

# Favorable Neurocognitive Outcome with Low Tidal Volume Ventilation after Cardiac Arrest

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## Abstract

**Rationale:** Neurocognitive outcome after out-of-hospital cardiac arrest (OHCA) is often poor, even when initial resuscitation succeeds. Lower tidal volumes ( $V_T$ s) attenuate extrapulmonary organ injury in other disease states and are neuroprotective in preclinical models of critical illness.

**Objective:** To evaluate the association between  $V_T$  and neurocognitive outcome after OHCA.

**Methods:** We performed a propensity-adjusted analysis of a two-center retrospective cohort of patients experiencing OHCA who received mechanical ventilation for at least the first 48 hours of hospitalization.  $V_T$  was calculated as the time-weighted average over the first 48 hours, in milliliters per kilogram of predicted body weight (PBW). The primary endpoint was favorable neurocognitive outcome (cerebral performance category of 1 or 2) at discharge.

**Measurements and Main Results:** Of 256 included patients, 38% received time-weighted average  $V_T$  greater than 8 ml/kg PBW during the first 48 hours. Lower  $V_T$  was independently

associated with favorable neurocognitive outcome in propensity-adjusted analysis (odds ratio, 1.61; 95% confidence interval [CI], 1.13–2.28 per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.008$ ). This finding was robust to several sensitivity analyses. Lower  $V_T$  also was associated with more ventilator-free days ( $\beta = 1.78$ ; 95% CI, 0.39–3.16 per 1-ml/kg PBW decrease;  $P = 0.012$ ) and shock-free days ( $\beta = 1.31$ ; 95% CI, 0.10–2.51;  $P = 0.034$ ).  $V_T$  was not associated with hypercapnia ( $P = 1.00$ ). Although the propensity score incorporated several biologically relevant covariates, only height, weight, and admitting hospital were independent predictors of  $V_T$  less than or equal to 8 ml/kg PBW.

**Conclusions:** Lower  $V_T$  after OHCA is independently associated with favorable neurocognitive outcome, more ventilator-free days, and more shock-free days. These findings suggest a role for low- $V_T$  ventilation after cardiac arrest.

**Keywords:** out-of-hospital cardiac arrest; cardiac arrest; ventilator-induced lung injury; acute lung injury; cerebral ischemia

Nontraumatic out-of-hospital cardiac arrest (OHCA) affects an estimated 424,000 people in the United States annually (1). Even when initial resuscitation succeeds, patient outcomes often are poor. More than half of successfully resuscitated patients experiencing OHCA do not survive to hospital discharge (2),

and cognitive impairment occurs in half of survivors (3).

After successful resuscitation, cardiovascular dysfunction, global ischemia–reperfusion, and systemic inflammation contribute further to multiorgan dysfunction and brain injury (4). This response, termed post–cardiac arrest

syndrome (PCAS) (5), evolves over subsequent hours to days and represents a narrow window within which targeted therapies may be effective.

Mechanical ventilation is a central component of postarrest care, for which neither current routine practice nor optimal management is well defined. Recent

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## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Patients suffering cardiac arrest have several risk factors for lung injury and often experience poor neurocognitive outcome. Low tidal volumes ( $V_T$ s) attenuate pulmonary and extrapulmonary organ injury in patients at risk of ventilation-induced lung injury. Experimental data suggest low  $V_T$  also may be neuroprotective. It is unknown whether low  $V_T$  improves neurocognitive outcome postarrest.

### What This Study Adds to the

**Field:** In patients suffering nontraumatic out-of-hospital cardiac arrest, lower  $V_T$  during the first 48 hours of intensive care unit admission was associated with improved neurocognitive outcome at hospital discharge, more ventilator-free days, and more shock-free days. In context with current understanding of lung–brain crosstalk, these findings suggest low- $V_T$  ventilation may improve neurocognitive outcome after cardiac arrest.

international consensus guidelines do not recommend a particular tidal volume ( $V_T$ ) strategy postarrest, noting a paucity of data on the subject; rather, they urge caution regarding low- $V_T$  strategies owing to potential harm from hypercapnia that could result (5, 6).

In patients with existing lung injury, high  $V_T$  ventilation causes further mechanical lung injury that propagates systemic inflammation and contributes to extrapulmonary organ injury (7–12). Among patients with acute respiratory distress syndrome (ARDS), lower  $V_T$  increases survival and attenuates both pulmonary and extrapulmonary organ dysfunction (8, 9). Even if overt ARDS is not present, clinical data suggest low  $V_T$  may improve outcomes among patients at risk of lung injury (13).

Long-term cognitive impairment occurs in the majority of ARDS survivors and is not fully explained by hypoxemia alone (14–16). Expanding preclinical evidence suggests mechanical lung injury may cause brain injury via several complex pathways (17–21), paralleling

clinical trials data that have revealed lung-protective ventilation attenuates other extrapulmonary organ dysfunctions (8, 9).

Patients admitted after OHCA have several risk factors for lung injury, including pulmonary ischemia–reperfusion, pulmonary aspiration, mechanical injury from chest compressions and associated thoracic fractures, and systemic inflammation characteristic of PCAS. Therefore, we reasoned lower  $V_T$  may be both lung protective and neuroprotective after successful resuscitation from OHCA. In the present study, we hypothesized that lower  $V_T$  is associated with improved neurocognitive outcome at hospital discharge and more rapid resolution of respiratory failure among patients hospitalized after OHCA.

