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ORIGINAL ARTICLE

Intermediate tidal volume is an acceptable option for ventilated patients with acute respiratory distress syndrome

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KEYWORDS
Acute respiratory distress syndrome;
Mechanical ventilation;
Tidal volume;
Ventilator-induced lung injury

Abstract
Objective: Evidence only proves low surpasses high tidal volume (V_T) for acute respiratory distress syndrome (ARDS). Intermediate V_T is a common setting for ARDS patients and has been demonstrated as effective as low V_T in non-ARDS patients. The effectiveness of intermediate V_T in ARDS has not been studied and is the objective of this study.
Design: A retrospective cohort study.
Setting: Five ICUs with their totally 130 beds in Taiwan.
Patients or participants: ARDS patients under invasive ventilation.
Interventions: No.
Main variables of interest: 28-D mortality.
Result: Totally 382 patients, with 6958 ventilator settings eligible for lung protection, were classified into low (mean $V_T = 6.7$ ml/kg), intermediate (mean $V_T = 8.9$ ml/kg) and high (mean $V_T = 11.2$ ml/kg) V_T groups. With similar baseline ARDS and ICU severities, intermediate and low V_T groups did not differ in 28-D mortality (47% vs. 63%, $P = 0.06$) or other outcomes such as 90-D mortality, ventilator-free days, ventilator-dependence rate. Multivariate analysis revealed high V_T was independently associated with 28-D and 90-D mortality, but intermediate V_T was not significantly associated with 28-D mortality (HR 1.34, CI 0.92–1.97, $P = 0.13$) or 90-D mortality. When the intermediate and low V_T groups were matched in propensity scores ($n = 66$ for each group), their outcomes were also not significantly different.

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Conclusion: Intermediate V_T, with its outcomes similar to small V_T, is an acceptable option for ventilated ARDS patients. This conclusion needs verification through clinical trials.

PALABRAS CLAVE
Síndrome de dificultad respiratoria aguda;
Ventilación mecánica;
Volumen corriente;
Lesión pulmonar inducida por ventilación

El volumen tidal intermedio es una opción aceptable para pacientes ventilados con síndrome de dificultad respiratoria aguda

Resumen
Objetivo: La evidencia solo demuestra que el volumen tidal (V_T) bajo supera al alto para el síndrome de dificultad respiratoria aguda (ARDS). La V_T intermedia es un escenario común para los pacientes con ARDS y se ha demostrado que es tan eficaz como la V_T baja en pacientes sin ARDS. No se ha estudiado la eficacia de la V_T intermedia en el ARDS y es el objetivo de este estudio.
Diseño: Un estudio de cohorte retrospectivo.
Ámbito: Cinco UCI con un total de 130 camas en Taiwán.
Pacientes o participantes: Pacientes con ARDS bajo ventilación invasiva.
Intervenciones: No.
Variables de interés principales: Mortalidad 28-D.
Resultado: Un total de 382 pacientes, con 6958 configuraciones de ventilador elegibles para protección pulmonar, se clasificaron en bajo (V_T medio = 6,7 ml/kg), intermedio (V_T medio = 8,9 ml/kg) y alto (V_T medio = 11,2 ml/kg). Grupos de V_T. Con un ARDS inicial similar y una gravedad en la UCI, los grupos de V_T intermedia y baja no difirieron en la mortalidad 28-D (47% vs. 63%, p = 0,06) u otros resultados como mortalidad 90-D, días sin ventilador, dependencia del ventilador índice. El análisis multivariado reveló que la V_T alta se asoció de forma independiente con la mortalidad 28-D y 90-D, pero la V_T intermedia no se asoció significativamente con la mortalidad 28-D (HR 1,34, IC 0,92-1,97, p = 0,13) o la mortalidad 90-D. Cuando los grupos de V_T intermedia y baja se emparejaron en puntajes de propensión (n = 66 para cada grupo), sus resultados tampoco fueron significativamente diferentes.
Conclusión: La V_T intermedia, con resultados similares a la V_T pequeña, es una opción aceptable para pacientes con ARDS ventilados. Esta conclusión necesita verificación a través de ensayos clínicos.

