7]. Even though protective ventilation strategies have been associated with decreased levels of pro-inflammatory cytokines and improved lung mechanics, its impact on other postoperative long-term outcomes such as PPCs and hospital length of stay (LOS) remains unclear.

A comprehensive review of current literature was carried out aiming to describe the pulmonary physiopathological changes experienced by patients undergoing cardiac surgery with and without CPB and treated under different ventilation strategies. Likewise, the incidence of PPCs in patients with and without continuous MV during CPB was analyzed.

METHODS

A literature search on PubMed, Embase, and Cochrane Library databases was carried out in order to identify manuscripts published between 01 Jan 2014 and 31 Jan 2019 describing MV and pulmonary complications in patients undergoing CPB surgery. We used Medical Subject Headings involving the terms “MV” (combined with “CPB”, “CPB and lung injury”, “CPB and morbidity”, “CPB and mortality”, “CPB and pulmonary perfusion”, “cardiac surgery and oxygen diffusion”), “CPB” [combined with “pulmonary complications”, “CPAP”, “positive end-expiratory pressure (PEEP)”, “lung injury”, “lung mechanics”], and “lung protective ventilation in CPB surgery”. Our search was limited to manuscripts in English language, involving adult patients only, clinical trials (including phase I-IV studies), narrative reviews, and systematic reviews (with or without meta-analysis). Case reports were only considered if they were needed to support specific clinical findings not previously discussed. Moreover, we excluded manuscripts referring to CPB surgery outside the scope of this review, conference abstracts, thesis, and trials involving children or patients undergoing other cardiac surgeries different from CPB.

RESULTS

Initially, we identified 207 manuscripts out of which 46 were duplicates. After title/abstract screening, 113 manuscripts were out of the scope of this review and thereby excluded. Therefore, 48 articles qualified for full-text revision. Thirty-five ($n = 35$) articles were excluded due to no CPB surgery or intraoperative ventilation was discussed ($n = 27$), case reports ($n = 2$), protocol design ($n = 2$), trials involving cardiac surgeries in children ($n = 1$), thesis ($n = 1$), and no full-text available ($n = 2$). Therefore, 13 articles were included for further description in our qualitative analysis: systematic review and meta-analysis ($n = 1$)^[2], meta-analysis ($n = 1$)^[8], randomized clinical trials or RCTs ($n = 3$)^[9-11], prospective observational ($n = 1$)^[12], and reviews ($n = 7$)^[4-6,13-16]. **Figure 1** describes the flow diagram corresponding to our search.

MV during CPB and serum inflammatory markers

A total of 3 RCTs and 1 prospective observational trial ($n = 157$ patients) studied the impact of intraoperative MV on inflammatory markers such as cytokines in patients undergoing cardiac surgery with CPB [Table 1]^[9-12]. Two RCTs involved one group with low V_T (3-4 mL/kg) MV and PEEP whereas no ventilation was administered in a second group^[9,10]. Another RCT assigned patients to either one of the following groups: patients without MV (MV group), patients receiving protective ventilation with continuous low V_T ventilation (LTV), and patients with CPAP of 10 cmH₂O (CPAP group)^[11]. Moreover, one prospective observational study allocated patients into 2 groups based on: MV or apnea with PEEP

