High Tidal Volumes in Mechanically Ventilated Patients Increase Organ Dysfunction after Cardiac Surgery

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ABSTRACT

Background: High tidal volumes in patients with acute respiratory distress syndrome and acute lung injury lead to ventilator-induced lung injury and increased mortality. We evaluated the impact of tidal volumes on cardiac surgery outcomes.

Methods: We examined prospectively recorded data from 3,434 consecutive adult patients who underwent cardiac surgery. Three groups of patients were defined based on the tidal volume delivered on arrival at the intensive care unit: (1) low: below 10, (2) traditional: 10–12, and (3) high: more than 12 ml/kg of predicted body weight. We assessed risk factors for three types of organ failure (prolonged mechanical ventilation, hemodynamic instability, and renal failure) and a prolonged stay in the intensive care unit.

Results: The mean tidal volume/actual weight was 9.2 ml/kg, and the tidal volume/predicted body weight was 11.5 ml/kg. Low, traditional, and high tidal volumes were used in 724 (21.1%), 1567 (45.6%), and 1,143 patients (33.3%), respectively. Independent risks factors for high tidal volumes were body mass index of 30 or more (odds ratio [OR] 6.25; CI: 5.26–7.42; $P < 0.001$) and female sex (OR 4.33; CI: 3.64–5.15; $P < 0.001$). In the multivariate analysis, high and traditional tidal volumes were independent risk factors for organ failure, multiple organ failure, and prolonged stay in the intensive care unit. Organ failures were associated with increased intensive care unit stay, hospital mortality, and long-term mortality.

Conclusion: Tidal volumes of more than 10 ml/kg are risk factors for organ failure and prolonged intensive care unit stay after cardiac surgery. Women and obese patients are particularly at risk of being ventilated with injurious tidal volumes.

What We Already Know about This Topic

- High tidal volume in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) lead to ventilator-induced lung injury and increased mortality, but optimal tidal volume for mechanically ventilated patient without ALI/ARDS remains controversial.

What This Article Tells Us That Is New

- After cardiac surgery, tidal volume above 10 ml/kg predicted body weight is a significant risk factor for organ failure, multiple organ failure, and prolonged stay in the intensive care unit. Women and obese patients are particularly exposed to high tidal volume.

HIGH tidal volumes in mechanically ventilated patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) lead to baro- and bio-trauma[1,2] and increased mortality.[3,4] Few studies have investigated patients without ALI/ARDS, but several suggest that high tidal volumes may also be deleterious for them.[5–9] It has recently been shown that ventilation with high tidal volumes is a risk factor for acquired ALI in a medical population.[5,6,10] Some authors plead for the generalization of a protective ventilatory strategy to many mechanically ventilated patients, especially in those at risk of developing lung injury.[11] In the case of cardiac surgery, most patients have normal lungs before surgery. Although mechanical ventilation is usually delivered for several hours, respiratory mechanics are transiently affected within the first few hours of surgery.[12] In addition, systemic inflammation because of different causes (cardiopulmonary bypass, multiple transfusions) is frequent after cardiac surgery and may be further aggravated by injurious ventilation, even if it is only delivered for a few hours.[13] However, low tidal volumes are not recommended in surgi-

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cal settings[14,15] because a reduction in tidal volume is associated with hypoxemia, probably by promoting atelectasis.[16,17] The aim of this study was to evaluate the clinical impact of high tidal volumes after cardiac surgery. Our hypothesis was that use of high tidal volumes delivered immediately after cardiac surgery increases organ failure.

Materials and Methods

Patients

We examined prospectively recorded data of adult patients who underwent coronary-artery bypass grafting, cardiac-valve surgery, or a combination of procedures with sternotomy and cardiopulmonary bypass at the Quebec Heart and Lung Institute from January 30, 2004, to March 30, 2006. We excluded patients who had received heart transplants, mechanical heart support, or descending aorta surgery, as well as patients who had received other infrequent surgical procedures such as minimally invasive valve surgery. Standard practices for cardiac surgery and anesthesiology during the period under study did not vary. The lungs were not ventilated during cardiopulmonary bypass. After cardiopulmonary bypass, connection to the ventilator was followed by recruitment maneuvers. The ventilator mode was synchronized intermittent mandatory ventilation with respiratory rate usually set at 10 breaths/min, the positive end-expiratory pressure (PEEP) at 5 cm H_2O, and fraction of inspired oxygen (F_{IO_2}) ranged from 70 to 100%, as recommended in anesthesiology textbooks.[14,15] Patients were managed using fast-track procedures, with early termination of sedation (propofol) and minimal analgesic (fentanyl) after rewarming at 36°C.[18] Patients were extubated as soon as possible when their hemodynamic, ventilatory, and neurologic states were deemed to be stable by the attending physician, and in the absence of severe bleeding. The ventilatory protocol for the postoperative period was managed by respiratory therapists for the F_{IO_2} weaning and for the switch to pressure support ventilation. Modifications of other ventilatory parameters (mainly respiratory rate and tidal volume) were managed by anesthesiologists or intensive care physicians based on arterial blood gas results.

Data Sources

We used the cardiac surgery database of our institution. Data are prospectively collected by clinical coordinators (surgeons, anesthesiologists, perfusionists, and research nurses) concurrently with patient care and are entered into the database by two trained full-time data-management personnel. We used the initial tidal volume on arrival at the intensive care unit (ICU) for all the analyses; 84% of patients were ventilated with this initial tidal volume during the entire time spent on synchronized intermittent mandatory ventilation. The remaining 16% had a tidal volume reduction after arterial blood gases analysis, but they were exposed to the tidal volume used for analysis for a minimum of 63 ± 26 min after the surgery. The patients were measured with a height gauge before surgery. Predicted body weight was calculated using a reference formula.[3] The cardiac surgery database was approved by the ethics committee of our institution (Comité d'éthique de la recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec, Canada) for research use without the need for patient consent.