Introduction

Mechanical ventilator support remains the cornerstone of acute respiratory distress syndrome (ARDS) management. Many harmful effects of mechanical ventilation, such as ventilator-induced lung injury (VILI), have been recognized and led to the development of a lung-protective ventilatory strategy, mainly by keeping tidal volume (V_T) low. A well-known study by the ARDS Network in 2000 demonstrated that low V_T (6 ml/kg predicted body weight, PBW) is better than high V_T (12 ml/kg PBW) in terms of mortality and ventilator-free days.[1] The superiority of low V_T in this study may stem more from avoiding the harmful effects of high V_T (12 ml/kg PBW) and plateau pressure (up to 50 cmH_2O) than strict adherence to low V_T per se. This speculation was supported by 3 futile clinical trials in low V_T before the year 2000.[2–4] With V_T around 10 ml/kg PBW and plateau pressure less than 31 cmH_2O in the control groups, the beneficial effects of low V_T were completely abolished in these 3 studies.[5] Therefore, we hypothesize that intermediate V_T (7.5–10 ml/kg PBW), by shunning the deleterious effects of high V_T, could also be lung-protective as low V_T.

Two decades after the publication of the landmark study,[1] low V_T adherence remains poor throughout the world.[6,7] A survey of Chicago physicians found that more than 92% knew that patients with ARDS warranted low V_T ventilation, but they ordered low V_T in only 7% (0–14%) of their eligible patients.[8] The reasons for nonadherence to low V_T ventilation are complex. Some physicians are skeptical about applying evidence derived from randomized control trials to critical care practice,[9,10] some may concern complications of low V_T such as hypercapnia,[11] air hunger sensation[12] and possible self-inflicted lung injury if there is no adequate sedation or paralysis.[13] Therefore, many physicians adopt a less strict version of lung protection ventilation. Intermediate V_T was found in some studies to be the most commonly applied ventilator setting for patients with ARDS.[14,15]

Intermediate V_T has been shown to be as effective as low V_T for ventilated patients without ARDS in terms of mortality and other clinical outcomes.[16–18] However, the role of intermediate V_T in patients with ARDS has not been

carefully studied. Data inferred from a study of 111 real-world patients with ARDS suggest that the mean V_T of 9.5 ml/kg PBW is not inferior to 6.1 ml/kg PBW in terms of 28-day or 1-year mortality rate.[19] In this study, we retrospectively compared the clinical outcomes of patients with ARDS who received intermediate and low V_T.

Method

Patient enrollment

We retrospectively collected invasively ventilated patients with ARDS admitted to Changhua Christian Hospital, a medical center with a total of 130 ICU beds in 5 separate wards, between January 2012 and November 2018. These patients were identified by their discharge diagnoses of ARDS and acute respiratory failure in electronic archives. Each diagnosis of ARDS was defined by the Berlin definition[20] and was reconfirmed by one of our pulmonologists (SHW or YCH). Exclusion criteria include age less than 20 or over 90 years, actual body weight less than 40 or over 100 kg, been transferred to other hospital or discharged against medical advice without traceable clinical outcome, a total duration of invasive ventilation less than 48 h, using airway pressure release ventilation or high-frequency oscillation ventilation or extracorporeal membrane oxygenation during the ARDS period, been withdrawn from the ventilator due to hospice, co-morbidities of metastatic malignancy, end-stage heart failure (left ventricular ejection fraction less than 35%) or ventilator-dependence (invasive ventilation lasting over 21 days before the onset of ARDS), been enrolled in other ARDS-related clinical trials. The patients were followed until death or the 90th day after ARDS was diagnosed. The study was approved by the institutional review board of Changhua Christian Hospital (Approval No. 181214). The Board has waived the requirement for informed consent from participants.

Characteristics of the patients and treatment variables

Baseline variables when ARDS was diagnosed for the first time were collected. They include age, sex, body mass index, acute physiology and chronic health evaluation II (APACHE II) score,[21] sequential organ failure assessment (SOFA) score,[22] co-morbidity, predisposing factors for ARDS and type of ICU admitted. Whether patients received sedation, muscle relaxant, systemic steroid, vasopressor, hemodialysis, continuous hemofiltration, prone position, or total parenteral nutrition during the ARDS period were recorded.

