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CRITICAL CARE

COMMENTARY

Diaphragmatic dysfunction in the intensive care unit: caught in the cross-fire between sepsis and mechanical ventilation

Basil J Petrof

See related research by Supinski and Callahan, http://ccforum.com/content/17/3/R120

Abstract

Accumulating evidence indicates that diaphragmatic weakness is common and frequently severe in mechanically ventilated patients. Supinski and Callahan now report that infection is a major risk factor for diaphragmatic weakness in this patient population. Importantly, they show that patients with the greatest levels of diaphragmatic dysfunction have a much poorer prognosis in terms of more prolonged ventilation as well as higher mortality. Mechanical ventilation itself has also been found to induce diaphragmatic weakness along with cellular changes resembling those found in sepsis. Future studies should be directed at understanding the interaction between sepsis and mechanical ventilation, and to developing therapeutic approaches that target their common cellular pathways implicated in diaphragmatic weakness.

Mechanical ventilation is one of the most frequently employed interventions in the intensive care unit (ICU). Although it is a life-saving measure, much time and effort is spent in trying to wean patients from the ventilator as quickly as possible, since mechanical ventilation is also a cause of numerous complications. In a recent issue of *Critical Care*, Supinski and Callahan [1] report that infection is a significant risk factor for diaphragmatic weakness and failure to wean patients from mechanical ventilation. The authors employed state of the art methods (transdiaphragmatic pressure measurements during bilateral magnetic stimulation of the phrenic nerves), and found that patients with evidence of infection had less than half the diaphragmatic pressure-generating ability of uninfected patients. In addition, patients with the most severe diaphragmatic weakness had a markedly worse prognosis. This consisted not only of a more prolonged need for ventilator support, but was also reflected in substantially higher mortality. Indeed, diaphragmatic function appeared to be a better prognostic indicator than other more conventional indices of critical illness severity, such as the Sequential Organ Failure Assessment score. Interestingly, the treating physicians in the ICU dramatically underestimated (in 90% of patients) the degree of diaphragmatic weakness present in their mechanically ventilated patients.

These findings should be an eye opener for practicing clinicians. They point to a need for greater awareness of the very high prevalence of diaphragmatic weakness in mechanically ventilated patients. The inability to successfully wean patients from mechanical ventilation has been closely linked to an unfavorably elevated level of the respiratory muscle work load/capacity ratio [2,3]. Although great emphasis is appropriately placed upon reducing the numerator in this relationship through attempts at improving respiratory system mechanics, the denominator (reflecting respiratory muscle function) is more difficult to assess and often neglected. Nevertheless, several studies have now shown that diaphragmatic weakness is common and frequently profound in mechanically ventilated patients [4-6], although the precise reasons for this are not well understood.

Based upon the fact that even uninfected patients in the study by Supinski and Callahan exhibited a large decrease (to approximately 50% of normal values) of diaphragmatic force-generating capacity, it seems clear that a major component of the diaphragmatic weakness observed in mechanically ventilated patients must be caused by additional factors other than infection. In this regard, another recent study reported that diaphragmatic

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weakness was present on the very first day of admission to the ICU in patients requiring mechanical ventilation for a variety of conditions, including, but not limited to, sepsis [7]. The study by Supinski and Callahan did not specifically evaluate the time course for developing diaphragmatic dysfunction, either from the time of ICU admission and initiation of mechanical ventilation, or from the onset of infection. When taken together, however, the above studies strongly suggest that diaphragmatic dysfunction constitutes a distinct, common, and under-recognized form of organ failure that occurs with many types of critical illness, and especially during sepsis.

The results of these studies in ICU patients are also consistent with a large body of data from different animal models, which have consistently demonstrated impaired diaphragmatic function during sepsis [8]. There is limited information about the impact of mechanical ventilation upon sepsis-induced diaphragmatic dysfunction, but the interaction between the two appears to be complex. Although mechanical ventilation may mitigate the adverse effects of sepsis upon diaphragmatic function and oxygen demand to the muscle very early in its course [9], there are several reasons to believe that mechanical ventilation will either worsen or impede recovery from sepsis-induced diaphragmatic dysfunction over the longer term. In this regard, mechanical ventilation itself leads to diaphragmatic atrophy and weakness in non-septic animals and humans, a phenomenon referred to as ventilator-induced diaphragmatic dysfunction (VIDD) [10]. Furthermore, sepsis-induced diaphragmatic dysfunction and VIDD appear to share many of the same pathogenetic mechanisms, such as increased oxidative stress and mitochondrial dysfunction within diaphragm muscle fibers [11]. Therefore, the combination of sepsis and VIDD could create a 'perfect storm', with mechanical ventilation either exacerbating the magnitude of diaphragmatic weakness caused by infection or slowing the subsequent recovery of diaphragmatic function once sepsis has resolved. Further studies will be required to specifically address these questions, and there is a clear need for novel therapeutic approaches that can either reverse or limit the development of diaphragmatic weakness in mechanically ventilated patients. The presence of common cellular mechanisms implicated in sepsis-induced diaphragmatic dysfunction and VIDD raises the possibility that pharmacologic agents directed at their shared molecular targets might be effective therapies for both conditions.

Abbreviations

ICU: Intensive care unit; VIDD: Ventilator-induced diaphragmatic dysfunction.

Competing interests

The author declares that he has no competing interests.

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Diaphragm weakness in mechanically ventilated critically ill patients

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Running Title: Diaphragm weakness in mechanical ventilation

Abstract

Introduction: Studies indicate that mechanically ventilated patients develop significant diaphragm muscle weakness, but the etiology of weakness and its clinical impact remain incompletely understood. We assessed diaphragm strength in mechanically ventilated medical intensive care unit (MICU) patients, correlated the development of diaphragm weakness with multiple clinical parameters, and examined the relationship between the level of diaphragm weakness and patient outcomes.

Methods: Transdiaphragmatic twitch pressure (PdiTw) in response to bilateral magnetic stimulation of the phrenic nerves was measured. Diaphragm weakness was correlated with the presence of infection, blood urea nitrogen, albumin, and glucose levels. The relationship of diaphragm strength to patient outcomes, including mortality and the duration of mechanical ventilation for successfully weaned patients, was also assessed.

Results: We found that infection is a major risk factor for diaphragm weakness in mechanically ventilated MICU patients. Outcomes for patients with severe diaphragm weakness (PdiTw < 10 cm H_2O) were poor, with a markedly increased mortality (49%) compared to patients with PdiTw ≥ 10 cm H_2O (7% mortality, P=0.022). In addition, survivors with PdiTw < 10 cm H_2O required a significantly longer duration of mechanical ventilation (12.3 ± 1.7 days) than those with PdiTw ≥ 10 cm H_2O (5.5 ± 2.0 days, P=0.016).

Conclusions: Infection is a major cause of severe diaphragm weakness in mechanically ventilated patients. Moreover, diaphragm weakness is an important determinant of poor outcomes in this patient population.