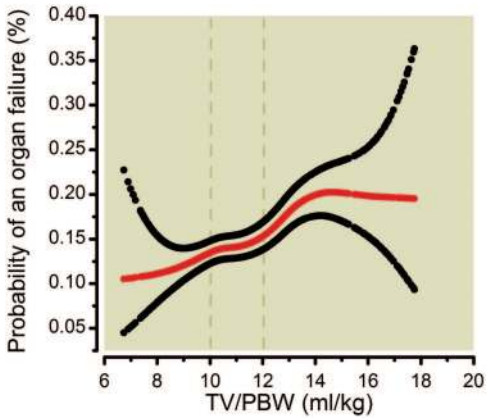

Fig. 1. Statistical model of a nonparametric logistic regression showing the dose-response relationship between the tidal volume at intensive care unit admission (ml/kg of predicted body weight) and the probability of an organ failure. TV/PBW = tidal volume/predicted body weight.

Definition of the Groups

We defined three groups of patients based on initial tidal volume on arrival to the ICU: (1) low tidal volumes (less than 10 ml/kg of predicted body weight), (2) traditional tidal volumes (10–12 ml/kg of predicted body weight), and (3) high tidal volumes (more than 12 ml/kg of predicted body weight). The choice of these tidal volume ranges was based on the literature[3,11,14,15] and on a model describing the impact of tidal volume on organ failure (fig. 1).

Study Outcomes

Our primary endpoint was organ dysfunction: prolonged mechanical ventilation (more than 24 h), prolonged hemodynamic instability (use of inotropes or vasopressors for more than 48 h after surgery), or renal failure (increase in creatinine levels more than 50 μM after surgery compared with baseline values). These complications are defined in the adult cardiac surgery database of the Society of Thoracic Surgeons.# The choice of these organ failures has several advantages: their definitions rely on objective criteria and they are associated with poor long-term outcome (fig. 2). We have considered the presence of one organ failure as well as multiple organ failure (at least two).

Our secondary endpoints were duration of mechanical ventilation, ICU and hospital stay, and ICU, hospital, and long-term mortality. We obtained the follow-up survival status from the Quebec Registry of the Social Security Death

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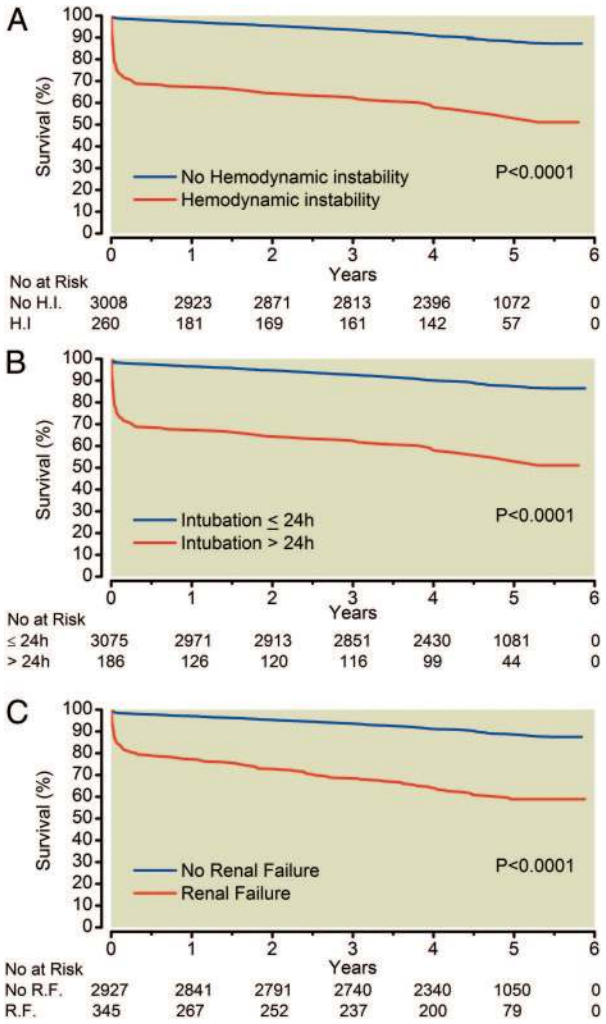

Fig. 2. Probability of long-term survival (with a 6-yr follow-up) of patients with and without organ failure. Hemodynamic instability (*A*), prolonged mechanical ventilation more than 24 h (*B*), or renal failure (*C*) are shown. The occurrence of organ failure as defined in our study had a marked impact on long-term survival. H.I. = hemodynamic instability; R.F. = renal failure.

Index. The closing date for the data were December 31, 2009.

Statistical Analysis

Continuous variables are expressed as means (SD) and categorical variables as percentages. Group comparisons were analyzed using one-way ANOVA for continuous variables and the chi-square test for categorical variables. *Post hoc* comparisons were performed using the Tukey *post hoc* test. A logistic regression analysis was performed to identify variables independently associated with organ failure definitions. Continuous variables were checked for the assumption of linearity in the logit using quartiles of the distribution and fractional polynomials before building the model in order to obtain the correct relationships. The graphic representations suggested linear relationships with the logit for all continuous variables. Variables from univariate logistic regressions with $P < 0.20$ were candidates for the multivariate regression model building. The variables were selected using two statistical approaches. First, stepwise and backward selections of variables were used in the multivariate regression model. Both approaches gave similar results. An alternative procedure to select variables was to use the best subset selection containing two to nine variables. Akaike and Sawa Bayesian information criteria were computed to validate the model selected. Conclusions were similar for both methods. To assess goodness-of-fit (calibration) for the model, a Hosmer-Lemeshow decile of risk test, Osius-Rojek normal approximation of the Pearson chi-square statistic distribution, and Stukel two degree-of-freedom test were performed. In order to appreciate the appropriate functional form between organ failure definitions and tidal volume/predicted body weight, a generalized additive model was built using the binary distribution. Smoothing was performed by spline fitting (df = 4). A linear regression analysis was performed to identify variables independently associated with length of ICU stay. The dependant variable was log-transformed to respect the linearity assumption with the continuous independent variables. The selection variables were performed using the stepwise and backward selections and the use of the best subset selection. Akaike and Sawa Bayesian information criteria were computed to validate the model selected, and conclusions were similar for both statistical approaches. As the statistics may vary from sample to sample and inference about the population must take into account these variations, we used the bootstrap technique to approximate the sampling distribution; 1,000 samples with replacement were performed. Kaplan–Meier analysis was used to examine differences in unadjusted survival without or with organ failure, with the log-rank tests used for comparison. Two-tailed values of $P < 0.05$ were considered significant. The univariate normality assumptions were verified using the Shapiro-Wilk test. Brown and Forsythe's variation of Levene's test statistic was used to verify the homogeneity of variances. All analyses were conducted using the SAS statistical package, version 9.2 (SAS Institute Inc., Cary, NC).