Some of the data from this study have been reported previously in the form of a conference abstract (22).

## Methods

### Study Population

This two-center retrospective cohort study included mechanically ventilated adults aged 18 years or older admitted after nontraumatic OHCA who required conventional mechanical ventilation for at least the first 48 hours of hospitalization. Patients were excluded for outside hospital stay longer than 24 hours before transfer, intracranial hemorrhage, chronic mechanical ventilation, use of airway pressure release mode of ventilation, extracorporeal membrane oxygenation, and missing ventilator data or height (required to calculate predicted body weight) (Figure 1). Each participating hospital's review board approved the study with waiver of consent.

Patient records for inclusion were identified via a previously validated approach (23). Potentially relevant admissions between 2008 and 2014 were screened by searching all inpatient records for prespecified International Classification of Diseases 9th revision and Current Procedural Terminology codes corresponding to ventricular arrhythmia, cardiac arrest, hypothermia, and cardiopulmonary resuscitation (23). Each identified chart was reviewed by study physicians to confirm diagnosis of OHCA and eligibility criteria.

### Determination of $V_T$

The primary exposure of interest was time-weighted average  $V_T$  in milliliters per kilogram predicted body weight (PBW) during the first 48 hours of intensive care unit (ICU) admission postarrest. Weighted-average  $V_T$  was calculated as the area under the  $V_T$ -versus-time plot (24), constructed using a last-value-forward step-function to reflect abrupt changes in  $V_T$  that would be expected in response to ventilator adjustments (*see* online supplement). The 48-hour interval was selected based on prior reports that systemic inflammation in PCAS is most pronounced during this time (4), likely increasing lung injury risk. Values for preset and exhaled  $V_T$  in volume- and pressure-targeted modes were used, respectively.  $V_T$  was scaled to PBW to account for between-patient differences in normal lung volumes; PBW was calculated via the NHLBI ARDS Network equation (9).

### Covariates

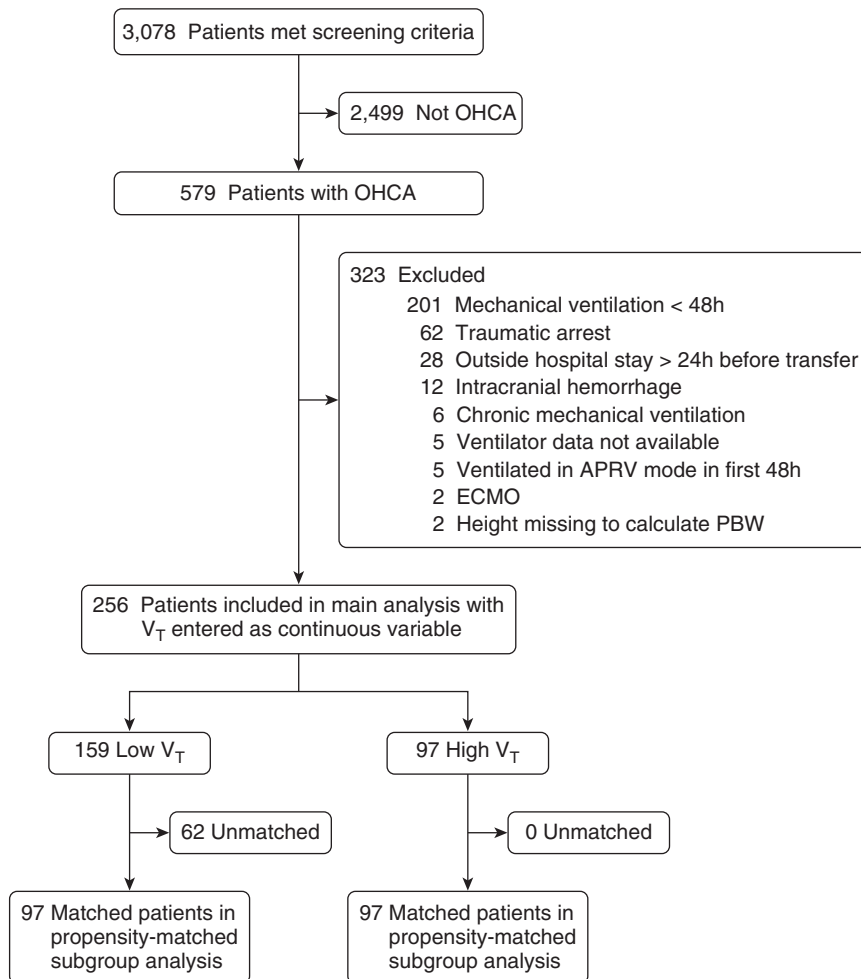
Cardiac arrest data were collected following revised Utstein template definitions (25). Additional information extracted from medical record review included anthropometrics, illness severity scores (Acute Physiology and Chronic Health Evaluation [APACHE]-II, Sequential Organ Failure Assessment [SOFA]), ventilator and respiratory data, hemodynamic parameters, temperature management strategy, and laboratory data. All data were sourced directly from each patient's hospital record and extracted for this study.

### Primary Outcome

The prespecified primary outcome was favorable neurocognitive outcome at hospital discharge, defined as cerebral performance category (CPC) of 1 or 2 (26–29). CPC scale ranges from 1 to 5, with 1 indicating normal function or minor neurocognitive deficit, 2 moderate disability, 3 severe disability, 4 coma/vegetative state, and 5 death or brain death. CPC was ascertained for all patients via chart review by two physician-investigators blinded to  $V_T$  and other respiratory and illness severity measures (*see* online supplement). Discordant ratings were resolved by consensus.

