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Review Article

Risk Factors for Prolonged Mechanical Ventilation after Cardiopulmonary Bypass for Open-Heart Surgery in Adults

Govender M[1]*, Bihari S[1,2] and Dixon DL[1,2]

[1]*Department of Critical Care Medicine, Flinders University, Australia*
[2]*Intensive and Critical Care Unit, Flinders Medical Centre, Australia*

***Corresponding author**
Govender M, Department of Critical Care Medicine, Flinders University, Adelaide, SA, Australia, 61-882-045-494; Fax: 61-882-045-751; Email: gove0014@flinders.edu.au

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Abstract

Cardiopulmonary bypass [CPB] during open-heart surgery is associated with pulmonary complications, such as atelectasis, acute respiratory distress syndrome [ARDS], pulmonary vascular injury and respiratory failure. Many patients require prolonged mechanical ventilation [PMV] as a result. PMV is associated with longer time in hospital, slowed recovery and increased mortality and morbidity. Therefore, it is beneficial for the patient and the hospital that pre-operative, intra-operative, and post-operative risk factors for PMV after CPB are identified and reduced. In this review we have identified risk factors for PMV after CPB for open-heart surgery in adults in order to provide a summary of these risk factors, and potential means by which these risk factors may be reduced. We conclude that there is a need for more studies in this area utilizing larger sample sizes and meta-analyses, in order to adequately identify the factors that are consistently associated with PMV risk. This may allow development of a scoring system for PMV risk, so that high-risk patients could be identified prior to cardiac surgery.

ABBREVIATIONS

PMV: Prolonged Mechanical Ventilation; CPB: Cardiopulmonary Bypass; ICU: Intensive Care Unit; SIRS: Systemic Inflammatory Response Syndrome; CABG: Coronary Artery Bypass Graft; BMI: Body Mass Index; Pao_2: Partial Pressure Of Oxygen; Fio_2: Fraction Of Inspired Oxygen; NYHA: New York Heart Association; EF: Ejection Fraction; AF: Atrial Fibrillation; ACC: Aortic Cross Clamp; IABP: Intra-Aortic Balloon Pump; COPD: Chronic Obstructive Pulmonary Disease; TRALI: Transfusion-Related Acute Lung Injury; STS: Society of Thoracic Surgeons.

INTRODUCTION

Patients receiving open-heart surgery normally remain intubated post-surgery to improve gas exchange and work of breathing, and to lower rates of hypertension and myocardial ischemia [1,2]. In operations using CPB, the majority of patients are extubated within 6-8 hours post-surgery [3]. However, up to 20% require mechanical ventilation for > 48 hours postoperatively [4]. PMV is most commonly defined as ≥ 24 hrs, but has been variously defined as a cumulative duration of mechanical ventilation for ≥6 hrs, ≥ 8 hrs, ≥ 24 hrs, ≥ 72hrs, or as long as ≥ 14 days.

There are many complications associated with PMV, including vocal cord granulomas and ulcerations [5], oxygen toxicity, and local inflammation [6]. Early extubation decreases intensive care unit [ICU] costs [7], and a shorter hospital stay is associated with decreased morbidity and mortality [8-10]. CPB is associated with longer ventilation times, as it can induce a systemic inflammatory response syndrome [SIRS] triggered by exposure of blood to the foreign surface of the extracorporeal circuit, amongst other factors. SIRS can result in pulmonary oedema, surfactant dysfunction, and pulmonary hypertension [11].

This comprehensive review of the current literature demonstrates that CPB has been found to be a direct risk factor for PMV in most studies, as well as indirectly increasing risk of other factors that are associated with causing PMV. The number of people requiring open-heart surgery will grow in the next decade due to the obesity epidemic. By identifying and scaling the impact of risk factors for PMV, it may be possible to create a patient scoring system of PMV risk that could potentially be used to decrease risk of PMV before and during cardiac surgery.

METHODOLOGY

For the purposes of this review, we have analyzed the relevant studies without setting a particular inclusion criterion for PMV definition. Studies must include use of CPB during cardiac surgery procedures, which can include coronary artery bypass graft [CABG] or valvular procedures. Studies employing univariate and/or multivariate analyses were included, but for those studies that included both we only considered the data obtained for multivariate analysis. Since there was a lack of studies on some factors that could potentially contribute to PMV risk, we included within our search any studies relevant to PMV, irrespective of date of publication or patient demographics.

