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REPORTS OF ORIGINAL INVESTIGATIONS

Prolonged mechanical ventilation after cardiac surgery: substudy of the Transfusion Requirements in Cardiac Surgery III trial

Ventilation mécanique prolongée après chirurgie cardiaque : étude auxiliaire de l'étude sur les besoins de transfusion en chirurgie cardiaque (TRICS III)

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Abstract

Purpose *Prolonged mechanical ventilation (MV) is a major complication following cardiac surgery. We conducted a secondary analysis of the Transfusion Requirements in Cardiac Surgery (TRICTS) III trial to describe MV duration, identify factors associated with prolonged MV, and examine associations of prolonged MV with mortality and complications.*

Methods *Four thousand, eight hundred and nine participants undergoing cardiac surgery at 71 hospitals worldwide were included. Prolonged MV was defined based on the Society of Thoracic Surgeons definition as MV lasting 24 hr or longer. Adjusted associations of patient and surgical factors with prolonged MV were examined using multivariable logistic regression. Associations of prolonged MV with complications were assessed using odds ratios, and adjusted associations between prolonged MV and mortality were evaluated using multinomial regression. Associations of shorter durations of MV with survival and complications were explored.*

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Results *Prolonged MV occurred in 15% (725/4,809) of participants. Prolonged MV was associated with surgical factors indicative of complexity, such as previous cardiac surgery, cardiopulmonary bypass duration, and separation attempts; and patient factors such as critical preoperative state, left ventricular impairment, renal failure, and pulmonary hypertension. Prolonged MV was associated with perioperative but not long-term complications. After risk adjustment, prolonged MV was associated with perioperative mortality; its association with long-term mortality among survivors was weaker. Shorter durations of MV were not associated with increased risk of mortality or complications.*

Conclusion *In this substudy of the TRICS III trial, prolonged MV was common after cardiac surgery and was associated with patient and surgical risk factors. Although prolonged MV showed strong associations with perioperative complications and mortality, it was not associated with long-term complications and had weaker association with long-term mortality among survivors.*

Study registration *www.ClinicalTrials.gov (NCT02042898); registered 23 January 2014. This is a substudy of the Transfusion Requirements in Cardiac Surgery (TRICS) III trial.*

Résumé

Objet *La ventilation mécanique (VM) prolongée est une complication majeure après chirurgie cardiaque. Nous avons effectué une analyze secondaire de l'étude TRICS III sur les besoins de transfusion au cours de la chirurgie cardiaque pour décrire la durée de la VM, identifier les facteurs associés à une VM prolongée et examiner les associations de la VM prolongée avec la mortalité et les complications.*

Méthodes *Quatre mille huit cent neuf participants subissant une chirurgie cardiaque dans 71 hôpitaux à travers le monde ont été inclus. La VM prolongée a été définie à partir de la définition de la Society of Thoracic Surgeons comme un événement durant 24 heures ou plus. Des associations ajustées de facteurs liés aux patients et à la chirurgie avec la VM prolongée ont été examinées en utilisant une régression logistique multifactorielle. Des associations de la VM prolongée avec des complications ont été évaluées en utilisant des rapports de cotes; les associations ajustées entre VM prolongée et mortalité ont été évaluées au moyen d'une régression multinominale. Les associations d'une VM de plus courte durée avec la survie et des complications ont été explorées.*

Résultats *La VM prolongée est survenue chez 15 % (725/4 809) des participants. Une VM prolongée a été associée à des facteurs chirurgicaux indicateurs de complexité (comme une chirurgie cardiaque antérieure, la durée de la circulation extracorporelle et les tentatives de débranchement) et à des facteurs liés au patient (comme un état préopératoire critique, une défaillance ventriculaire gauche, une insuffisance rénale et une hypertension pulmonaire). La VM prolongée a été associée à des complications périopératoires, mais pas à des complications à long terme. Après ajustement pour le risque, la VM prolongée a été associée à la mortalité périopératoire; son association avec la mortalité à long terme des survivants a été plus faible. Les durées plus courtes de VM n'ont pas été associées à une augmentation du risque de mortalité ou à des complications.*

Conclusion *Dans cette étude auxiliaire de l'essai TRICS III, la VM prolongée a été fréquente après chirurgie cardiaque et a été associée à des facteurs de risque liés au patient et à la chirurgie. Bien que la VM prolongée ait présenté de fortes associations avec les complications périopératoires et la mortalité, elle n'a pas été associée avec des complications à long terme et était plus faiblement associée à la mortalité à long terme parmi les survivants.*

Enregistrement de l'étude *www.ClinicalTrials.gov (NCT02042898); enregistrée le 23 janvier 2014. Il s'agit d'une étude auxiliaire de l'étude TRICS III sur les besoins de transfusion en chirurgie cardiaque.*

Keywords Critical care · Critical care outcomes · Mechanical · Postoperative complications · Pulmonary medicine · Thoracic surgery · Ventilators

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Prolonged mechanical ventilation (MV) is a major complication following cardiac surgery and has previously been linked to increased mortality, diminished quality of life, and significant economic burden.[1–4] The most recent guidelines from the Society of Thoracic Surgeons (STS) consider duration of MV longer than 24 hr as a major morbidity end-point following cardiac surgery.[5] Mechanical ventilation longer than 24 hr is endorsed by the National Quality Foundation and was selected by the STS as a quality measure since it is associated with higher mortality and is an independent predictor for readmission to the intensive-care unit (ICU), and since shorter ventilation times are linked to high quality of care.[6] The incidence of prolonged MV following cardiac surgery in previous studies has ranged from 2.6 to 22.7%,[1–4,7–14] with the definition of prolonged MV ranging from 24 hr to 14 days. These studies proposed a variety of perioperative risk factors for prolonged MV, including type of cardiac surgery and duration of cardiopulmonary bypass.[3,4,8–11,13,14]

The existing literature has significant shortcomings. Several studies included patients treated more than one decade ago and may no longer reflect contemporary perioperative practice.[1,2,8,10] Furthermore, most prior studies involved cohorts from a single institution, which limits generalizability.[1,2,8–10,14] In addition, outcome definitions for prolonged MV were heterogeneous across studies.[1–4,8–14] A contemporary study examining MV following cardiac surgery would inform risk discussions, enhance patient–physician communication, and provide insight into the long-term recovery of cardiac surgery patients. Identifying risk factors for prolonged MV will further enable study into strategies that promote liberation from MV in high-risk patients.