### Secondary Outcomes

Secondary outcomes included ventilator-free days, extrapulmonary organ failure-free



**Figure 1.** Study flow diagram. Of 579 patients with out-of-hospital cardiac arrest (OHCA), 256 were included in the main analyses. Of these, 194 patients (97 pairs) were included in a sensitivity analysis of patients matched by propensity to receive low  $V_T$  ( $\leq 8$  ml/kg predicted body weight [PBW]). APRV = airway pressure release ventilation; ECMO = extracorporeal membrane oxygenation.

days, ICU-free days, and hospital-free days through Day 28, and vital status at hospital discharge. Ventilator-free days were calculated as the time between successful liberation from mechanical ventilation and study Day 28 (30). A value of zero ventilator-free days was assigned for patients not surviving to hospital discharge to avoid misleading conclusions for patients who might get extubated but not survive hospitalization. Extrapulmonary organ failure-free days, ICU-free days, and hospital-free days were calculated similarly. Shock was defined as systolic blood pressure less than or equal to 90 mm Hg or vasopressor use; patients transferred out of intensive care who survived to discharge were assumed to be shock-free for days spent out of ICU. Renal, hepatic, and

coagulation failures were ascertained using Brussels score definitions (31) with one modification: patients not requiring dialysis at time of live hospital discharge were considered not to have renal failure after discharge. Patients who received chronic outpatient dialysis before arrest were excluded from analysis of renal failure-free days. When data were unavailable on a particular study day during hospitalization, the last observed value was carried forward, conservatively biasing results toward the null if blood tests were checked less frequently as health improved. Organ failures otherwise were considered resolved after live hospital discharge.

Associations between  $V_T$  and mean arterial pressure, arterial oxygen tension, and arterial carbon dioxide tension were

evaluated as safety and mechanistic endpoints. Time-weighted average values over the first 48 hours were calculated as above. In addition, we specifically evaluated the association of  $V_T$  with hypercapnia, defined as  $Pa_{CO_2}$  greater than 45 mm Hg (6), given the potential for lower  $V_T$  to induce hypercapnia if alveolar ventilation were not maintained. These assessments also sought to determine whether low  $V_T$  might simply be a marker of ventilator management more adherent with existing guidelines (6).

### Statistics

Descriptive statistics are presented as mean  $\pm$  SD, median (interquartile range), or number (%). Results were compared with unpaired or paired  $t$  test, Wilcoxon rank-sum test, or chi-square test, as appropriate.

**$V_T$  strategy assessment.** Logistic regression models were developed to identify independent predictors of receiving  $V_T$  less than or equal to 8 ml/kg PBW during the first 48 hours. Candidate predictor variables consisted of all those entered in the propensity score as described below. Backward elimination was used to develop the final model, applying threshold  $P = 0.05$  to remain in the model.

**Primary analysis of clinical endpoints.**  $V_T$  in milliliters per kilogram PBW over the first 48 hours, the exposure of interest, was entered as a continuous variable for all primary analyses of clinical endpoints.

Propensity score covariate adjustment was selected as the primary analysis technique for all clinical endpoints to account for the many factors that may influence  $V_T$  strategy after OHCA. The propensity score was developed using logistic regression to estimate the probability of receiving low ( $\leq 8$  ml/kg PBW) compared with high ( $> 8$  ml/kg PBW)  $V_T$ . This dichotomized  $V_T$  threshold was chosen to reflect current standard practice for lung-protective  $V_T$ , stemming from the ARDS Network protocol that targeted  $V_T$  of 4 to 8 ml/kg PBW (9) and the U.S. Critical Illness and Injury Trials Group Checklist for Lung Injury Prevention recommendation for  $V_T$  of 6 to 8 ml/kg PBW in patients at risk for lung injury (32, 33). The final propensity model was chosen to represent current understanding of underlying biology and ensure face validity. Relevant

covariates were identified from literature review and consideration of clinical relevance to postarrest biology. In addition, factors known to predict neurocognitive outcome were entered into the propensity model, regardless of their potential association with  $V_T$ , to optimize precision of the final effect estimate. Model discrimination and calibration were assessed with the *c*-statistic and Hosmer-Lemeshow goodness-of-fit test, respectively.

**Sensitivity analyses.** Several sensitivity analyses were performed for the primary endpoint, neurocognitive outcome at hospital discharge, to confirm results were not dependent on the method of covariate adjustment or formatting of either  $V_T$  or CPC scale. Alternative methods used for covariate adjustment included multivariable logistic regression, propensity quintile adjustment (34), inverse-probability-of-treatment weighting (35), and propensity-matched analysis (36–38). To evaluate if results were dependent on entering  $V_T$  as a continuous variable,  $V_T$  was recoded as high ( $>8$  ml/kg PBW) versus low ( $\leq 8$  ml/kg PBW)  $V_T$  and entered as a categorical predictor in a propensity-adjusted model. Finally, to evaluate if results were dependent on dichotomizing CPC, propensity-adjusted analysis with continuous  $V_T$  was repeated using ordinal logistic regression, with CPC scale entered as an ordinal dependent variable. Additional details are provided in the online supplement.