Results

During the 26-month study period (January 2004–March 2006), 4,203 patients underwent cardiac surgery, and 3,434 patients were included in the analysis (fig. 3).

Among the included patients, coronary artery bypass graft alone was performed in 453 (62.6%), 1,057 (67.5%), and 741 patients (64.8%) respectively for low, traditional, and high tidal volumes, respectively. Valve repair alone were performed in 77 (10.1%), 133 (8.5%), and 140 patients (12.2%) for low, traditional, and high tidal volumes, respectively. Finally, combined surgery (coronary artery bypass graft surgery + valves or more than one valve repair)

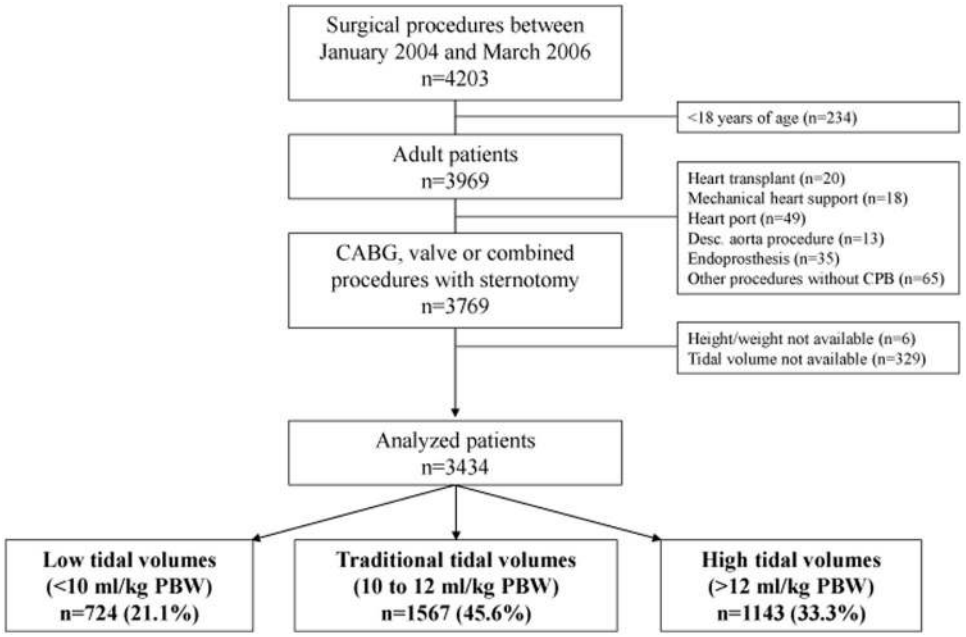

Fig. 3. Flow chart of the study and the study groups based on the initial tidal volume. CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; PBW = predicted body weight.

were performed in 170 (23.5%), 355 (22.6%), and 239 patients (20.9%) for low, traditional, and high tidal volumes, respectively.

Mean tidal volume/actual weight and mean tidal volume/predicted body weight were 9.2 ± 1.3 and 11.1 ± 1.5 in men ($P < 0.001$) and 9.1 ± 1.4 and 12.5 ± 2.2 in women ($P < 0.001$). Tidal volume distribution differed when using tidal volume/predicted body weight or tidal volume/actual weight (figs. 4 and 5). Table 1 lists the pre-, per-, and postoperative characteristics of the patients receiving low, traditional, and high tidal volumes as well as the organ failure frequency for each group.

Impact of Tidal Volume

The rate of organ failure increased with tidal volume, prolonged intubation (4.3% *vs.* 5.4% *vs.* 7.6%, $P = 0.006$), hemodynamic instability (5.4% *vs.* 7.9% *vs.* 10.1%, $P = 0.001$), and renal failure (7.9% *vs.* 10.4% *vs.* 12.7%, $P = 0.004$) for low, traditional, and high tidal volumes, respectively (table 1). In the univariate analysis, the presence of organ failure was associated with high tidal volumes (table 2). In the multivariate analysis, high tidal volume was an independent risk factor for organ failure and multiple organ failure (table 3), for mechanical ventilation lasting more than 24 h (high *vs.* low: OR: 2.0 [1.12–3.44], $P = 0.02$) and hemodynamic instability

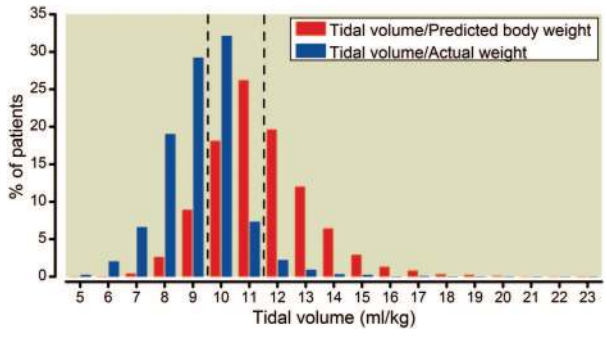

Fig. 4. Distribution of tidal volumes after cardiac surgery. The number (percentage) of patients with tidal volumes less than 10, 10–12, and more than 12 ml/kg were 724 (21.1%), 1,567 (45.6%), and 1,143 (33.3%), respectively, when predicted body weight was used. The number (percentage) of patients with tidal volumes less than 10, 10–12, and more than 12 ml/kg were 1,956 (57.0%), 1,429 (41.6%), and 49 (1.4%), respectively, when actual body weight was used.