In view of these limitations, we conducted this substudy of the Transfusion Requirements in Cardiac Surgery (TRICS) III trial, a randomized controlled trial of moderate and high-risk patients undergoing cardiac surgery with cardiopulmonary bypass where a restrictive approach to red-cell transfusion was non-inferior to a liberal approach.[15,16] In this substudy, we sought to describe contemporary MV practices following cardiac surgery; identify preoperative patient factors and intraoperative surgical factors associated with prolonged postoperative MV; examine associations of prolonged MV with postoperative and long-term complications; and assess long-term survival of patients requiring prolonged MV after cardiac surgery. Given the substantial interest in cardiac fast-track programs that prioritize early extubation,[17,18] we also explored associations of shorter durations of MV with mortality and complications.

Methods

The Transfusion Requirements in Cardiac Surgery (TRICS) III study was registered at ClinicalTrials.gov (NCT02042898; principal investigators, C. D. M, N. S.; date of registration, 23 January 2014). The trial protocol was approved by appropriate institutional ethics committees (St. Michael's Hospital Research Board, protocol #13-295), and participating patients provided written informed consent prior to enrollment. Protocol details and trial results, including details on participating sites, have previously been published.[15,16,19] In brief, TRICS III was an international, open-label, randomized, controlled, non-inferiority trial comparing restrictive and liberal red-cell transfusion strategies among adults aged 18 yr or older at moderate-to-high predicted risk of death undergoing cardiac surgery with cardiopulmonary bypass. Patients were allocated in a 1:1 ratio to either restrictive (to receive red-cell transfusion if their hemoglobin concentration was less than 7.5 $g \cdot dL^{-1}$ intraoperatively or postoperatively) or liberal (to receive red-cell transfusion if their hemoglobin concentration was less than 9.5 $g \cdot dL^{-1}$ intraoperatively or postoperatively in the ICU, or less than 8.5 $g \cdot dL^{-1}$ in the non-ICU ward) strategies. Outcome adjudicators were unaware of treatment allocation. All other aspects of the patients care, including management of MV, were left to the discretion of the attending clinicians.

Inclusion and exclusion criteria

Patients meeting TRICS III inclusion and exclusion criteria who subsequently underwent surgery were included in this substudy. Patients who died within 24 hr of surgery were excluded, as they were ineligible to meet prolonged MV criteria (Electronic Supplementary Material eFigure).

Outcomes

The primary outcome for this substudy was the duration of MV, calculated as the time from the end of index surgery to extubation. Among patients who were not extubated, the duration of MV was defined as the time from the end of surgery to the time when the patient began unsupported spontaneous breathing that lasted for at least 48 hr with no pressure support, continuous positive airway pressure, or positive end-expiratory pressure. If patients were reintubated, the time from reintubation to subsequent extubation was added to generate the cumulative duration of MV.

Perioperative complications were assessed within 30 days of surgery and included myocardial infarction, new renal failure, new focal neurologic deficits, infection, gut infarction, acute kidney injury, seizures, encephalopathy, and delirium. Patients were contacted by the study team for long-term follow-up at six months following surgery. The date of surgery and the date of final follow-up were collected. At final follow-up, outcomes of interest included mortality (including date of death), any rehospitalization following index surgery, any emergency room visit following index surgery, myocardial infarction, stroke, any revascularization procedure, or new onset of dialysis.

Measurements

Preoperative demographic characteristics, surgical history, cardiac status and function, comorbidities, and medications were recorded, as were operative characteristics including type of surgery, emergency status, and duration of cardiopulmonary bypass. Patients were defined as being in a *critical preoperative state* if they required preoperative MV, preoperative cardiac massage, preoperative ionotropic support, or intra-aortic balloon counter-pulsation; if they had preoperative acute renal failure (anuria or oliguria < 10 mL·h^{-1}); or if they had ventricular tachycardia or fibrillation. Patients were followed prospectively, and clinical outcomes were assessed by blinded outcome adjudicators at either hospital discharge or on postoperative day 28.

Predictors of prolonged mechanical ventilation

The following predictors were evaluated based on clinical sensibility.[2,4,7,10,11,13,20] Preoperative factors included: age, sex, body mass index (BMI), transfusion strategy, previous cardiac surgery, critical preoperative state, recent myocardial infarction, left ventricular function, diabetes, hypertension, chronic lung disease, renal function, and pulmonary hypertension. Intraoperative factors included: type of surgery, surgical urgency, duration of cardiopulmonary bypass, and separation attempts from cardiopulmonary bypass.

Analyses

We used descriptive statistics to characterize the cohort. Categorical variables are described using counts and frequencies, and continuous variables are described using means with standard deviations (SDs) or medians with interquartile ranges [IQRs].

Duration of MV is described based on plots of its distribution (in hours) using a histogram and appropriate summary statistics. We calculated the incidence of prolonged MV based on the STS definition of cumulative MV of 24 hr or longer.[5,21,22] We also calculated the incidence of prolonged MV using a cumulative MV threshold of 48 hr.

We examined the association of pre- and intraoperative patient and surgical factors with prolonged MV, based on the STS definition of MV longer than 24 hr, in unadjusted analyses using frequency tables, odds ratios (ORs), and the Chi square statistic. We created a multivariable logistic regression to examine the adjusted association of pre- and intraoperative factors with prolonged MV. Model covariates were chosen *a priori* based on previous literature and clinical sensibility.[2,4,7,10,11,13,20] We assessed multicollinearity between predictor variables using the variance inflation factor (VIF); no predictor variables showed collinearity based on a VIF threshold of 2.5. Potential non-linear relationships between continuous variables and outcomes were explored using four-knot restricted cubic splines; all observed relationships were linear based on a likelihood ratio test and splines were not required. Adjusted estimates of association are reported as ORs with associated 95% confidence intervals (CIs). To quantify optimism and address over-fitting, the adjusted model was internally validated using bootstrap resampling. The optimism-corrected C index was derived from 1,000 bootstrap resamples of the original study. Model calibration was assessed by plotting fitted *vs* observed likelihoods of events among 1,000 bootstrap samples. Underlying model assumptions were verified.