For all hypothesis testing, a two-sided  $\alpha$  threshold of 0.05 was considered statistically significant.

## Results

Screening identified 579 patients admitted to study hospitals for OHCA during the study period. Of these, 323 were excluded from analysis, the most common reasons being mechanical ventilation less than 48 hours before extubation or death ( $n = 201$ ), traumatic cause of arrest ( $n = 62$ ), and initial admission after arrest to a nonstudy hospital lasting more than 24 hours ( $n = 28$ ). In total, 256 patients were included in the final analysis (Figure 1).

OHCA was witnessed in 76% of included patients, and 51% of patients had an initial rhythm of ventricular tachycardia or ventricular fibrillation.

Study patients had high acuity on admission, as evidenced by high APACHE-II and SOFA scores. More than two-thirds had shock in the first 24 hours, and 86% had  $Pa_{O_2}:Fi_{O_2}$  less than or equal to 300. Additional patient characteristics are presented in Table 1.

### $V_T$ Strategy

Mean  $V_T$  over the first 48 hours was  $7.9 \pm 1.4$  ml/kg PBW (range, 4.9–14.3 ml/kg PBW). Thirty-eight percent of patients received an average  $V_T$  greater than 8 ml/kg PBW over the first 48 hours, and just 4% received an average  $V_T$  less than or equal to 6 ml/kg PBW during this time. Average  $V_T$  over the first 48 hours did not differ significantly from initial  $V_T$  at ICU admission (mean difference, 0.1; 95% confidence interval [CI], 0.0–0.3 ml/kg PBW;  $P = 0.070$ ).

In multivariable analysis, only height (odds ratio [OR], 1.19; 95% CI, 1.13–1.24 per 1-cm increase;  $P < 0.001$ ), weight (OR, 0.98; 95% CI, 0.97–1.00 per 1-kg increase;  $P = 0.037$ ), and hospital of admission (OR, 2.89; 95% CI, 1.50–5.59;  $P = 0.002$ ) were significantly predictive of receipt of low- $V_T$  ventilation. With just these three covariates in a model predicting receipt of low  $V_T$ , model discrimination and calibration were high (*c*-statistic = 0.844; Hosmer-Lemeshow goodness-of-fit  $P = 0.949$ ).

### Propensity Model for $V_T$ over First 48 Hours

The final propensity model predicting  $V_T$  included as covariates age, anthropometrics (height, weight, sex), measures of illness severity (APACHE-II, circulatory shock on Day 1), arrest characteristics (witnessed arrest, bystander cardiopulmonary resuscitation, initial shockable rhythm, hospital of admission, receipt of therapeutic hypothermia), and respiratory characteristics (initial pH,  $Pa_{CO_2}$ , and peak inspiratory pressure; lowest  $Pa_{O_2}:Fi_{O_2}$  in first 24 h). The model exhibited high discrimination (*c*-statistic = 0.862) and calibration (Hosmer-Lemeshow goodness-of-fit  $P = 0.877$ ) for predicting  $V_T$ .

### Low $V_T$ and Neurocognitive Outcome

In unadjusted analysis, lower  $V_T$  was significantly associated with favorable neurocognitive outcome (OR, 1.47; 95% CI, 1.12–1.92 per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.005$ ). In the prespecified primary analysis, after adjusting for propensity score, lower  $V_T$  remained significantly associated

with favorable neurocognitive outcome (OR, 1.61; 95% CI, 1.13–2.28 per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.008$ ).

The association between lower  $V_T$  and favorable neurocognitive outcome was robust to method of covariate adjustment and handling of the independent and dependent variables of primary interest. Alternative covariate adjustment techniques used included multivariable regression, propensity quintile adjustment, inverse-probability-of-treatment weighting, and propensity matching (Figure 2).

In the propensity-matched sensitivity analysis, each patient receiving high  $V_T$  was successfully matched with a patient receiving low  $V_T$  ( $n = 97$  per group), with balance achieved between groups for all available biologically relevant covariates (Table 1). In this cohort, lower  $V_T$  again was significantly associated with favorable neurocognitive outcome (OR, 1.68; 95% CI, 1.11–2.55 per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.014$ ). Figure 3 presents Kaplan-Meier estimated probability of discharge with favorable neurocognitive outcome for patients receiving high versus low  $V_T$  in the total study cohort without adjustment (log-rank  $P = 0.008$ ) and propensity-matched cohort (log-rank  $P = 0.021$ ).

Reanalysis using ordinal logistic regression, entering CPC as an ordinal dependent variable and adjusting for propensity score, confirmed that the association between  $V_T$  and neurocognitive outcome was not dependent on dichotomizing CPC scale (OR, 1.30; 95% CI, 1.02–1.68 per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.038$ ; score test for proportional odds assumption  $P = 0.073$ ). Reanalysis entering  $V_T$  as a dichotomized variable and adjusting for propensity score similarly found an association between lower  $V_T$  and favorable neurocognitive outcome (OR, 2.95; 95% CI, 1.22–7.12;  $P = 0.016$ ).