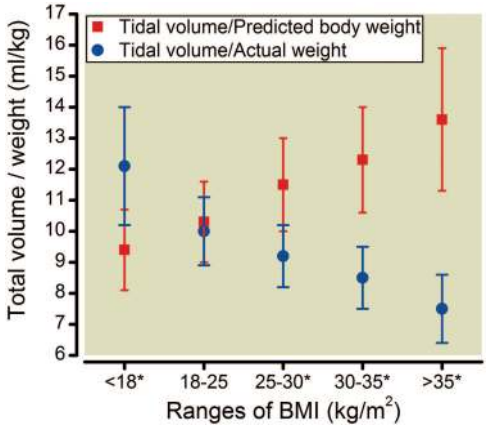

Fig. 5. Tidal volumes expressed in ml per kg of actual body weight (*blue circles*) and tidal volumes expressed in ml/kg of predicted body weight (*orange squares*) for different body mass index ranges. BMI = body mass index. * $P < 0.05$ for comparison between tidal volumes expressed with actual and predicted body weight.

Table 1. Pre-, Per-, and Postoperative Characteristics of the Patients (n = 3,434) in the Three Study Groups: Low Tidal Volume (Less Than 10 ml/kg of Predicted Body Weight [PBW]), Traditional Tidal Volumes (10–12 ml/kg of PBW), and High Tidal Volumes (More Than 12 ml/kg of PBW)

	Tidal Volumes (ml/kg of PBW)			
	Less Than 10 (n = 724)	10–12 (n = 1,567)	More Than 12 (n = 1,143)	*P* Value
Preoperative Data				
Age (years)	65 ± 12	65 ± 11	66 ± 10	0.009 (‡)
Age 65 yr or older, n (%)	415 (57)	839 (53)	631 (55)	0.23
Female sex, n (%)	106 (15)	319 (20)	514 (45)	<0.001 (*, †, ‡)
BMI (kg/m^2)	24 ± 4	27 ± 4	31 ± 5	<0.001 (*, †, ‡)
BMI more than 30 kg/m^2, n (%)	65 (9)	310 (20)	586 (51)	<0.001 (*, †, ‡)
Actual weight (kg)	72 ± 15	76 ± 15	79 ± 16	<0.001 (*, †, ‡)
Predicted body weight (kg)	66 ± 8	63 ± 9	55 ± 10	<0.001 (*, †, ‡)
Height (cm)	171 ± 8	168 ± 8	160 ± 9	<0.001 (*, †, ‡)
Logistic Euroscore (%)	3.3 (1.6–6.7)	3 (1.5–6.5)	3.4 (1.7–7)	0.52
Priority emergency, n (%)	257 (35)	579 (37)	366 (32)	0.03 (‡)
Previous cardiac surgery, n (%)	64 (8.8)	131 (8.4)	83 (7.3)	0.42
LVEF less than 40%, n (%)	69 (24)	135 (47)	82 (29)	0.19
LVEF (%)	57 ± 14	58 ± 14	58 ± 14	0.0003 (†)
Intubation before surgery, n (%)	4 (0.6)	13 (0.8)	11 (1.0)	0.63
Cerebrovascular disease, n (%)	45 (6.2)	97 (6.2)	63 (5.5)	0.73
Diabetes mellitus, n (%)	154 (21)	428 (27)	416 (36)	<0.001 (*, †, ‡)
Arterial hypertension, n (%)	368 (51)	901 (58)	779 (68)	<0.001 (*, †, ‡)
COPD, n (%)	97 (13)	190 (12)	176 (15)	0.05
Previous renal failure, n (%)§	29 (4.0)	94 (6.0)	55 (4.8)	0.11
Hemodialysis, n (%)	2 (0.3)	12 (0.8)	4 (0.3)	0.19
Peripheral vascular disease, n (%)	82 (11)	172 (11)	156 (14)	0.09
Previous atrial fibrillation, n (%)	80 (11)	143 (9)	104 (9)	0.28
Previous infarction, n (%)	282 (39)	616 (39)	416 (36)	0.27
Intra-aortic balloon pumping (preop), n (%)	31 (4.3)	72 (4.6)	34 (3.0)	0.09
Per- and Postoperative Data				
Respiratory rate (breath/min)	11 ± 2	10 ± 1	10 ± 1	<0.001 (*, ‡)
Tidal volume (ml) per kg of actual weight	8.7 ± 1.3	9.3 ± 1.2	9.4 ± 1.3	<0.001 (*, †, ‡)
Tidal volume (ml) per kg of PBW	9.2 ± 0.7	11.0 ± 0.6	13.5 ± 1.4	<0.001 (*, †, ‡)
Coronary artery bypass graft alone, n (%)	453 (63)	1,057 (67)	741 (65)	0.06
Cardiopulmonary bypass time (min)	89 ± 36	90 ± 37	91 ± 41	0.57
Prolonged cardiopulmonary bypass time, n (%)‖	109 (15)	254 (16)	186 (16)	0.74
Aortic cross-clamping time (min)	64 ± 29	64 ± 30	64 ± 31	0.85
Total transfusion	0 (0–2)	0 (0–2)	3.4 (1.7–7)	0.87
Multiple transfusions (5 or fewer units), n (%)	111 (15)	225 (14)	141 (12)	0.15
Intra-aortic balloon pumping (per- and postop), n (%)	11 (1.5)	33 (2.1)	39 (3.4)	0.02 (†)
Drained pleural effusion (postop), n (%)	47 (6.5)	138 (8.8)	126 (11.0)	0.004 (†)
Pulmonary infection (post-op), n (%)	64 (8.8)	110 (7.0)	101 (8.8)	0.15
Septicemia (postop), n (%)	4 (0.6)	20 (1.3)	16 (1.4)	0.21
Cerebrovascular accident (postop), n (%)	18 (2.5)	36 (2.3)	27 (2.4)	0.96
Atrial fibrillation (postop), n (%)	272 (38)	587 (37)	416 (36)	0.82
Reoperation for bleeding, n (%)	43 (5.9)	76 (4.9)	50 (4.4)	0.31
Outcome Data				
Duration of mechanical ventilation (hours)	6.0 (5–12)	6.5 (4.5–13)	7.4 (4.8–14.9)	<0.001 (†)
Reintubation, n (%)	25 (3.5)	72 (4.6)	64 (5.6)	0.10
Intubation more than 24 h, n (%)	31 (4.3)	84 (5.4)	87 (7.6)	0.006 (†)
Intubation more than 48 h, n (%)	11 (1.5)	46 (2.9)	44 (3.9)	0.01 (†)
Intubation more than 7 d, n (%)	3 (0.4)	9 (0.6)	11 (1.0)	0.30
Hemodynamic instability, n (%)	39 (5.4)	124 (7.9)	115 (10.1)	0.001 (†)
Renal failure, n (%)	57 (7.9)	163 (10.4)	145 (12.7)	0.004 (†)
Hemodialysis, n (%)	9 (1.2)	47 (3.0)	36 (3.2)	0.02 (*, †)