Pre-operative risk factors for prolonged mechanical ventilation

Age and sex

Age appears to be a clear risk factor for PMV (Tables 1,2), with risk increasing as age increases, most probably due to co-morbidities complicating recovery and an impaired bodily response to combat injury and cope with the stress of surgery. For example**,** compared to age ≤65, those 65-75yrs old had a 2.2 times increased risk of PMV, those 75-80yrs old had a 4.8 times increased risk, and age >80yrs had a risk 5.5 times greater [12]. Another study found a 0.3% increase in risk of severe hypoxemia, and therefore PMV, after CPB for every year above the age of 34 [13].Most studies did not find that sex was a risk factor [13-15] as illustrated in Table 1, but results might have been affected by the relatively small sample size in many of these studies.

Body weight

Obesity decreases functional residual capacity, expiratory reserve volume, partial pressure of oxygen [PaO_2]and compliance of the chest wall, and increases the alveolar-arterial [A-a] oxygen gradient, and thereby has the potential to contribute to PMV [16].One study that only looked at the effect of obesity found that obesity [BMI 30-40 kg/m^2] and extreme obesity [BMI ≥40 kg/m^2] was associated with increased risk of PMV since BMI is inversely related to PaO2/FiO2 ratio, with 30.6% of patients analyzed having post-operative hypoxemia, defined as PaO_2/FiO_2 ratio <200 [17]. A retrospective study by Faritous et al of women undergoing cardiac surgery found that the risk of post-operative hypoxemia increased 1.7 fold for each incremental BMI class [18].However, most studies have not found an association between BMI and PMV [12,15,19,20], possibly due to a broader examination of variables affecting PMV risk reducing the significance of BMI under multivariate analysis.

Diabetes mellitus

As a result of surgical stress, there is an increase in gluconeogenesis and glycogenolysis causing hyperglycaemia even in patients who had normal blood glucose levels before surgery [21]. Hyperglycaemia decreases endothelium-derived vasodilators, and increases release of vasoconstrictors and reactive oxygen species that exacerbate SIRS [21].The PaO_2/FiO_2 ratio is lower and the A-a oxygen gradient is higher in diabetics before cardiac surgery, with these indices being poorer after CBP [22-24].The number of diabetic patients with HbA_{1c}> 6.5% requiring mechanical ventilation after CPB was higher compared to diabetic patients with better glycaemic control [25], relating to a higher incidence of pneumonia [25,26] and transfusion requirement [25], which are both associated with PMV. Diabetes mellitus occurs in one-third of patients with chronic renal disease undergoing CABG surgery [27], which has been found in some studies to be an independent risk factor for PMV. In spite of these results, conflicting studies concluded that diabetes mellitus was not a risk factor for PMV [12,13,15] which again may be due to relatively low sample sizes.

Systemic hypertension

Hypertension [>140mmHg systolic and/or >90mmHg diastolic] can be pre-existing, or may be acutely increased before surgery due to anxiety [28]. Acute rises in systemic hypertension can exacerbate underlying left ventricular systolic dysfunction, thereby leading to acute pulmonary oedema [28]. Suematsu and colleagues [2001] found that hypertension was an excellent predictor of PaO_2/FiO_2 ratio <350 [29] and hypertension was a significant risk factor for PMV [30,31]. However, Ji et al [2013] and Jian et al [2013] studying patients of differing demographics to Suematsu et al [2001], did not find hypertension was significant for PMV or re-intubation, respectively [32,33].

Cardiovascular disease and atrial fibrillation

Pre-operative congestive heart failure was found to be a risk factor for PMV [15,24,31,33]. As expected, the higher the New York Heart Association [NYHA] class, the greater the risk of PMV in these studies. For example, compared to ejection fraction [EF] >55%, those with EF <55% had ~1.8x increased risk of severe hypoxemia, and thus increased incidence of PMV [13]. Pre-existing ventricular failure may be worsened after cardiac surgery, which can cause cardiogenic pulmonary oedema, pulmonary hypertension and hypoxemia. Recent myocardial infarction [<90 days] is a predictor of post-operative respiratory problems after CBP [34]. Pre-operative atrial fibrillation [AF] increased duration of mechanical ventilation to >24hrs [35], and increased the incidence of acute renal failure, itself a risk factor for PMV [35]. AF contributes to lowering post-operative cardiac output, which leads to cardiogenic pulmonary oedema and decreased renal blood flow [35].

