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Impact of sex on use of low tidal volume ventilation in invasively ventilated ICU patients—A mediation analysis using two observational cohorts

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Abstract

Background

Studies in patients receiving invasive ventilation show important differences in use of low tidal volume (V_T) ventilation (LTVV) between females and males. The aims of this study were to describe temporal changes in V_T and to determine what factors drive the sex difference in use of LTVV.

Methods and findings

This is a posthoc analysis of 2 large longitudinal projects in 59 ICUs in the United States, the 'Medical information Mart for Intensive Care III' (MIMIC III) and the 'eICU Collaborative Research DataBase'. The proportion of patients under LTVV (median V_T < 8 ml/kg PBW), was the primary outcome. Mediation analysis, a method to dissect total effect into direct and indirect effects, was used to understand which factors drive the sex difference. We included 3614 (44%) females and 4593 (56%) males. Median V_T declined over the years, but with a persistent difference between females (from median 10.2 (9.1 to 11.4) to 8.2 (7.5 to 9.1) ml/kg PBW) vs. males (from median 9.2 [IQR 8.2 to 10.1] to 7.3 [IQR 6.6 to 8.0] ml/kg PBW) (*P* < .001). In females versus males, use of LTVV increased from 5 to 50% versus from 12 to 78% (difference, −27% [−29% to −25%]; P < .001). The sex difference was mainly driven by patients' body height and actual body weight (adjusted average causal mediation effect, −30% [−33% to −27%]; *P* < .001, and 4 [3% to 4%]; *P* < .001).

Conclusions

While LTVV is increasingly used in females and males, females continue to receive LTVV less often than males. The sex difference is mainly driven by patients' body height and actual body weight, and not necessarily by sex. Use of LTVV in females could improve by paying more attention to a correct calculation of V_T, i.e., using the correct body height.

Introduction

Before a landmark study regarding the benefit of so-called low V_T ventilation (LTVV) was published in 2000 [1], it was common practice in critically ill patients to use a high tidal volume (V_T) during invasive ventilation, as this increased minute ventilation necessary to compensate for an often present disease–induced increase in dead space [2], and because this potentially reduced atelectases thereby reducing the need for high oxygen fractions (FiO_2) and positive end–expiratory pressure (PEEP) [3]. Convincing evidence for harm from ventilation with a high V_T in patients with acute respiratory distress syndrome (ARDS) [1] resulted in worldwide introduction of LTVV often also in patients without ARDS. Indeed, a noticeable decline in V_T size was seen in critically ill patients [4], albeit that many patients continued to receive ventilation with a too high V_T [5, 6].

Often–cited challenges with LTVV include alleged increases in sedation need due to the higher respiratory rate necessary to compensate for a decline in minute volume with use of a low V_T. This could induce or worsen delirium, and may increase the risk for patient–ventilator asynchronies [7–9], although this was never confirmed in observational studies [10, 11]. Another practical problem with LTVV is that V_T needs to be titrated against predicted body weight (PBW), which is a function of a patient's body height [1]––however, body height is often not known at the time of ICU admission, taking a patient's body height in a supine position can be difficult [12–16], and estimates of body height are frequently inaccurate in the ICU setting [13, 17–20]. Apart from this, doctors and nurses need to apply a not so easy equation at the bedside to calculate PBW, which could be challenging. For these reasons it has been proposed to use a 'default' V_T [9]. This practice seemed to have been implemented widespread, as a 'rounded' absolute V_T is often used [5, 6].

Two large observational studies, one in critically ill patients with ARDS [21], and one in patients receiving intraoperative ventilation during general anaesthesia for surgery [22], show that females receive LTVV much less often than males. We aimed to determine whether this sex difference in use of LTVV has narrowed over the years, we assessed the databases of 2 large longitudinal projects, the 'Medical Information Mart for Intensive Care III' (MIMIC–III) [23, 24] and the 'eICU Collaborative Research DataBase' (eICU) [25]. We also wished to determine which factors drive the sex difference. The aims were achieved, by testing the following hypotheses (1) that the difference in use of LTVV between females vs. males has narrowed, and (2) that the sex difference is mediated more by differences in patients' body height and weight, than by the use of a default V_T or sex per se.

Methods

For this analysis, data were retrieved from 2 conveniently–sized longitudinal projects, of which the databases contain granular data on ventilation management in ICU patients in the US between 2001 and 2015––the 'Medical Information Mart for Intensive Care III' (MIMIC–

III) v1.4 [23, 24], and the 'eICU Collaborative Research Database' (eICU) [25]. An elaborative description of these high temporal resolution databases can be found in the **S1 File**.

Ethical approval

The Institutional Review Board of the Beth Israel Deaconess Medical Center (2001–P–001699/14) and the Massachusetts Institute of Technology (No. 0403000206) approved the MIMIC III project. Requirement for individual patient consent was waived because the project did not impact clinical care and all protected health information was deidentified. The eICU was exempt from institutional review board approval due to its retrospective design, lack of direct patient intervention, and the security scheme, for which the re–identification risk was certified as meeting the safety standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219–2).

Patient selection

Patients were selected for inclusion in the current analysis if: 1) aged $\geq$ 16 years; and 2) having had received invasive ventilation for at least 48 consecutive hours from start of ventilation. Patients were excluded if death occurred before 48 hours, and if ventilation was provided through a tracheostomy cannula at any time during the first 48 hours of ventilation. Patients who had incomplete datasets or datasets that did not sufficiently capture absolute V_T, body height or actual body weight (ABW) were also excluded. In patients who were admitted for ventilation more than one time, only data of the first ICU admission of the first hospitalization were used.