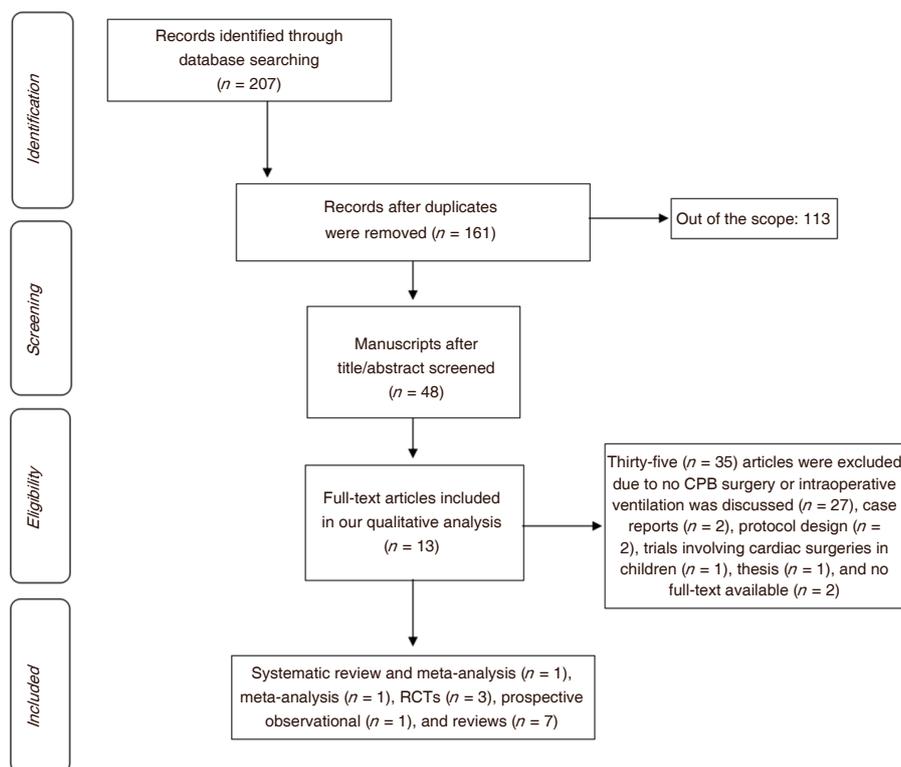


Figure 1. Flow diagram

received during CPB^[12]. Analyzed inflammatory markers varied among studies: chemokines (CCL2, CCL4, CCL20)^[9]; matrix metalloproteinase (MMP)-8, MMP-9 and lipocalin-2^[10]; tumor necrosis factor alpha (TNF- α) and interleukin (IL)-10^[12]; and IL-6, IL-8, and IL-10^[11]. Table 1 summarizes the main reported findings for each study.

MV during CPB and perioperative outcomes

Perioperative clinical outcomes (e.g., atrial fibrillation, perioperative myocardial infarction, and pericardial tamponade) and 28-day mortality after cardiac surgery were assessed in 2 of the RCTs included in this review^[9,10]. Moreover, the ratio between the arterial oxygen partial pressure (PaO₂) and the inspired fraction of oxygen (FiO₂) or PaO₂/FiO₂ ratio was reported in the only prospective observational study^[12]. Likewise, one meta-analysis by Chi *et al.*^[8] included 17 trials and 1,162 patients undergoing cardiac surgery evaluating the oxygenation index (PaO₂/FiO₂ ratio) and the alveolar to arterial oxygen difference (AaDO₂) after CPB. Rate of PPCs, shunt fraction, hospital LOS, and postoperative AaDO₂ (4 h after CPB) were also estimated. Authors used the GRADE system to assess the level of evidence for each outcome [Table 1].

A recent systematic review and meta-analysis described the impact of different MV strategies during CPB on postoperative outcomes in adult patients undergoing cardiac surgery. A total of 15 RCTs were included in this analysis, 13 trials in patients undergoing coronary artery bypass grafting (CABG) and 2 trials in patients undergoing valve surgery. Subsequently, only 5 studies (134 patients in total) reported the use of CPAP during CPB and its impact on oxygenation. Other primary end-points were PaO₂/FiO₂ ratio (5 studies), the alveolar-arterial O₂ gradient or P(A-a)O₂ (9 studies), hospital LOS (6 studies), and the duration of postoperative MV (6 studies)^[2].

Seven review manuscripts have summarized some of the current findings in terms of MV strategies and perioperative lung mechanics in patients undergoing cardiac surgery. Table 1 describes the main reported conclusions for each one of them^[4-6,14-16].