The association of prolonged MV with postoperative and long-term complications among survivors was examined using unadjusted ORs and the Chi square statistic.

We assessed the association of MV status with mortality by computing time to death from the date of index surgery with censoring at the time of final follow-up. We generated Kaplan–Meier curves and used the log-rank test to determine whether survival differed based on prolonged MV status. We performed multivariable regression to evaluate associations of prolonged MV status with mortality accounting for the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, a validated predictor of in-hospital mortality risk after major cardiac surgery.[23] Cox proportional hazards modeling was attempted, but the proportional hazards assumption was violated. Subsequent attempts to generate parametric survival models with log-normal and log-logistic distributions did not show adequate fit. Ultimately, a multinomial regression model was developed with three end-points assigned: alive at long-term follow-up, perioperative mortality (within 30 days of index surgery), and long-term mortality (death between postoperative day 30 and time of follow-up). Adjusted estimates of association were reported as adjusted ORs with associated 95% CIs.

Among patients who did not experience prolonged MV, associations between shorter durations of MV with survival and complications were explored. Durations of MV were categorized based on clinical sensibility into 0–6 hr, 6–12 hr, and 12–24 hr. Kaplan–Meier curves were generated to plot survival by duration of MV. Associations of duration of MV with postoperative and long-term complications were examined using the Chi square statistic. Occurrence of reintubation, ICU length-of-stay, and hospital length-of-stay are also reported by duration of MV.

Statistical analyses were performed using the R statistical package, version 3.2.4 (R Core Team [2016], www.r-project.org) with the "hmisc," "rms," "lubridate," "tidyverse," "survminer," "nnet," and "pmsampsize" packages.

Power

For a logistic regression model predicting prolonged MV with 25 parameters, assuming an outcome incidence of 12.5% and a c-statistic of 0.7, a sample size of 3,878 with 485 outcome events would be sufficiently powered to conduct this analysis.

Missing data

There was minimal missing data in the cohort (< 1% overall; with n = 3 [0%] observations missing at 30 days and n = 32 [1%] missing at six months). Survival analyses censored patients at the time of last contact; their final status (alive *vs* dead) was determined at last contact.

Results

This analysis included 4,809 patients, whose characteristics are presented in Table 1. The mean age of patients was 72 yr, 65% of patients were male, and the mean BMI was 28 kg·m^{-2}. Fifty-one percent of patients were assigned to the restrictive transfusion strategy and 49% to the liberal transfusion strategy. Common comorbidities included treated hypertension (74%), moderate renal impairment (46%), and diabetes mellitus (27%). Patients underwent a range of surgical procedures, including isolated valve surgery (29%) and isolated coronary artery bypass graft (coronary artery bypass grafting; 26%). The mean duration of cardiopulmonary bypass was 121 min; most patients required a single attempt to separate from cardiopulmonary bypass.

The median [IQR] duration of MV was 8.9 [5.2–17.7] hr. A histogram of duration of MV is presented in Fig. 1. About 15% (725/4,809) received MV for longer than 24 hr, while 9% (430/4,809) required MV for longer than 48 hr.

Unadjusted associations of prolonged MV status with preoperative and intraoperative factors are also presented in Table 1. Patient factors associated with prolonged MV included age, restrictive transfusion strategy, previous cardiac surgery, diminished left ventricular function, critical preoperative state, impaired renal function, and pulmonary hypertension. Prolonged MV was associated with certain types of surgery, longer duration of cardiopulmonary bypass, greater cardiopulmonary bypass separation attempts, and return to the operating room after index surgery.

Adjusted associations of prolonged MV status with preoperative characteristics and intraoperative factors are presented in Table 2. The following factors were associated with prolonged MV following risk adjustment: previous cardiac surgery, impaired left ventricular function, critical preoperative state, impaired renal function, and pulmonary hypertension. Duration of cardiopulmonary bypass, and cardiopulmonary bypass separation attempts were also associated with prolonged MV. The model was well calibrated and did not show evidence of meaningful overfitting, with an optimism-corrected c-statistic of 0.712.

Prolonged MV was associated with increased odds of various postoperative complications (Table 3). The most frequent postoperative complications were acute kidney injury, delirium, infection, and myocardial infarction. Among survivors, there was limited evidence of association of prolonged MV with long-term complications such as hospitalization following index surgery, emergency visit since index surgery, myocardial infarction, stroke, revascularization procedure, or dialysis.

Prolonged MV was associated with lower odds of survival following surgery (log-rank test, $P < 0.001$). Kaplan–Meier curves illustrating the unadjusted association of prolonged MV with survival are presented in Fig. 2. The survival probability at six months was 81% for the prolonged MV group, compared with 97% for the routine MV group.

Multivariable analysis using multinomial regression modeling was performed to evaluate the adjusted association between prolonged MV with mortality while adjusting for the EuroSCORE II (Table 3). After adjustment, prolonged MV was strongly associated with increased odds of perioperative mortality within 30 days (adjusted odds ratio [aOR], 16.0; 95% CI, 10.9 to 23.6); among perioperative survivors, it was also associated with increased odds of long-term mortality at six months (aOR, 2.2; 95% CI, 1.4 to 3.4).

Among patients who did not experience prolonged MV, shorter duration of MV (< six hours) was not associated with increased risk of mortality (Fig. 3) and perioperative or long-term complications including reintubation, ICU length-of-stay, or hospital length-of-stay (Table 4).