(*continued*)

Table 1. Continued

	Tidal Volumes (ml/kg of PBW)			
	Less Than 10 (n = 724)	10–12 (n = 1,567)	More Than 12 (n = 1,143)	*P* Value
Any organ failure, n (%)	82 (11)	230 (15)	206 (18)	<0.001 (†)
Multiple organ failure, n (%)	21 (2.9)	74 (4.7)	70 (6.1)	0.006 (†)
ICU length of stay (days)	1.0 (1.0–2.2)	1.2 (0.9–2.6)	1.8 (1.0–3.0)	<0.001 (†, ‡)
ICU length of stay more than 24 h, n (%)	478 (20)	1,036 (45)	814 (35)	0.003 (†, ‡)
ICU length of stay more than 48 h, n (%)	225 (31)	518 (33)	447 (39)	<0.001 (†, ‡)
ICU length of stay more than 7 d, n (%)	19 (16)	46 (38)	57 (47)	0.005 (†, ‡)
Hospital length of stay (days)	6 (5–8)	6 (5–8)	7 (5–9)	0.06
ICU mortality, n (%)	13 (1.8)	30 (1.9)	29 (2.5)	0.44
Hospital mortality, n (%)	22 (3.0)	49 (3.1)	43 (3.8)	0.59
Hospital and late mortality, n (%)	91 (13)	208 (13)	154 (13)	0.85

Results are presented as means ± SD or median (25th–75th percentiles) for continuous data and absolute (n) and relative frequency (%) for categorical data. *P* value is provided for the variance analysis, and differences with $P < 0.05$ between groups are provided.

* P <10 *vs.* 10–12. † P < 10 *vs.* >12. ‡ P 10–12 *vs.* >12. § Previous renal failure defined by preoperative creatininemia more than 150 μM. ‖ Cardiopulmonary bypass time of more than 120 min.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; LVE = left ventricular ejection fraction.

(high *vs.* low: OR: 2.4 [1.53–3.64], $P = 0.007$). Traditional tidal volume was an independent risk factor for hemodynamic instability (traditional *vs.* low: OR: 1.8 [1.17–2.75], $P < 0.001$). An internal validation of the logistic model by bootstrap analyses demonstrated similar results.

Higher tidal volume was associated with longer stay in the ICU (2.0 ± 1.9 *vs.* 2.3 ± 3.2 *vs.* 2.7 ± 3.9 days, $P < 0.001$). High tidal volume was an independent risk factor for prolonged ICU stay of more than 48 h (high *vs.* low: OR: 1.4 [1.17–1.79], $P < 0.001$) and more than 1 week (high *vs.* low: OR: 1.8 [1.01–3.09], $P = 0.04$). There were no differences in hospital mortality and long-term mortality among the patient groups classified by tidal volume.

In the case of organ failure, the frequency of prolonged ICU stay and ICU mortality, hospital mortality, and long-term mortality increased (table 1, table 2, fig. 2).

Risk Factors Related to High Tidal Volumes

The percentage of women who received low, traditional, or high tidal volumes was 14.6, 20.4, and 45.0%, respectively ($P < 0.001$). The mean body mass indexes (BMI) of the three groups were 24.3 ± 4.0, 27.0 ± 4.1, and 30.8 ± 5.1 kg/m^2, respectively ($P < 0.001$). In the multivariate analysis, a BMI of more than 30 kg/m^2 and female sex were risk factors when high tidal volumes were used (table 4).

Discussion

In this observational study, we demonstrated the impact of tidal volumes used immediately after cardiac surgery on postoperative complications and patient outcomes. Traditional tidal volumes (10–12 ml/kg of predicted body weight) and high tidal volumes (more than 12 ml/kg of predicted body weight) were associated with prolonged mechanical ventilation, hemodynamic instability, renal failure, and prolonged stay in the ICU among patients who underwent cardiac surgery, compared with low tidal volumes (less than 10 ml/kg of predicted body weight). Use of high tidal volume was an independent risk factor for prolonged mechanical ventilation, hemodynamic instability, multiple organ failure, and prolonged ICU stay. Women and obese patients were more at risk of receiving injurious ventilation.

