

# Risk Factors of Prolonged Mechanical Ventilation in Patients Undergoing Redo Valve Surgery

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## ABSTRACT

**Background:** Prolonged mechanical ventilation (PMV) after cardiac surgery is associated with high morbidity and mortality. Patients following redo valve surgery possess many attributes that place them at risk for PMV, yet few studies particularly focused on them. The purpose of this study was to identify perioperative variables associated with PMV in redo valve surgery.

**Methods:** A retrospective study, including 117 patients who underwent redo valve surgery from November 2017 to September 2021, was performed. The potential perioperative risk factors for PMV were collected. PMV was defined as the need for intubation and mechanical ventilation for >24 h, after completion of the operation. The clinical data were analyzed with univariate and multivariate analyses to identify risk factors for PMV following redo valve surgery.

**Results:** The incidence of PMV was 38.5% ( $N = 45$ ). Multiple logistic regression analysis showed perioperative risk factors for PMV included advanced age (age > 57 years) [odds ratio (OR) 3.043, 95% confidence interval (CI) 1.172–7.905,  $P = 0.022$ ], low weight (weight  $\leq 58$  kg) (OR 2.798, 95% CI: 1.088–7.199,  $P = 0.033$ ), EuroSCORE II  $\geq 6.8\%$  (OR 3.467, 95% CI: 1.364–8.817,  $P = 0.009$ ), and VIS at 12 hours post ICU admission (VIS12) > 10 (OR 5.613, 95% CI: 2.211–14.249,  $P < 0.001$ ).

**Conclusions:** In adult patients undergoing redo valve surgery, advanced age, low weight, high EuroSCORE II and a high VIS at 12 hours post-ICU admission were associated with PMV. Hemodynamic status after operation were more important than preoperative and intraoperative variables in predicting PMV.

## INTRODUCTION

As the number of patients who have undergone valve surgery has increased and life expectancy prolonged, the frequency of redo heart valve surgery also has increased.

Perivalvular leakage, mechanical valve thrombosis, biological valve dysfunction, and prosthetic valve endocarditis all are reasons for reoperation [Furukawa 2014].

Patients undergoing redo valvular surgery always had a long preoperative course and poor cardiac function, usually with more comorbidity. Furthermore, the duration of surgery is longer than common operations, due to tissue adhesion and coagulation abnormality. All of the above influence postoperative recovery, resulting in prolonged mechanical ventilation (PMV). On one hand, mechanical ventilation can reduce oxygen consumption and support cardiopulmonary function recovery; on the other hand, PMV can aggravate the primary disease, increase the incidence of postoperative infection and other complications, prolong the length of ICU and hospital stay, and increase mortality of the patients.

Even though there is a reasonable amount of literature available that reports the risk factors for PMV after cardiac surgery, few studies particularly focused on patients who underwent redo valve surgery [Trouillet 2009; Sharma 2017]. The aim of this study was to investigate the incidence, risk factors, and outcomes of PMV after redo valve surgery.

## MATERIALS AND METHODS

This study was conducted in accordance with the ethical standards of our hospital's IRB. Informed consent was not required because this observational study did not modify existing diagnostic or therapeutic strategies.

**Patient population and data:** We retrospectively analyzed a series of 118 consecutive adult patients, who underwent redo valve surgery at our institution between November 2017 and September 2021. One patient, who did not survive until the defined cut-off point of PMV, was excluded from the study. The remaining 117 patients composed the study population (control group:  $N = 72, 61.5\%$ ; PMV group:  $N = 45, 38.5\%$ ).

**Prolonged mechanical ventilation:** PMV was defined as the need for intubation and mechanical ventilation for >24 h, after completion of the operation. This includes both patients with early and persistent ventilatory dependency who were not extubated within the initial 24 h ( $N = 35, 78\%$ ) and those who had one or more unsuccessful extubation attempts ( $N = 10, 22\%$ ) eventually accumulating >24 h of endotracheal intubation and mechanical ventilation.