Current smoking, chronic obstructive pulmonary disease and pulmonary hypertension

Pre-existing respiratory disease in patients is exacerbated following cardiac surgery. Respiratory compliance is typically decreased within the first three days post-surgery, which may prolong intubation in these patients. Indeed, one study specifically looking at pre-operative PaO_2 found that it was an excellent predictor of post-operative PaO_2/FiO_2 ratio <350 [29]. Studies looking at multiple variables found that current smoking was not a variable associated with increased risk of PMV [12,13,33]. However, four prospective cohort studies specifically looking at smoking, found that cessation for >20 years to >3 months prior to cardiac surgery significantly decreased duration of mechanical ventilation [36-39]. This was in contrast to Reddy and colleagues who found that smoking caused a 1.7 times increased risk of PMV, with forced expiratory volume in one second [FEV_1] <70% being associated with a 2.01 increased risk of PMV [12]. Chronic obstructive pulmonary disease [COPD] was not a risk factor for PMV in most studies [13,20,24] while Jian et al who used a larger sample size did find an association [33]. Systolic pulmonary artery pressures >35mmHg has been associated with increased risk of PMV, with increasing severity of pulmonary hypertension

Table 1: Outline of results, definitions of PMV and patient populations for major studies analyzing the effect of several variables on PMV risk for patients undergoing cardiac surgery using CPB.

Study	Definition of PMV	Sample size and patient demographics	Factors significantly associated with increasing risk of PMV
Reddy et al 2007	>48hrs	12,662 patients undergoing cardiac surgery between Apr 1997-Mar 2005; prospective analysis; UK	Increasing age above 65 years; current smoker; increasing serum creatinine>125µmol/L; EF <30%; myocardial infarction <90 days; urgent surgery; emergency surgery; use of CPB
Ji et al 2013	>48hrs or re-intubation following cardiac surgery	143 patients undergoing cardiac surgery between Jan 2005-Dec 2012; retrospective analysis; Shanghai.	Increasing age above 65 years; pre-operative CHF; pre-operative PaO_2; CPB duration; intra-operative phrenic nerve injury; post-operative acute kidney injury
Siddiqui et al 2012	>24hrs	1,617 patients undergoing cardiac surgery between Mar 2009- May 2011; retrospective analysis; Pakistan	Pre-operative renal failure; emphysema; EF <30%; urgent operation; prolonged CPB; prolonged aortic cross clamp time; complex surgical procedures; peri-operative myocardial infarction
Faritous et al 2011	Uninterrupted mechanical ventilation of ≥14 complete days.	5,497 female patients undergoing CABG between Apr 2002-Mar 2008; retrospective analysis; Iran	Increasing age ≥70 years; EF ≤30%; pre-operative respiratory or renal disease; emergency or re-do operation; use of pre-operative inotropic agents
Giakoumidakis et al 2011	No set definition	48 patients undergoing cardiac surgery between Oct 2010-Dec 2010, Observational prospective analysis; Greece	Older age; prolonged duration of cardiac surgery
Yende et al 2002	>24hrs	400 patients undergoing cardiac surgery between June 1999-Oct 2000; observational Prospective analysis; USA.	Post-operative bleeding; hypoxemia
Ji et al 2012	>48hrs	588 patients undergoing cardiac surgery between Jan 2003- Dec 2008; retrospective analysis; Shanghai	Pre-operative CHF; pre-operative hypoalbuminemia; pre-operative PaO_2; post-operative anaemia
Suematsu et al 2000	>24hrs	167 patients undergoing cardiac surgery between 1994-1998; retrospective analysis; Japan	Older age; longer duration of surgery; peri-operative heart failure; glucose level; post-operative transfusion; low PaO_2/FiO_2 ratio
Dunning et al 2003	>24hrs	3,070 patients undergoing cardiac surgery between Apr 1998-May 2002; retrospective analysis; UK	Parsonnetscore >7;low EF; emergency operation;low PaO_2; older age
Knapik et al 2011	>48hrs	2 cohorts: July 2007 - Dec 2008, n = 2165; Jan 2009 - July 2010, n = 2192. Retrospective analysis; Poland.	Aortic aneurysm surgery; emergency surgery; combined procedures; valve procedures; pre-operative renal dysfunction; pre-operative stroke or transient ischemic attack
Totonchi et al 2014	>48hrs	743 patients; observational prospective analysis; Iran.	Gender; COPD; chronic kidney disease; endocarditis; type of surgery; length of operation; CPB time; transfusion; post-operative bleeding; inotrope-dependency
Wong et al 1999	>10hrs	885 patients; prospective analysis; Canada.	Increased age; female gender; post-operative use of intra-aortic balloon pump; use of inotropes; post-operative bleeding; atrial fibrillation
Cislaghi et al 2009	>12hrs	5,123 patients undergoing cardiac surgery from Jan 2000-Dec 2006; observational prospective analysis.	Age >65 years; chronic renal failure; COPD; redo surgery; emergency surgery; NYHA class >2; EF< 30%; transfusion; CPB time >77 min
Natarajan et al 2006	≥24hrs	470 patients undergoing CABG between Jan-June 2002; retrospective analysis; Chennai.	EF <40%; pre-operative renal dysfunction; prolonged CPB >120 min; re-exploration/re-intubation in the ICU