### Low $V_T$ and Secondary Clinical Outcomes

In propensity-adjusted analyses, lower  $V_T$  was associated with more ventilator-free days ( $\beta = 1.78$ ; 95% CI, 0.39–3.16 for change in ventilator-free days per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.012$ ) and shock-free days ( $\beta = 1.31$ ; 95% CI, 0.10–2.51 for change in shock-free days per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.034$ ).  $V_T$  was not significantly associated

**Table 1.** Baseline Characteristics According to High versus Low V<sub>T</sub>

	Total Study Population				Propensity-matched Subgroup Analysis*	
	High V <sub>T</sub> (n = 97)	Low V <sub>T</sub> (n = 159)	SMD	P	Low V <sub>T</sub> (n = 97)	SMD
Age, years	66 ± 17	59 ± 17	0.389	0.001	61 ± 17	0.249
Height, cm	165 ± 10	177 ± 8	-1.280	<0.001	173 ± 8	-0.889
Weight, kg	81 ± 21	88 ± 24	-0.299	0.023	84 ± 22	-0.132
Female	45 (46)	31 (19)	0.597	<0.001	28 (29)	0.368
Comorbidities						
Coronary disease	31 (32)	43 (27)	0.108	0.478	28 (29)	0.067
Congestive heart failure	24 (25)	35 (22)	0.065	0.648	18 (19)	0.151
Chronic pulmonary disease	20 (21)	24 (15)	0.145	0.306	16 (16)	0.106
Arrest characteristics						
Witnessed arrest	77 (79)	117 (74)	0.137	0.367	76 (78)	0.025
Bystander CPR	57 (59)	90 (57)	0.044	0.795	55 (57)	0.042
Time from collapse to CPR initiation, min	2 (0-8)	1.5 (0-5)	0.208	0.326	1 (0-5)	0.212
Duration of CPR before sustained ROSC, min	15 (10-33)	16 (10-30)	0.069	0.878	15 (9-30)	0.150
Initial rhythm ventricular tachycardia or ventricular fibrillation	48 (49)	82 (52)	-0.042	0.797	51 (53)	-0.062
Comatose after ROSC	93 (96)	154 (97)	0.052	0.734	93 (96)	0.000
Therapeutic hypothermia after ROSC	74 (76)	139 (87)	-0.292	0.025	80 (82)	-0.153
Hospital A admission	53 (55)	110 (69)	-0.303	0.023	61 (63)	-0.168
Illness severity						
APACHE-II	34 ± 6	34 ± 6	0.020	0.875	34 ± 6	0.060
SOFA on Day 1	11 ± 3	11 ± 3	-0.016	0.692	11 ± 3	-0.083
Shock in first 24 h <sup>†</sup>	71 (73)	109 (69)	0.102	0.482	72 (74)	-0.023
Initial lactate, mmol/L	5.3 ± 4.7	4.6 ± 3.7	0.173	0.247	4.5 ± 3.3	0.194
Peak lactate in first 24 h, mmol/L	5.3 ± 4.6	4.8 ± 3.7	0.126	0.357	4.8 ± 3.3	0.145
Initial respiratory characteristics						
Tidal volume, ml	541 ± 88	514 ± 77	0.316	0.013	496 ± 76	0.543
Tidal volume, ml/kg PBW	9.3 ± 1.8	7.3 ± 1.0	1.401	<0.001	7.4 ± 1.1	1.287
Tidal volume averaged over first 48 h, ml/kg PBW	9.3 ± 1.2	7.1 ± 0.6	2.294	<0.001	7.2 ± 0.6	2.207
Total respiratory rate, breaths/min	20 ± 6	21 ± 6	-0.138	0.287	20 ± 7	-0.084
Minute volume, L/min	10.4 ± 3.4	10.7 ± 3.6	-0.086	0.510	10.1 ± 3.5	0.073
PEEP, cm H <sub>2</sub> O	5 (5-5)	5 (5-8)	-0.241	0.176	5 (5-8)	-0.204
Peak inspiratory pressure, cm H <sub>2</sub> O	27 ± 7	26 ± 8	0.186	0.154	27 ± 8	0.068
Mean airway pressure, cm H <sub>2</sub> O	12 ± 3	11 ± 4	0.087	0.498	11 ± 4	0.057
F <sub>IO<sub>2</sub></sub>	1.0 (0.6-1.0)	1.0 (0.6-1.0)	0.101	0.400	1.0 (0.6-1.0)	0.091
pH	7.23 ± 0.18	7.25 ± 0.16	-0.069	0.586	7.25 ± 0.16	-0.099
Pa <sub>CO<sub>2</sub></sub> , mm Hg	47 ± 16	49 ± 17	-0.117	0.369	48 ± 17	-0.058
Pa <sub>O<sub>2</sub></sub> , mm Hg	235 ± 133	222 ± 150	0.089	0.497	233 ± 159	0.013
Pa <sub>O<sub>2</sub></sub> :F <sub>IO<sub>2</sub></sub>	266 ± 150	257 ± 167	0.059	0.650	269 ± 176	-0.014
Pa <sub>O<sub>2</sub></sub> :F <sub>IO<sub>2</sub></sub> ≤ 300 in first 24 h	82 (85)	138 (87)	-0.064	0.711	84 (87)	-0.059
Lowest Pa <sub>O<sub>2</sub></sub> :F <sub>IO<sub>2</sub></sub> in first 24 h	165 ± 113	166 ± 113	-0.005	0.967	173 ± 115	-0.074

*Definition of abbreviations:* APACHE-II = Acute Physiology and Chronic Health Evaluation-II score; CPR = cardiopulmonary resuscitation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; ROSC = return of spontaneous circulation; SMD = standardized mean difference; SOFA = Sequential Organ Failure Assessment score.