**ICU management:** At the end of the operation, patients were admitted directly to the cardiac surgery ICU. Initial hemodynamic management (adequate volume therapy,

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inotropes, and/or vasopressors) was tailored to patients' status and type of operation. Arterial blood pressure and central venous pressure continuously were monitored on a routine basis, a pulmonary artery catheter or pulse index continuous cardiac output (PiCCO) in the case of hemodynamic instability. The patients were ventilated by the synchronized intermittent mandatory ventilation mode with a tidal volume of 8 to 10 ml/kg predicted body weight. The fraction of inspired oxygen (FiO<sub>2</sub>) and respiratory rate adjustments were made according to routine blood-gas analyses to maintain partial pressure of arterial oxygen (PaO<sub>2</sub>) between 80 and 100 mmHg and partial pressure of arterial carbon between 35 and 40 mmHg. Postoperative sedation with remifentanyl and propofol was adjusted to achieve a sedation level at which the patient responds to gentle shaking, corresponding to a Ramsay sedation score of 4 or 3. Patients were tested for tracheal extubation when circulation was stable. Blood loss had to be less than 100 mL/h, with a trend toward decreased fluid drainage from chest drains. The decision to extubate a patient was made after a trial of spontaneous breathing or a trial under low-level pressure support. Before extubation, the patient had to be neurologically alert and oriented, able to move equally all four limbs, breathe spontaneously, and obey commands.

**Data collection:** Potential predictor variables for PMV were prespecified based on clinical judgment, literature review and availability in our hospital. The preoperative baseline characteristics included age, sex, body mass index, weight, NYHA classification of cardiac function, EuroSCORE II, echocardiography result, some laboratory data, cardiothoracic ratio, and preoperative complications.

Intraoperative factors included cardiopulmonary bypass time and aortic cross-clamp times, volume of blood transfusion, and types of surgery.

Postoperative factors included vasoactive-inotropic score (VIS) at 0 and 12 hours post-ICU admission and fluid balance on the first two days at ICU, other postoperative outcomes, namely, mechanical ventilation time, length of stay in ICU, length of stay in hospital, in-hospital mortality, the incidence of ventilator-associated pneumonia, and tracheostomy.

The VIS score was calculated as dopamine dose ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ) + dobutamine dose ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ) + 100  $\times$  epinephrine dose ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ) + 100  $\times$  norepinephrine dose ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ) + 10,000  $\times$  vasopressin dose (U  $\text{kg}^{-1} \text{ min}^{-1}$ ) + 10  $\times$  milrinone dose ( $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ).

Fluid balance (ml  $\text{kg}^{-1}$ ) was calculated: Fluid balance = [(amount of crystalloids + colloids + packed red cell + plasma + platelets + enteral nutrition) – (blood loss + urine output + gastrointestinal losses + drain losses + dialysis or ultrafiltrate)]/weight.

**Statistical analysis:** Descriptive statistics are expressed as median (25th percentile, 75th percentile) or the means  $\pm$  standard deviation (SD) for continuous variables and as n (%) for categorical variables. We used the Student t test or the Mann-Whitney U test, when the distribution was not normal, to compare continuous variables, and the  $\chi^2$  test or Fisher's exact test to compare percentages, as appropriate.

Univariable analysis was used to identify parameters associated with PMV. Thereafter, a Forward stepwise multivariable

logistic regression analysis was used to determine factors independently associated with PMV. Variables were entered into the model based on a univariable analysis significance threshold of  $P < 0.05$ . All continuous variables were transformed into categorical variables before the analysis. The cut-off was considered as the 50th percentile of the recorded values and clinically appropriate. Odds ratio and 95% confidence intervals were calculated. IBM SPSS 21.0 (SPSS Inc., Chicago, IL, USA) was used to analyze data.

Collinearity between variables was assessed by Pearson pairwise correlation coefficient and variance inflation factors (VIF) statistics;  $r > 0.7$  and  $\text{VIF} > 10$  are cut-off values for multicollinearity in the regression model. Consequently, the factors that indicated multicollinearity were removed from the model. The Hosmer-Lemeshow goodness-of-fit test was used to assess the validity of the regression model. The criterion for statistical significance was set at a value of  $P < 0.05$ .