Ventilator setting and monitoring parameters when eligible for lung protection

Ventilator settings were recorded every 8 h until ventilator discontinuation or the 28th day after diagnosing ARDS. If a fraction of inspired oxygen (F_IO_2) $\geq$ 50% and positive end-expiratory pressure (PEEP) was greater than 5 cmH_2O, it was considered eligible for lung protection. This definition of eligibility was made because it approximated the threshold for a trial of spontaneous breathing without further restriction in V_T or plateau pressure in the ARDS Network ventilation protocol.[23] V_T and other ventilator parameters were counted and analyzed only when the occasions were eligible for lung protection. The mean V_T was categorized based on each patient's predicted body weight[1] into low (<7.5 ml/kg PBW),[19,24,25] intermediate (7.5–10 ml/kg PBW)[18] and high (>10 ml/kg PBW).[16] Other parameters collected include airway pressure (peak, mean, plateau, driving), PEEP, respiratory system compliance (C_{RS}), and arterial oxygenation (P_aO_2, S_pO_2, P_aO_2/F_IO_2 ratio). When patients were under pressure-targeted ventilation and their plateau pressures were not measured directly, we used the peak airway pressure or the sum of PEEP and set increment of inspiratory pressure to represent plateau pressure.[23]

Outcome assessment

The primary outcome was mortality rate of 28 days. Secondary outcome included a 90-day mortality rate, ventilator-free days during the initial 28 days, and ventilator-dependence rate on day 28 (excluding the patient who died within 28 days).

Statistical analysis

Data were expressed as a number (percent), mean $\pm$ standard deviation or median, interquartile range (IQR). Each variable was tested for normal distribution using the Kolmogorov–Smirnov test. For the comparison of three groups of continuous variables, we used the analysis of variance or the Kruskal–Wallis analysis of variance test. Regarding categorical variables, the Chi-square or Fisher's exact test was used when appropriate. The Bonferroni-adjusted post hoc significance test was used to compare low and intermediate V_T. Uni- and multi-variate Cox proportional hazards regression with backward selection procedure were used to assess hazard ratios (HR) and 95% confidence interval (CI) of mortality. V_T category was retained in the models as a priori basis. Variables with a *P*-value of less than 0.10 in the crude model entered the multivariate model during backward selection. The propensity score was calculated by non-parsimonious multivariable logistic regression. All variables, except respiratory parameters, were considered. Propensity score matching was performed to balance the distributions of measured covariates in the low- and intermediate-V_T groups. We matched each patient in the low V_T group with one of the intermediate V_T group based on propensity scores with a caliper of 0.1 standard deviation unit. All respiratory parameters were tested for collinearities using the variance inflation factor (VIF). A VIF over 2 indicates the presence of collinearity and it was excluded from the model. A *P*-value of less than 0.05 was considered significant. All statistical analyses were performed using the SPSS statistical package (IBM SPSS Statistics, version 20, IBM Corporation, Chicago, IL, USA).