Table 1 Sample description with unadjusted associations of pre- and intraoperative factors by mechanical ventilation status

Characteristic	Routine MV *N* = 4,084	Prolonged MV *N* = 725	*P* value
Patient factors			
Age (yr), mean (SD)	73 (10)	71 (11)	0.001
Male sex, *n*/total *N* (%)	2,617/4,084 (64%)	490/725 (68%)	0.07
Body mass index ($kg\cdot m^{-2}$), mean (SD)	28 (5)	28 (6)	0.10
Transfusion strategy, *n*/total *N* (%)	2,018/4,084 (49%)	396/725 (55%)	0.01
Restrictive			
Liberal	2,066/4,084 (51%)	329/725 (45%)	
Previous cardiac surgery, *n*/total *N* (%)	447/4,084 (11%)	145/725 (20%)	< 0.001
Recent myocardial infarction, *n*/total *N* (%)	974/4,084 (24%)	171/725 (24%)	0.92
Left ventricular function, *n*/total *N* (%)*			< 0.001
Good	2,600/4,084 (64%)	388/725 (54%)	
Moderately reduced	1,163/4,084 (29%)	252/725 (35%)	
Poor	250/4,084 (6%)	67/725 (9%)	
Very poor	70/4,084 (2%)	17/725 (2%)	
Critical preoperative state, *n*/total *N* (%)	138/4,084 (3%)	57/725 (8%)	< 0.001
Preoperative mechanical ventilation, *n*/total *N* (%)	5/4,084 (0%)	4/725 (1%)	0.03
Diabetes mellitus, *n*/total *N* (%)	1100/4084 (27%)	216/725 (30%)	0.12
Treated hypertension, *n*/total *N* (%)	3,004/4,084 (74%)	551/725 (76%)	0.18
Chronic lung disease, *n*/total *N* (%)	635/4,084 (16%)	118/725 (16%)	0.65
Renal function, *n*/total *N* (%)†			< 0.001
Normal	1,537/4,084 (38%)	224/725 (31%)	
Moderate impairment	1,883/4,084 (46%)	328/725 (45%)	
Severe impairment	619/4,084 (15%)	154/725 (21%)	
Use of dialysis	43/4,084 (1%)	19/725 (3%)	
Pulmonary hypertension, *n*/total *N* (%)‡			< 0.001
Moderate	623/4,084 (15%)	168/725 (23%)	
Severe	268/4,084 (7%)	85/725 (12%)	
Operative factors			
Type of surgery, *n*/total *N* (%)			< 0.001
Isolated CABG	1,104/4,084 (27%)	143/725 (20%)	
Isolated valve surgery	1,226/4,084 (30%)	188/725 (26%)	
CABG + valve surgery	947/4,084 (23%)	237/725 (33%)	
CABG + non-valve surgery	120/4,084 (3%)	23/725 (3%)	
Valve + non-CABG surgery	566/4,084 (14%)	114/725 (16%)	
Other non-CABG non-valve surgery	121/4,084 (3%)	20/725 (3%)	
Surgical urgency, *n*/total *N* (%)			0.06
Emergency	2,902/4,084 (71%)	488/725 (67%)	
Urgent	1138/4,084 (28%)	232/725 (32%)	
Elective	44/4,084 (1%)	5/725 (1%)	
Duration of cardiopulmonary bypass, mean (SD)	115 (49)	153 (82)	< 0.001
Cardiopulmonary bypass separation attempts, *n*/total *N* (%)			< 0.001
1	3,849/4,084 (95%)	599/725 (83%)	
2	197/4,084 (5%)	93/725 (13%)	
3+	24/4,084 (1%)	31 (4%)	

Table 1 continued

Characteristic	Routine MV*N* = 4,084	Prolonged MV*N* = 725	*P* value
Return to operating room, *n*/total *N* (%)	257/4,084 (6%)	253 (35%)	< 0.001

* Left ventricular function was defined according to the following categories: good (left ventricular ejection fraction, ≥ 51%), moderately reduced (31–50%), poor (21–30%), and very poor (≤ 20%).

† Renal function was defined according to the following categories: normal (creatinine clearance, > 85 mL·min^{-1}), moderately impaired (50–85 mL·min^{-1}), severely impaired (< 50 mL·min^{-1}), and use of dialysis (regardless of creatinine clearance).

‡ Pulmonary hypertension was defined according to the following categories: moderate (pulmonary artery systolic pressure 31–55 mm Hg) and severe (pulmonary artery systolic pressure > 55 mm Hg).

CABG = coronary artery bypass grafting; MV = mechanical ventilation; SD = standard deviation

Discussion

Among moderate- to high-risk patients who underwent a range of cardiac surgery procedures across 71 study sites, this study found that prolonged MV was common, occurring in 15% of patients. While prolonged MV was associated with a restrictive transfusion strategy in unadjusted analyses, the magnitude of this association diminished with risk adjustment. Risk-adjusted predictors of prolonged MV included surgical factors such as previous cardiac surgery, duration of cardiopulmonary bypass, and number of separation attempts; and patient factors such as critical preoperative state, impaired left ventricular function, renal impairment, and pulmonary hypertension. Prolonged MV was associated with perioperative morbidity and mortality; its association with long-term mortality at six months was diminished and it was not associated with long-term complications among survivors. Among patients not experiencing prolonged MV, shorter durations of MV (six hours or less) were not associated with increased risk of mortality or either postoperative or long-term complications compared with longer durations.

In our study, surgical factors associated with prolonged MV in risk-adjusted analyses included difficulty separating from cardiopulmonary bypass, previous cardiac surgery, and duration of bypass. Difficulty separating from cardiopulmonary bypass was associated with two times the odds of prolonged MV for two separation attempts, and more than four times the odds of prolonged MV with three or more attempts. Separation from cardiopulmonary bypass is affected by ventricular function, hypovolemia, vasoplegia, and surgical complications.[24,25] These each require expedient management and can be associated with significant end-organ dysfunction, including cardiorespiratory complications requiring MV. Difficulty separating from bypass has been independently associated with mortality and adverse outcomes following cardiac surgery in prior research; our study affirms its importance.[24] Previous cardiac surgery (1.5 times increase in odds) and duration of cardiopulmonary bypass (9% increase in odds per ten-minute increase in duration) were also associated with prolonged MV. These factors have been previously described, and likely point to increased surgical complexity.[5,11,12] Cardiopulmonary bypass itself is associated with profound physiologic changes, including initiation of systemic inflammatory responses and increased capillary permeability, which may contribute to pulmonary edema and prolonged ventilation.[26–28]