Tidal volume reduction is a standard of care for patients with ALI and ARDS.[19] There is no consensus for other patients, but some authors advocate broader applicability of protective ventilation.[11] Several studies have demonstrated a link between high tidal volumes and the development or aggravation of local and systemic inflammation in patients with normal lungs.[8,9,13,20–22] However, several studies did not observe such an effect.[23–26] The studies suggesting that tidal volume reduction has a protective effect included patients who underwent surgery with one-lung ventilation,[7,8] prolonged surgical procedures,[9,20] and cardiac surgery.[13,21,22] In a recently published paper by Kor *et al.* it was shown that this latter group was at risk to develop early postoperative acute lung injury.[27] In the present study we showed that tidal volume was independently associated with patient outcomes after cardiac surgery. In this population, several studies showed that a protective ventilatory strategy can reduce systemic and pulmonary inflammation.[13,21,22] In a group of 40 patients who underwent coronary artery bypass graft surgery, Zupancich *et al.* demonstrated that pulmonary and systemic proinflammatory cytokines levels increase in patients ventilated with high tidal volumes but not in those ventilated with low tidal volumes.[13] In a recently published study, Sundar *et al.* compared ventilation with 10 *versus* 6 ml/kg tidal volumes after cardiac surgery.[28] The authors demonstrated that in the

Table 2. Univariate Analysis of Variables Influencing the Occurrence of an Organ Failure or Multiple Organ Failures (at Least Two) after Cardiac Surgery

	Any Organ Failure (n = 518)	No Organ Failure (n = 2,916)	*P* Value	Multiple Organ Failure (n = 165)	No Multiple Organ Failure (n = 3,269)	*P* Value
Tidal Volumes at ICU Admission						
Less than 10 ml/kg of PBW	82 (16)	642 (22)	<0.001‡	21 (13)	703 (21)	0.005‡
10–12 ml/kg of PBW	230 (44)	1,337 (46)	—	74 (45)	1,493 (45)	—
More than 12 ml/kg of PBW	206 (40)	937 (32)	—	70 (42)	1,073 (33)	—
Preoperative Data						
Age (years)	64 ± 11	69 ± 11	<0.001	70 ± 10	65 ± 11	<0.001
Age 65 yr or older, n (%)	361 (70)	1,524 (52)	<0.001	118 (71)	1,767 (54)	<0.001
Female sex, n (%)	171 (33)	768 (26)	0.002	56 (34)	883 (27)	0.06
BMI (kg/m^2)	28 ± 5	28 ± 5	0.33	28 ± 6	28 ± 5	0.90
BMI more than 30 kg/m^2, n (%)	165 (32)	796 (27)	0.04	52 (31)	909 (28)	0.33
Actual weight (kg)	76 ± 17	76 ± 15	0.88	76 ± 19	76 ± 16	0.70
Predicted body weight (kg)	61 ± 10	60 ± 10	0.05	61 ± 10	60 ± 10	0.24
Height (cm)	165 ± 10	166 ± 9	0.13	165 ± 9	166 ± 9	0.37
Logistic Euroscore (%)	7.3 (2.0–6.0)	2.7 (1.5–5.8)	<0.001	12.7 (6.2–27.8)	3.0 (1.5–6.3)	<0.001
Priority emergency, n (%)	239 (46)	963 (33)	<0.001	91 (55)	1,111 (34)	<0.001
Previous cardiac surgery, n (%)	71 (14)	207 (7.1)	<0.001	35 (21)	243 (7.4)	<0.001
LVEF less than 40%, n (%)	90 (18)	196 (7)	<0.001	41 (27)	245 (8)	<0.001
LVEF (%)	58 ± 13	53 ± 15	<0.001	51 ± 14	48 ± 16	<0.001
Intubation before surgery, n (%)	19 (3.8)	9 (0.3)	<0.001	12 (7.3)	16 (0.5)	<0.001
Cerebrovascular disease, n (%)	57 (11)	148 (5)	<0.001	20 (12)	185 (6)	0.002
Diabetes mellitus, n (%)	187 (36)	811 (28)	<0.001	59 (36)	939 (29)	0.06
Arterial hypertension, n (%)	316 (61)	1,732 (60)	0.43	97 (59)	1951 (60)	0.87
COPD, n (%)	104 (20)	359 (12)	<0.001	40 (24)	423 (13)	<0.001
Previous renal failure, n (%)*	85 (16)	93 (3)	<0.001	28 (17)	150 (5)	<0.001
Hemodialysis, n (%)	10 (2)	8 (0.3)	<0.001	1 (0.6)	17 (0.5)	0.59
Peripheral vascular disease, n (%)	91 (18)	319 (11)	<0.001	35 (21)	375 (11)	<0.001
Previous atrial fibrillation, n (%)	109 (21)	218 (7.5)	<0.001	47 (28)	280 (8.6)	<0.001
Previous infarction, n (%)	222 (43)	1,092 (37)	0.02	66 (40)	1,248 (38)	0.68
Intra-aortic balloon pumping (preop), n (%)	81 (16)	52 (2)	<0.001	21 (13)	116 (4)	<0.001
Per- and Postoperative Data						
Coronary artery bypass graft alone, n (%)	224 (43)	2027 (69)	<0.001	47 (28)	2,204 (67)	<0.001
Cardiopulmonary bypass time (min)	113 ± 55	86 ± 33	<0.001	138 ± 65	88 ± 35	<0.001
Prolonged cardiopulmonary bypass time, n (%)†	172 (33)	377 (13)	<0.001	90 (55)	459 (14)	<0.001
Aortic cross-clamping time (min)	79 ± 40	61 ± 27	<0.001	93 ± 46	63 ± 28	<0.001
Total transfusions	2.0 (0–9)	0 (0 to 1)	<0.001	7.0 (1–15)	0 (0–2)	<0.001
Multiple transfusions (5 or more units), n (%)	159 (31)	318 (11)	<0.001	85 (51)	392 (12)	<0.001
Intra-aortic balloon pumping (per- and postop), n (%)	63 (12)	20 (0.7)	<0.001	39 (24)	44 (1.4)	<0.001
Duration of mechanical ventilation (hours)	14.4 (7.2–36.0)	7.2 (4.8–12.0)	<0.001	55.2 (19.2–132.0)	7.2 (4.8–12.0)	<0.001
Drained pleural effusion (postop), n (%)	119 (23)	192 (7)	<0.001	55 (33)	256 (8)	<0.001
Pulmonary infection (postop), n (%)	155 (30)	120 (4)	<0.001	88 (53)	187 (6)	<0.001
Septicemia (postop), n (%)	33 (6)	7 (0.2)	<0.001	15 (9)	25 (0.8)	<0.001
Cerebrovascular accident (postop), n (%)	40 (8)	41 (1)	<0.001	21 (13)	60 (2)	<0.001