Keywords: diaphragm weakness, mechanical ventilation, infection, weaning, ICU mortality

Introduction

The number of mechanically ventilated patients in medical intensive care units (MICUs) in the United States has increased dramatically over the past 20 years. Currently 800,000 patients per year require mechanical ventilation [1]. Many of these patients die, with a yearly mortality exceeding 200,000 [2]. In addition, survivors often require prolonged, expensive hospital stays to achieve liberation from mechanical ventilation [3]. In the past it was thought that the severity of lung disease was the major determinant of outcomes in MICU patients, but recent work indicates that mechanically ventilated patients develop significant diaphragm weakness [4-6].

Diaphragm weakness is primarily thought to occur as a consequence of ventilator induced diaphragm inactivity, with weakness progressing as duration of mechanical ventilation increases [7, 8]. Theoretically, however, there are other mechanisms by which diaphragm weakness can develop. Animal studies indicate that experimental models of infection induce significant diaphragm weakness [9, 10]. In addition, data suggest that azotemia, hyperglycemia, and low systemic albumin levels are risk factors for prolonged mechanical ventilation and could theoretically be associated with the development of respiratory muscle weakness [11-13]. The importance of infection, azotemia, hyperglycemia, and reduced albumin levels as risk factors for the development of diaphragm weakness in mechanically ventilated patients is, however, unknown.

It is also commonly thought that diaphragm weakness predisposes patients to sustained respiratory failure, greatly prolonging the time required to wean patients from mechanical ventilation and worsening clinical outcomes. No previous study, however,

has examined the quantitative relationship of diaphragm function, assessed using a purely objective, nonvolitional technique (such as bilateral anterior magnetic phrenic nerve stimulation) to clinical outcomes in mechanically ventilated patients.

The purpose of the present study, therefore, was to objectively measure diaphragm strength in a cross section of mechanically ventilated MICU patients and test the specific hypothesis that the severity of diaphragm weakness would correlate with one or more of the following clinical factors: the presence of infection, blood urea nitrogen level, serum albumin level, and/or blood glucose level. We also ascertained the relationship of diaphragm strength to patient outcomes, including mortality, rate of transfer to long-term acute care facilities (LTAC), and the subsequent duration of mechanical ventilation in MICU survivors who were successfully extubated. Finally, to determine if clinicians were cognizant of the severity of diaphragm weakness present in their patients, we asked the attending MICU physicians to estimate diaphragm strength and compared these estimates to objectively determined measurements.

Methods

Study Protocol

Studies were performed on adult ICU patients requiring mechanical ventilation in the University of Kentucky Medical Intensive Care Unit for more than 24 hours. The protocol was approved by the University of Kentucky Institutional Review Board and informed consent was obtained from subjects and their surrogates. The following were recorded: (a) diaphragm strength by measuring PdiTw (transdiaphragmatic twitch pressure), (b) respiratory static system compliance and airway resistance using the

mechanical ventilator diagnostic module, (c) basic clinical data, (d) clinician estimates of diaphragm strength, and (e) outcomes, including mortality, rate of transfer to long-term acute care facilities (LTAC), and additional days required for continued mechanical ventilation until successful extubation.

Exclusion Criteria

If the attending physician anticipated that the patient would be successfully weaned from mechanical ventilation in less than 24 hours, or determined that the patient was too unstable to tolerate the measurements, subjects were not screened for study inclusion. Exclusion criteria included: (a) requirement for high dose pressors (≥15 mcg/min of norepinephrine or ≥15 mg/kg/min of dopamine), (b) elevated PEEP (≥15 cm H_2O), (c) presence of a cardiac pacemaker or implanted defibrillator, (d) administration of neuromuscular blocking agents within 48 hours prior to study entry, (e) recent variceal bleeding, (f) pregnancy, (g) incarceration, or (h) institutionalization.

Determination of Pdi Twitch

Diaphragm strength was assessed by measuring transdiaphragmatic twitch pressure (PdiTw) in response to bilateral anterior magnetic stimulation of the phrenic nerves. PdiTw is an objective, non-volitional technique that has been verified in previous studies to provide the most accurate assessment of diaphragm strength in humans [14-16]. Moreover, previous studies demonstrate that this technique can reliably and reproducibly measure diaphragm contractile strength in mechanically ventilated ICU patients [4-6]. Subjects were studied in the supine position with the head of the bed

elevated at 30 degrees. Two sterile commercially available balloon tipped catheters (Ackred Medical, NJ) were passed through the nose after application of local anesthetic (1 cc of 1% Lidocaine gel); one catheter was placed in the stomach while the other was placed in the esophagus. Following initial placement, catheters were connected to Validyne pressure transducers (Validyne Engineering, Northridge, CA) to verify correct positioning. Correct placement of the gastric balloon was confirmed by demonstrating a positive pressure in response to pressure applied over the stomach; correct placement of the esophageal balloon was verified by demonstrating that the pressure waveform had an end-expiratory pressure similar to the total PEEP level and also mirrored airway pressure changes with inspiratory efforts during airway occlusion. After confirming accurate balloon placement, subjects were left to breathe quietly for 10 minutes before further assessment. Figure of eight magnetic coils attached to dual Magstim 200 stimulators (Jali Medical, Inc., Waltham, MA,) were then placed bilaterally over the phrenic nerves adjacent to the border of the sternocleidomastoid muscles. Magnetic field strength was adjusted to maximal levels (100%) and simultaneous supramaximal magnetic pulses were delivered to the phrenic nerves bilaterally to elicit maximal twitch transdiaphragmatic pressures (i.e. Pdi twitch). Stimuli were interpolated between adjacent ventilator breaths and the transdiaphragmatic pressures elicited by these stimuli were recorded while simultaneously and transiently occluding the external circuit connecting the endotracheal tube to the ventilator with a pneumatic valve. A minimum of five twitches were recorded, with at least 30 seconds between adjacent stimuli. To verify stimuli were supramaximal, additional twitches were performed at reduced magnetic field strengths (90-95%). Pdi twitch was calculated as follows: Pdi twitch = Δ

gastric pressure - Δ esophageal pressure. The best three measurements in response to 100% levels of magnetic stimulation were averaged for each subject and recorded as the Pdi twitch.

Measurement of Respiratory System Static Compliance and Airway Resistance

For these assessments, the ventilator was set to a square-wave flow pattern with an inspiratory plateau. Ventilator rate was then transiently increased (e.g. 30-60 seconds) to suppress spontaneous respirations. After reaching a steady state, peak pressure (Ppeak) and plateau pressure (Pplat), were recorded and intrinsic PEEP (PEEPi) was determined using an end-expiratory occlusion maneuver. Inspiratory airway resistance of the respiratory system was calculated as (Ppeak – Pplat)/inspiratory flow, and the effective static compliance of the respiratory system was calculated as Vt/(Pplat – (total PEEP)). Once measurements were completed, the ventilator was returned to its previous mode and settings.