Certain patient factors showed associations with prolonged MV after risk adjustment. Patients in a critical preoperative state had a greater than two times increase in odds of prolonged MV, as they likely required time-sensitive operations with limited opportunity for optimization. The presence of comorbid conditions including impaired left ventricular function (up to 1.8 times increase in odds), renal impairment (2.5 times increase in odds for those on dialysis) and pulmonary hypertension (up to two times increase in odds) were also associated with prolonged MV. Patients with these comorbidities have increased risk of severe cardiac dysfunction[29,30] and limited physiologic reserve;[31,32] they may therefore be prone to postoperative complications contributing to prolonged MV. Very poor left ventricular function did not exhibit a strong statistical association with prolonged MV; this was likely related to its infrequent occurrence in our cohort. Finally, the restrictive transfusion strategy was associated with increased odds of prolonged MV. This may have been related to the unblinded nature of the study, with clinicians choosing to delay extubation in more anemic patients. Further research is also needed to potentially investigate whether volume status management using crystalloids *vs* colloids affected heart–lung interactions and risk of prolonged MV.

Though the incidence and risk factors for prolonged MV following cardiac surgery have been previously examined, there is a relative paucity of evidence examining the postoperative trajectory of patients requiring prolonged

Table 2 Adjusted associations of preoperative and intraoperative factors with prolonged mechanical ventilation

Factor	Adjusted odds ratio (95% CI)	*P* value
Age (yr) per 10-year increase	1.02 (0.92 to 1.13)	0.68
Male sex	1.06 (0.88 to 1.28)	0.51
Body mass index, per 5-kg·m^{-2} increase	0.96 (0.88 to 1.04)	0.29
Transfusion strategy		0.01
Restrictive	1.23 (1.04 to 1.46)	
Liberal	Reference	
Previous cardiac surgery	1.56 (1.22 to 2.00)	0.001
Recent myocardial infarction	1.18 (0.92 to 1.52)	0.19
Left ventricular function*		0.001
Good	Reference	
Moderately reduced	1.37 (1.13 to 1.66)	
Poor	1.82 (1.31 to 2.52)	
Very poor	1.54 (0.85 to 2.79)	
Critical preoperative state	2.18 (1.51 to 3.16)	< 0.001
Diabetes mellitus	1.17 (0.96 to 1.43)	0.11
Treated hypertension	1.22 (0.99 to 1.50)	0.07
Chronic lung disease	1.13 (0.90 to 1.43)	0.29
Renal function†		< 0.001
Normal	Reference	
Moderate impairment	1.32 (1.08 to 1.62)	
Severe impairment	1.79 (1.37 to 2.32)	
Use of dialysis	2.43 (1.32 to 4.50)	
Pulmonary hypertension‡		< 0.001
Moderate	1.78 (1.44 to 2.21)	
Severe	1.97 (1.47 to 2.65)	
Type of surgery		0.56
Isolated CABG	Reference	
Isolated valve surgery	1.12 (0.82 to 1.51)	
CABG + valve surgery	1.28 (0.97 to 1.69)	
CABG + non-valve surgery	1.16 (0.69 to 1.95)	
Valve + non-CABG surgery	1.10 (0.78 to 1.55)	
Other non-CABG non-valve surgery	0.99 (0.55 to 1.78)	
Surgical urgency		0.52
Elective	Reference	
Urgent	0.98 (0.80 to 1.19)	
Emergency	0.52 (0.18 to 1.58)	
Duration of cardiopulmonary bypass, per 10-minute increase	1.09 (1.07 to 1.11)	< 0.001
Cardiopulmonary bypass separation attempts		< 0.001
1	Reference	
2	2.02 (1.51 to 2.70)	
3+	4.43 (2.45 to 8.02)	

Optimism-corrected c-statistic = 0.712

* Left ventricular function was defined according to the following categories: good (left ventricular ejection fraction, ≥ 51%), moderately reduced (31–50%), poor (21–30%), and very poor (≤ 20%).

† Renal function was defined according to the following categories: normal (creatinine clearance, > 85 mL·min^{-1}), moderately impaired (50–85 mL·min^{-1}), severely impaired (< 50 mL·min^{-1}), and use of dialysis (regardless of creatinine clearance).

‡ Pulmonary hypertension was defined according to the following categories: moderate (pulmonary artery systolic pressure 31–55 mm Hg) and severe (pulmonary artery systolic pressure > 55 mm Hg).

CABG = coronary artery bypass grafting; CI = confidence interval

Table 3 Unadjusted associations (*upper panel*) of prolonged mechanical ventilation status with postoperative (30-day) and long-term (six-month) complications. Adjusted association (*lower panel*) of prolonged mechanical ventilation status (exposure) with long-term status (alive, postoperative mortality, long-term mortality) adjusting for the EuroSCORE II

Unadjusted associations Outcome	Routine MV *N* = 4,084	Prolonged MV *N* = 725	Odds ratio (95% CI)
Postoperative complications, *n*/total *N* (%)			
Death	38/4,084 (1%)	101/725 (14%)	17.2 (11.8 to 25.5)
Myocardial infarction	193/4,084 (5%)	61/725 (8%)	1.9 (1.4 to 2.5)
Infection	83/4,084 (2%)	154/725 (21%)	13.0 (9.8 to 17.3)
Acute kidney injury	1,219/4,084 (30%)	434/725 (60%)	3.5 (3.0 to 4.1)
Gut infarction	3/4,084 (0%)	14/725 (2%)	25.7 (8.3 to 116.7)
Focal neurologic deficit	46/4,084 (1%)	46/725 (6%)	6.0 (3.9 to 9.0)
Seizures	37/4,084 (1%)	56/725 (8%)	9.1 (6.0 to 14.1)
Delirium	389/4,084 (10%)	216/725 (30%)	4.0 (3.3 to 4.9)
Encephalopathy	10/4,084 (0%)	21/725 (3%)	12.0 (5.8 to 27.0)
Long-term complications, *n*/total *N* (%)	Routine MV *N* = 3,924	Prolonged MV *N* = 610	Odds ratio (95% CI)
Death	82/3,924 (2%)	31/610 (5%)	2.5 (1.6 to 3.8)
Hospitalization since index surgery	985/3,924 (25%)	166/610 (28%)	1.1 (0.9 to 1.4)
Emergency room visit since index surgery	1,038/3,924 (27%)	170/610 (28%)	1.1 (0.9 to 1.3)
Myocardial infarction	37/3,924 (1%)	6/610 (1%)	1.1 (0.4 to 2.4)
Stroke	58/3,924 (2%)	11/610 (2%)	1.3 (0.6 to 2.3)
Revascularization procedure	33/3,924 (1%)	3/610 (1%)	0.6 (0.1 to 1.7)
Dialysis	45/3,924 (1%)	11/610 (2%)	1.6 (0.8 to 3.0)