Table 1. Summary of the manuscripts included in our review

Authors	Year	Research Method	Sample Size	Main outcome	Comments
Bechtel <i>et al.</i> ^[13]	2014	Review	NA	Describe current literature about anesthetic management in patients undergoing CPB	Protecting ventilation techniques during CPB may be associated with decreased inflammatory response. However, no significant overall improvement in respiratory and oxygenation parameters has been reported
Beer <i>et al.</i> ^[9]	2014	RCT	30	Chemokines serum levels	CCL4 serum levels from POD1 to POD5 were significantly reduced in the ventilated patients when compared to the non-ventilated group ($P < 0.05$). Perioperative clinical outcomes and 28-day mortality were comparable among groups
Young ^[14]	2014	Review	NA	To describe current strategies to reduce the postoperative inflammatory lung injury in patients undergoing CPB	Increased resistance in the pulmonary circuit may result from no ventilation during CPB. Further RCTs are required to elucidate the impact of mechanical ventilation during CPB on postoperative pulmonary outcomes
Beer <i>et al.</i> ^[10]	2015	RCT	30	Matrix metalloproteinases levels	Matrix metalloproteinases levels were significantly reduced at different time-points in patients who underwent mechanical ventilation during CPB. However, clinical implications should be addressed in future trials
Ferrando <i>et al.</i> ^[5]	2015	Review	NA	Review pulmonary protective strategies during CPB	CPAP, recruitment maneuvers, and low V_T during CPB have been associated with better postoperative lung mechanics. In addition, maintaining certain level of pulmonary perfusion during CPB may positively impact these outcomes
Gaudriot <i>et al.</i> ^[12]	2015	Prospective Observational	50	Impact of Mechanical ventilation during CPB on postoperative immune response	Pro-inflammatory TNF- α and immunosuppressive IL-10 were significantly reduced in patients who received mechanical ventilation during CPB ($P < 0.05$). Moreover, non-ventilated patients had a lower postoperative lymphocyte count when compared with the ventilated group ($P = 0.04$).
Huffmyer <i>et al.</i> ^[6]	2015	Review	NA	Pulmonary complications after CPB: etiology, risk factors, and prophylaxis	Intermittent ventilation, low V_T and recruitment maneuvers have been associated with reduced atelectasis and improved lung mechanics. Mixed results have been reported in terms of inflammatory markers and clinical outcomes.
Lellouche <i>et al.</i> ^[15]	2015	Review	NA	Mechanical ventilation strategies in patients undergoing cardiac surgery	Protective ventilation strategies are associated with improved lung mechanics, decreased pro-inflammatory cytokines, and reduced postoperative intubation time and ICU LOS
Bignami <i>et al.</i> ^[16]	2016	Review	NA	Postoperative lung dysfunction and mechanical ventilation strategies to prevent it in patients undergoing CPB	No ventilation during CPB has been linked to increased lysosomal enzymes in lungs circulation and increased incidence of ARDS. Low V_T , 6-8 mL/Kg of IBW, PEEP, recruitment maneuvers, and $FiO_2 < 80\%$ have been associated with decreased morbidity, hospital LOS, and PPCs. Ventilation before and after the CPB may significantly affect lung mechanics as well. Mixed results have been reported in terms of CPAP use during CPB and its association with improved postoperative pulmonary outcomes. Only one trial has reported high-frequency ventilation during CPB with no significant respiratory improvements reported
Chi <i>et al.</i> ^[8]	2017	Meta-analysis	NA	Impact of mechanical ventilation during CPB on PPCs when compared to non-ventilated patients	Mechanical ventilation during CPB results in an improved oxygenation and gas exchanged. However, comparable incidences of PPCs and hospital LOS have been reported among groups
Toikkanen <i>et al.</i> ^[11]	2017	RCT	47	Mechanical ventilation and its effect on cytokines levels after CABG	CABG with CPB is associated with an increased pro-inflammatory cytokines pulmonary passage when compared to patients where CPB was not used. Moreover, lung ventilation did not change cytokines concentration in patients undergoing CABG with CPB. Main limitation: sample size, patient selection (e.g., lung disease was excluded), and no subgroups (ventilation vs. non-ventilation) in patients undergoing CABG without CPB
Bignami <i>et al.</i> ^[4]	2018	Review	NA	Describe current status of protective ventilation strategies and their impact on postoperative outcomes	In patients undergoing cardiothoracic surgery, protective ventilation strategies are associated with a decreased inflammatory response and should be considered in patients at high risk of PPCs. CPAP, low V_T , and non-ventilated lungs are among the options for mechanical ventilation during CPB

Wang <i>et al.</i> ^[2]	2018	Systematic Review and Meta-analysis	NA	Different strategies used for mechanical ventilation during CPB and postoperative outcomes	CPAP between 5-15 cm H ₂ O during CPB may be associated with short-term benefits such as improved gas exchange and oxygenation. However, no significant differences in these variables were found when comparing patients undergoing mechanical ventilation during CPB and those non-ventilated
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CPB: cardiopulmonary bypass; RCT: randomized clinical trial; CCL: chemokine ligand; POD: postoperative day; CPAP: continuous positive airway pressure; VT: tidal volume; TNF- α : tumor necrosis factor alpha; IL: interleukin; ICU: intensive care unit; LOS: length of stay; IBW: ideal body weight; PEEP: positive end-expiratory pressure; FiO₂: inspired fraction of oxygen; PPCs: postoperative pulmonary complications; CABG: coronary artery bypass graft; ARDS: acute respiratory distress syndrome

DISCUSSION

Multifactorial mechanisms affecting pulmonary function during and after CPB

Postoperative respiratory dysfunction is the most common postoperative complication in patients undergoing cardiac surgery under CPB affecting 10% to 25% of these patients and also associated with high mortality rates^[17-19]. Patient-specific, anesthesia- and surgery-related factors contribute to the onset of a complex mosaic of pathophysiological events that result in severe respiratory mechanics and gas exchange impairment ensuing postoperative pulmonary dysfunction^[18,20-23].