Abbreviations: EF: Ejection Fraction; CPB: Cardio Pulmonary Bypass; CHF: Congestive Heart Failure; NYHA: New York Heart Association; FEV_1: Forced Expiratory Volume In 1 Second; BMI: Body Mass Index; Pao_2: Partial Pressure Of Oxygen; Fio_2: Fraction Of Inspired Oxygen; CABG: Coronary Artery Bypass Graft; COPD: Chronic Obstructive Pulmonary Disease.

being associated with a higher risk [40].

Chronic renal disease

Chronic renal disease impairs the ability to excrete fluid, causing pulmonary oedema [41]. The sedative, analgesic and anxiolytic drugs used peri-operatively have a decreased metabolism and clearance due to renal dysfunction, thus causing a prolonged decrease in respiratory drive [41]. As a result, there is a need for PMV, this being correlated with increasing stage of severity [30,42-47]. For example, compared to a creatinine

Table 2: Summary of the strength of the association for analyzed factors effecting PMV risk.

Factor effecting PMV risk	Strength of association of the factor in increasing PMV risk
Pre-operative	
Increasing age Congestive heart failure [including low EF and NYHA class] Recent myocardial infarction Atrial fibrillation	Strong
Current/recent smoker	Moderate
Sex Diabetes mellitus Systemic hypertension Chronic obstructive pulmonary disease Chronic renal disease Urgent or emergency operation	Weak
Intra-operative	
Increasing duration of cardiopulmonary bypass	Strong
Length of operation	Moderate
Increasing aortic cross clamp time Hypothermia Complexity of surgery Haemodilution/low haematocrit	Weak
Post-operative	
Delirium Blood transfusion Re-exploration for bleeding	Strong
Myocardial infarction Atrial fibrillation Post-operative bleeding	Moderate
Acute kidney injury	Weak

level of ≤125μmol/L, those with >125-≤175μmol/L had a 1.09 odds ratio of PMV, whilst those with >175μmol/L had a 4.0 odds ratio [P<0.001] [32]. Chronic renal disease also increases risk of peri-operative AF, post-operative bleeding, re-exploration for bleeding, need for transfusion, post-operative acute kidney injury and new myocardial infarction, which have been found to be independent risk factors for PMV in some studies [48]. Post-operative bleeding due to platelet dysfunction and impaired erythropoietin synthesis causes anaemia of chronic disease that may exacerbate post-operative hypoxemia, leading to PMV [41]. Despite this, some studies found no significant association with chronic renal disease [13, 20, 24, 29, 30],which may again be due to differing patient demographics and sample sizes.

Urgency of operation

Patients with acute coronary syndromes are given anti-platelet and anti-thrombotic drugs to improve survival, but this increases the risk of bleeding when emergency surgery is performed [49]. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists found that emergency surgery was associated with increased transfusion requirement, which may be exacerbated by re-exploration for bleeding [50], both of which have been associated as risk factors for PMV. Reddy et al found that compared to elective surgery, urgent surgery had a 1.6 odds and emergency surgery had a 2.1 odds of PMV [1]. Studies demonstrating a significant association with emergency surgery [42,44,51] are evenly matched with studies which found no relationship [13,43,52] therefore it is difficult to form a conclusion and more studies are required in this area.