Data extraction

Sex, body height and ABW data were extracted, in addition to other demographic data, including reason for and type of ICU admission, reason for invasive ventilation, and comorbidities. Body weight and height were collected from the medical records, i.e., the body weight and height as used for decisions in care. These could either be based on measurement at earlier contacts with a patient, measurements in the ward, or at admission to the ICU. Presence of ARDS was scored and classified, or re–classified when previous definitions were used, as 'mild', 'moderate' or 'severe' according to current Berlin definition for ARDS [26]. Ventilatory variables and parameters were extracted as the highest and the lowest values per time frame of 6 hours during the first 48 hours of ventilation. These values were summarized as the mean for every 6 hours and then as the median for the first 48 hours. V_T was collected and normalized for ABW and PBW, as follows:

$$VT, ABW = absolute\ VT\ [ml]/ABW\ [kg] \tag{Eq 1}$$

And

$$VT, PBW = absolute\ VT\ [ml]/PBW\ [kg] \tag{Eq 2}$$

PBW was calculated as follows:

$$PBW = 45.5 + 0.90 * ([body\ height\ in\ cm] - 152.4)(in\ females) \tag{Eq 3A}$$

And

$$PBW = 50.0 + 0.90 * ([body\ height\ in\ cm] - 152.4)(in\ males). \tag{Eq 3B}$$

LTVV was defined as having had received a median V_T over the first 48 hours $\leq$ 8 ml/kg PBW, a low V_T was defined as $V_{T,\ PBW} \leq$ 8 ml/kg PBW. A patient was defined as possibly having had received ventilation with a default V_T when the first two reported absolute V_T were 'rounded numbers' i.e., a V_T of 200, 250, 300, 350, 400, 450, 500, 550, 600 or 650 ml.

The primary outcome was use of LTVV. We also analysed which factors mediate the sex difference in use of LTVV.

Statistical analysis

No assumptions were made for missing data. Descriptive statistics were reported for the study population stratified according to sex, and as number and relative proportions for categorical variables and median [IQR] for continuous variables. For baseline characteristics, the groups were compared using Fisher exact tests for categorical variables and Wilcoxon rank–sum test for continuous variables. For all analyses, males were used as the reference.

All analyses were performed using multilevel (patients nested in hospitals, within the datasets), mixed modelling with hospitals as random effect and dataset as a fixed effect. Heterogeneity between datasets was determined by fitting a fixed interaction term between sex and dataset, while overall sex effect was reported with dataset treated as a fixed effect and hospitals treated as a random effect.

Ventilatory variables and parameters where compared over time, and between males and females, and absolute differences with the respective 95%–confidence interval (CI) were calculated as the absolute difference from a mixed–effect linear model considering the dataset as a fixed effect and the year of admission and centres as random effect to account for within–centre and year clustering. Categorical variables were compared as the risk difference from the same model.

Cumulative distribution plots were used to plot the cumulative distribution frequency of ventilation variables and parameters, for males and females according to tertiles of year of admission. The mode, and median with interquartile range [IQR] of absolute V_T, $V_{T,\ ABW}$, and $V_{T,\ PBW}$ were calculated. V_T, $V_{T,\ ABW}$, and $V_{T,\ PBW}$ were further assessed according quintiles of body height and ABW.

Temporal shifts in body height, ABW, absolute V_T, $V_{T,\ ABW}$, and $V_{T,\ PBW}$ over the calendar years were compared between females and males using mixed–effect longitudinal models with patients and centres as random effect, and the dataset, year, sex and an interaction of year and sex as fixed effects. Two P–values were reported: 1) P–value for sex differences, reflecting the overall test for difference between sex across the years; and 2) P–values for the sex x year interaction, evaluating if change over time differed by sex. In addition, a P–value from a three–way fixed interaction between dataset, sex a year was reported to assess the consistency of the findings among the datasets assessed.

The proportion of patients having had received LTVV were described and an unadjusted mixed–effect generalized linear model was used to extract the risk difference among sex. To further assess if use of LTVV is associated with sex, even after adjustment for confounders, a mixed–effect multivariable model with centres and years as random effect was done. The model was adjusted by covariates according to clinical relevance and when unbalanced among the groups, namely: age, body height, ABW, Oxford Severity of Illness Score (OASIS), Sequential Organ Failure Assessment (SOFA), type of admission, pH, $PaCO_2$, and use of a titrated (i.e., non–default) V_T. In all models, continuous variables were standardized to improve convergence, and absolute differences represents changes according to one standard deviation increase in the predictor.

To investigate whether the difference in the use of LTVV between females and males are due to differences in body height, ABW or the use of a 'fixed' possibly sex–specific V_T, a mixed–effect multivariable mediation model was used. In a first step in the mediation analysis, we assessed the individual impact of body height, ABW and having had received a default V_T as potential mediators for the difference in use of LTVV between sex in an univariable and multivariable model adjusted by all the covariates described above. For this model, Quasi–Bayesian 95% confidence intervals were estimated after 10,000 simulations. In a second step, body height, ABW, and having had received a default V_T were included simultaneously in the model to assess the impact and importance of each. In this second model the confidence intervals were estimated from robust clustered standard errors. All mediation models included year and centres as random effect.

All analyses were conducted in R v.3.60 and a P–value < 0.05 was considered statistically significant.