Data presented as mean ± SD, median (interquartile range), or n (%). Data presented with patients grouped according to high V<sub>T</sub> (>8 ml/kg PBW) versus low V<sub>T</sub> (≤8 ml/kg PBW), the V<sub>T</sub> threshold used for developing the propensity score. Primary analyses of all outcomes used the full cohort with V<sub>T</sub> entered as a continuous variable and propensity score entered as a model covariate. Propensity matching was performed in a secondary sensitivity analysis to confirm that the main finding was not dependent on method of covariate adjustment.

\*SMD compared to high-V<sub>T</sub> population, with whom matching was performed. Each patient in high-V<sub>T</sub> group was successfully matched with a low-V<sub>T</sub> patient with specified match criteria.

<sup>†</sup>Shock was defined as systolic blood pressure ≤ 90 mm Hg or vasopressor use.

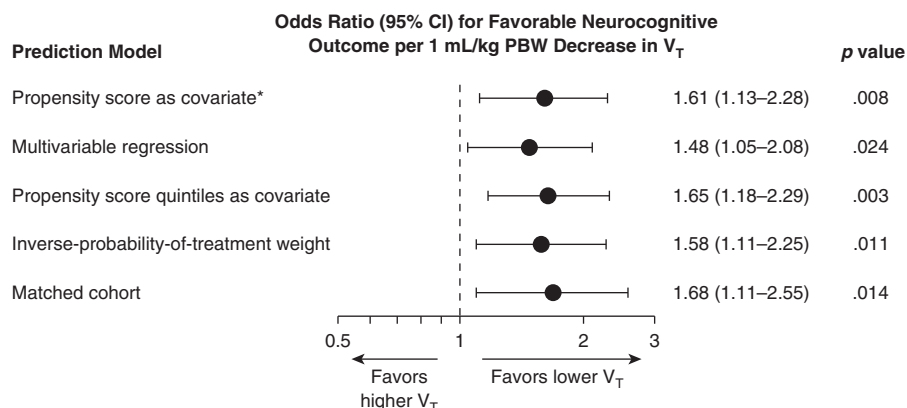
with renal, hepatic, or coagulation failure-free days (Figure 4).

Lower V<sub>T</sub> also was associated with more ICU-free days (β = 1.38; 95% CI, 0.13-2.63; P = 0.030) and hospital-free days (β = 1.07; 95% CI, 0.04-2.09; P = 0.042) in propensity-

adjusted analyses. V<sub>T</sub> was not significantly associated with survival to hospital discharge in propensity-adjusted analysis, although the direction of change favored lower V<sub>T</sub> (OR for survival, 1.23; 95% CI, 0.95-1.60 per 1-ml/kg PBW decrease in V<sub>T</sub>; P = 0.115).

#### Alternative Mechanistic and Safety Endpoints

V<sub>T</sub> was not associated with mean arterial pressure over the first 48 hours (β = -0.82; 95% CI, -9.25 to 7.60 for change in mean arterial pressure per



**Figure 2.**  $V_T$  and neurocognitive outcome after out-of-hospital cardiac arrest. Sensitivity analyses performed for primary endpoint, favorable neurocognitive outcome at hospital discharge, to determine whether results were dependent on method of covariate adjustment. Odds ratios represent odds of favorable versus unfavorable neurocognitive outcome (cerebral performance category 1–2 vs. 3–5) per 1-ml/kg predicted body weight (PBW) decrease in  $V_T$ . Additional sensitivity analyses (not shown in figure) yielded similar results with  $V_T$  reentered as a binary variable and with use of ordinal logistic regression to model cerebral performance category as an ordinal outcome. \*Indicates prespecified primary outcome analysis. CI = confidence interval.

1-ml/kg decrease in  $V_T$ ;  $P = 0.847$ ).  $V_T$  demonstrated no association with arterial oxygen or arterial carbon dioxide tension over the first 48 hours ( $Pa_{O_2}$ :  $\beta = -2.23$ ; 95% CI,  $-6.53$  to  $2.07$  for change in  $Pa_{O_2}$  per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.307$ ;  $Pa_{CO_2}$ :  $\beta = 0.46$ ; 95% CI,  $-0.13$  to  $1.05$  for change in  $Pa_{CO_2}$  per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.127$ ). Exposure to hypercapnia, defined as average arterial oxygen tension greater than 45 mm Hg during the first 48 hours, was similar between patients receiving higher versus lower  $V_T$  (10.7% vs. 10.3%;  $P = 1.00$ ).