Operative risk factors for PMV

Cardiopulmonary bypass duration, aortic cross clamp duration, length of operation, complexity of surgery: As shown in Table 1, longer durations of CPB was a consistent risk factor for PMV across most studies reviewed [12, 13, 15, 24, 30, 31, 42], with CPB >120mins being a significant risk factor in most [13,30,42]. For example, Szeles et al found that compared to not using CPB, duration of CPB <120 min had a ~2.3 odds of PMV, and duration >120 mins had a ~3.2 odds [13]. Aortic cross clamp [ACC] time was largely insignificant as a risk factor [15,24,29-31,33]. Length of the operation has been found to be significant in some studies as shown in Table 1, but not in others since it is related to the duration of CPB, so became insignificant after multivariate analysis. However, increased length of operation may also indicate surgical or anesthetic difficulties, which could be independently associated with PMV. Complexity of the surgery, such as combined CABG and valvular surgery and multiple valve surgery, was largely non-significant in conferring risk of PMV [20,30,32]. This may be dependent on surgical technique, as well as patient specific factors such as age and co-morbidities that may affect the patient's ability to recover from more complex surgeries.

Use of an intra-aortic balloon pump

A randomized controlled trial was conducted by Onorati et al of 50 COPD patients either receiving non-pulsatile CPB or intra-aortic balloon pump [IABP]-induced pulsatile CPB. It was found that the latter group had a shorter intubation time [8.3±5.1 hours versus the former group: 13.2±6.0; P = 0.001], better PaO_2/FiO_2 at aortic de-clamping and at 24 hours post-surgery, and better scores on blinded chest radiographs [53]. CPB alone produces non-pulsatile blood flow, whilst pulsatile blood flow reduces tissue vasoconstriction, optimizes tissue oxygen consumption and decreases tissue acidosis throughout the body [53]. This is expected to decrease SIRS, and improve blood flow through the pulmonary arteries during CPB, so is expected to offer better pulmonary outcomes [53]. IABP-induced pulsatile CPB had a lower incidence of acute renal failure and transfusions in a study conducted on 80 patients >70 years of age [54]. Therefore, the use of IABP-induced pulsatile CPB seems promising, but there is conflicting evidence where peri-operative use of an IABP was not associated with PMV [14,15,24,55], which could be related to differences in technique.

Hypothermia

Patients are at a greater risk of morbidity and mortality after CPB if their ICU admission temperature was <36°C [56]. For example, the risk of AF increases as the body temperature decreases, and may progress to ventricular tachycardia [57], being found to be highest at 27.2°C, between 30-33°C and between 22-32°C [58].Bladder core temperature <36°C in the ICU post-CPB was associated with PMV [59] in a retrospective database analysis of 5,701 patients over 2 years [57]. However, hypothermia (34°C) was not a significant factor for PMV in a randomized controlled trial (n=144) in which nasopharyngeal temperatures were measured [60]. This might be due to the different bodily locations of measurement, the different methods of data collection or the large difference in sample size.

Altered blood physiology and intra-operative bleeding

Haemodilution and systemic heparinisation used during CPB, coupled with the non-pulsatile blood flow, all effect normal blood physiology and increase risk of bleeding [61]. Excessive haemodilution is an important factor in the development of lung injury [62-64], and is associated with increased risk of post-operative acute kidney injury [65]. Haematocrit levels <22% due to blood loss increased the incidence of pulmonary oedema, re-operation due to bleeding, stroke, myocardial infarction and renal failure, which have been associated with PMV [66]. Hypervolemia may also lead to delirium, which can potentially increase risk of PMV. However, there have only been a few studies analyzing the effects of these factors.

Post-operative risk factors for prolonged mechanical ventilation

Myocardial infarction and atrial fibrillation: Post-operative acute myocardial infarction and AF are moderate risk factors for PMV (Table 2). Myocardial infarction increases the risk of pulmonary oedema, which leads to hypoxemia and pulmonary hypertension, and increases risk of acute renal failure. Time on CPB was 33% longer in patients who developed an infarction [67]. AF is the most common arrhythmia following cardiac surgery, occurring in 20-40% of patients [69]. There was a significant increase in monocytes and polymorphonuclear cells after cardiac surgery in patients with CPB who developed AF [70]. Post-operative AF increases risk of new myocardial infarction, congestive heart failure, post-operative bleeding due to anticoagulation and delirium, therefore may only indirectly increase risk of PMV, so was insignificant as a risk factor for PMV in two studies [32, 33]. However, AF has been found to increase risk of re-intubation post-surgery [71], and increase the risk of ventilation for >24hrs in other studies [72].