Clinical Parameters

Data for the following clinical parameters were collected as close as possible to the time of determination of PdiTw levels: age, gender, clinical diagnoses, the presence of positive cultures for infectious agents, antibiotic regimen, glucose, albumin, blood urea nitrogen (BUN), SOFA scores, Charlson comorbidity indexes, vital signs, duration of mechanical ventilation prior to PdiTw measurement, mechanical ventilation mode, FiO_2, tidal volume and rate, % patient triggered breaths, and most recent arterial blood gas values. All recorded values were obtained within 24 hours of PdiTw assessment.

Clinician Estimates

Attending physicians were asked to estimate the level of diaphragm strength using a form with qualitative descriptors of muscle weakness (see Additional file 1 Methods).

Statistics

Whenever data were normally distributed and variances were similar, parametric tests were used to compare groups. When these conditions were not met, non-parametric tests were used to make comparisons. Data analyzed using parametric tests are presented as mean ± 1 standard error of the mean. Data analyzed using nonparametric tests are presented as median ± confidence intervals. Linear regression was utilized to assess the relationship of BUN, albumin, glucose and duration of prior mechanical ventilation to PdiTw level. Analysis of variance was employed to compare PdiTw across cohorts of patients with different levels of ventilator triggering. Fisher exact testing and receiver operating curve analyses were used to determine the boundary between weak and strong PdiTw groups that best discriminated between survival and mortality [17].

Results

Diaphragm Strength in MICU Patients

Sixty subjects were recruited into the study. PdiTw could not be measured in three subjects because the magnetic coils could not be effectively positioned due to anatomic constraints (Subjects # 18, 43, and 48). Detailed information for the 57 subjects in whom PdiTw measurements were successfully performed is provided in Additional file

2, Table 1. To verify that we achieved supramaximal levels of magnetic stimulation, we plotted the PdiTw values achieved with using 95% magnetic field strength levels against PdiTw values attained using 100% magnetic field strength, as shown in Figure 1A. The PdiTw levels obtained using 95% and 100% field strength levels were virtually identical, arguing that supramaximal neural stimulation was achieved when employing 100% magnetic field strength for these studies. Moreover, the twitch determinations were highly reproducible in individual subjects, with a coefficient of variation for the best three measurements performed at 100% stimulator output averaging 7% for the 57 subjects. High levels of PEEP can alter the relationship between the actual intrinsic diaphragm strength and the measured PdiTw. In the present cohort of patients, however, only one study subject had a PEEP level greater than 8 cm H_2O. As a result, PEEP induced hyperinflation did not appreciably impact our data analysis (see Additional file 3, Figure S1).

This cohort of 57 mechanically ventilated subjects had a mean PdiTw of 7.9 ± 0.6 cm H_2O. This value is similar to values reported previously in mechanically ventilated critically ill patients [4-6]. For comparison, normal healthy adults average a PdiTw of 29.3 ± 2.8 cm H_2O in our laboratory; this value is similar to that reported for healthy adults in the literature [4, 14]. Estimates of diaphragm strength from the attending physicians were obtained for 51 subjects. Clinicians did not accurately predict the level of diaphragm strength of their patients (Figure 1B). In many cases, patients with profound levels of diaphragm weakness were thought to have normal strength. Strength was overestimated in 46 of 51 patients, correctly estimated in 5 patients, and was never underestimated.

Risk Factors for the Development of Diaphragm Weakness

Data were analyzed to determine which factors correlated with the level of diaphragm weakness in mechanically ventilated subjects. We found a strong relationship between the presence of infection and diaphragm weakness. In all, 41 subjects were classified as being infected based on a positive test for a pathogenic organism from a sterile site (40 patients) or a clinical diagnosis of bacterial pneumonia (1 patient; cultures were lost for this individual). All 41 subjects that were classified as infected were thought to be infected clinically by the attending physicians who were providing care for these patients and all 41 of these patients received antibiotic therapy (Tables 2 and 3). The remaining 16 patients were classified as non-infected (see Table 2). Infected patients had a median PdiTw of only 5.5 cm H_2O (25%-75% confidence levels of 4.0-7.9 cm H_2O), while patients without clinical evidence of infection had a median PdiTw of 13.0 cm H_2O (25%-75% confidence levels of 11.0-14.7, $p<0.001$) (Figure 2A). Of interest, while infection was associated with greater diaphragm weakness, infected patients did not have significantly different respiratory mechanical parameters (i.e. respiratory system static compliance and airway resistance) than non-infected patients (Figure 2B and 2C).

We also found that there was no significant correlation between PdiTw and either BUN, albumin, or glucose levels (Figures 3A, 3B, and 3C). While many patients were receiving steroids (regimens provided in Table 3), we found no correlation between steroid dosage and PdiTw values (see Additional file 4, Figure S2). In addition, we found no relationship between the number of days subjects had been on mechanical

ventilation prior to testing and the level of PdiTw (Figure 4A). This finding contrasts with recent reports suggesting that patients on mechanical ventilation for longer durations have progressively lower levels of diaphragm strength [6, 23]. One potential explanation for this difference is that the patients examined in the present study were all ventilated with assist modes of mechanical ventilation, while previous work which demonstrated a strong relationship between mechanical ventilation and the development of diaphragm weakness specifically restricted examination to patients who were on controlled mechanical ventilation with little or no spontaneous respiratory activity [23]. As shown in Figure 4B, our patient population had a high level of spontaneous respiratory activity, with the majority of patients triggering more than 75% of ventilator breaths. Of interest, we also found that PdiTw was similar over the range of levels of ventilator triggering observed in the present study (Figure 4C).

Relationship of Diaphragm Strength to Patient Outcomes

To assess the relationship between diaphragm strength and mortality, we plotted PdiTw against patient days of survival (Figure 5A). Patients that died were significantly weaker than survivors, with PdiTw averaging 6.3 ± 0.6 and 8.9 ± 0.9 cm H_2O, respectively, for these two groups ($p<0.04$). To further analyze this relationship, we used Fisher exact testing and ROC curve analyses to determine the level of PdiTw that best discriminated between survival and mortality [17]. Both forms of testing found this boundary to be 10 cm H_2O. Patients with a PdiTw ≥ 10 cm H_2O had only a 7% mortality (1 death out of 14 patients) while patients with a PdiTw < 10 cm H_2O had a 49% mortality (17 deaths out of 35 patients, $p=0.022$ for comparison of the two groups,

Figure 5B). Because indices of lung function may influence mortality, we also compared respiratory system static compliance and airway resistance between patients with PdiTw ≥ 10 cm H_2O and patients with Pdi < 10 cm H_2O (Figures 5C and 5D). Lung mechanics were not significantly different between these two groups of patients, indicating that level of diaphragm function, not lung function, best correlated with survival in our patients. In addition, patients with PdiTw ≥ 10 cm H_2O and PdiTw < 10 cm H_2O had similar SOFA scores (7.6 ± 0.6 and 6.9 ± 0.4, respectively) and Charlson Comorbidity Indices (2.7 ± 0.5 and 2.5 ± 0.3, respectively).