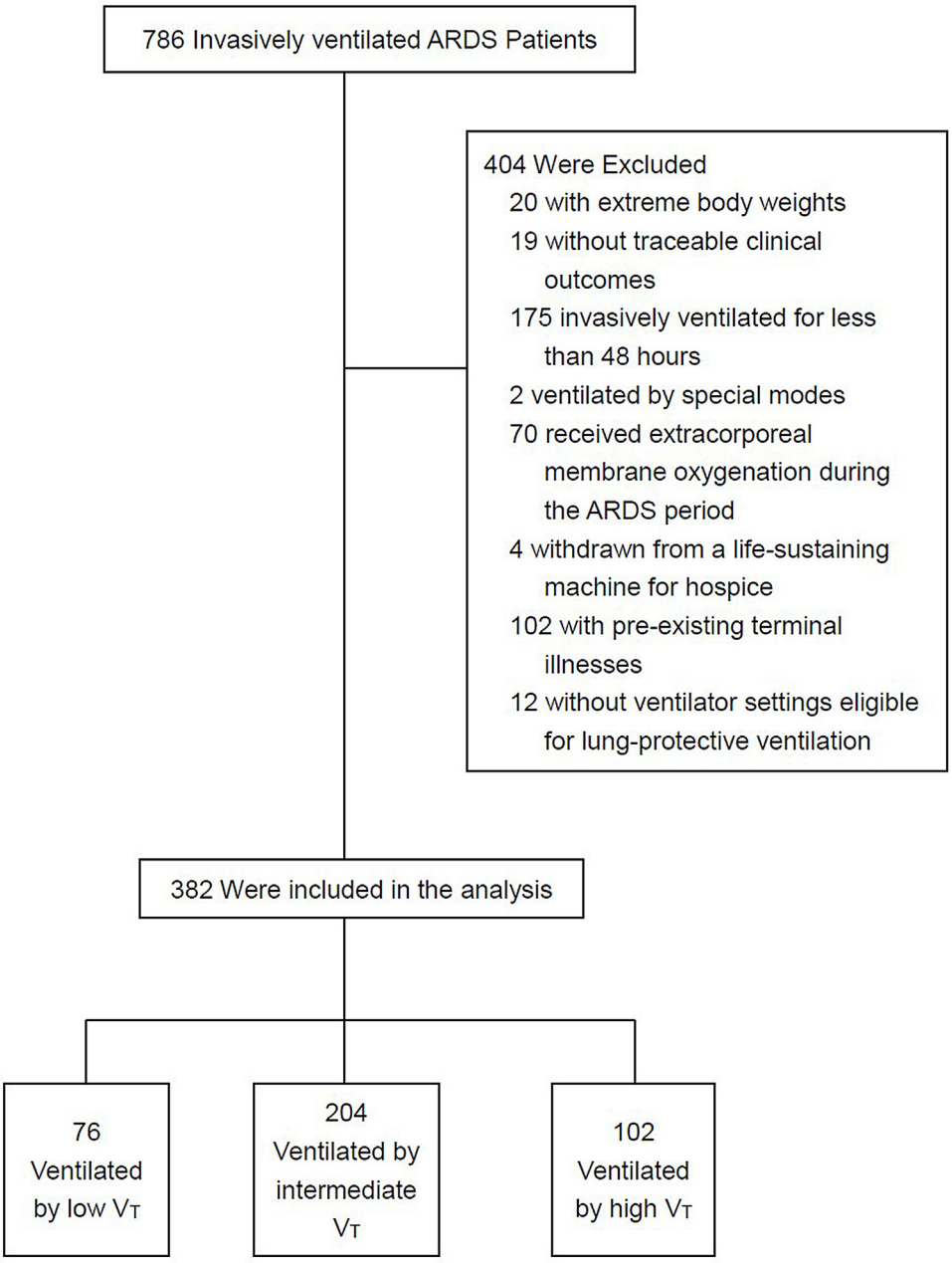

Figure 1 Flowchart of patients included in the final analysis.

Result

Totally 786 patients were invasively ventilated for their ARDS and acute respiratory failure. Four hundred and four patients were excluded because of 20 with extreme body weights, 19 without traceable clinical outcomes, 175 invasively ventilated for less than 48 h, 2 ventilated by special modes, 70 received extracorporeal membrane oxygenation during the ARDS period, 4 withdrawn from a life-sustaining machine for hospice, 102 with pre-existing terminal illnesses and 12 without ventilator settings eligible for lung-protective ventilation. Therefore, 382 patients, with a total of 6958 ventilator settings eligible for lung-protective ventilation, were analyzed. A flowchart of patients included in the final analysis was presented in Fig. 1.

The patients were classified into low (mean V_T = 6.7 ml/kg PBW, n = 76, 19.9%), intermediate (mean V_T = 8.9 ml/kg PBW, n = 204, 53.4%) and high (mean V_T = 11.2 ml/kg PBW, n = 102, 26.7%) V_T groups according to their mean V_T while eligible for lung protection. Their baseline characteristics, treatment, and ventilator setting variables are summarized in Table 1. Intermediate and low V_T groups did not differ in their baseline APACHE II or SOFA scores. Both groups also have a comparable baseline ARDS severity distribution. The driving pressures the patients received were not significantly different.

Table 1 Baseline characteristics and treatment variables.