Acute kidney injury

Acute renal failure following CPB occurs in 8% of adult patients who had pre-operative renal impairment and in 3–4% of patients without pre-operative renal impairment [73]. Pre-operative diabetes mellitus, peripheral artery disease, congestive heart failure, advanced age, duration of CPB and longer cross-clamp time, also increase risk of acute kidney injury [74]. The use of haemodilution in CPB, as well as the non-pulsatile blood flow and SIRS could be contributing factors [75]. Acute kidney injury causes water retention, leading to congestive heart failure and pulmonary oedema, which ultimately results in hypoxemia [33]. Acute kidney injury was a significant risk factor for PMV in some studies [15, 32, 33] but not all (Table 1).

Delirium

Longer durations of CPB may incur increased risk of central nervous system injury [76, 77], due to SIRS, a higher rate of particulate and gaseous micro emboli [78, 79], and increases the risk of delirium post-operatively [80],which is associated with PMV [56, 80, 81].There is limited coordination between the respiratory system and the brain, needing a longer time for mechanical ventilation [76]. Conversely, longer duration of mechanical ventilation also increases risk of delirium [56, 80]. Transfusion, older age [56, 76, 78], a history of major depression [76], pre-operative cognitive impairment [82, 83],post-operative renal failure [78], and AF [56], were other risk factors for post-operative delirium.

Blood transfusion

Blood transfusion is used to improve haemostasis, enhance oxygen carrying capacity, and provide volume support for cardiac output after cardiac surgery [50]. However, the use of transfusion increases the incidence of acute kidney injury, worsens cardiac outcomes, and increases risk of stroke and mortality [50]. Transfusion-related acute lung injury [TRALI] may also occur, which is the leading cause of transfusion-related mortality across cardiac and non-cardiac surgeries [52]. It develops during or within 6 hours of being transfused, and is defined by a PaO_2/FiO_2<300mmHg [52]. It is characterized by non-cardiogenic pulmonary oedema. Multiple transfusions increase the risk TRALI [odds ratio of 4.5 for 3-9 units vs 1-2 units] [52, 62], with a higher volume of banked blood transfused increasing the risk of PMV [13, 24, 84, 85].

Re-exploration for bleeding

Biancari et al conducted a systematic review with meta-analysis on the impact of re-exploration for bleeding after cardiac surgery on the immediate postoperative outcome. They found that those at a higher risk for re-exploration were often older males, patients with peripheral vascular disease, patients who were taking aspirin pre-operatively, and who underwent urgent/emergency surgery [88]. Four out of eight of the studies in the systematic review found that re-exploration was significantly related to increased risk of PMV, with a combined risk ratio of PMV of 3.39 (95% CI 2.28-5.05; P≤0.001) [88]. Re-exploration was associated with a prolonged CPB time, and was a strong risk factor for ARDS [84]. Excessive post-operative bleeding was a significant risk factor for PMV in some studies (Table 1) as it requires transfusion and can increase the risk of renal failure [89-91]. CPB was associated with greater degree of post-operative bleeding [52].

Difficulties with creating scoring systems for prolonged mechanical ventilation

Problems that arise when creating a scoring system for PMV include breadth of application limited to the particular patient demographic of the institution in which it was developed, and that the system may need to be modified overtime within an institution as the patient demographic changes. For example, the study by Knapik and colleagues compared two different cohorts of patients in one institution retrospectively across two different time periods (cohort 1: July 2007 – Dec 2008 and cohort 2: Jan 2009 – July 2010) [44]. This allowed them to test the validity of their prediction model of PMV risk over time. In the second time period, the technique of post-operative ventilation had changed, and there was a drop in the use of CPB as there were more patients >65yrs needing surgery who were typically treated off-pump [44]. Age >65yrs, NYHA class >II, urgent surgery and CABG surgery were no longer risk factors in the new prediction model for the second time period, since the elderly tended to have NYHA class III or IV, tended to require CABG surgery over valvular surgery, and more frequently had elective surgery [44]. This shows that risk factors change over time even within institutions, highlighting the need for continual re-assessment of risk factors to keep scoring systems accurate.