## RESULTS

During the observation period, 118 redo valvular surgery patients were evaluated, of whom one was excluded because the patient died within 24 hours after the operation. The patients were divided into control group ( $N = 72$ , 61.5%) and PMV group ( $N = 45$ , 38.5%). The median extubation time was 20.0 hours, with a range of 5 to 471 hours. The distribution of extubation time had a highly skewed pattern and was illustrated in Figure 1. (Figure 1)

A number of perioperative factors were associated with PMV in univariate analysis. The preoperative risk factors were age, weight, NYHA class III–IV, EuroSCORE II, glomerular filtration rate (GFR), hemoglobin, and total bilirubin. (Table 1)

Intraoperative risk factors were cardiopulmonary bypass (CPB) time, aortic cross-clamp time, and blood transfusion. There was no difference in operation types between the two groups. (Table 2)

VIS at ICU admission (VIS0) and VIS at 12 hours post

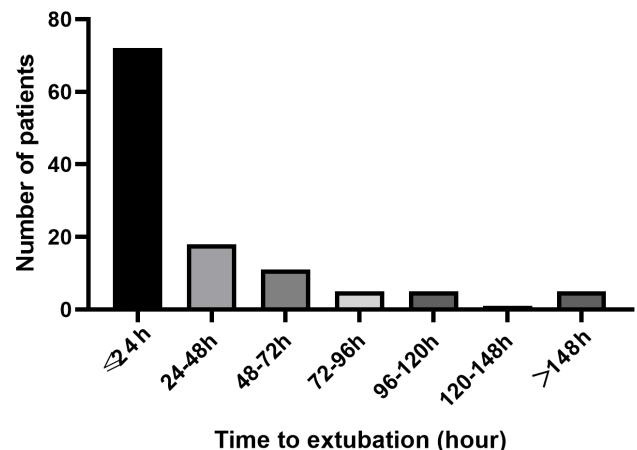


Figure 1. Graph illustrating the distribution of extubation time ( $N = 117$ ).

ICU admission (VIS12) were postoperative risk factors associated with PMV. Also, fluid balance in the first day was associated with PMV. (Table 3)

Eleven factors entered multivariate analysis, aortic cross clamp time and VIS0 were removed from the model because of multicollinearity. Multivariate analysis revealed advanced age (age>57 years), low weight (weight ≤58 kg), EuroSCORE II ≥6.8%, and VIS12>10 as independent risk factors for PMV following surgery. (Table 4) Calibration with the Hosmer-Lemeshow Test showed a good fit ( $\chi^2=8.298$ ,  $P=0.141$ ).

Postoperative outcomes are presented in Table 5. (Table 5) The median mechanical ventilation time was 18 hours in the control group. By contrast, it was 62 hours in the PMV group. The ICU and hospital LOS were significantly longer in the PMV group. The overall incidence of in-hospital mortality was 5.1% ( $N=6$ ), which was observed only in patients who had delayed extubation. Ventilator associated pneumonia (VAP) occurred in 11 patients. Tracheostomy was performed in four patients (8.9%). Among them, three were weaned from the ventilator and successfully extubated and survived

well. One older woman was transferred to another hospital and died after two months. The patients who needed renal replacement therapy were much more in the PMV group than in the control group.

## DISCUSSION

The present study investigated the incidence, risk factors, and outcomes of PMV after redo valve surgery. We found that advanced age, low weight, high EuroSCORE II, and high VIS12 were independent risk factors for PMV following surgery. There were several studies on risk factors of PMV after cardiac surgery before, however, most of them included heterogeneous groups of patients undergoing different cardiac or cardiovascular surgical procedures [Trouillet 2009; Sharma 2017; Murthy 2007; Bartz 2015]. Some of the studies focused on patients undergoing coronary artery bypass grafting (CABG) [Saleh 2012; Hsu 2019] or aortic dissection surgery [Maisat 2020; Miyashita 2021], and few studies were