We also evaluated the possible mechanism(s) by which diaphragm weakness may have influenced the incidence of death. In this cohort, five of the patients with PdiTw < 10 cm H_2O that died were receiving vasopressors when care was withdrawn; vasopressors and mechanical ventilation were stopped simultaneously in these patients and death occurred as a result of combined respiratory failure and hypotension. In the remaining 12 patients with PdiTw < 10 cm H_2O that died, none met criteria for brain death, all maintained motor drive to the respiratory pump, none were on vasopressors, and the only form of continuous life support that these patients were receiving was mechanical ventilation. Prior weaning trials had been attempted and all 12 patients had failed to reach extubation criteria. Death occurred in these 12 patients when mechanical ventilation was withdrawn. These data suggest that the presence of severe diaphragm weakness limited weaning trial success in these 12 patients and may have influenced the decision to withdraw care.

With respect to other outcome measures, seven patients with PdiTw < 10 cm H_2O were transferred to a long term ventilator facility (LTAC) while only one of the patients

with PdiTw ≥ 10 cm H_2O was transferred to an LTAC. In addition, the time required to wean survivors from mechanical ventilation was a function of PdiTw, with time to wean increasing significantly for patients with PdiTw values below 10 cm H_2O (Figure 6A). On average, duration of mechanical ventilation after PdiTw measurements was 12.3 ± 1.7 days for patients with PdiTw <10 cm H_2O but only 5.5 ± 2.0 days for patients with PdiTw ≥ 10 cm H_2O (p=0.016). In contrast, duration of mechanical ventilation had no relationship to either respiratory system static compliance (Figure 6B) or airway resistance (Figure 6C).

Discussion

The present study indicates that diaphragm weakness is a significant determinant poor outcomes in mechanically ventilated MICU patients. We found that the incidence of death was 49% in the patients with the weakest diaphragms (i.e. with PdiTw < 10 cm H_2O) but only 7% for patient with PdiTw levels ≥ 10 cm H_2O. One possible explanation for the far greater mortality in the patients with PdiTw < 10 cm H_2O could be that weakness is simply a marker for multi-organ system failure and that damage to these other organs was primarily responsible for patient deaths. Surprisingly, however, we found that indices of disease severity (e.g. lung mechanics, SOFA scores, Charlson Comorbidity Indexes) were almost identical in patients with PdiTw levels ≥ 10 cm H_2O and in patients with PdiTw < 10 cm H_2O, suggesting that the relationship between diaphragm weakness and mortality is not simply an epiphenomenon. Moreover, the majority of patient deaths (12 of 18) were the direct result of withdrawal of mechanical ventilatory support in weak patients and, in each case, occurred after unsuccessful

weaning attempts. It is likely that weakness contributed to the inability to wean these patients from mechanical ventilation and thereby may have influenced the decision to withdraw care.

We also found that a high percentage of patients with PdiTw < 10 cm H_2O required transfer to LTAC units. Reports indicate that long term outcomes for this group of patients are poor, with a high percentage (51%) dying within one year [18]. As a result, the high rate of transfer of weak patients to these units represents a poor outcome. In addition, we found that the relationship between diaphragm strength and duration of mechanical ventilation for patients that did not die and remained in the ICU was curvilinear, with duration increasing progressively as PdiTw levels fell to lower values (Figure 6A). Weak patients with PdiTw <10 cm H_2O required more than twice as long to wean from mechanical ventilation than stronger patients with PdiTw levels ≥ 10 cm H_2O. Moreover, the duration of mechanical ventilation did not correlate with the level of lung dysfunction but only with the level of diaphragm strength.

We also evaluated our data to ascertain the role of infections, BUN, albumin and glucose levels in the induction of diaphragm weakness in mechanically ventilated patients. We found the level of diaphragm weakness in mechanically ventilated MICU patients did not correlate with BUN, glucose, or albumin levels despite previous reports associating these factors with prolonged mechanical ventilation [11-13]. In contrast, we found that evidence of infection was a predictor of strikingly lower levels of diaphragm strength than that observed for non-infected patients. This finding is consistent with multiple previous animal studies demonstrating that infection rapidly reduces diaphragm

force generation, decreases diaphragm mitochondrial function, activates diaphragm proteolytic pathways, and reduces diaphragm contractile protein function [9, 25-31].

While infected patients had the weakest diaphragms, even the non-infected mechanically ventilated patients in our study had a median level of PdiTw (13 cm H_2O) that is substantially lower than that observed for normal healthy adults (30 cm H_2O). There are two likely explanations for the weakness observed in the non-infected patients. First, many of the patients in our study were chronically ill, with multiple illnesses including heart failure, malignancy, liver and renal diseases. Each of entities has negative effects on muscle function, and it is possible that the pre-intubation muscle function of these patients may have been appreciably lower than that observed in normal subjects.

In addition, use of mechanical ventilation can result in diaphragm inactivity and atrophy [19-22]. Numerous animal studies have provided evidence of this phenomenon, and more recently, several elegant studies indicate that loss of diaphragm function occurs in patients who are subjected to controlled mechanical ventilation with minimal or no spontaneous respirations [19, 23]. Our patients were all ventilated using assisted modes of mechanical ventilation and may therefore have had less inactivity induced diaphragm dysfunction than observed in patient populations ventilated with controlled modes of mechanical ventilation. Nevertheless, it is still possible that ventilator induced inactivity contributed to the level of diaphragm weakness observed in our non-infected patients. As a corollary, the level of weakness observed in our infected patients may represent the combined effects of chronic illness, ventilator induced inactivity, and infection induced diaphragm dysfunction.

It is worth noting, however, that the non-infected patients had a level of PdiTw (median of 13 cm H_2O) that was sufficiently high that this group of patients would be expected to have good outcomes (i.e. a low death rate and an average wean time from mechanical ventilation of about 5 days) according to the data presented in Figures 5 and 6. Only the infected mechanically ventilated patients, as a group, had low enough PdiTw levels (median of 5.5 cm H_2O) to expect poor outcomes (i.e. a high mortality and a protracted need for mechanical ventilation). These data argue, therefore, that even if all the diaphragm weakness observed in our non-infected patients was a consequence of ventilator induced inactivity, this level of weakness alone would not be expected to result in poor patient outcomes. Our data would suggest, instead, that only the combination of ventilator induced inactivity and infection may produce sufficient diaphragm weakness to negatively influence patient survival and duration of mechanical ventilation.

Conclusions

In summary, we found that mechanically ventilated MICU patients have severe diaphragm weakness, that the clinicians caring for these patients greatly underestimate the severity of diaphragm weakness present, and that infections are a major risk factor for the development of diaphragm weakness in this population. We also found that diaphragm weakness was associated with poor patient outcomes, including a significantly increased mortality, an increased transfer to LTACs and a markedly longer duration required for weaning from mechanical ventilation.

Diaphragm weakness appears to be a major risk factor for respiratory failure and death in mechanically ventilated MICU patients; theoretically, pharmacological treatments that improve diaphragm strength should reduce the duration of mechanical ventilation and MICU mortality. Currently no such agents are used in clinical practice, but recent experimental studies indicate that pharmacological inhibition of selected cellular pathways can prevent diaphragm weakness in animal models of critical illness [32, 33]. There is an urgent need to translate these pharmacological treatments from the bench to the bedside in order to prevent or reverse diaphragm weakness in mechanically ventilated MICU patients. Such therapies are likely to influence both acute and long term outcomes.