Posthoc analyses.   We performed two posthoc analyses. The first posthoc analysis concerned patients who were admitted because of sepsis, and including patients with pneumo–sepsis. In this analysis we repeated the main analysis to compare temporal shifts in absolute V_T, $V_{T, ABW}$, and $V_{T, PBW}$ over the calendar years between females and males.

In a second posthoc analysis we explored the differences between sexes during controlled ventilation versus spontaneous ventilation. Also here we followed the main analysis.

Results

Patients

After exclusion of patients not meeting inclusion and exclusion criteria, a total of 8207 patients (44% females; 56% males) remained for the final analysis––3846 patients in the MIMIC III database, and 4361 patients in the eICU database (**Fig 1 in S1 File**). Females were slightly older, appeared sicker on admission, and more often had a history of chronic obstructive pulmonary disease (**Tables 1 and 2 in S1 File**). Females were shorter than males, and had a lower ABW. Body height did not change, but ABW increased over the years, in females and in males (**Fig 2 in S1 File**).

Median absolute V_T, median peak, plateau and driving pressure, median minute ventilation, median respiratory rate and median mechanical power declined over the years, in females and males (**Fig 1**, **Table 1**; **Table 3 in S1 File**). Females received ventilation with a default V_T more often than males (**Fig 3 in S1 File**). While $V_{T, ABW}$ was similar in females versus males, $V_{T, PBW}$ remained persistently higher in females.

Use of LTVV

LTVV was increasingly used over the years, in females and males (**Fig 2**). In females versus males, use of LTVV increased from 5 to 50% versus from12 to 78% (difference, –27% [–29% to –25%]; P $<$ .001).

Mediation analysis

Results from the multivariate model are presented in **Table 2**; **Table 4 in S1 File**.

In the multivariable multiple mediation models, body height and ABW mediated the sex inequality in use of LTVV (**Table 3**). Use of default V_T mediated the sex difference in use of LTVV in a model that only used this factor (P = 0.021), but not in the model using also patients' body height and ABW.

Table 1. Ventilatory parameters in the first two days of ventilation[*].

	Females	Males	Absolute Difference[**]	p value
	(*n* = 3614)	(*n* = 4593)	(95% CI)	
First day of ventilation				
Tidal volume				
Absolute, mL	472 (412–518)	550 (500–615)	-86.45 (-89.95 to -82.95)	< 0.001
Mode	500	600	---	---
mL/kg PBW	8.6 (7.7–9.7)	7.6 (6.8–8.5)	1.00 (0.93 to 1.07)	< 0.001
Mode	8.0	6.8	---	---
mL/kg ABW	6.4 (5.2–7.9)	6.4 (5.3–7.6)	0.05 (-0.02 to 0.13)	0.161
Mode	8.0	6.1	---	---
Use of default tidal volume	1705 / 3468 (49.2)	1965 / 4443 (44.2)	4.93 (2.72 to 7.14)	< 0.001
PEEP, cmH$_2$O	5 (5–8)	5 (5–8)	-0.19 (-0.31 to -0.07)	0.002
Respiratory rate, mpm	18 (15–21)	18 (15–21)	-0.01 (-0.20 to 0.17)	0.886
Plateau pressure, cmH$_2$O	21 (17–25)	20 (16–24)	0.99 (0.73 to 1.25)	< 0.001
Driving pressure, cmH$_2$O	14 (12–18)	13 (11–16)	1.14 (0.92 to 1.36)	< 0.001
Peak pressure, cmH$_2$O	26 (21–30)	25 (20–29)	0.90 (0.61 to 1.19)	< 0.001
Minute ventilation, L/min	8.5 (7.0–10.1)	10.0 (8.2–12.0)	-1.59 (-1.69 to -1.49)	< 0.001
L/min PBW	0.15 (0.13–0.19)	0.14 (0.11–0.16)	0.02 (0.02 to 0.02)	< 0.001
Mechanical power, J/min	15.0 (11.0–20.0)	17.1 (12.4–23.5)	-2.71 (-3.04 to -2.39)	< 0.001
J/min PBW	0.27 (0.20–0.37)	0.23 (0.17–0.33)	0.04 (0.03 to 0.04)	< 0.001
Ventilatory ratio	1.90 (1.51 to 2.42)	1.74 (1.41 to 2.19)	-0.18 (-0.24 to -0.14)	< 0.001
Second day of ventilation				
Tidal volume				
Absolute, mL	455 (400–507)	550 (500–605)	-87.30 (-90.91 to -83.69)	< 0.001
Mode	500	600	---	---
mL/kg PBW	8.4 (7.6–9.6)	7.5 (6.8–8.4)	0.94 (0.87 to 1.01)	< 0.001
Mode	7.9	6.8	---	---
mL/kg ABW	6.3 (5.1–7.8)	6.3 (5.2–7.5)	0.03 (-0.05 to 0.10)	0.492
Mode	10.0	6.1	---	---
PEEP, cmH$_2$O	5 (5–8)	5 (5–9)	-0.28 (-0.41 to -0.15)	< 0.001
Respiratory rate, mpm	18 (15–21)	18 (15–21)	-0.05 (-0.25 to 0.15)	0.606
Plateau pressure, cmH$_2$O	21 (17–25)	20 (17–24)	0.70 (0.45 to 0.96)	< 0.001
Driving pressure, cmH$_2$O	14 (11–17)	13 (10–16)	0.95 (0.74 to 1.16)	< 0.001
Peak pressure, cmH$_2$O	25 (21–30)	25 (20–29)	0.31 (0.02 to 0.59)	0.035
Minute ventilation, L/min	8.2 (6.8–10.0)	9.9 (8.1–11.9)	-1.62 (-1.72 to -1.52)	< 0.001
L/min PBW	0.15 (0.12–0.18)	0.13 (0.11–0.16)	0.02 (0.01 to 0.02)	< 0.001
Mechanical power, J/min	14.5 (10.5–19.6)	17.0 (12.3–23.8)	-3.11 (-3.45 to -2.77)	< 0.001
J/min PBW	0.26 (0.19–0.36)	0.23 (0.16–0.33)	0.03 (0.02 to 0.04)	< 0.001
Ventilatory ratio	1.75 (1.40 to 2.20)	1.59 (1.28 to 1.98)	-0.15 (-0.19 to -0.12)	< 0.001

Data are median (quartile 25%–quartile 75%).