Table 1. Preoperative factors for prolonged mechanical ventilation

Variables	All (N = 117)	Control (N = 72)	PMV (N = 45)	P-value
Age (y)	57 (49.0, 67.5)	54.5 (39.0, 63.0)	64 (56.0, 69.5)	<0.001
Male sex	53 (45.3)	35 (48.6)	18 (40.0)	0.363
BMI (kg/m <sup>2</sup> )	21.5±3.15	21.7±3.12	21.2±3.21	0.393
Weight	58.3±10.19	60.0±10.59	55.6±8.98	0.022
NYHA class III-IV	100 (85.5)	57 (79.2)	43 (95.6)	0.014
EuroSCORE II (%)	6.79 (4.41, 11.19)	5.57 (3.96, 8.99)	10.50 (6.46, 15.43)	<0.001
LVEF (%)	61.2±9.79	61.3±9.49	61.0±10.37	0.890
LAd	58 (51, 65.5)	58 (48, 66)	60 (53, 64.5)	0.282
LVEDD	5.12±0.96	5.16±0.94	5.07±0.99	0.606
Severe PH	42 (35.9)	23 (31.9)	19 (42.2)	0.260
Scr	78 (62.5, 97.0)	75 (60.0, 86.0)	81 (64.5, 122.0)	0.057
GFR	84.8 (60.1, 100.0)	88.9±21.83	69.6±25.30	<0.001
Hb	112.4±25.99	117.4±26.79	104.4±22.71	0.008
Serum albumin	40.0 (37.4, 42.2)	40.6 (38.4, 42.6)	39.0 (36.9, 41.4)	0.073
Total Bilirubin	20.9 (14.7, 34.7)	17.7 (12.9, 29.8)	23.9 (15.7, 40.1)	0.037
BNP	220.2 (94.1, 438.6)	177.3 (81.0, 341.9)	305.5 (114.4, 571.4)	0.072
CTR	0.63 (0.58, 0.71)	0.62 (0.58, 0.70)	0.63 (0.59, 0.76)	0.140
Preoperative Af or AF	91 (77.8)	52 (72.2)	39 (86.7)	0.067
COPD	4 (3.4)	2 (2.8)	2 (4.4)	0.638
Previous stroke or TIA	4 (3.4)	3 (4.2)	1 (2.2)	1.000
Diabetes mellitus	5 (4.3)	4 (5.6)	1 (2.2)	0.648

BMI, body mass index; NYHA, New York Heart Association; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; LAd, left atrial diameter; LVEDD, left ventricular end diastolic diameter; Severe PH, severe pulmonary hypertension, means pulmonary artery systolic pressure>55 mmHg; Scr, serum creatinine; GFR, glomerular filtration rate; Hb, hemoglobin; BNP, brain natriuretic peptide; CTR, cardiothoracic ratio; Af, atrial fibrillation; AF, atrial flutter; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack

Table 2. Intraoperative factors for prolonged mechanical ventilation

Variables	All (N = 117)	Control (N = 72)	PMV (N = 45)	P-value
CPB time (min)	185 (134.5, 230.5)	158.5 (122.5, 210.8)	212.0 (151.5, 277.5)	0.001
Aortic cross-clamp time	122 (89.5, 167.5)	114.5 (85.5, 152.3)	150 (102.5, 188.0)	0.005
Blood transfusion (ml)	1080 (600, 1869.5)	840 (540, 1595)	1360 (740, 2230)	0.012
Operations				
MVR	48 (41.0)	34 (47.2)	14 (31.1)	0.085
AVR	23 (19.7)	12 (16.7)	11 (24.4)	0.303
MVR + AVR	19 (16.2)	9 (12.5)	10 (22.2)	0.165
TVR	9 (7.7)	4 (5.6)	5 (11.1)	0.303
TVP	78 (66.7)	45 (62.5)	33 (73.3)	0.227
MVP	6 (5.1)	5 (6.9)	1 (2.2)	0.404
Repair of perivalvular leakage	13 (11.1)	8 (11.1)	5 (11.1)	1.000