Key Messages

- Recent work indicates that many mechanically ventilated MICU patients have severe diaphragm weakness, but the causes and consequences of this weakness remain controversial.
- The present study indicates that infection is a major risk factor for development of diaphragm weakness in medical intensive care unit patients treated with assist modes of mechanical ventilation.
- This work also demonstrates that the level of diaphragm weakness is a novel predictor of clinical outcomes; the weakest patients have a high mortality and require prolonged durations of mechanical ventilation.
- This study indicates that clinicians underestimate the severity of diaphragm dysfunction in mechanically ventilated critically ill patients.

Abbreviations: BUN = blood urea nitrogen, H_2O = water, ICU = intensive care unit, LTAC = long term acute care, MICU = medical intensive care unit, PdiTw = transdiaphragmatic twitch pressure in response to bilateral anterior magnetic stimulation of the phrenic nerves, SOFA = Sequential Organ Failure Assessment,

Competing Interests

Both authors declare that they have no competing interests.

Author's Contributions

G.S.S. drafted the protocol, performed the measurements, analyzed the pressure tracings, obtained patient data, interpreted the data, drafted and revised the final manuscript. L.A.C. assisted in performing the measurements, obtaining patient data, had a major impact on the interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

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Figure Legends

Figure 1: PdiTw: Measured Levels and Physician Estimates

The left panel (A) displays PdiTw levels for the 57 subjects included in the analysis. Each symbol represents a single subject and plots the PdiTw level obtained in response to stimulation of the phrenic nerves with a 95% of maximum magnetic field strength (y axis) against the PdiTw obtained in response to stimulation of the phrenic nerves with 100% of maximum magnetic field strength (x axis). All of the data cluster along the line of identity, indicating that supramaximal stimulation was achieved during 100% magnetic field stimulation. If supramaximal conditions had not been achieved, data points would have fallen to the right of the line of identity. In the right panel (B), measured PdiTw levels are compared to levels predicted for each subject by their attending physicians; each symbol represents data from a single patient. Red symbols that are below the line (46 out of 51 determinations) indicate determinations for which physicians overestimated diaphragm strength (i.e. PdiTw).

Figure 2: Infection and Diaphragm Weakness

The top panel (A) compares Pdi Twitch (PdiTw) measurements for non-infected and infected patients. Data from individual patients is shown for each group on the right, while plots on the left for each group show mean (■), median levels (middle line of box), 25% and 75% confidence intervals (upper and lower borders of the box) and 1% and 99% intervals (whiskers above and below the box). Infection was associated with significant lower Pdi Twitch values (* indicates statistical significance). Bottom panels display respiratory system static compliance (i.e. RS Static Compliance, 2B) and

inspiratory airway resistance (2C) for non-infected and infected patients; there was no difference in these indices of lung function between non-infected and infected groups.

Figure 3: Correlation of PdiTw to BUN, Albumin, and Glucose Levels.

This figure displays PdiTw as a function of blood urea nitrogen (BUN, 3A), albumin (3B), and glucose levels (3C). There was no significant correlation between any these parameters and PdiTw. Specifically, correlation coefficients and p values for regression of PdiTw to parameters were, respectively, 0.146 and 0.277 for BUN, 0.072 and 0.596 for albumin, and 0.032 and 0.815 for glucose levels (all NS).

Figure 4: Relationship of Prior Duration of Mechanical Ventilation and Ventilator Triggering to Diaphragm Strength

Figure 4A displays PdiTw as a function of the duration of mechanical ventilation prior to measurement of PdiTw. There was no statistically significant correlation of PdiTw to duration of ventilation prior to measurement, with a correlation coefficient of 0.020 and a p value of 0.881 for this assessment (NS). Figure 4B demonstrates that the majority of subjects actively initiated (i.e. triggered) ventilator breaths more than 75% of the time. Figure 4C shows that the level of diaphragm strength (PdiTw) did not correlate with the level of triggering with the same PdiTw observed at all triggering levels.

Figure 5: Relationship of Diaphragm Strength to Survival

Figure 5A displays the survival of patients (days after measurement, x axis) as a function of PdiTw level (y axis). Patients that died had low average PdiTw levels (6.3 ±

0.6 cm H_2O) while survivors had higher PdiTw levels (8.9 ± 0.9 cm H_2O, p=0.044). Figure 5B displays survival curves for subjects with PdiTw ≥ 10 cm H_2O (n=15) and PdiTw < 10 cm H_2O (n=42). Weak subjects had a significantly higher mortality (49%) than strong subjects (7%, p=0.022). To exclude the possibility that the greater mortality in the weakest patients may have been due to the presence of more severe lung dysfunction, we also examined respiratory system (RS) static compliance (Figure 5C) and airway resistance (Figure 5D). There was no significant difference in RS static compliance or airway resistance for patients with PdiTw ≥ 10 cm H_2O and PdiTw < 10 cm H_2O, indicating that the greater mortality ion the weakest patients was not due to concomitant lung dysfunction.

Figure 6: Relationship of Diaphragm Strength to ventilator Weaning Duration

Figure 6A displays the duration of mechanical ventilation after measurement of PdiTw as a function of the level of PdiTw; each symbol represents data from a single subject. Patients with PdiTw ≥ 10 cm H_2O required significantly shorter times to wean from mechanical ventilation when compared to patients with PdiTw < 10 cm H_2O (p=.016). The time required to wean from mechanical ventilation bore no relationship, however, to the respiratory system (RS) static compliance (Figure 6B) or the airway resistance (Figure 6C).

Table 1. Characteristics of Non - Infected and Infected Study Subjects

	Non-Infected (n=16)	**Infected (n=41)**
Age (Years)	52.4 ± 14.1	55.5 ± 16.7
Gender	Male 44%, Female 56%	Male 49%, Female 51%
BMI	30.3 ± 9.2	29.8 ± 9.5
Total ICU Days	15.1 ± 9.8	34.9 ± 40.2
Days of MV Before PdiTw Measurement	9.1 ± 8.9	10.4 ± 12.4
Steroid Usage (%)	50%	51%

Data presented as mean ± SD

Table 2. Criteria for Classification of 57 Subjects According to the Presence or Absence of Active Infection at the Time of PdiTw Measurements

Subject #	Infected	Site	Organism(s) Isolated From Site(s)	Dx of Infection by Attending	AB Tx	Pulmonary Infiltrates
1	No			No	No	No
2	Yes	Liver abscess	*Staphylococcus sp., Fusobacterium necrophorum*	Yes	Yes	Yes
3	No			No	No	No
4	Yes	PAL	*Streptococcus pneumoniae*	Yes	Yes	Yes
5	No			No	No	No
6	Yes	Blood	Gram + bacteria**	Yes	Yes	Yes
7	Yes	PAL	*Pseudomonas aeruginosa*	Yes	Yes	Yes
8	Yes	Blood	*Staphylococcus species*	Yes	Yes	Yes