**Post Hoc Analyses for Residual Confounding**

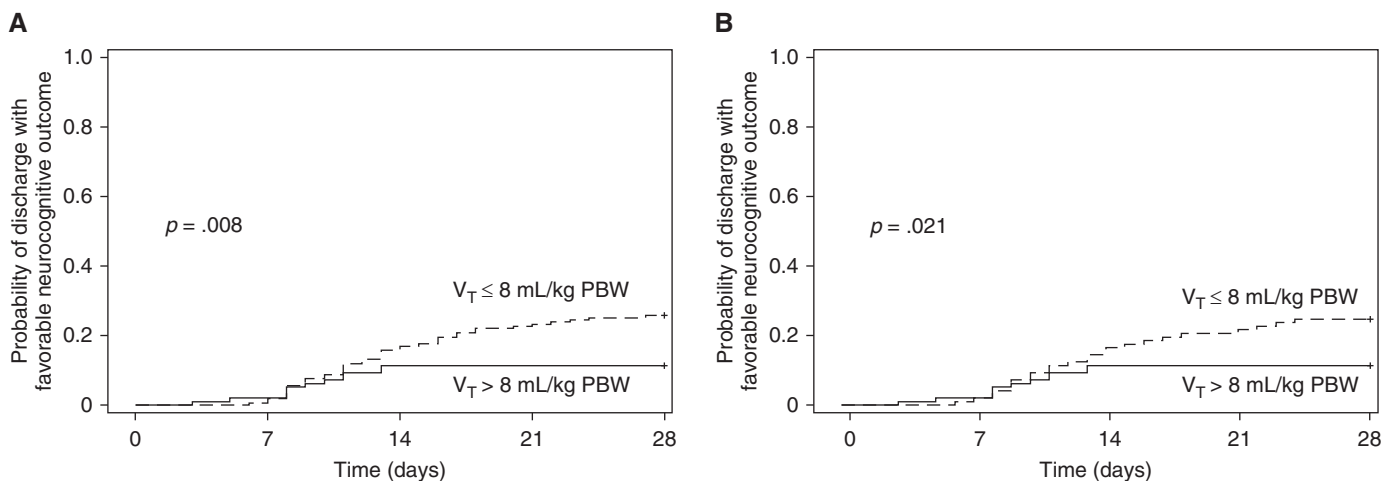
Therapeutic hypothermia was prescribed more commonly among patients receiving lower  $V_T$  in unadjusted analysis, driven by its use in patients without an initial shockable rhythm (84% versus 69% with low versus high  $V_T$ , respectively;  $P = 0.045$ ). After adjusting for propensity score, therapeutic hypothermia was not associated with  $V_T$  in the full study cohort ( $\beta = 0.14$ ; 95% CI,  $-0.19$  to  $0.47$  for change in  $V_T$  [in ml/kg PBW] associated with use of therapeutic hypothermia;

$P = 0.413$ ), and its use did not differ by high versus low  $V_T$  in the matched cohort ( $P = 0.375$ ). In addition, therapeutic hypothermia was not associated with favorable neurocognitive outcome in unadjusted analysis ( $P = 0.757$ ) or in the multivariable regression sensitivity analysis ( $P = 0.516$ ).

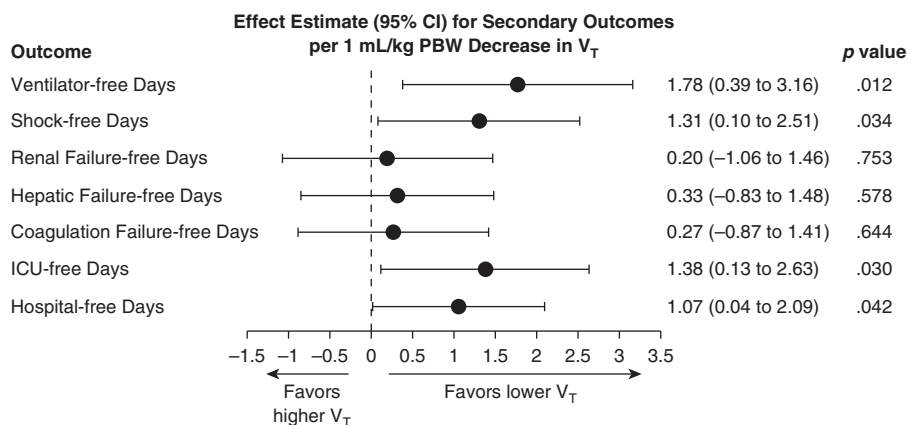
Because hospital of admission predicted receipt of low  $V_T$ , additional *post hoc* analyses were performed to evaluate for residual confounding related to unmeasured hospital-specific aspects of care. Hospital of admission was not associated with favorable neurocognitive outcome in unadjusted analysis ( $P = 0.747$ ) or in the multivariable regression sensitivity analysis ( $P = 0.588$ ).  $V_T$  remained significantly associated with favorable neurocognitive outcome in separate univariable models constructed for each site (hospital A: OR, 1.50; 95% CI, 1.04–2.17 per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.022$ ; hospital B: 1.46; 95% CI, 0.98–2.17 per 1-ml/kg PBW decrease in  $V_T$ ;  $P = 0.042$ ). Limited sample size precluded separate multivariable analyses by site.

**Discussion**

In this study, lower  $V_T$  during the first 48 hours of admission was independently associated with favorable neurocognitive outcome after OHCA. This finding was consistent across several sensitivity analyses, indicating conclusions were not dependent on statistical approach. Lower  $V_T$  also was



**Figure 3.** Probability of discharge with favorable neurocognitive outcome through Day 28. Kaplan-Meier estimates stratified according to time-weighted average  $V_T$  received during the first 48 hours of admission. (A) Entire study cohort ( $n = 256$ ), unadjusted analysis. (B) Cohort matched by propensity for receiving low- $V_T$  ventilation ( $n = 194$ ). PBW = predicted body weight.



**Figure 4.**  $V_T$  and secondary outcomes. Effect estimates with 95% confidence intervals (CI) for secondary outcomes from linear regression models, propensity score–adjusted analyses. Effect estimate refers to the change in the outcome variable per 1-ml/kg predicted body weight (PBW) decrease in tidal volume. ICU = intensive care unit.

independently associated with more ventilator-free days and shock-free days. In the context of existing data on lung–brain interaction in critical illness, these results suggest a neuroprotective role for lower  $V_T$  in patients hospitalized after OHCA.