CPB, cardiopulmonary bypass; MVR, mitral valve replacement; AVR, aortic valve replacement; TVR, tricuspid valve replacement; TVP, tricuspid valvuloplasty; MVP, mitral valvuloplasty

Table 3. Postoperative factors for prolonged mechanical ventilation

Variables	All (N = 117)	Control (N = 72)	PMV (N = 45)	P-value
VIS				
VIS0	9 (5, 16)	7 (5, 12)	14 (8, 21)	<0.001
VIS12	10 (8, 15.5)	8 (6, 11)	17 (10, 24)	<0.001
Fluid balance (ml/Kg)				
The first day	-11.6 (-21.8, -2.3)	-14.5(-23.5, -7.7)	-4.5(-12.6, 7.6)	<0.001
The second day	-15.5±16.13	-15.84±12.69	-14.96±20.63	0.798

VIS, Vasoactive-inotropic score; VIS0, Vasoactive-inotropic score at ICU admission; VIS12, Vasoactive-inotropic score at 12 hours post ICU admission

particular to reoperative cardiac surgery. To our knowledge, we are the first to evaluate it in adult patients undergoing redo valve surgery.

Prevalence of PMV after cardiovascular surgery varying from 3% to 22% [Murthy 2007]. This wide variability is in large part attributable to the discrepant definitions of PMV in the literature, which varies from 24 hours to 14 days [Bartz 2015; Legare 2001; Pappalardo 2004; Rajakaruna 2005]. In this study, we found that the incidence of PMV after redo valve surgery was 38.5%, which was much higher than common cardiac surgery. This mainly is because redo valve surgery was a complex procedure, with a higher rate of perioperative morbidity and mortality; another reason was 24 hours of cumulative intubation was used to define PMV. It has been demonstrated that early tracheal extubation is safe, cost beneficial, and can improve resource use in cardiac surgery. Fast-track cardiac anesthesia strives to achieve endotracheal extubation within 1 to 6 hours after cardiac surgery [Cheng 1998], and ultrafast-track extubation is defined as immediate

post-surgical weaning from mechanical ventilation and endotracheal extubation [Varghese 2016]. In our center, most surgery patients could be extubated within 24h after surgery, therefore, we thought that the definition of PMV we adopted was reasonable.

In this study, we found that advanced age was an independent risk factor of PMV. Advanced age is a marker of reduced physiological reserve and multiple comorbidities and has been consistently demonstrated to be a predictor of PMV [Murthy 2007; Saleh 2012; Legare 2001; Reddy 2007]. Except advanced age, low weight also was found to be an independent risk factor of PMV. The weight of patients in the PMV group was lower than the control group, the odds ratio of PMV in patients with weight lower than 58 kg was 2.798-fold of patients with weight higher than 58 kg. The probable reason is that low weight means slow recovery, and the strength of respiratory muscle was weak. Similarly, previous study showed low BMI is associated with higher incidence of severe complications and increased morbidity and mortality

Table 4. Multivariate analysis of perioperative factors for prolonged mechanical ventilation

Variables	Beta coefficient	Standard error	Odds ratio (95% confidence interval)	P-value
Age	1.113	0.487	3.043 (1.172-7.905)	0.022
Weight	1.029	0.482	2.798 (1.088-7.199)	0.033
EuroSCORE II	1.243	0.476	3.467 (1.364-8.817)	0.009
VIS12	1.725	0.475	5.613 (2.211-14.249)	<0.001
Constant	-3.237	0.639	0.039	<0.001

EuroSCORE, European System for Cardiac Operative Risk Evaluation; VIS12, Vasoactive-inotropic score at 12 hours post ICU admission