9	No			No	No	Yes[†]
10	Yes	PAL	*Pseudomonas aeruginosa*	Yes	Yes	Yes
11	No			No	No	No
12	Yes	Sinuses Nasopharyngeal Swab	*Bacteroides capillosus, Fusobacterium sp., β strep. Gp C* Influenza A	Yes	Yes	Yes
13	No			No	No	No
14	Yes	Jejunal drain	VRE, *Pseudomonas aeruginosa*	Yes	Yes	Yes
15	Yes	Blood	*Staphylococcus aureus*	Yes	Yes	No
16	No			No	No	No
17	Yes	PAL Blood	*Staphylococcus species* *Staphylococcus species*	Yes	Yes	Yes

19	Yes	PAL	*Klebsiella pneumoniae*	Yes	Yes	Yes
20	Yes	Blood	*Staphylococcus aureus*	Yes	Yes	No
21	Yes	Neck abscess	*Streptococcus sp.*	Yes	Yes	No
22	Yes	Sputum	*Hemophilus parainfluenza*	Yes	Yes	Yes
23	Yes	Stage IV Decubitus Urine	*Pseudomonas aeruginosa, Proteus mirabilis* *Pseudomonas aeruginosa*	Yes	Yes	No
24	No			No	No	No
25	No			No	No	No
26	No			No	No	No
27	Yes	Subphrenic abscess	*Candida glabrata*	Yes	Yes	Yes

28	No			No	No	No
29	Yes	BAL	*Escherichia coli* *Klebsiella pneumoniae*	Yes	Yes	Yes
30	No			No	No	No
31	No			No	No	Yes[†]
32	Yes	Blood	*Enterococcus faecalis*	Yes	Yes	No
33	Yes	PAL	*Staphylococcus aureus*	Yes	Yes	Yes
34	Yes	Blood	Gram + cocci*	Yes	Yes	Yes
35	Yes	ET aspirate Blood	*Acinetobacter calcoaceticus,* *Enterobacter cloacae* *Candida*	Yes	Yes	Yes
36	Yes	PAL Central Venous Catheter	*Achromobacter xyloxosidans* *Pseudomonas aeruginosa*	Yes	Yes	Yes

37	Yes	PAL	*Pseudomonas aeruginosa*	Yes	Yes	Yes
38	Yes	Liver abscess	*Escherichia coli*	Yes	Yes	Yes
39	Yes	PAL	*Staphylococcus sp., Enterobacter aerogenes, Escherichia coli*	Yes	Yes	Yes
40	Yes	PAL Blood	MRSA MRSA	Yes	Yes	Yes
41	Yes	Nasopharyngeal swab	Influenza B	Yes	Yes	Yes
42	Yes	Blood Leg abscess Osteomyelitis	MRSA MRSA MRSA	Yes	Yes	Yes
44	No			No	No	Yes[†]
45	No			No	No	No
46	Yes	Sputum	MRSA	Yes	Yes	Yes

47	Yes	PAL	*Streptococcus pneumoniae*	Yes	Yes	Yes
49	No			No	No	No
50	Yes	Pleural fluid Pleural tissue	*Acinetobacter baumannii*, VRE *Acinetobacter baumannii*, VRE	Yes	Yes	Yes
51	Yes	Blood	*Bacillus circulans*	Yes	Yes	Yes
52	Yes	Blood	VRE	Yes	Yes	Yes
53	Yes	PAL Nasopharyngeal Swab	*Pseudomonas aeruginosa* H1N1	Yes	Yes	Yes
54	Yes	Blood Tracheal aspirate	VRE *Stenotrophomonas maltophilia*	Yes	Yes	Yes
55	Yes	PAL	MRSA	Yes	Yes	Yes
56	Yes	Blood Sputum	MRSA, *Pseudomonas aeruginosa*, VRE *Pseudomonas aeruginosa*	Yes	Yes	Yes

57	Yes	BAL	samples lost††	Yes	Yes	Yes
58	Yes	Tracheal aspirate	*Hemophilus influenza*	Yes	Yes	Yes
59	Yes	Blood	*Staphylococcus species*	Yes	Yes	No
60	Yes	Urine PAL	*Enterobacter cloacae* *Streptococcus sp*.	Yes	Yes	Yes

* Data not included for subjects 18, 43, and 48 because PdiTw measurements not obtained due to anatomic constraints
† Patient with pulmonary infiltrates but without evidence of infection (Subject 9 with non-pulmonary acute lung injury, Subject 31 with pulmonary fibrosis, Subject 44 with ARDS)
** Organism not speciated-subject treated with antibiotics prior to transfer
†† Bronchoscopy performed with purulent exudates noted; specimens lost in transit to lab

Abbreviations: AB Tx = Patient on antibiotic therapy at the time of PdiTw measurement, BAL= bronchoalveolar lavage, Dx = Diagnosis, MRSA = methicillin resistant Staphylococcal aureus, PAL = protected alveolar lavage, VRE = Enterococcus faecium (vancomycin resistant)

Table 3. Medication Regimen in 57 Subjects* at the Time of PdiTw Measurements

Subject #	Antibiotics	Other Medications	Steroid Regimen Over Entire ICU Stay
1		Midazolam, Metoprolol, Hydralazine, Calcium acetate, Famotidine	
2	Piperacillin/Tazobactam , Vancomycin, Levofloxacin, Flagyl	Enoxaparin , Omeprazole, Dobutamine	Hydrocortisone 100 mg q 8 hrs x 4 days
3		Metoprolol, Haloperidol, Insulin, Aspirin	
4	Piperacillin/Tazobactam, Vancomycin, Levofloxacin	Midazolam, Fentanyl, Pantoprazole	
5		Famotidine, Trazadone	Methylprednisolone 1 gm/d x 3 days, Prednisone 60 mg/d x 2 days , 40 mg/d x 3 days, 30 mg/d x 2 days , 20 mg/d x 2 days , 10 mg/d x 2 days
6	Piperacillin/Tazobactam , Vancomycin, Fluconazole	Midazolam, Fentanyl, Insulin, Lactulose, Levothyroxine, Norepinephrine, Pantoprazole	Hydrocortisone 50 mg q 6 hrs x 1 day
7	Piperacillin/Tazobactam	Midazolam, Alprazolam, Fentanyl, Insulin, Famotidine, Heparin	
8	Vancomycin	Midazolam, Fentanyl, Insulin, Famotidine, Heparin, Simvastatin, Gabapentin, Venlafaxine, Calcium gluconate	Hydrocortisone 50 mg q 8 hrs x 8 days