ABW: actual body weight; mpm: movements per minute; PBW: predicted body weight; PEEP: positive end–expiratory pressure.

[*] Data was aggregated as the median of 4 values per day (measured every 6 hours).

[**] Absolute difference calculated from a mixed–effect linear model with dataset and sex as fixed effect and hospitals as random effect.

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Posthoc analyses

The results of the posthoc analysis concerning 973 female and 1058 male patients with sepsis, did not change the findings, albeit that the differences did not reach statistical significance (**Fig

Table 2. Effect on low tidal volume ventilation*.

	Absolute Difference (95% CI)	*p* value
Female sex	-0.06 (-2.84 to 2.70)	0.964
Age	-1.12 (-2.19 to -0.05)	0.040
Weight	-8.10 (-9.22 to -6.99)	< 0.001
Height	22.97 (21.50 to 24.44)	< 0.001
OASIS	1.40 (0.18 to 2.63)	0.025
SOFA	-0.63 (-1.85 to 0.60)	0.314
Type of admission		
Elective surgery	0 (Reference)	- - -
Medical admission	8.36 (4.85 to 11.88)	< 0.001
Urgent surgery	4.79 (-1.43 to 11.01)	0.131
pH	-0.11 (-1.28 to 1.05)	0.847
$PaCO_2$	5.80 (4.65 to 6.95)	< 0.001
Use of titrated tidal volume	-4.30 (-6.39 to -2.19)	< 0.001

OASIS: Oxford acute severity of illness score; SOFA: Sequential Organ Failure Assessment.

* Absolute difference calculated from a mixed–effect multivariable model with centers and years as random effect.

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4 in S1 File). The second analysis in 1901 patients during controlled ventilation and 1190 patients during assisted ventilation illustrates that differences between the sexes were consistently present during controlled and spontaneous ventilation (**Fig 5 in S1 File**).

Discussion

The results of this analysis of 2 longitudinal projects can be summarized as follows: (1) the proportion of females and males receiving LTVV increased over the last decades, but females remained at a higher risk of not receiving LTVV; (2) modus and median absolute V_T, $V_{T, ABW}$, and $V_{T, PBW}$ declined, both in females and males, but $V_{T, PBW}$ remained persistently higher in
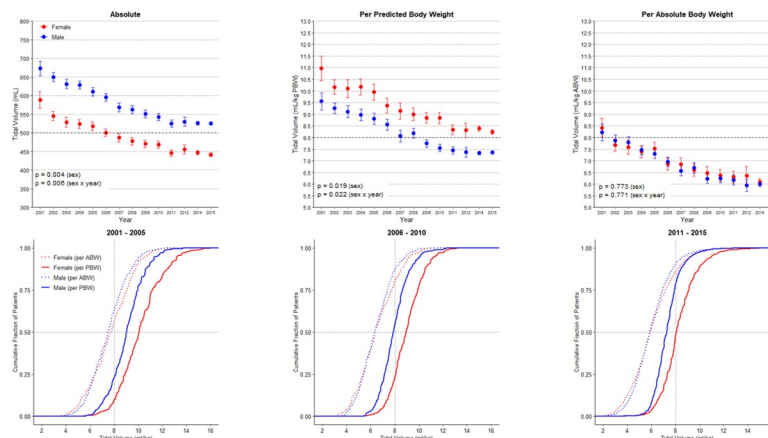
Fig 1. Absolute tidal volume and corrected tidal volume (by predicted body weight or absolute body weight) over years and according to tertiles of year. PBW: predicted body weight; ABW: actual body weight. *p* values for the sex reflect the overall test for difference between sex over the years while *p* values for the sex x year interaction evaluate if change over time differed by sex. There is no interaction between dataset and sex ($p = 0.311$, $p = 0.100$, $p = 0.483$ for absolute, corrected by PBW or ABW, respectively), or dataset and sex x year interaction ($p = 0.310$, $p = 0.100$, $p = 0.482$ for absolute, corrected by PBW or ABW, respectively).

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Table 3. Mediation analysis.