Adjusted association Outcome	Routine MV	Prolonged MV - Adjusted odds ratio (95% CI)
Postoperative mortality	Ref	16.0 (10.9 to 23.6)
Long-term mortality	Ref	2.2 (1.4 to 3.4)

CI = confidence interval; MV = mechanical ventilation

MV. One study of three centers in Spain identified multiple organ failure and sepsis as important causes of death in patients requiring prolonged MV.[3] An American retrospective study from a statewide consortium identified factors, such as requirement for extracorporeal support, that were associated with mortality among patients requiring prolonged MV.[33] In our study, prolonged MV was associated with all examined perioperative complications. Further, prolonged MV showed strong associations with mortality within 30 days after surgery, despite adjustment using a validated risk index predicting mortality following cardiac surgery.

Prolonged MV showed strong associations with postoperative complications, the most frequent of which were acute kidney injury, delirium, myocardial infarction, and infection. After adjustment for the EuroSCORE II, prolonged MV was strongly associated with mortality within 30 days following surgery. These findings support the use of this metric as a quality measure by the STS. Among survivors, there was limited evidence of association between prolonged MV and long-term complications assessed at six months. To our knowledge, long-term outcomes among patients requiring prolonged MV following cardiac surgery have not previously been explored. Survivors of the perioperative period in this study were at no increased risk of complications at six months. Following risk adjustment, the magnitude of association between prolonged MV and long-term mortality was not as high as its association with perioperative mortality.

In our study, 30-day mortality for cardiac surgery patients with prolonged MV was 14%, compared with 1% for patients without prolonged MV. A prospective study in

Table 4 Exploratory associations of duration of intubation with postoperative complications among patients ventilated < 24 hr

Outcome	0–6 hours	6–12 hours	12–24 hours	*P* value*
Postoperative complications, *n*/total *N* (%)				
Death	16/1,569 (1%)	10/1,456 (1%)	12/1,059 (1%)	0.46
Myocardial infarction	68/1,569 (4%)	65/1,456 (4%)	60/1,059 (6%)	0.24
Infection	19/1,569 (1%)	28/1,456 (2%)	36/1,059 (3%)	< 0.001
Acute kidney injury	453/1,569 (29%)	387/1,456 (27%)	379/1,059 (36%)	< 0.001
Gut infarction	1/1,569 (0%)	0/1,456 (0%)	2/1,059 (0%)	0.27
Focal neurologic deficit	9/1,569 (1%)	14/1,456 (1%)	23/1,059 (2%)	< 0.001
Seizures	7/1,569 (0%)	10/1,456 (1%)	20/1,059 (2%)	< 0.001
Delirium	141/1,569 (9%)	135/1,456 (9%)	113/1,059 (11%)	0.33
Encephalopathy	2/1,569 (0%)	2/1,456 (0%)	6/1,059 (1%)	0.07
Reintubation	3/1,569 (0%)	8/1,456 (1%)	19/1,059 (2%)	< 0.001
ICU length-of-stay (days), median [IQR]	1 [1–3]	1 [1, 2]	3 [2–4]	< 0.001
Hospital length-of-stay (days), median [IQR]	8 [6–10]	8 [7–10]	9 [7–13]	< 0.001
Long-term complications, *n*/total *N* (%)				
Death	22/1,511 (1%)	30/1,399 (2%)	30/1,013 (3%)	0.03
Hospitalization since index surgery	365/1,511 (24%)	341/1,399 (24%)	279/1,013 (28%)	0.11
Emergency room visit since index surgery	403/1,511 (27%)	354/1,399 (25%)	281/1,013 (28%)	0.37
Myocardial infarction	21/1,511 (1%)	6/1,399 (0%)	10/1,013 (1%)	0.027
Stroke	21/1,511 (1%)	25/1,399 (2%)	12/1,013 (1%)	0.45
Revascularization procedure	17/1,511 (1%)	10/1,399 (1%)	6/1,013 (1%)	0.29
Dialysis	11/1,511 (1%)	15/1,399 (1%)	19/1,013 (2%)	0.03

*The 0–6-hr, 6–12-hr, and 12–24-hr groups were compared for each complication using a Chi square test; for ICU and hospital length-of-stay, the forestated groups were compared using the Kruskal–Wallis test

ICU = intensive-care unit; IQR = interquartile range

361 ICUs in 20 countries found that ICU mortality for all adults receiving MV for 12 hr or more was 31%.[34] A systematic review including 57,420 adult patients with COVID-19 who received any MV found an estimated case fatality rate of 45%.[35] This information is informative to practitioners and will reassure patients and their families that prolonged MV following cardiac surgery does not portend as dire a prognosis as MV in the context of other systemic critical illness.

Shorter durations of MV (six hours or less), as targeted in fast-track programs, were not associated with increased risk of mortality, postoperative or long-term complications including reintubation, ICU length-of-stay or hospital length-of-stay. There is increasing interest in fast-track cardiac care that prioritizes early extubation after surgery as a means of reducing time in the ICU and associated hospital costs.[17,18] Given the paucity of intensive-care resources during the ongoing pandemic, these concerns are heightened. Our work adds to a growing body of evidence suggesting that early extubation is not associated with increased mortality or complications, and can be safely conducted in selected patients. Within the limitations of our study design, we are unable to comment on improved outcomes in these patients.