Patient-specific factors

Chronic obstructive pulmonary disease, low ventricular ejection fraction (EF) (i.e., EF < 30%), hypertension, blood transfusions, emergency surgery, previous cardiac surgery, combined procedures (i.e., cardiac and aortic procedures), active endocarditis, age > 70 are some of the patient-related risk factors associated with respiratory insufficiency after cardiac surgery^[24-26].

Anesthesia-related factors

Several reports identified a strong association between general anesthesia and impaired postoperative pulmonary function. Prolonged time in supine position and muscle relaxation have been linked to a significant reduction in both, functional residual capacity (FRC) and lung volume, resulting from a cephalic displacement of the diaphragm and the loss of balance between the elastic recoil of the lung and the outward forces of the chest wall. This reduction in FRC promotes alveolar collapse (i.e., atelectasis) and increases airway resistance with subsequent increased resistance to thoracic blood flow circulation. Furthermore, the volatile agents inhibit pulmonary hypoxic vasoconstriction whereas intravenous agents may decrease the hypoxic and hypercapnic ventilatory response. Intubation along with the aforementioned mechanisms may result in ventilation-perfusion mismatch, abnormal shunt fraction, and wider AaDO₂^[27,28].

Surgery-related factors

Sternotomy incision, sternosynthesis, and left internal mammary artery dissection

Numerous reports describe the association between the surgical technique and changes in respiratory mechanics and lung function^[22,29-33]. Median sternotomy disrupts sternum integrity, provokes chest wall instability (i.e., uncoordinated rib cage expansion, decrease compliance), and reduces lung volumes with subsequent impaired pulmonary mechanics^[29,31]. The combination of sternotomy and dissection of the left internal mammary artery (LIMA) has a significant impact on respiratory mechanics^[29,31]. LIMA harvesting maneuvers not only interfere with sternum stability but also may affect blood supply to the sternum, intercostal muscles, and left phrenic nerve functionality. Moreover, instillation of saline slush in the pericardial cavity has been also associated with phrenic nerve injury or dysfunction during cardiovascular surgery^[22]. Therefore, chest wall mechanics and diaphragm mobility impairment results in significant changes from pre-sternotomy breathing patterns (abdominal) to an upper thoracic pattern with reduced lung volumes thereby, promoting atelectasis^[34]. Retraction of the chest wall during LIMA harvesting produces additional trauma to the costovertebral joints ensuing an unstable rib cage with impaired diaphragm contraction^[34,35]. Likewise, altered thoracic wall mechanics and diaphragmatic dysfunction have been associated to a reduced postoperative abdominal motion^[22,29,31,34,36]. Nevertheless, disruption of the anterior insertions of the diaphragm seems to recover shortly after surgery^[37].

In addition to direct nerve injury (i.e., neuropraxia), the LIMA retractor has been also associated with lesion of the left internal oblique abdominal, external oblique abdominal and rectus abdominis muscles^[35,38,39]. In contrast, sternotomy with intact pleura maintains respiratory system and chest wall elastance unchanged. However, the opening of the parietal pleura leads to lung collapse with decreased lung elastance and resistance^[32]. In addition, the use of LIMA for grafting requires the insertion of a pleural subxyphoid or left intercostal tube for drainage, being subxyphoid placement associated with lesser impairment and postoperative pain when compared to intercostal insertion^[33,40,41].

Blood transfusion

Blood transfusion is used in 30%-60% of patients undergoing cardiac surgery and the reported incidence of transfusion-related acute lung injury (TRALI) is 2.5%^[42-44]. Blood transfusion has been linked to an increased risk of postoperative morbid events^[45], being transfusion of > 3 red blood cells units an independent risk factor for increased hospital LOS after cardiac surgery^[46]. Presence of bioactive lipids and antibodies in the stored blood, and the activation of transfused neutrophils in the setting of an exacerbated host's systemic and pulmonary inflammatory response are some of the mechanisms involved in the TRALI^[47].