	Adjusted Absolute Difference (95% CI)[a]	p value
Univariable Mediation Model[b]		
Body height as mediator		
Total effect of sex	-27.6 (-29.7 to -26.0)	< 0.001
Average causal mediation effect of body height	-27.7 (-29.7 to -26.0)	< 0.001
Average direct effect of female sex	0.1 (-2.5 to 3.0)	0.940
Body weight as mediator		
Total effect of sex	-27.6 (-29.7 to -26.0)	< 0.001
Average causal mediation effect of body weight	1.0 (0.4 to 2.0)	< 0.001
Average direct effect of female sex	-28.6 (-30.7 to -26.0)	< 0.001
Default V_T as mediator		
Total effect of sex	-27.7 (-29.8 to -26.0)	< 0.001
Average causal mediation effect of titrated V_T	0.0 (-0.0 to 0.0)	0.150
Average direct effect of female sex	-27.7 (-29.9 to -26.0)	< 0.001
Body height, weight and titrated V_T as mediators*		
Total effect of sex	-28.0 (-32.2 to -23.9)	< 0.001
Average causal mediation effect of height	-30.7 (-34.2 to -27.2)	< 0.001
Average causal mediation effect of weight	3.3 (2.7 to 4.0)	< 0.001
Average causal mediation effect of titrated V_T	0.0 (-0.1 to 0.1)	0.818
Average direct effect of female sex	-0.7 (-3.8 to 2.5)	0.671
Multivariable Mediation Model[c]		
Body height as mediator**		
Total effect of sex	-28.4 (-30.7 to -26.0)	< 0.001
Average causal mediation effect of body height	-28.4 (-30.4 to -26.0)	< 0.001
Average direct effect of female sex	-0.0 (-2.8 to 3.0)	0.960
Body weight as mediator***		
Total effect of sex	-0.3 (-3.1 to 3.0)	0.820
Average causal mediation effect of body weight	-0.3 (-0.8 to 0.0)	0.310
Average direct effect of female sex	-0.0 (-2.8 to 3.0)	0.970
Default V_T as mediator****		
Total effect of sex	0.1 (-2.6 to 3.0)	0.939
Average causal mediation effect of titrated V_T	0.2 (0.0 to 0.0)	0.021
Average direct effect of female sex	-0.0 (-2.8 to 3.0)	0.968
Body height, weight and titrated V_T as mediators*		
Total effect of sex	-27.0 (-31.3 to -22.7)	< 0.001
Average causal mediation effect of body height	-30.1 (-33.5 to -26.6)	< 0.001
Average causal mediation effect of body weight	3.6 (2.9 to 4.4)	< 0.001
Average causal mediation effect of titrated V_T	0.1 (-0.1 to 0.2)	0.459
Average direct effect of female sex	-0.7 (-3.9 to 2.5)	0.679

[a] All estimated generated after 10,000 simulations if not otherwise indicated.

[b] Mixed–effect mediation model with Quasi–Bayesian confidence intervals, with hospitals and year as random effects and dataset as fixed effect.

[c] Mixed–effect mediation model with Quasi–Bayesian confidence intervals, with hospitals and year as random effects and dataset as fixed effect and adjusted for: age, OASIS, SOFA, type of admission, pH and $PaCO_2$.

* Confidence intervals estimated from robust clustered standard errors.

** Further adjusted by weight and titrated tidal volume.

*** Further adjusted by height and titrated tidal volume.

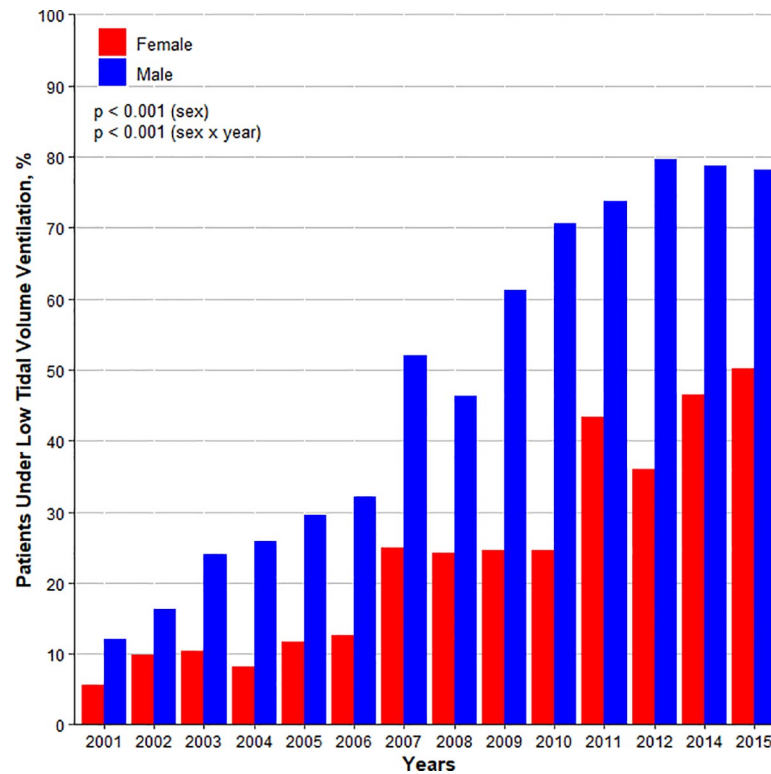**** Further adjusted by weight and height.

Fig 2. Percentage of patients receiving low tidal volume ventilation. Low tidal volume ventilation defined as a median of tidal volume in the first 48 hours of ventilation $\leq$ 8 ml/kg PBW. The overall difference on the use of low tidal volume ventilation among females and males corrected by the years is -26.7% (-28.8 to -24.6)%; $p < 0.001$. There is an interaction between dataset and sex ($p = 0.004$), and dataset and sex x year interaction ($p = 0.004$).

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females; and (3) differences in use of LTVV between females and males were almost completely mediated by differences in body height and ABW between the sexes.