Early extubation has been used as a measure of successful implementation of enhanced recovery after surgery programs and fast-track extubation protocols.[36,37] Some studies have shown that fast-track protocols can be safely used to decrease time to extubation, even in high-risk patients.[37] Nevertheless, studies have failed to consistently show that a benchmark of six hours to extubation improves patient outcomes. While some previous work showed that an early extubation protocol can reduce ventilator time without reducing ICU or hospital length-of-stay,[38] patients who are selected for fast-track extubation may be those with fewer comorbidities and a lower degree of surgical complexity.[39] Early extubation may thus be a marker of appropriate progression of care in well-selected patients.[40] In contrast, prolonged MV is a marker of a complicated perioperative course portending greater morbidity and mortality, as shown by our results.

This work has important clinical implications. The frequency of prolonged MV is an important part of preoperative discussions with patients who are candidates

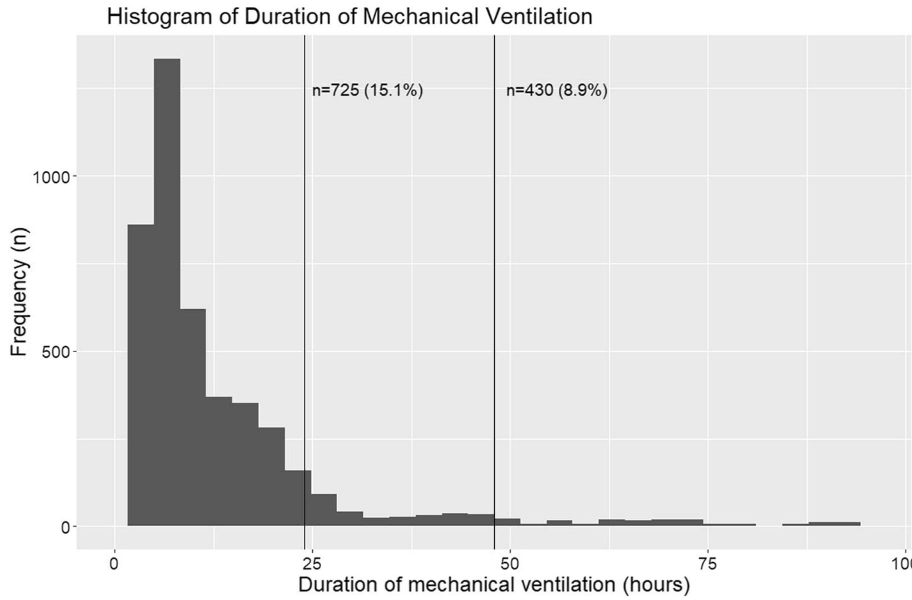

Fig. 1 Duration of mechanical ventilation

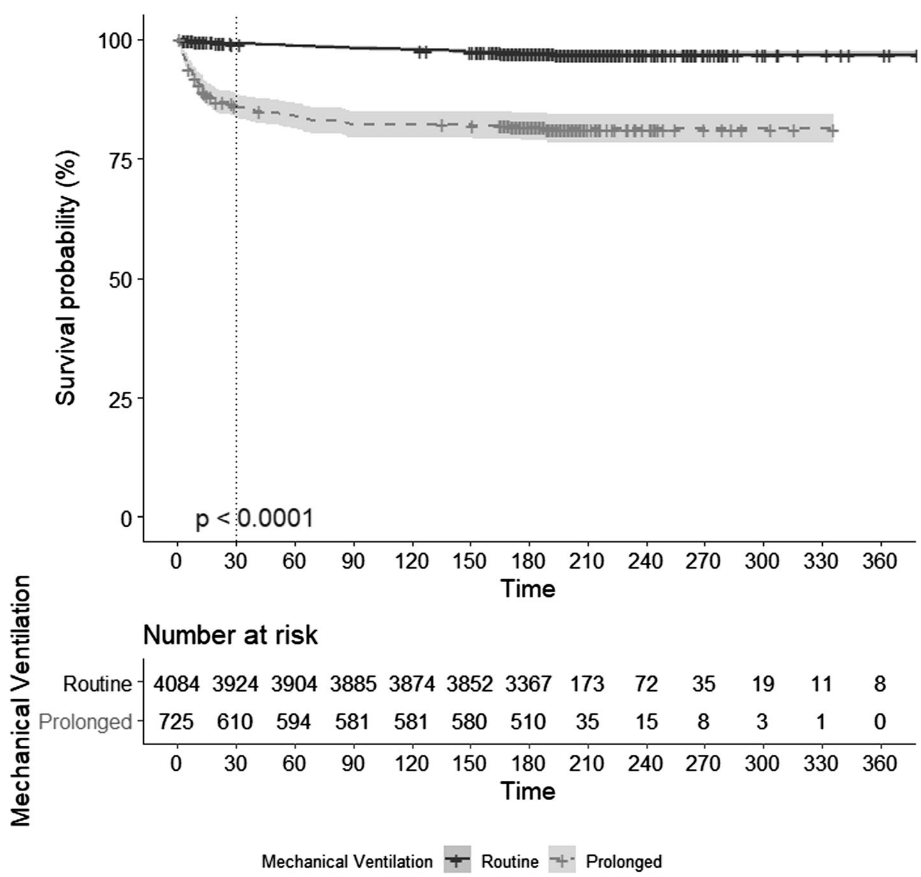

Fig. 2 Unadjusted survival curves based on mechanical ventilation status

for cardiac surgery; this study sets the stage for further work developing a risk score to predict prolonged MV.[20] In addition, our study findings can help facilitate planning intensive-care resources and project hospital-level costs to care for high-risk cardiac surgery patients. A novel addition to the literature is our finding of limited evidence of association of prolonged MV with long-term complications, and weak adjusted associations of prolonged MV with long-term mortality among survivors. These findings suggest that with appropriate treatment of perioperative complications, these patients have favorable long-term prognoses. This work will reassure patients and