Cardiotomy for suction

Tissue plasminogen activating factor, pro-inflammatory mediators (i.e., cytokines, activated leukocytes, lipids), pro-coagulants, and platelet factors are present in the cardiomy suction blood. Numerous reports have shown the detrimental effects associated with these mediators during re-transfusion of unwashed blood collected in the pericardium including an increased inflammatory response with impaired lung function and hemostasis^[48,49]. Cell salvage devices helps to remove these activated mediators from the blood obtained from cardiomy suction^[50,51].

Extracorporeal circulation

In spite of innovations in biocompatibility of CPB circuit's surfaces, the inflammatory response associated to extracorporeal circulation with subsequent anti-inflammatory response as well as the ischemia-reperfusion injury, continue to have a significant impact on postoperative morbidity and mortality after cardiac surgery^[52]. The exposure of plasma proteases to CPB circuit's non-endothelial surface ("contact activation") immediately activates the complement pathways and factor XII (XIIa). Likewise, classic complement pathway is activated by heparin-protamine complexes, coagulation and fibrinolysis byproducts (from the activation of the extrinsic coagulation pathway after vascular injury). Activation of classical and alternative pathway promotes the release of pro-inflammatory cytokines (TNF α , IL-1, IL-2, and IL-8), production of activated-polymorphonuclear leukocytes, endothelial cell damage, and capillary permeability^[21,52-54]. The combination of the aforementioned factors along with ischemia-reperfusion injury results in endothelial, alveolar and interstitial edema, increased airway resistance and atelectasis^[21]. Moreover, hemodilution (required to prevent embolism and hemolysis during CPB) may exacerbate pulmonary edema^[55].

Cessation of ventilation and altered surfactant production and function

Type II alveolar cell dysfunction, inactivation of large aggregate by alveolar edema fluid, and/or large aggregate leakage across the damaged alveolar capillary membrane are some of the effects of apnea and lung collapse to FRC during CPB, being the inflammatory response triggered by the use of a foreign bypass circuit during extracorporeal circulation^[56]. These biochemical and functional disturbances significantly affect surfactant concentration and functionality, contributing to the onset of atelectasis. Cyclic alveoli stretch is necessary to produce a signal transduction responsible of stimulating surfactant secretion by Type II alveolar cell^[57-59]. Therefore, apnea during CPB may significantly reduce surfactant secretion. Govender *et al.*^[60] reported that patients who underwent off-pump coronary bypass with MV using PEEP experienced higher postoperative large aggregate concentrations when compared to patients who

underwent CABG under CPB. Moreover, absence of ventilation has been associated with hydrostatic pulmonary edema, poor pulmonary compliance, and higher incidence of lung infections^[61,62].

Ischemia-reperfusion injury

Under physiologic conditions, bronchial circulation represents 3%-4% of the pulmonary blood flow and may decrease during CPB^[63]. The ischemic phase depletes the energy stores (i.e., ATP), increasing lactate levels in the pulmonary blood flow^[53,64]. The reperfusion and re-oxygenation phase after aortic cross-clamp release stimulates the production of reactive oxygen species (ROS) resulting in dysregulation of intracellular and mitochondrial calcium transport, increased inflammatory response (i.e., cytokines, complement and activation of neutrophils), endothelial cell damage, and increased vascular permeability^[60,65-67]. The systemic and pulmonary inflammatory states originated during and after CPB generate a compensatory anti-inflammatory response characterized by the production of anti-inflammatory cytokines (IL-10) and leukocytes^[68,69]. Monocytes downregulation follows this chain of events resulting in an increased susceptibility to postoperative infections^[52,70].

Hyperoxia

Increased oxygen concentrations are commonly administered during CPB in order to avoid cellular hypoxia, reduce gaseous micro-embolism, and improve neutrophils' functionality^[71]. Nonetheless, enhanced production of ROS, cardiovascular dysregulation, and increased injury due to ischemia-reperfusion are some of the systemic effects linked to hyperoxia^[72,73].

Could MV be a mechanistic strategy to protect the lungs during CPB?

Different strategies such as CPAP with and without PEEP have been implemented during MV under CPB. Current evidence about the use of MV as a mechanistic strategy for lung protection during CPB remains controversial. Early studies examined the effects of CPAP during CPB without showing any significant beneficial effects on oxygenation^[74,75]. Nevertheless, recent studies have reported that CPAP pressures of 10 cmH₂O were more effective in achieving and maintaining better postoperative PaO₂/FIO₂ ratio than lower CPAP pressures in patients undergoing cardiac surgery with CPB^[61].