Strengths of this analysis are the use of 2 conventionally–sized high temporal resolution databases that contain granular ventilation data of two well–defined cohorts of patients from several centres from 2001 to 2015. In addition, all ventilation data comprised measurements realized every 6 hours in the first 48 hours of ventilation, instead of once a daily timepoints. This made it possible to analyse temporal changes and to better understand which factors are associated with V_T titrations. The strict analysis plan, sophisticated statistical computations, and the mediation analysis made it possible to explain the difference in use of LTVV between females and males.

The finding that females receive ventilation with a higher $V_{T,\ PBW}$ than males is in line with results from previous investigations. Indeed, differences in median V_T of ~1 to ~1.5 ml/kg PBW have been reported in general ICU populations [21, 27–29], as well as in specific groups like patients with ARDS [30] or with sepsis–related lung injury [31]. and in organ donors [32]. The same was found in patients receiving intraoperative ventilation [22, 33–37]. In patients undergoing prolonged elective abdominal surgery it were the females, patients with shorter stature or higher BMI that seemed more likely to receive large tidal volumes during general anaesthesia [33]. This association was also found in studies of patients undergoing intraoperative ventilation during general anaesthesia for surgery [34, 35]. The current study adds to these findings by showing that, the ICU sex inequality in use of LTVV is not a 'sex–issue', as differences in V_T are driven by differences in patients' body height and weight and not by sex per se.

In the ICU setting, body height is frequently overestimated [17, 18], in particular in shorter patients [13, 19, 20]. In the here analysed cohorts, males were median 15 cm taller than females, which mirrors previous findings that worldwide males are on average >10 cm taller than females [5, 6, 31]. This difference could explain, at least in part, why females, who are thus usually shorter, are at a higher risk of not receiving LTVV [30, 31]. This is exactly what the mediation analysis suggests––body height is the most important mediator of the sex difference in LTVV.

A possible explanation could be a mismeasurement of body height. In ICU patients, ABW is frequently overestimated [13, 18–20], and it are the shorter patients in whom this happens most often [19]. The median difference in ABW between females and males of 14 kg in the here analysed cohorts, resembles findings in another study [18]. While V_T should be titrated to PBW, and not to the ABW, this was often neglected [38, 39]. When V_T is erroneously titrated to ABW, and if ABW is overestimated more often in shorter individuals, this could be another reason for why females receive LTVV less often than males. Yet, this is what was also suggested by the mediation analysis, albeit that it was a less important mediator than body height.

ICU patients frequently receive ventilation with a default V_T [30]. The findings of the current analysis suggest that the proportion of females and males who possibly received ventilation with a default V_T evolved in opposite ways, i.e., a decrease in females versus an increase in males. The reason for this remains unexplained. The benefits from using default V_T are that this approach is more straightforward and easier to implement than performing a difficult calculation at the bedside. However, using a default V_T has the potential to harm females more since their shorter body height makes that they are at greatest risk of receiving higher V_T [40]. Nevertheless, use of default V_T was associated with increased use of LTVV. Of note, the mediation analysis suggested that use of a default V_T had a very small, actually negligible effect on the sex difference in use of LTVV.

There is abundant and convincing evidence that the use of an incorrect (i.e., too high) V_T is associated with higher mortality and morbidity in ICU patients [21, 28, 29, 41–43]. In fact, V_T is one of the key elements of lung–protective ventilation. Critically ill females tend to develop ARDS more often, and also have higher mortality rates [21, 28]. In addition, in female patients after cardiac surgery, a higher V_T was found to have independent associations with organ dysfunction and prolonged ICU stay [29]. Whether the temporal changes in the current analysis translate in better outcomes, and whether this is different for females and males, cannot be reliably determined since we could not correct for temporal changes in other care processes that certainly have an impact on outcome as well. This analysis has a number of limitations. First, it was a posthoc analysis. Second, the present findings cannot be translated to patients ventilated through a tracheostomy canula or who died in the first 48 hours, since these patients were excluded from the current analysis. Only patients who received invasive ventilation for at least 48 hours were considered, this cohort will therefore consist of a selection of more severely ill patients, and may not generalize to the patients admitted to the ICU receiving invasive ventilation that are extubated within 48 hours. Third, the current analysis is the assumption that a rounded V_T is a default V_T. Fourth, differences between the sexes in the posthoc analysis considering only patients with sepsis were not statistically significant. This, however, was probably to a lack of power since the number of patients used for this analysis was smaller. Of note, we only had information on ventilatory mode in the MIMIC-III database, as this was not collected in the eICU study.

Conclusion

In these 2 large longitudinal projects spanning 2 decades of ventilation care for critically ill patients, we noticed a clear trend towards increased use of LTVV in females and males.

However, females continued to receive LTVV less often than males, a difference that seems mainly driven by differences in patients' body height and ABW, and not by sex or the use of a default V_T. These findings point out the importance to obtain a better insight into the practical challenges of titrating V_T and the influence of these challenges on the use of LTVV.