Limitations of the studies analyzed

A lack of consensus on the definition of PMV (Table 1) has led to inconsistent conclusions regarding whether certain factors carry significant risk for PMV. These inconsistencies may also be attributed to the large differences in sample sizes between some studies and the retrospective nature of many of the studies (Table 1), which relies on accurate data recording and appropriate collation and storage of data, as well as accurate assessment of patients for pre-operative factors. Similarly, there are differences across institutions as to routine practice for cardiac surgery and CPB, and post-operative patient management, particularly for those requiring mechanical ventilation in the ICU. All of these factors may influence the extent to which the duration of CPB, ACC and cardiac surgery as well as the complexity of surgery, impact on PMV risk. Furthermore, the factors assessed differed between studies.

Since some studies have been conducted on non-Western populations (Table 1), different patient demographics are also likely to have affected both the risk factors studied and the degree of associated risk for PMV. The time over which studies were conducted varied markedly as well (Table 1), and it would be expected that the results of those studies conducted over a longer period could be affected by changing patient demographic and changing surgical/CPB methods over time. Despite disparities over whether certain risk factors are important or not, it would be beneficial to treat each factor analyzed as a 'potential' risk factor for PMV for the patient, and thus try to minimize the effects of these factors on mechanical ventilation time.

Summary of the risk factors for prolonged mechanical ventilation with recommendations for decreasing risk

Since age is a strong risk factor for PMV, this suggests that the elderly should undergo off-pump surgery where possible to avoid SIRS. Minimally invasive cardiac surgery should also be used where possible, since it decreases blood loss, lowers risk of infection and decreases ventilation time [93]. There have been differing results regarding sex of the patient and obesity as risk factors for PMV. Diabetes mellitus is associated with increased risk of post-operative infections, including pneumonia, and also increased risk of post-operative acute kidney injury, but there lacks consensus as to whether it increases PMV risk (Table 2). Despite this, Suematsu et al (2000) suggests that normo-glycaemia should be aimed for during CPB [13], but further studies are required. Reducing weight and controlling diabetes before surgery is recommended, because although it is difficult to say whether these are significant risk factors, it would be beneficial to the patient's health and recovery after surgery if these were managed.

It appears that a higher NYHA class, lower EF, recent myocardial infarction and pre-operative AF are clearly risk factors for PMV (Table 2), but there needs to be further studies with larger sample sizes to adequately assess whether pre-operative systemic hypertension is of significance. Overall, it appears that current smoking and pre-operative pulmonary hypertension may be associated with increased risk of PMV, since underlying respiratory disease is exacerbated following cardiac surgery. Low pre-operative PaO_2 has a strong association with PMV risk, but there is still inconsistency about COPD being a risk factor for PMV. There appears to be a correlation between increasing levels of creatinine and increasing risk of PMV, but chronic renal disease has been inconsistently associated with increased risk of PMV. Whether the urgency of the operation is a risk factor for PMV is still debatable. However, emergency surgery and chronic renal disease increase risk of post-operative bleeding, transfusion and re-exploration for bleeding, which are themselves potential risk factors for PMV.

It would be beneficial for lung outcomes and overall patient health post-surgery if the patient had adequate treatment for pre-existing lung disease, congestive heart failure, systemic hypertension, atrial fibrillation and chronic renal disease well before surgery. This should involve symptom control and delay of disease progression, where possible. It would also mean that those at high risk of such conditions could potentially be identified and managed to prevent them from getting these conditions, to improve outcomes post-surgery. Smoking cessation started as soon as possible before cardiac surgery is recommended as it could decrease risk, although it is expected that cessation too close to surgery would not significantly improve risk.

Most of the studies concur that the duration of CPB is a risk factor for PMV due to SIRS. CPB duration >120 minutes carries the highest risk, so longer operation time is indirectly associated with risk of PMV. Surgeons should try to avoid CPB use where possible, or at least minimize CPB duration. The use of total vital capacity maneuvers immediately before termination of CPB may decrease incidence of intrapulmonary shunting and atelectasis caused by CPB, so may be used as techniques to decrease intubation duration [94]. The use of an ACC is an insignificant risk factor for PMV. Studies differ as to whether complexity of surgery or hypothermia is direct risk factors for PMV, but hypothermia may indirectly contribute to PMV risk by increasing the risk of AF. The use of IABP-induced pulsatile CPB has been shown to lower intubation times, incidence of acute renal injury and transfusion requirement, which also confer better lung outcomes. However, results are still inconsistent over the use of IABP. Since the use of an IABP has been associated with better outcomes, it would be worthwhile for more studies to be conducted. Although few studies have looked at the direct effect of low haematocrit levels and haemodilution, it has been shown that they are associated with worse lung outcomes.