9		Midazolam, Lorazepam, Omeprazole, Ursodiol, Clonidine, Levetiracetam, Ondansetron, Metaclopramide, Hydralazine, Heparin	
10	Piperacillin/Tazobactam, Vancomycin	Midazolam, Famotidine, Aspirin, Clopidogrel, Insulin, Heparin, Metaclopramide, Docusate	Prednisone 20 mg/d x 3 days, Hydrocortisone 100 mg q 8 hrs x 2 days
11		Midazolam, Protonix, Amitryptyline, Bupropion, Carvedilol, Clonazepam, Folic acid, Acetaminophen, Digoxin, Ondansetron, Heparin, Tacrolimus	Methylprednisolone 60 mg q12 hrs x 3 days
12	Vancomycin, Clindamycin, Tamiflu	Midazolam, Fentanyl, Morphine, Heparin, Insulin, Pantoprazole, Bumetanide	Methylprednisolone 60 mg /d x 4 days, Prednisone 40 mg/d X 3 days
13		Midazolam, Enoxaparin, Famotidine, Insulin, Metoprolol, Aspirin, Hydralazine, Lisinopril, Simvastatin	
14	Vancomycin, Levofloxacin, Flagyl, Aztreonam	Midazolam, Fentanyl, Heparin	Methylprednisolone 60 mg q12 hrs x 6 days
15	Vancomycin	Propofol, Omeprazole, Heparin, Amlodipine	
16		Midazolam, Fentanyl, Protonix, Ondansetron, Darbepoetin, Folic acid, Cyanocobalamin, Hydralazine, Amldipine, Lisinopril	
17	Vancomycin, Levofloxacin	Midazolam, Fentanyl, Protonix, Insulin, Lactulose, Levothyroxine, Sertraline, Hydralazine, Gabapentin, Carvedilol	

19	Vancomycin, Piperacillin/Tazobactam, Levofloxacin	Heparin, Hydralazine, Labetalol, Metoprolol, Levetiracetam, Lorazepam, Omeprazole, Phenytoin	Prednisone 20 mg/d x 2 days
20	Vancomycin	Midazolam, Morphine, Amlodipine, Labetalol, Metoprolol, Protonix, Phenytoin, Heparin	
21	Vancomycin, Tobramycin, Ampicillin/sulbactam	Midazolam, Fentanyl, Heparin, Ibuprofen, Amiodarone, Metoprolol, Omeprazole	
22	Vancomycin, Levofloxacin	Famotidine, Heparin, Metaclopramide, Diphenhydramine	
23	Vancomycin, Doripenem, Colistin	Bumetanide, Midazolam, Ascorbic acid, Famotidine, Insulin, Vitamin A, Zinc, Aripiprazole, Escitalopram, Heparin	
24		Paroxetine, Pramipexole, Simvastatin, Omeprazole, Heparin, Midazolam, Insulin, Metoprolol, Bumetanide	
25		Midazolam, Heparin, Omeprazole, Haloperidol, Olanzapine, Insulin	Prednisone 40 mg/d x 6 days
26		Famotidine, Darbepoetin, Amlodipine, Labetolol, Folic acid, Thiamine, Dexmedetomidine, Heparin	
27	Doripenem, Doxycycline, Micafungin, Flagyl	Midazolam, Fentanyl, Promethazine, Pantoprazole, Levetiracetam, Propofol, Lactulose	Prednisone 50 mg q 8 hrs x 8 days

28		Midazolam, Haloperidol, Omeprazole, Levothyroxine, Heparin, Insulin, Furosemide	
29	Doripenem, Tobramycin, Fluconazole, Erythromycin	Morphine, Ondansetron, Rifaximin, Pantoprazole, Lactulose, Insulin, Aspirin, Heparin, Levetriacetam, Midazolam, Phenytoin, Vasopressin	
30		Aspirin, Benztropine, Famotidine, Gabapentin, Hydrochlorothiazide, Metoclopramide, Miralax, Insulin, Heparin, Valproic acid, Docusate	Methylprednisolone 125 mg q 6 hrs x 2 days
31		Azathioprine, Bumetanide, Clopidogrel, Ezetimibe, Famotidine, Fentanyl, Furosemide, Heparin, Metoprolol, Midazolam, Nitroglycerin patch, Omeprazole, Provastatin	Methylprednisilone 125 mg q 6 hrs x 3 days, 40 mg q 6 hrs x 2 days, Prednisone 60 mg/d x 5 days
32	Vancomycin, Gentamycin, Aztreonam	Midazolam, Fentanyl, Aspirin, Carbemazepam, Haloperidol, Metoprolol, Omeprazole, Phenytoin, Insulin, Heparin	Methylprednisolone 60 mg q 6 hrs x 6 days
33	Linezolid	Midazolam, Lorazepam, Fentanyl, Aspirin, Digoxin, Insulin, Metoprolol, Famotidine, Heparin	
34	Vancomycin, Piperacillin/Tazobactam , Micofungin	Midazolam, Fentanyl, Insulin, Aspirin, Amlodipine, Metaclopramide, Famotidine, Heparin	Methylprednisolone 100 mg q12 hrs x 9 days
35	Vancomycin, Piperacillin/Tazobactam , Micofungin, Colistin, Bactrim	Foscarnate, Pantoprazole, Diphenhydramine, Insulin, Fludrocortisone, Levothyroxine, Ursodiol	Methylprednisolone 10 mg X 1 day

36	Vancomycin, Meraopenum, Valgancyclovir, Cefipime, Dapsone, Levofloxacin	Ondansetron, Omeprazole, Metoprolol, Mycophenolate mofetil, Sildenafil	Prednisone 25 mg/d x 250 days
37	Piperacillin/Tazobactam , Vancomycin,Levofloxacin	Midazolam, Fentanyl, Aspirin, Heparin, Omeprazole, Simvastatin	Methylprednisolone 40 mg/d x 2 days, Prednisone 40 mg/d x1 day, Prednisone 20mg/d x 3 days
38	Flagyl, Levofloxacin, Aztreonam	Midazolam, Fentanyl, Morphine, Norepinephrine, Vasopressin, Famotidine, Heparin	
39	Doripenam, Colistimethate, Vancomycin	Midazolam, Fentanyl, Lortab, Zolpidem, Metoprolol, Omeprazole, Heparin	
40	Vancomycin, Piperacillin/Tazobactam , Levofloxacin	Midazolam, Fentanyl, Metaclopramide, Aspirin, Azathioprine, Clopidogrel, Furosemide, Ondansetron, Simvastatin, Famotidine, Heparin	Prednisone 20 mg/d x 7 days
41	Vancomycin, Piperacillin/Tazobactam , Clindamycin	Midazolam, Fentanyl, Propofol, Insulin, Omeprazole	
42	Vancomycin, Cefipime, Levofloxacin, Acyclovir	Midazolam, Fentanyl, Ondansetron, Pantoprazole, Heparin	
44		Midazolam, Fentanyl, Haloperidol, Insulin, Famotidine, Heparin	Methylprednisolone 125 mg q 6 hrs x 2 days
45		Midazolam, Fentanyl, Ondansetron, Insulin, Omeprazole, Heparin	Hydrocortisone 100 mg q 8 hrs x 3 days
46	Linezolid, Piperacillin/Tazobactam , Tobramycin	Midazolam, Diltiazem, Mycophenolate mofetil, Tacrolimus, Famotidine, Insulin, Heparin	Hydrocortisone 100 mg q 8 hrs x 6 days, Prednisone 40 mg/d x 3 days