(*continued*)

Table 2. Continued

	Any Organ Failure (n = 518)	No Organ Failure (n = 2,916)	*P* Value	Multiple Organ Failure (n = 165)	No Multiple Organ Failure (n = 3,269)	*P* Value
Atrial fibrillation (postop), n (%)	317 (61)	958 (33)	<0.001	116 (70)	1,159 (35)	<0.001
Reoperation for bleeding, n (%)	56 (11)	113 (3.9)	<0.001	30 (18)	139 (4.3)	<0.001
Outcome Data						
ICU length of stay (days)	4.0 (1.9–6.4)	1.1 (0.9–2.1)	<0.001	6.9 (4.1–12.3)	1.2 (0.9–2.3)	<0.001
ICU length of stay more than 48 h, n (%)	371 (72)	819 (28)	<0.001	150 (91)	1,040 (32)	<0.001
ICU length of stay more than 7 days, n (%)	107 (21)	15 (0.5)	<0.001	78 (48)	44 (1.4)	<0.001
Hospital length of stay (days)	10.0 (7.0–17.0)	6.0 (5.0–7.0)	<0.001	15.0 (9.0–27.0)	6.0 (5.0–8.0)	<0.001
ICU mortality, n (%)	64 (12)	8 (0.3)	<0.001	47 (28)	25 (0.8)	<0.001
Hospital mortality, n (%)	91 (18)	23 (0.8)	<0.001	63 (38)	51 (1.6)	<0.001
Hospital and late mortality, n (%)	184 (35)	269 (9.0)	<0.001	90 (55)	363 (11)	<0.001

Results are presented as means ± SD or median (25th–75th percentiles) for continuous data and absolute (n) and relative frequency (%) for categorical data.

* Previous renal failure defined by preoperative creatininemia more than 150μM. † Cardiopulmonary bypass time more than 120 min. ‡ Pair comparisons for the different tidal volumes: TV/PBW less than 10 *vs.* TV/PBW 10–12, $P = 0.03$; TV/PBW less than 10 *vs.* TV/PBW 10–12, $P = 0.04$; TV/PBW less than 10 *vs.* TV/PBW more than 12, $P < 0.001$; TV/PBW less than 10 *vs.* TV/PBW more than 12, $P = 0.001$; TV/PBW 10–12 *vs.* TV/PBW more than 12, $P = 0.01$; TV/PBW 10–12 *vs.* TV/PBW more than 12, $P = 0.12$.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; LVEF = left ventricular ejection fraction; PBW = predicted body weight; TV = tidal volume.

small tidal volumes group, fewer patients were intubated after 6 h, which may be related to the significantly higher $Paco_2$ levels in this group. Also, fewer patients were reintubated in this group.[28] However, this study did not include enough patients to demonstrate differences on ICU length of stay, and data on organ dysfunction were not reported. It is likely that in the high tidal volume group, inflammation was increased as previously demonstrated.[13] Recently, it was demonstrated that increased inflammatory markers were independent predictors of major adverse cardiac events after cardiac surgery.[29] The present study is the first to demonstrate that high tidal volumes have an impact on cardiac surgery outcomes.

Although several studies have investigated the impact of high tidal volumes on lung dysfunction, few have evaluated the impact on other organs.[11] In the present study, high and traditional tidal volumes were associated with hemodynamic and renal failure. High tidal volumes have been associated with an increase in local and systemic inflammation and a decrease in mean arterial pressure compared with protective ventilation.[13] Another study has shown that protective ventilatory strategies decrease systemic and local inflammation, cardiac dysfunction, perivascular edema, and vascular congestion compared with high tidal volumes.[30] In the present study, both traditional and high tidal volumes were independent risk factors for hemodynamic instability. Renal failure can be induced by hemodynamic instability related to high tidal volumes[31] as well as by systemic inflammation as demonstrated in animal[30,32] studies. An injurious ventilatory strategy can lead to increased rates of epithelial cell apoptosis in the kidney and increased serum creatinine levels.[32] High tidal volumes can also result in reduced urine output and plasma creatinine clearance compared with protective ventilatory strategies.[30]

We found that tidal volumes were independent predictors of prolonged ICU stays. To our knowledge, this is the first time that such a relationship has been reported in patients without ARDS. It must be acknowledged that the time when the patient is able to be discharged from the ICU and the time when the patient is actually discharged from the ICU may be different. We conducted analysis with both variables and found similar results. A prolonged ICU stay after cardiac surgery is associated with poor long-term outcomes and increased costs.[33] In the Kern *et al.* study, 9% of the patients received more than 48 h of mechanical ventilation but accounted for 43% of the overall costs after cardiac surgery. In addition, mortality was 0.5% in patients ventilated for less than 48 h but rose to 11% in patients ventilated for more than 48 h.[34] Our results were similar to those of the Kern *et al.* study in that the 202 patients (6%) ventilated for more than 48 h accounted for 2% of the number of days in the ICU, whereas mortality was 2.2% in patients ventilated for less than 48 h but rose to 42% in patients ventilated for more than 48 h.

In our study, patients with a high BMI were ventilated with a low tidal volume/actual body weight but a high tidal volume/predicted body weight. A similar pattern was recently reported with a large cohort of mechanically ventilated patients.[35] This underscores the need to use predicted body

Table 3. Multivariate Analysis of Risk Factors for an Organ Failure or Multiple Organ Failures (at Least Two) after Cardiac Surgery