β-blockers, sotalol, and amiodarone all reduced risk of post-operative AF, with no marked difference in efficacy between them [7]. Acute kidney injury after cardiac surgery also appears to be a risk factor for PMV. Some drugs such as frusemide, natriuretic peptide and low dose dopamine have shown efficacy in decreasing severity of renal dysfunction and volume overload post-surgery [34]. There is a need for adequate perioperative hydration, and fluid balance monitoring. Nephrotoxic drugs should be discontinued before surgery. Post-operative delirium appears to be a clear risk factor for PMV, and results in a longer ICU and hospital stay [77]. It would be favorable for those predisposed to delirium to be screened for their risk of post-operative delirium using cognitive testing. CPB duration should be minimized, off-pump surgery should be used were possible, and pain should be adequately controlled for those predisposed to delirium.

Transfusion appears to be a clear risk factor PMV since it is related to TRALI (Table 2), with multiple transfusions conferring a higher risk. Post-operative bleeding increases the risk of multiple transfusions and renal dysfunction, so is indirectly associated with increased risk of PMV. Re-exploration for bleeding appears to be a strong risk factor for PMV (Table 2). Surgical technique should be re-assessed in institutions where there is a higher percentage of patients requiring re-exploration, as well as management of pre-operative coagulopathy to decrease bleeding [85]. The need for transfusion can be reduced by preventing haemodynamic instability [86]. In order to facilitate peri-operative blood conservation, the use of anti-fibrinolytic drugs, off-pump surgery where possible, and erythropoietin to increase pre-operative blood volume has been recommended by the Society of Thoracic Surgeons [STS] [51]. They also recommend implementing a blood conservation program within institutions that involves transfusion algorithms to guide transfusion decisions [51].

The use of pre-operative corticosteroids may decrease pro-inflammatory cytokines and increase anti-inflammatory cytokines after CPB, with better lung outcomes [95]. Administration of aprotinin, a serum protease inhibitor, in the pulmonary artery during CPB may also improve lung outcomes [96]. However, aprotinin use remains controversial, since it may increase risk of myocardial infarction, heart failure, acute renal failure and stroke. It is recommended by the STS, with the caveat of caution due to the increased risk of renal dysfunction [51]. The STS also recommends the use of two lysine analogues that inhibit fibrinolysis: epsilon-aminocaproic acid and tranexamic acid, and are safer drugs than aprotinin[51]. The STS commented that leukocyte filters lack clinical benefit and may even activate leukocytes so they do not recommend its use [51].

CONCLUSION

The major limitation to this study was difficulty in comparing studies due to inconsistency in the definition of PMV, as well as variations in sample sizes, patient demographics and patient management. As a result, there were inconsistencies amongst the findings for many of the factors analyzed, so it has been difficult to confidently comment on whether certain factors carry risk of PMV. There is a need for institution-wide studies in this area, in particular the effect of the sex of the patient, BMI, diabetes mellitus, hypothermia, pre-operative systemic hypertension, urgency and complexity of surgery, and use of an IABP. Providing more evidence of factors that are consistently associated with PMV risk may allow development of a scoring system to stratify patients into low, moderate or high-risk groups. This could be used to tailor their management peri-operatively. Such a scoring system could be specific to a particular institution, but modifiable to reflect changes overtime to surgical technique and patient demographics.

The following appear to be clear risk factors for PMV: increasing age [especially >65 years], higher NYHA class, lower EF, recent myocardial infarction, pre-operative AF, longer duration of CPB [especially >120 minutes], post-operative delirium, use of transfusion [especially multiple transfusions], and re-exploration for bleeding. Off-pump cardiac surgery and minimally invasive cardiac surgery should be used where possible. Otherwise, CPB duration should be minimized. This review has provided a preliminary summary of factors contributing to PMV risk specifically related to CPB, and we encourage further research in this area given that PMV increases hospital costs and mortality and morbidity following cardiac injury.

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