Several possible mechanisms could explain a link between low- $V_T$  ventilation and favorable neurocognitive outcome: attenuation of lung injury–mediated systemic inflammation, pulmonary mechanotransduction, lung–brain crosstalk, differences in blood oxygen or carbon dioxide tension, and hemodynamic effects of lower mean airway pressures.

Pulmonary mechanotransduction, independent of tissue hypoxia, produces several responses that may precipitate brain injury. Overdistension lung injury induces local and systemic cytokine release (11) that may heighten systemic inflammation already present from ischemia–reperfusion injury. Peripheral cytokine signaling in turn is transmitted to the brain via vagal afferents, circumventricular organs, and transport of cytokines or downstream molecules across the blood–brain barrier (39–43). Insults ranging from acute myocardial infarction (44, 45) to sepsis (46, 47) have been shown to increase intracerebral proinflammatory cytokine levels and associated neuronal injury. Several studies similarly have implicated lung injury as a precipitant of neuroinflammation and brain injury (17–20). Even absent preexisting lung injury, recent data suggest lung mechanotransduction during high- $V_T$  ventilation may induce vagal afferent-

mediated apoptotic pathways in the brain (17, 18).

Such lung–brain communication appears to be bidirectional. Massive brain injury increases susceptibility to lung injury (48). In preclinical studies, bilateral vagotomy exacerbated lung injury from ischemia–reperfusion and high  $V_T$ , whereas vagal stimulation attenuated lung injury (49). ARDS is relatively common in brain-injured patients with respiratory failure, in whom high  $V_T$  appears to be an independent risk factor for developing lung injury (50, 51). Thus, in PCAS, ventilation-induced lung injury may increase risk of postarrest brain injury and vice versa in a deleterious positive feedback loop mediated in part by the neuroinflammatory reflex (17, 39, 40). Improvements in neurocognitive outcome, ventilator-free days, and shock-free days associated with lower  $V_T$  in the present study together support systemic benefits of low- $V_T$  ventilation in PCAS.

Although an important potential safety concern, lower  $V_T$  was not associated with hypercapnia in our cohort. Thus, low  $V_T$  likely can be prescribed in most patients with PCAS while adhering to treatment guidelines recommending eucapnia by increasing respiratory rate (6). In addition, lower  $V_T$  was not simply a marker of improved adherence to guidelines for oxygenation management in our study. The lack of association between  $V_T$  and mean arterial pressure argues against differences in cerebral perfusion as an explanatory mechanism. Reduced cerebral venous and

lymphatic drainages with higher  $V_T$  are potential contributory mechanisms, although their roles in disease pathophysiology and relationship to mechanical ventilation are poorly understood (52–55).

Although our findings support a role for low  $V_T$  in PCAS, results are not conclusive. First, causation cannot be inferred from this observational study design. Several features of this study argue against residual confounding: (1) the biological approach used in developing the propensity score, which incorporated several baseline illness severity measures; (2) the finding of height, weight, and hospital as the only independent predictors of low  $V_T$  in this cohort; and (3) similarities in intraarrest characteristics, APACHE-II, Day 1 SOFA, and shock incidence in the first 24 hours among patients receiving higher versus lower  $V_T$ . Although CPC is a standard outcome in cardiac arrest studies (25), its sensitivity and discriminatory power for mild to moderate brain injury are controversial (56, 57). Such may be limited further by relying on chart review alone to determine CPC. Prospective validation of our findings in a clinical trial with rigorous cognitive testing and functional outcomes measures is warranted.

Receipt of a low- $V_T$  strategy could be an epiphenomenon that marks better care, but similar adherence to oxygenation and eucapnia targets do not support such in this study. Lower  $V_T$  was associated with increased use of therapeutic hypothermia in the unmatched, unadjusted analysis due to differences in use for patients with a nonshockable arrest. Postarrest targeted hypothermia remains controversial, is unproven in patients without a shockable rhythm at arrest (27), and was not associated with neurocognitive outcome in our cohort in either unadjusted or multivariable analyses.  $V_T$  also differed by hospital of admission, but hospital was not associated with neurocognitive outcome in unadjusted or multivariable analyses. Moreover, in separate hospital-specific models, the association between  $V_T$  and neurocognitive outcome remained significant, and ORs were strikingly similar between hospitals. Adjusting for both hypothermia use and admitting hospital via the propensity score and separately as

covariates in the multivariable sensitivity analysis did not change the finding that lower  $V_T$  predicts favorable neurocognitive outcome, making them unlikely to explain this association.

Finally, precise causal mechanisms cannot be inferred from this analysis. Several pathways of lung–brain crosstalk have been described in other

disease states with biological similarities to PCAS (44–47). Additional preclinical and clinical investigations are needed to determine their relevance to cardiac arrest and elucidate other mechanisms that may be unique to the constellation of injuries comprised by PCAS.

In conclusion, lower  $V_T$  was independently associated with favorable neurocognitive outcome among patients

hospitalized after nontraumatic OHCA. Lower  $V_T$  also was associated with earlier liberation from mechanical ventilation and more days free from circulatory shock. These results suggest a role for lung-protective ventilation to improve patient outcomes after OHCA. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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