	Low V_T ($n = 76$)	Intermediate V_T ($n = 204$)	High V_T ($n = 102$)	*P*-value	Adjusted *P*-value[c] of intermediate vs. low V_T
Age (year), mean ± SD	61 ± 17	64 ± 16	66 ± 15	0.17	0.70
Male, No. (%)	61 (80)	145 (71)	58 (57)	<0.01	0.36
Body mass index, median (IQR), (kg/m²)	22 (19–24)	23 (20–26)	23 (21–26)	0.01	0.01
APACHE II Score, median (IQR)	25 (21–30)	25 (19–29)	21 (17–30)	0.21	1.00
SOFA score, median (IQR)	7 (5–10)	8 (5–10)	7 (5–9)	0.65	1.00
Severity of ARDS at diagnosis					
mild, No. (%)	16 (21)	41 (21)	26 (28)	0.55	0.99
moderate, No. (%)	30 (40)	92 (48)	48 (51)	0.58	0.48
severe, No. (%)	29 (39)	60 (31)	20 (21)	0.02	0.21
P_aO_2/F_IO_2 at diagnosis	119 (90–176)	126 (95–180)	154 (109–208)	0.03	0.98
Etiology					
Sepsis, No. (%)	32 (42)	80 (39)	42 (41)	0.91	1.00
Pneumonia, No. (%)	62 (82)	149 (73)	60 (59)	<0.01	0.47
Pancreatitis, No. (%)	1 (1)	9 (4)	3 (3)	0.42	0.64
Aspiration, No. (%)	4 (5)	14 (7)	8 (8)	0.80	1.00
Blood transfusion, No. (%)	7 (9)	25 (12)	15 (15)	0.54	1.00
Others or Unknown, No. (%)	9 (12)	27 (13)	26 (26)	0.04	1.00
Comorbidity					
Chronic obstructive pulmonary disease, No. (%)	27 (36)	71 (35)	29 (28)	0.48	1.00
Diabetes mellitus, No. (%)	35 (46)	73 (36)	32 (31)	0.12	0.35
Hypertension, No. (%)	28 (37)	98 (48)	55 (54)	0.08	0.28
Chronic kidney disease, No. (%)	11 (14)	27 (13)	13 (13)	0.94	1.00
Heart failure, No. (%)	20 (26)	66 (32)	33 (32)	0.60	0.99
Cerebral vascular accident, No. (%)	13 (17)	56 (27)	22 (22)	0.16	0.22
Liver cirrhosis, No. (%)	8 (10)	25 (12)	11 (11)	0.89	1.00
Malignancy, No. (%)	23 (30)	44 (22)	22 (22)	0.28	0.39
Immunosuppressed, No. (%)	15 (20)	30 (15)	26 (25)	0.07	0.92
Surgical ICU admission, No. (%)	5 (7)	22 (11)	30 (29)	<0.01	0.87
Cumulative fluid balance in the 1st week, median (IQR), (L)	5 (2–9)	4 (1–8)	4 (0–7)	0.55	1.00
Treatment received during ARDS					
Sedation, No. (%)	73 (96)	187 (92)	93 (91)	0.40	0.62
Muscle relaxant, No. (%)	75 (99)	189 (93)	80 (78)	<0.01	0.08
Single shot facilitating intubation	1 (1)	6 (3)	7 (9)	0.13	0.10
Continuous infusion facilitating synchrony	65 (87)	150 (79)	63 (79)		
For both intubation and synchrony	9 (12)	33 (17)	10 (12)		
Vasopressor, No. (%)	62 (82)	160 (78)	74 (73)	0.32	1.00
Total parenteral nutrition, No. (%)	13 (17)	36 (18)	26 (25)	0.22	1.00
Systemic steroid, No. (%)	69 (91)	172 (84)	81(79)	0.12	0.49
Prone position, No. (%)	15 (20)	25 (12)	2 (2)	<0.01	0.34
Hemodialysis, No. (%)	13 (17)	27 (13)	10 (10)	0.36	1.00
Continuous hemofiltration, No. (%)	35 (46)	72 (35)	20 (20)	<0.01	0.30

Table 1 (*Continued*)

	Low V_T ($n=76$)	Intermediate V_T ($n=204$)	High V_T ($n=102$)	*P*-value	Adjusted *P*-value[c] of intermediate vs. low V_T
Respiratory parameters when eligible for lung protection, median (IQR)					
V_T/PBW (ml/Kg)	6.7 (6.2–7.1)	8.9 (8.3–9.4)	11.2 (10.6–12.0)	<0.01	<0.01
C_{RS}[a] (ml/cmH_2O)	21 (18–26)	27 (23–31)	29 (24–34)	<0.01	<0.01
Plateau pressure[b] (cmH_2O)	33 (31–35)	32 (30–34)	32 (29–34)	0.02	0.04
PEEP (cmH_2O)	12 (10–14)	11 (10–12)	10 (9–10)	<0.01	<0.01
Driving pressure[b] (cmH_2O)	21 (18–24)	21 (18–23)	22 (20–25)	0.04	1.00

[a] C_{RS}: respiratory-system compliance.
[b] Putative numbers, subject to over-estimation. See Method section for details.
[c] Bonferroni-adjusted post hoc significance test.

Table 2 Outcomes of ARDS patients receiving various V_T.