	Organ Failure*		
Variable	Odds Ratio	95% CI	*P* Value
Septicemia (postop)	13.10	5.00–34.30	<0.001
Intra-aortic balloon pumping (per- and postop)	12.12	6.55–22.40	<0.001
Pulmonary infection (postop)	5.25	3.80–7.25	<0.001
Previous renal failure†	3.75	2.56–5.49	<0.001
Cerebrovascular accident (postop)	3.64	2.11–6.26	<0.001
Cardiopulmonary bypass time (min)	2.45	1.78–3.38	<0.001
Drained pleural effusion (postop)	2.13	1.55–2.94	<0.001
Atrial fibrillation (postop)	2.13	1.69–2.69	<0.001
Logistic Euroscore (%)	1.75	1.54–1.99	<0.001
Cerebrovascular disease	1.58	1.06–2.63	0.02
TV/PBW more than 12 *vs.* less than 10	1.54	1.09–2.19	0.02
Priority emergency	1.46	1.15–1.85	0.002
Diabetes mellitus	1.33	1.04–1.70	0.02
BMI more than 30 kg/m^2	1.32	1.00–1.73	0.05
TV/PBW 10–12 *vs.* less than 10	1.32	0.96–1.83	0.09

	Multiple Organ Failure‡		
Variable	Odds Ratio	95% CI	*P* Value
Intra-aortic balloon pumping (per- and postop)	11.06	5.84–20.95	<0.001
Pulmonary infection (postop)	9.92	6.47–15.23	<0.001
Cerebrovascular accident (postop)	4.97	2.47–9.97	<0.001
Cardiopulmonary bypass time (min)	3.07	1.78–5.31	<0.001
Multiple transfusions (5 or more units)	2.47	1.58–3.87	<0.001
Logistic Euroscore (%)	2.34	1.87–2.93	<0.001
Atrial fibrillation (postop)	2.34	1.52–3.59	<0.001
TV/PBW more than 12 *vs.* less than 10	2.26	1.20–4.25	0.01
Drained pleural effusion (postop)	2.13	1.32–3.42	0.002
TV/PBW 10–12 *vs.* less than 10	1.83	0.99–3.38	0.05
Diabetes mellitus	1.55	1.00–2.40	0.05

* $P = 0.05$ (multivariate model), C index: 0.85, $P < 0.001$; Hosmer-Lemeshow chi-square = 8.34, $P = 0.40$. † Previous renal failure defined by preoperative creatininemia >150μM. ‡ $P = 0.04$ (multivariate model), C index: 0.94, $P < 0.001$; Hosmer-Lemeshow chi-square = 4.96, $P = 0.76$.

BMI = body mass index; PBW = predicted body weight; TV = tidal volume.

Table 4. Multivariate Analysis of Risk Factors for High Tidal Volumes after Cardiac Surgery

	Odds Ratio	95% CI	*P* Value
BMI more than 30 kg/m^2	6.25	5.26–7.42	<0.001
Female sex	4.33	3.64–5.15	<0.001

C index: 0.75, $P < 0.001$; Hosmer-Lemeshow chi-square = 0.33, *P* value: 0.85.

BMI = body mass index.

weight to set the optimal tidal volume in mechanically ventilated patients. Female sex was also an independent risk factor when high tidal volumes were used after cardiac surgery. Our results were in agreement with the study by Gajic *et al.*,[5] in which women received higher tidal volumes than men and tended to develop more ALI. This may in part explain the results of previous studies reporting that female sex is a risk factor for prolonged mechanical ventilation after cardiac surgery.[36]

There are several clinical implications of our findings. Our study provided an additional argument to promote the implementation of prophylactic protective ventilatory strategies, even in patients without ALI/ARDS. Many patients are exposed to possible causes of lung injury at admission[37] or during their ICU stay, including acquired sepsis,[38] transfusions,[39] ischemia, and reperfusion.[40] ALI/ARDS may occur several days after the beginning of mechanical ventilation, and the diagnosis is frequently underestimated. In the Herasevitch *et al.* study, only 26% of the clinicians detected ALI/ARDS the day it occurred.[41] A multiple hit theory has been proposed by which repeated injuries lead to the development of ALI/ARDS.[11] Tidal volume reduction at the initiation of mechanical ventilation may prevent an additional "hit." These results also demonstrate that some populations are at risk of being ventilated with high tidal volumes (obese patients and women), confirming that predicted body weight must be calculated and used to deliver protective ventilation.

Our study had a number of limitations. First, it was observational in design, as we did not randomize patients to different initial tidal volumes. Second, we compared different tidal volumes but did not evaluate PEEP. In most other studies, postsurgery protective ventilatory strategies combined high PEEP with low tidal volumes.[8,9,13,20–22] It is likely that tidal volume reduction should be delivered with a moderate increase in PEEP to prevent atelectasis, as with ARDS patients.[42] Third, the choice of tidal volume thresholds is open to discussion. In the nonparametric logistic regression showing the dose-response relationship between tidal volumes and organ dysfunction, three zones could be delineated, with different slopes for tidal volumes less than 10 ml/kg of predicted body weight and those more than 12 ml/kg (fig. 3). Schultz proposed 10 ml/kg of predicted body weight as the maximum tidal volume during mechanical ventilation.[11] Traditional tidal volumes (10–12 ml/kg) are in

line with those recommended in widely used anesthesiology textbooks.[14,15] Fourth, it may not be possible to transpose our results to all patients. For example, in relatively young patients undergoing elective noncardiac surgeries, high tidal volumes have no impact on systemic or pulmonary inflammation after 1[26] or 3 h.[25] These populations may not require the tidal volume to be adjusted, if no additional risk factors for acute lung injury are present. Also, it may be difficult to apply results of epidemiologic reports to individual clinical decision-making at the bedside. Multicenter randomized controlled studies are needed to confirm or refute these observations and to evaluate the external validity of the present results. Finally, we showed that the utilization of high tidal volumes is an independent predictor of organ dysfunction after cardiac surgery. However, an association and not a causality link could be demonstrated.

In conclusion, we found that traditional and high tidal volumes immediately after cardiac surgery are independent risk factors for organ dysfunction and prolonged ICU stay. Prophylactic protective ventilatory strategies should be provided in populations with an inflammatory state (virtually all critically ill patients) who are at risk of developing ventilator-induced lung injury. Women and obese patients are more at risk of being ventilated with injurious tidal volumes. As such, special care should be paid to ventilatory settings for these patients. In particular, predicted body weight rather than actual body weight should be used to set the tidal volumes in mechanically ventilated patients.

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