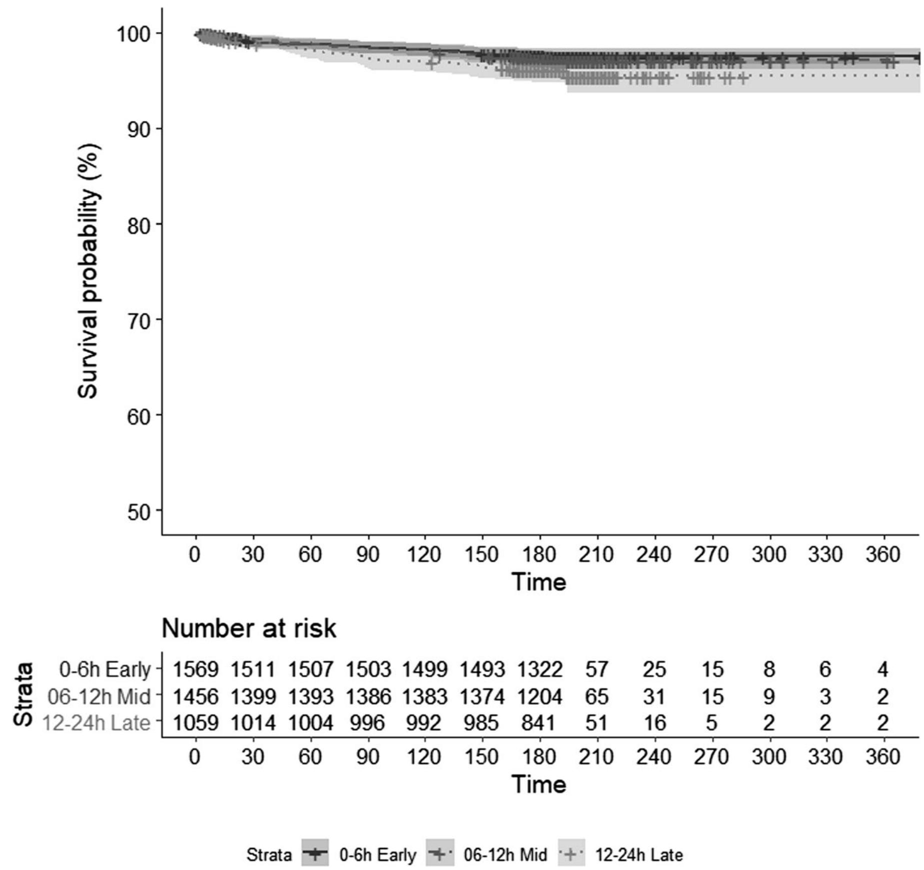

Fig. 3 Survival among patients ventilated < 24 hr

families and guide clinicians caring for acutely ill patients requiring prolonged MV following cardiac surgery. In keeping with previous findings, early extubation at less than six hours was not associated with an increase in-hospital length-of-stay or reintubation, although our ability to assess other safety and quality metrics was limited.

This study has several strengths. The robust conduct of the TRICS III trial involved standardized inclusion and exclusion criteria, a multicenter design with a large sample undergoing diverse surgical procedures, prospective data collection, masking of outcome assessors, and minimal loss to follow-up.[15,19]

This study also has limitations. First, although we examined associations between prolonged MV and postoperative complications, the causality of this association is difficult to ascertain. For instance, it is not known whether prolonged MV led to infections, such as ventilator-associated pneumonias, or whether other infectious processes necessitated prolonged MV.[41] Future work addressing the directionality of these associations is warranted. Second, the TRICS III trial included patients at moderate-to-high risk of death according to the EuroSCORE II;[15] the generalizability of study results to low-risk surgical populations may be limited. Third, data on intraoperative MV was not collected as part of this study. Emerging evidence points to an association between intraoperative ventilation parameters such as lower driving pressure and reductions in postoperative pulmonary complications among patients undergoing cardiac surgery.[42] Whether intraoperative ventilation parameters impact risk of postoperative ventilation requires further study. Fourth, other risk calculators for prolonged MV exist, including one from the STS that uses more than 65 predictors and includes predictors specific to the USA such as *primary* and *secondary payer*.[21,22] As these variables were not captured in TRICS III, a head-to-head comparison of our model with the STS model was not possible. Fifth, while we examined associations between prolonged MV and long-term complications such as stroke and myocardial infarction, patients' long-term trajectory will importantly be affected by factors such as long-term disability and neuropsychological outcomes, which we did not assess and warrant further study. Finally, we excluded patients who died within 24 hr of surgery, as these patients were ineligible to experience prolonged MV. Whether this exclusion biased results is unclear, though prior research has indicated that these deaths are often associated with surgical complications.[43] We found strong associations of surgical factors with prolonged MV despite excluding these patients; it is therefore unlikely that their inclusion would meaningfully impact our conclusions.

In summary, prolonged MV is common among patients at moderate-to-high risk of mortality undergoing cardiac surgery. Prolonged MV was associated with surgical factors, including previous cardiac surgery, duration of cardiopulmonary bypass, and difficulty of separation from bypass; and patient factors suggesting greater burden of illness, including critical preoperative state, left ventricular impairment, renal impairment, and pulmonary hypertension. Strong associations were noted between prolonged MV and short-term postoperative complications and mortality, but not long-term complications. Shorter durations of MV were not associated with complications or mortality. While this study describes the burden of prolonged MV, future work is needed to identify perioperative management strategies that improve outcomes for cardiac surgical patients requiring prolonged postoperative ventilation.

Author contributions *Ashwin Sankar*, *Alexandra Rotstein*, *Bijan Teja*, *François-Martin Carrier*, and *C. David Mazer* conceived and designed the study and were involved in drafting the manuscript. *Ashwin Sankar*, *Kevin Thorpe*, and *C. David Mazer* performed the data retrieval and *Ashwin Sankar*, *Alexandra Rotstein*, *Bijan Teja*, *François-Martin Carrier*, and *Kevin Thorpe* performed the statistical analyses. All authors were involved in the interpretation of the data, in drafting the manuscript, and made critical revisions to the discussion section. All authors read and approved the final version to be published.

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