	Low V_T ($n=76$)	Intermediate V_T ($n=204$)	High V_T ($n=102$)	*P*-value	Adjusted *P*-value for intermediate vs. low V_T[b]
Mortality at day 28 (%)	48 (63)	96 (47)	43 (42)	0.02*	0.06
Mortality at day 90 (%)	52 (68)	125 (61)	58 (57)	0.29	0.81
Ventilator-free days, day 1–28[a], median (IQR)	12 (2–18)	13 (0–18)	10 (0–19)	0.84	1.00
Ventilator dependence by day 28[a] (%)	8 (29)	40 (37)	23 (39)	0.62	1.00
Evolution of ARDS severity in the 1st week				0.16	0.93
Improved, No (%)	23 (30)	74 (36)	44 (43)		
Worsened, No (%)	21 (28)	64 (38)	33 (32)		
Stationary, No (%)	32 (42)	66 (32)	25 (24)		
Length of stay in ICU, median (IQR), day	11 (6–19)	13 (7–19)	13 (7–21)	0.70	1.00
Length of stay in hospital, median (IQR), day	14 (6–23)	16 (8–30)	18 (9–37)	0.06	0.40
Pneumothorax (%)	3 (4)	8 (4)	10 (10)	0.08	1.00
Subcutaneous emphysema (%)	6 (8)	9 (4)	6 (6)	0.51	0.75

[a] In patients surviving by day 28.
[b] Bonferroni-adjusted post hoc significance test was used.
* P-value < 0.05.

The outcomes of the three groups are shown in Table 2. Intermediate V_T has similar 28-day mortality with the low V_T group (47.1% vs. 63.2%, $P=0.06$). Intermediate and low V_T groups did not differ significantly in other outcomes, such as 90-day mortality, ventilator-free days, ventilator-dependence rate, or barotrauma rate. By Cox regression model analysis, high V_T (HR 1.78, 95% CI 1.08–2.94, $P=0.03$), male, low C_{RS}, liver cirrhosis, and high PEEP were independently associated with mortality at 28 days (Table 3). Intermediate V_T was not independently associated with 28-day mortality (HR 1.34, 95% CI 0.92–1.97, $P=0.13$). Factors independently associated with 90-day mortality include high V_T (HR 1.62, 95% CI 1.06–2.49, $P=0.03$), age, male, hypertension, liver cirrhosis, malignancy, low C_{RS}, high F_IO_2 and low P_aO_2 (Table s1). Again, intermediate V_T was not independently associated with mortality at 90 days. The collinearities of F_IO_2, P_aO_2, and C_{RS} were excluded due to their lower than 2 VIF values (Table s2).

Intermediate and low V_T cohorts matched with the propensity score were developed. Their characteristics and outcomes are presented in Table 4. Both groups did not differ in mortality (Fig. 2) and all other clinical outcomes. Multivariate analysis revealed that low C_{RS} and high F_IO_2 were independently associated with mortality rate of 28- or 90-days, while intermediate V_T was not (Table s3).

Discussion

According to several surveys,[14,17] intermediate V_T was commonly used in patients with or without ARDS throughout the

Table 3 Factors associated with 28-day mortality.

	Univariate analysis		Multivariate analysis			
	Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value
Low V_T	1					
Intermediate V_T	0.70 (0.50, 0.99)	0.04	1.44 (0.98, 2.14)	0.07	1.34 (0.92, 1.97)	0.13
High V_T	0.57 (0.38, 0.86)	0.01	1.86 (1.12, 3.10)	0.02	1.78 (1.08, 2.94)	0.03
Age, per year	1.00 (0.99, 1.01)	0.37				
Male	1.36 (0.99, 1.88)	0.06	2.01 (1.41, 2.86)	<0.01	2.09 (1.47, 2.98)	<0.01
Body mass index, per kg/m^2	0.97 (0.94, 1.00)	0.06	0.99 (0.95, 1.02)	0.42		
APACHE II score, per point	1.01 (0.99, 1.02)	0.53				
SOFA score, per point	1.02 (0.98, 1.06)	0.30				
P_aO_2/F_IO_2 at diagnosis	1.00 (0.99, 1.00)	0.35				
Chronic obstructive pulmonary disease	1.15 (0.86, 1.54)	0.36				
Diabetes mellitus	0.91 (0.68, 1.23)	0.53				
Hypertension	0.74 (0.55, 0.99)	0.04	0.84 (0.62, 1.13)	0.24		
Chronic renal failure	0.88 (0.59, 1.33)	0.55				
Heart failure	0.92 (0.68, 1.26)	0.61				
Liver cirrhosis	1.61 (1.08, 2.39)	0.02	1.61 (1.07, 2.41)	0.02	1.72 (1.15, 2.56)	0.01
Malignancy	1.57 (1.15, 2.14)	0.01	1.27 (0.92, 1.76)	0.15		
Continuous hemofiltration	2.01 (1.51, 2.68)	<0.01				
C_{RS}[b], per ml/cmH_2O	0.94 (0.92, 0.96)	<0.01	0.92 (0.89, 0.94)	<0.01	0.91 (0.89, 0.94)	<0.01
Plateau Pressure, per cmH_2O	1.00 (1.00, 1.01)	0.42				
PEEP, per cmH_2O	1.13 (1.06, 1.22)	<0.01	1.24 (1.15, 1.34)	<0.01	1.23 (1.14, 1.33)	<0.01

[a] Backward elimination selective procedure.
[b] C_{RS}: respiratory-system compliance.

world. However, our study is the first report on the clinical outcomes of the use of intermediate V_T in patients with ARDS.