Supporting information

S1 File. The supplement 'S1_File' contains all the supporting files for this submission. (DOCX)

Acknowledgments

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References

1. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000; 342(18):1301–8. https://doi.org/10.1056/NEJM200005043421801 PMID: 10793162

2. Pontoppidan H, Hedley-Whyte J, Bendizen HH, Laver MB, Radford EP Jr. Ventilation and oxygen requirements during prolonged artificial ventilation in patients with respiratory failure. N Engl J Med. 1965; 273:401–9. https://doi.org/10.1056/NEJM196508192730801 PMID: 14328102

3. Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. N Engl J Med. 1963; 269:991–6. https://doi.org/10.1056/NEJM196311072691901 PMID: 14059732

4. Schaefer MS, Serpa Neto A, Pelosi P, Gama de Abreu M, Kienbaum P, Schultz MJ, et al. Temporal Changes in Ventilator Settings in Patients With Uninjured Lungs: A Systematic Review. Anesth Analg. 2019; 129(1):129–40. https://doi.org/10.1213/ANE.0000000000003758 PMID: 30222649

5. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. Jama. 2016; 315(8):788–800. https://doi.org/10.1001/jama.2016.0291 PMID: 26903337

6. Neto AS, Barbas CSV, Simonis FD, Artigas-Raventos A, Canet J, Determann RM, et al. Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PRoVENT): an international, multicentre, prospective study. Lancet Respir Med. 2016; 4(11):882–93. https://doi.org/10.1016/S2213-2600(16)30305-8 PMID: 27717861

7. Ferguson ND. Low tidal volumes for all? Jama. 2012; 308(16):1689–90. https://doi.org/10.1001/jama.2012.14509 PMID: 23093167

8. Marini JJ. Lower tidal volumes for everyone: principle or prescription? Intensive Care Medicine. 2013; 39(1):3–5. https://doi.org/10.1007/s00134-012-2754-2 PMID: 23179334

9. Kilickaya O, Gajic O. Initial ventilator settings for critically ill patients. Critical Care. 2013; 17(2):123. https://doi.org/10.1186/cc12516 PMID: 23510269

10. Serpa Neto A, Simonis FD, Barbas CS, Biehl M, Determann RM, Elmer J, et al. Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis. Intensive Care Med. 2014; 40(7):950–7. https://doi.org/10.1007/s00134-014-3318-4 PMID: 24811940

11. Simonis FD, Binnekade JM, Braber A, Gelissen HP, Heidt J, Horn J, et al. PReVENT—protective ventilation in patients without ARDS at start of ventilation: study protocol for a randomized controlled trial. Trials. 2015; 16:226. https://doi.org/10.1186/s13063-015-0759-1 PMID: 26003545

12. L'Her E, Martin-Babau J, Lellouche F. Accuracy of height estimation and tidal volume setting using anthropometric formulas in an ICU Caucasian population. Ann Intensive Care. 2016; 6(1):55. https://doi.org/10.1186/s13613-016-0154-4 PMID: 27325410

13. Determann RM, Wolthuis EK, Spronk PE, Kuiper MA, Korevaar JC, Vroom MB, et al. Reliability of height and weight estimates in patients acutely admitted to intensive care units. Crit Care Nurse. 2007; 27(5):48–55; quiz 6. PMID: 17901460

14. Hemmes SNT, Ball L, Serpa Neto A, de Abreu MG, Pelosi P, Schultz MJ. Are height and weight estimates in ED patients reliable for setting the ventilator? Am J Emerg Med. 2017; 35(12):1963–4. https://doi.org/10.1016/j.ajem.2017.06.003 PMID: 28610772

15. O'Brien ID, Shacklock E, Middleditch A, Bigham C. Inaccuracies in calculating predicted body weight and its impact on safe ventilator settings. J Intensive Care Soc. 2016; 17(3):191–5. https://doi.org/10.1177/1751143715626163 PMID: 28979490

16. Stehman CR, Buckley RG, Dos Santos FL, Riffenburgh RH, Swenson A, Mulligan S, et al. Bedside estimation of patient height for calculating ideal body weight in the emergency department. J Emerg Med. 2011; 41(1):97–101. https://doi.org/10.1016/j.jemermed.2009.12.016 PMID: 20189741

17. Bloomfield R, Steel E, MacLennan G, Noble DW. Accuracy of weight and height estimation in an intensive care unit: Implications for clinical practice and research. Crit Care Med. 2006; 34(8):2153–7. https://doi.org/10.1097/01.CCM.0000229145.04482.93 PMID: 16763505

18. Maskin LP, Attie S, Setten M, Rodriguez PO, Bonelli I, Stryjewski ME, et al. Accuracy of weight and height estimation in an intensive care unit. Anaesth Intensive Care. 2010; 38(5):930–4. https://doi.org/10.1177/0310057X1003800519 PMID: 20865881

19. Sasko B, Thiem U, Christ M, Trappe HJ, Ritter O, Pagonas N. Size matters: An observational study investigating estimated height as a reference size for calculating tidal volumes if low tidal volume ventilation is required. PLoS One. 2018; 13(6):e0199917. https://doi.org/10.1371/journal.pone.0199917 PMID: 29958278

20. Bojmehrani A, Bergeron-Duchesne M, Bouchard C, Simard S, Bouchard PA, Vanderschuren A, et al. Comparison of usual and alternative methods to measure height in mechanically ventilated patients: potential impact on protective ventilation. Respir Care. 2014; 59(7):1025–33. https://doi.org/10.4187/respcare.02732 PMID: 24255160

21. McNicholas BA, Madotto F, Pham T, Rezoagli E, Masterson CH, Horie S, et al. Demographics, management and outcome of females and males with acute respiratory distress syndrome in the LUNG SAFE prospective cohort study. Eur Respir J. 2019; 54(4). https://doi.org/10.1183/13993003.00609-2019 PMID: 31346004

22. Nijbroek S, Serpa Neto A, Hemmes S, Schultz M. Intraoperative ventilation management differs between genders–insights from a worldwide prospective cohort study. European Respiratory Journal. 2020; 56(suppl 64):2598.

23. Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. Sci Data. 2016; 3:160035. https://doi.org/10.1038/sdata.2016.35 PMID: 27219127

24. Johnson AE, Stone DJ, Celi LA, Pollard TJ. The MIMIC Code Repository: enabling reproducibility in critical care research. J Am Med Inform Assoc. 2018; 25(1):32–9. https://doi.org/10.1093/jamia/ocx084 PMID: 29036464

25. Goldberger AL, Amaral LA, Glass L, Hausdorff JM, Ivanov PC, Mark RG, et al. PhysioBank, Physio-Toolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation. 2000; 101(23):E215–20. https://doi.org/10.1161/01.cir.101.23.e215 PMID: 10851218

26. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. Jama. 2012; 307(23):2526–33. https://doi.org/10.1001/jama.2012.5669 PMID: 22797452

27. ESICM LIVES 2018: Paris, France. 20–24 October 2018. Intensive Care Med Exp. 2018;6(Suppl 2):40.

28. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med. 2004; 32(9):1817–24. https://doi.org/10.1097/01.ccm.0000133019.52531.30 PMID: 15343007

29. Lellouche F, Dionne S, Simard S, Bussieres J, Dagenais F. High tidal volumes in mechanically ventilated patients increase organ dysfunction after cardiac surgery. Anesthesiology. 2012; 116(5):1072–82. https://doi.org/10.1097/ALN.0b013e3182522df5 PMID: 22450472

30. Walkey AJ, Wiener RS. Risk factors for underuse of lung-protective ventilation in acute lung injury. J Crit Care. 2012; 27(3):323.e1–9. https://doi.org/10.1016/j.jcrc.2011.06.015 PMID: 21855285

31. Han S, Martin GS, Maloney JP, Shanholtz C, Barnes KC, Murray S, et al. Short women with severe sepsis-related acute lung injury receive lung protective ventilation less frequently: an observational cohort study. Crit Care. 2011; 15(6):R262. https://doi.org/10.1186/cc10524 PMID: 22044724

32. Chapa J, Nonas S. Differences in lung protective ventilation use in female vs male organ donors. Chest. 2018; 154(4):1101A.

33. Fernandez-Bustamante A, Wood CL, Tran ZV, Moine P. Intraoperative ventilation: incidence and risk factors for receiving large tidal volumes during general anesthesia. BMC Anesthesiol. 2011; 11:22. https://doi.org/10.1186/1471-2253-11-22 PMID: 22103561

34. Wanderer JP, Ehrenfeld JM, Epstein RH, Kor DJ, Bartz RR, Fernandez-Bustamante A, et al. Temporal trends and current practice patterns for intraoperative ventilation at U.S. academic medical centers: a retrospective study. BMC Anesthesiol. 2015; 15:40. https://doi.org/10.1186/s12871-015-0010-3 PMID: 25852301

35. Bender SP, Paganelli WC, Gerety LP, Tharp WG, Shanks AM, Housey M, et al. Intraoperative Lung-Protective Ventilation Trends and Practice Patterns: A Report from the Multicenter Perioperative Outcomes Group. Anesth Analg. 2015; 121(5):1231–9. https://doi.org/10.1213/ANE.0000000000000940 PMID: 26332856

36. Karalapillai D, Weinberg L, Galtieri J, Glassford N, Eastwood G, Darvall J, et al. Current ventilation practice during general anaesthesia: a prospective audit in Melbourne, Australia. BMC Anesthesiol. 2014; 14:85. https://doi.org/10.1186/1471-2253-14-85 PMID: 25302048

37. Kowa CY, Jin Z, Longbottom R, Cullinger B, Walker P. Risk factors for excessive tidal volumes delivered during intraoperative mechanical ventilation, a retrospective study. Int J Physiol Pathophysiol Pharmacol. 2020; 12(2):51–7. PMID: 32419900

38. Kam EP, Eslick GD, James A, Benson JP. Acute respiratory distress syndrome (ARDS) and low tidal volume ventilation: the debate about weight. Intensive Care Med. 2004; 30(7):1502. https://doi.org/10.1007/s00134-004-2277-6 PMID: 15185067

39. Wolthuis EK, Korevaar JC, Spronk P, Kuiper MA, Dzoljic M, Vroom MB, et al. Feedback and education improve physician compliance in use of lung-protective mechanical ventilation. Intensive Care Med. 2005; 31(4):540–6. https://doi.org/10.1007/s00134-005-2581-9 PMID: 15731892

40. Schultz MJ, Karagiannidis C. Is gender inequity in ventilator management a "women's issue"? European Respiratory Journal. 2019; 54(4):1901588. https://doi.org/10.1183/13993003.01588-2019 PMID: 31624130

41. Lanspa MJ, Peltan ID, Jacobs JR, Sorensen JS, Carpenter L, Ferraro JP, et al. Driving pressure is not associated with mortality in mechanically ventilated patients without ARDS. Crit Care. 2019; 23(1):424. https://doi.org/10.1186/s13054-019-2698-9 PMID: 31881909

42. Madotto F, Pham T, Bellani G, Bos LD, Simonis FD, Fan E, et al. Resolved versus confirmed ARDS after 24 h: insights from the LUNG SAFE study. Intensive Care Med. 2018; 44(5):564–77. https://doi.org/10.1007/s00134-018-5152-6 PMID: 29632996

43. Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Biehl M, Binnekade JM, et al. Protective versus Conventional Ventilation for Surgery: A Systematic Review and Individual Patient Data Meta-analysis. Anesthesiology. 2015; 123(1):66–78. https://doi.org/10.1097/ALN.0000000000000706 PMID: 25978326