Even though only a small amount of patients undergoing cardiac surgery may develop acute respiratory distress syndrome (ARDS), the reported mortality rates may reach up to 50%^[17,24]. An increased body of evidence supports the benefits of PMV (low V_T, FiO₂, and PEEP) in patients with ARDS^[76-80]. The rationale for using PMV during CPB lies in the fact that postoperative pulmonary dysfunction in cardiac surgery is characterized by alterations in lung mechanics and gas exchange abnormalities, which may resemble some of the ARDS physiologic and clinical features. Although many surgeons prefer the lung collapsed during CPB in order to improve the surgical field, recent published reports suggest that PMV may be associated with a significant reduction of pathophysiological events and pulmonary dysfunction after cardiac surgery^[81-89]. However, MV also entails some risk of pulmonary damage such as alveolar over distension (resulting from high V_T), alveolar rupture (due to cyclic opening), inactivation of surfactant, and excessive lung stress inducing elevated transpulmonary pressure^[90-93].

John and Ervine^[84] randomized patients undergoing CABG under CPB to either MV with low V_T/no-PEEP (ZEEP) or non-ventilation. Patients who were ventilated during CPB presented lower extravascular lung water content and shorter extubation times when compared to the non-ventilation group (530 ± 50 mL vs. 672 ± 32 mL, *P* = 0.028 and 3.60 ± 0.3 h vs. 4.8 ± 0.4 h, *P* = 0.038 respectively). Paradoxically, the cyclic expansion of the lungs may further reduce the bronchial blood flow during the pulmonary exclusion phase of extracorporeal circulation^[94].

Gagnon *et al.*^[86] studied 40 patients undergoing CABG with CPB. Patients were randomized into two groups, no ventilation (group I) and ventilation with low V_T (3 mL/kg) and ZEEP during CPB. Endothelial function was assessed through the changes in pulmonary vascular resistance index (PVRI) after the injection of acetylcholine (ACh) into the pulmonary artery. Although patients in the ventilated group had a better vasodilatory response to ACh, the difference in PVRI between the two groups was not statistically significant neither after declamping of the aorta ($P = 0.32$) nor at 1 h after CPB ($P = 0.28$). In addition, LTV with or without PEEP has been associated with attenuation of the systemic and pulmonary immune-inflammatory response and thereby, its effect in the lungs^[9,10,12,87].

MV and pulmonary perfusion during CPB

Discontinuation of the pulmonary artery circulation during CPB significantly affects the bronchial blood flow and metabolic demand which results in ischemia-reperfusion injury. Nevertheless, maintaining pulmonary circulation and ventilation during CPB have been associated with reduced ischemia-reperfusion damage in preclinical models^[95].

In humans, the impact of continuous pulmonary perfusion during extracorporeal circulation on reducing postoperative lung injury remains controversial^[96-98]. Santini *et al.*^[96] compared pulsatile pulmonary perfusion during CPB with conventional CPB in patients undergoing cardiac surgery. The pulsatile pulmonary perfusion group showed increased $\text{PaO}_2/\text{FiO}_2$ and lung compliance with reduced neutrophils in the bronchoalveolar lavage when compared to the conventional group. Moreover, pulmonary perfusion has been also associated with an increased postoperative oxygenation when compared to the use of histidine-tryptophan-ketoglutarate solution during CPB in patients undergoing cardiac surgery^[97]. Even though pulmonary perfusion during CPB reduces the postoperative inflammatory response and improves oxygenation, long-term benefits are yet to be determined. However, its implementation may considerably increase surgeons' workload.

CONCLUSION

A variety of MV strategies may have potential benefits in patients undergoing cardiac surgery with CPB. PMV is a useful mechanistic strategy during CPB associated with reduced systemic and inflammatory responses and thereby, lung injury. Nevertheless, the impact of these findings on postoperative morbidity and mortality has not been clearly established. Future prospective RCTs should address the need for clinical data describing both, short- and long-term outcomes in patients undergoing cardiac surgeries with CPB under MV.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and outline of this manuscript: Echeverria-Villalobos M
Made substantial contributions to data search, interpretation, and writing: Echeverria-Villalobos M, Munlemvo DM, Fiorda-Diaz J, Essandoh MK

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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