Some animal studies have confirmed that high V_T contributes to VILI.[26,27] A recent study found that patients ventilated with V_T of 12 ml/kg PBW for as short as 4 days could induce lung inflammation.[28] The well-known study by the ARDS Network showed that high V_T has a worse outcome than low V_T.[1] Our results also confirm that high V_T is independently associated with mortality at 28 and 90 days in patients with ARDS. However, strict adhesion to low V_T may not be necessary. According to data from our study, intermediate V_T, by shunning the deleterious effect of high V_T, has comparable clinical outcomes with low V_T.

Low V_T is not by itself the only factor in preventing VILI. Amato et al. found that V_T divided by C_{RS}, or driving pressure, is most strongly associated with survival in ARDS.[29] Gattinoni et al. coined the term 'baby lung' to describe a fraction of the lung parenchyma that maintains normal inflation in patients with ARDS. They argued that V_T should be adjusted according to the size of the baby lung and the strain it received during mechanical inflation instead of ideal body weight.[30] They incorporated V_T and a bundle of respiratory parameters to measure the mechanical power lung received during ventilation,[31] which is considered more accurate in predicting the likelihood of VILI.[32] Since V_T per se is not of utmost importance in preventing VILI, more strict control of V_T (i.e., ultralow V_T) failed to produce additional benefit as some researchers expected.[33]

Strictly low V_T may not be necessary for all patients with ARDS. Several ARDS phenotypes have been identified. About 55% of patients who met the Berlin definition of ARDS do not have typical pathological diffuse alveolar damage. These patients tend to have milder symptoms and shorter clinical courses.[34] About 10–17% of patients with ARDS were extubated or no longer met the criteria for ARDS in less than 24 h.[14,35] These subsets of ARDS with their distinct clinical course may warrant personalized treatment. A recently published French trial tested personalized treatment by giving patients with ARDS with focal involvement a V_T of 8 ml/kg PBW and those without focal involvement a V_T of 6 ml/kg PBW in addition to a bundle of other related ventilatory maneuvers. The per protocol analysis showed that patients in the personalized treatment group have a survival advantage over the control group, who universally received a V_T of 6 ml/kg PBW.[36]

To classify V_T as low or not, some observational studies on ARDS only counted the V_T patients received in the initial few days.[6,19] However, this way of counting inappropriately neglected the influences of V_T patients received in subsequent days. We adopted the method of Needham et al. by counting all V_T patients received for up to 28 days if their ventilator settings were considered eligible for lung protection.[23] We recorded V_T three times per day, more frequently than Needham (twice per day). Based on the mean of all V_T patients received throughout the whole ventilation courses, we believe our categorization of V_T is more accurate than many previous observational studies on ARDS.

Table 4 Characteristics and outcomes of propensity score-matched cohorts.

	Low V_T ($n = 66$)	Intermediate V_T ($n = 66$)	*P*-value
Age (year)	62 ± 17	60 ± 16	0.53
Male (%)	52 (79)	57 (86)	0.25
Body mass index (kg/m²)	22 (19–24)	24 (22–26)	0.00
APACHE II score	25 (20–30)	25 (18–28)	0.47
SOFA score	7 (5–9)	8 (6–11)	0.21
Lung injury score	12 (11–13)	11 (10–13)	0.54
Comorbidity			
Chronic obstructive pulmonary disease (%)	22 (33)	20 (30)	0.71
Diabetes mellitus (%)	28 (42)	25 (38)	0.59
Hypertension (%)	26 (39)	22 (33)	0.47
Chronic renal failure (%)	9 (14)	7 (11)	0.59
Heart failure (%)	18 (27)	20 (30)	0.70
Cerebral vascular accident (%)	11 (17)	11(17)	1.00
Liver cirrhosis (%)	8 (12)	10 (15)	0.61
Malignancy (%)	20 (30)	22 (33)	0.71
Admission for surgical conditions (%)	5 (8)	11 (17)	0.11
V_T/predicted body weight (ml/kg)	6.7 (6.1–7.2)	9.0 (8.3–9.4)	0.00
C_{RS}[b] (ml/H_2O)	21 (17–25)	29 (25–33)	0.00
Driving pressure (cmH_2O)	21 (18–24)	21 (18–23)	0.20
F_IO_2 (%)	73 (64–89)	66 (59–77)	0.04
PaO_2/F_IO_2 ratio	127 (94–183)	127 (83–192)	0.76
Outcomes			
Ventilator-free days, day 1–28[a], median (IQR)	12 (2–18)	15 (3–19)	0.51
Ventilator dependence by day 28[a] (%)	7 (32)	8 (25)	0.58
28-Day mortality (%)	44 (67)	34 (52)	0.08
90-Day mortality (%)	47 (71)	37 (56)	0.07
Barotrauma (%)	6 (9)	5 (8)	0.75