Table 5. Postoperative outcomes

Variables	All (N = 117)	Control (N = 72)	PMV (N = 45)	P-value
MV time (hour)	20 (18, 48)	18 (16, 20)	62 (44.5, 101.5)	<0.001
ICU LOS (day)	4 (2, 5)	3 (2, 4)	6 (4, 9)	<0.001
Hospital LOS (day)	19 (14, 26.5)	16.5 (13, 21)	25 (20, 35)	<0.001
In-hospital mortality	6 (5.1)	0 (0)	6 (13.3)	0.003
VAP	11 (9.4)	0 (0)	11 (24.4)	<0.001
Tracheostomy	4 (3.4)	0 (0)	4 (8.9)	0.020
CRRT	13 (11.1)	3 (4.2)	10 (22.2)	0.002

Data were presented as median (25th percentile, 75th percentile) or n (%). MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit; VAP, ventilator associated pneumonia; CRRT, continuous renal replacement therapy

after CABG [Perrotta 2007]. Increased BMI also is associated with a higher incidence of PMV, Saleh et al. found increased body mass index (BMI > 35 kg/m<sup>2</sup>) was an independent predictor of PMV [Saleh 2012]. However, there was no significant difference in BMI between the two groups in our study.

In this investigation, PMV also was associated with a higher EuroSCORE II, in line with previous reports [Filsoufi 2008; Fernandez-Zamora 2018]. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a cardiac risk model for predicting mortality after cardiac surgery. It was published in 1999 and derived from an international European database of patients who had undergone cardiac surgery by the end of 1995 [Nashef 2012]. Because cardiac surgery has substantially improved with a sustained reduction of risk-adjusted mortality, EuroSCORE II was then constructed and tested in 2012. Ad et al. reported that EuroSCORE II had better predictive discrimination for operative mortality than EuroSCORE I, which greatly overestimated this risk. EuroSCORE II also fared well compared with the STS risk score [Ad 2016]. Our results demonstrated that EuroSCORE II was an independent risk factor of PMV following redo valve surgery.

In this study, the most powerful risk factor was VIS at 12 hours post-ICU admission (VIS12). The patients with a higher VIS12 (VIS12 >10) had a more than five-fold odds with PMV occurring, compared with VIS12 ≤10. The VIS is calculated as a weighted sum of all administered inotropes

and vasoconstrictors, reflecting pharmacological support of the cardiovascular system [Gaies 2010]. Studies have shown that higher VIS predicts unfavorable outcomes, including morbidity and mortality, after cardiac surgery in pediatric and adult populations [Gaies 2010; Davidson 2012; Koponen 2019]. Our study showed that VIS12 also was an independent risk factor of PMV, which can be explained by the fact that higher VIS means the patient was hemodynamically unstable, therefore, needing prolonged mechanical ventilation.

Although most previous studies found low left ventricular ejection fraction (LVEF) to be a risk factor for PMV [Reddy 2007; Filsoufi 2008], this association was not found in the present study. In fact, the values of LVEF were similar in these two groups. Moreover, an advanced NYHA class, another potential indicator of poor ventricular function, was statistically a significant factor, as shown by univariate analysis but was not significant in multivariate analysis. Similarly, cardiopulmonary bypass time and blood transfusion were not independent risk factors for PMV in our study, contrary to previous study [Sharma 2017; Bartz 2015].

In our cohort, PMV was associated with significant longer ICU and hospital LOS, increased in-hospital mortality, higher incident of VAP, tracheostomy, and renal replacement therapy. Unlike VAP and tracheostomy, we do not regard higher incident of renal replacement therapy as the result of PMV. We suggested that PMV and renal replacement therapy

were both the results of hemodynamic instability in the perioperative period.

**Study limitations:** This study has several limitations. First, this was a single-center, retrospective observational study with a small sample size, and conclusions are limited in their application. Second, because of the lack of pulmonary function test results, such as FEV1, the preoperative respiratory function of patients all were taken from medical history, which were not accurate enough. Finally, clinical outcome analysis focused on postoperative mortality and morbidity, and we were not able to provide information on late complications, quality of life, and cause of death following discharge.

## CONCLUSIONS

In adult patients undergoing redo valve surgery, advanced age, low weight, a higher EuroSCORE II, and VIS at 12 hours post-ICU admission are associated with PMV. Hemodynamic status after operation were more important than preoperative and intraoperative variables in predicting PMV.

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