[a] In patients surviving by day 28.
[b] C_{RS}: respiratory-system compliance.

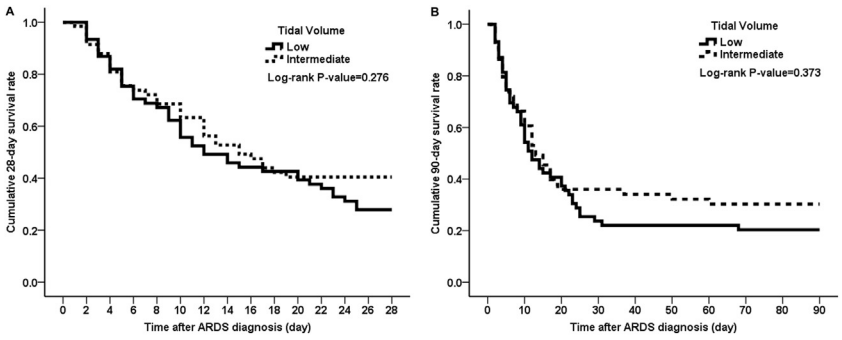

Figure 2 Kaplan–Meier survival curves by day 28 (A) and day 90 (B) for propensity score-matched patients of intermediate and low V_T groups.

The V_T received by our patients were not randomly assigned, but were given according to the in-charge doctors' choice. We find those receiving low V_T have lower C_{RS} (Table 1), which made higher V_T inappropriate because the limitation of plateau pressure could easily be exceeded. Whereas those with higher C_{RS} were more likely to receive intermediate, rather than low V_T. This practice was in line with the global tendency toward nonadherence to low V_T[6–8] as we have mentioned in our introduction.

Prone positioning has been proved effective for moderate to severe ARDS patients,[37] but only 12% and 20% (from intermediate and low V_T group respectively, both with a median of $P_aO_2/F_IO_2 < 150$ mmHg) of our patients received this adjunctive therapy. This was just another example of discrepancy between clinical trial and clinical practice. This trend was also universal. The LUNG SAFE study, involving 50 countries around the world, found prone was used in only 6% and 16% of the moderate and severe ARDS patients

respectively.[14] A recent survey of moderate-to-severe ARDS patients in the US found only 6% of them received prone in their early management.[38] Efforts are needed to find reasons behind the widespread nonadherence.

Liver cirrhosis was found to be an independent risk factor for 28- and 90-day mortality in our patients with ARDS. This finding was in accordance with previous studies.[39,40] Increased pro-inflammatory interleukine-6 and interleukine-8 in patients with decompensated cirrhosis were thought to contribute to lung injury in those at risk.[41]

There are several limitations to this study. First, it was a retrospective observation. The classification of V_T groups was not assigned randomly. Selection bias and unrecognized confounders are possible. Second, our data were all from one center. The generalizability of our conclusion can be limited. Third, for patients with pressure-targeted ventilation, plateau pressures were not measured directly. We used the peak airway pressure or the sum of PEEP and set increment of inspiratory pressure instead.[23] The plateau pressure derived by this way is prone to overestimation.[42] Driving pressure and C_{RS} calculated from this putative plateau pressure were all subject to imprecision.

In conclusion, we found that high V_T is harmful to patients with ARDS. Intermediate and low V_T and have similar clinical outcomes. Our results suggested that intermediate V_T is an acceptable option for ventilated patients with ARDS. This conclusion needs to be verified by randomized control trials.

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Authors' contributions

SHW drafted the manuscript. CTK analyzed the data and performed statistical calculations. CYL collected clinical data from study patients. YCH gave final approval of the version to be published.

Conflict of interest

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.medin.2022.03.016.

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