47	Vancomycin, Cefipime, Levofloxacin	Midazolam, Aspirin, Captopril, Furosemide, Simvastatin, Insulin	Prednisone 40 mg/d x 3 days, 30 mg/d x 2 days
49		Midazolam, Aspirin, Atorvastatin, Bisoprolol, Clopidogrel, Fluticasone, Folic acid, Pantoprazole, Heparin	Methylprednisolone 60 mg q 6 hrs x 4 days, 40 mg q 12 hrs x 2 days, Prednisone 40 mg/d x 1 day
50	Vancomycin, Aztreonam, Tobramycin, Daptomycin	Midazolam, Hydroxyzine, Darbepoetin, Levothyroxine, Ferrous sulfate, Ergocalciferol, Pancrelipase, Omeprazole	Hydrocortisone 20 mg q 12 hrs x 37 days
51	Vancomycin, Piperacillin/Tazobactam , Doripenam, Fluconazaole	Midazolam, Fentanyl, Furosemide, Pancrelipase, Magnesium oxide, Famotidine, Insulin, Heparin	
52	Vancomycin, Piperacillin/Tazobactam , Daptomycin	Midazolam, Fentanyl, Levothyroxine, Darbepoetin, Fluticasone, Lactulose, Paroxetime, Insulin, Heparin	Hydrocortisone 100 mg q 8 hrs x 5 days
53	Tamiflu, Piperacillin/Tazobactam , Cefipime, Daptomycin, Doripenam	Midazolam, Darbepoetin, Bumetanide, Famotidine, Insulin, Heparin	
54	Vancomycin, Piperacillin/Tazobactam	Morphine, Oxycodone, Furosemide, Famotidine, Insulin, Heparin	Hydrocortisone 50 mg q 6 hrs x 3 days
55	Vancomycin, Piperacillin/Tazobactam , Levofloxacin, Daptomycin	Ferrous sulfate, Folic acid, Levothyroxine, Metaclopramide, Pravastatin, Digoxin Tacrolimus, Omeprazole, Heparin	
56	Daptomycin, Linezolid, Tobramycin, Colistin, Zithromax	Midazolam, Fentanyl, Dexmedetomidine, Omeprazole, Heparin	

57	Vancomycin, Piperacillin/Tazobactam , Levofloxacin, Tamiflu	Midazolam, Fentanyl, Clonazepam, Gabapentin, Famotidine, Insulin, Heparin	
58	Piperacillin/Tazobactam	Midazolam, Morphine, Furosemide, Metoprolol, Citalopram, Pantoprazole, Aspirin, Acetazolamide, Insulin, Heparin	Methylprednisolone 60 mg q 8 hrs x 4 days, Prednisone 60 mg/d x 5 days, 40 mg/d x 5 days, 30 mg/d x 5 days
59	Vancomycin, Cefipime, Levofloxacin	Midazolam, Fentanyl, Dopamine, Norepinephrine, Simvastatin, Aspirin, Omeprazole, Heparin	Hydrocortisone 100 mg q 8 hrs x 3 days, 50 mg q 8 hrs x 2 day, 50 mg q 12 hrs x 7 days
60	Vancomycin, Cefipime, Tobramycin	Midazolam, Fentanyl, Norepinephrine, Pantoprazole, Heparin	

* Data not included for subjects 18, 43, and 48 because PdiTw measurements not obtained due to anatomic constraint

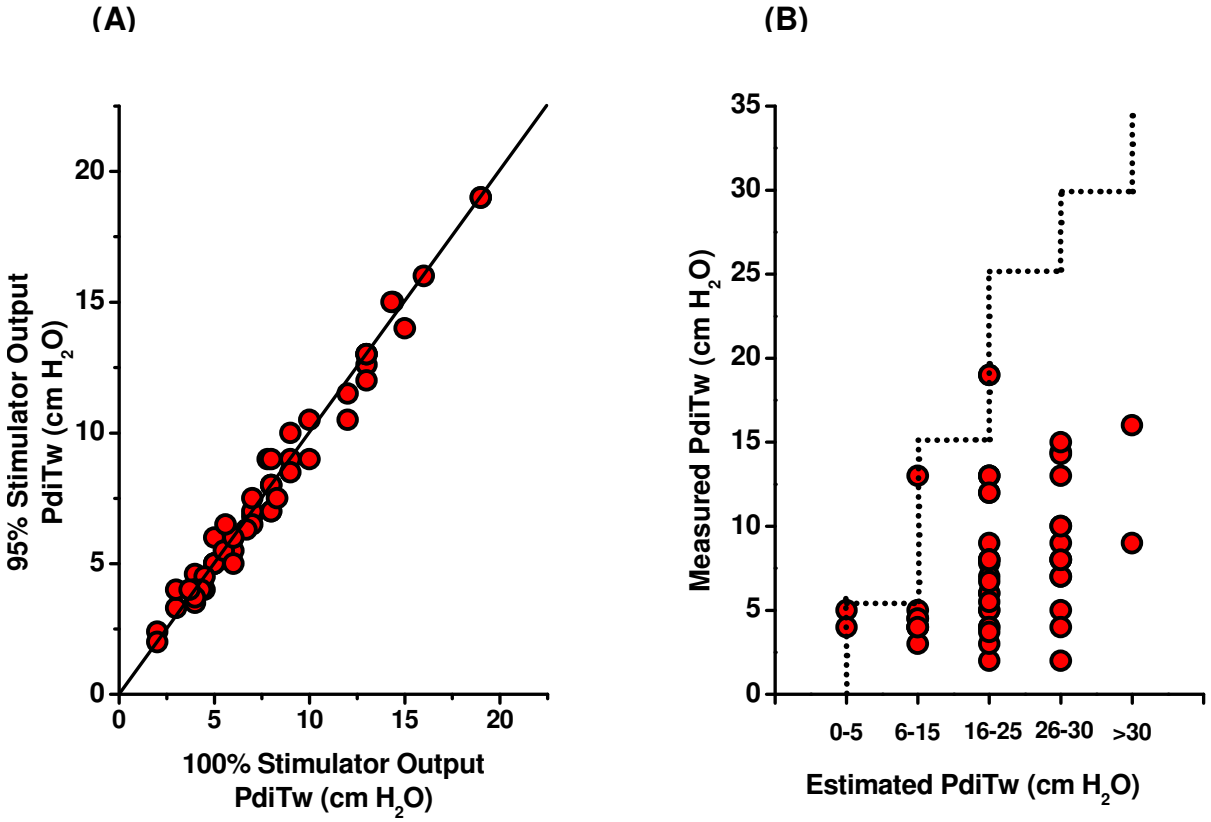
(A)
95% Stimulator Output PdiTw (cm H2O)
100% Stimulator Output PdiTw (cm H2O)
0
5
10
15
20
(B)
Measured PdiTw (cm H2O)
Estimated PdiTw (cm H2O)
0-5
6-15
16-25
26-30
>30
0
5
10
15
20
25
30
35

Figure 1

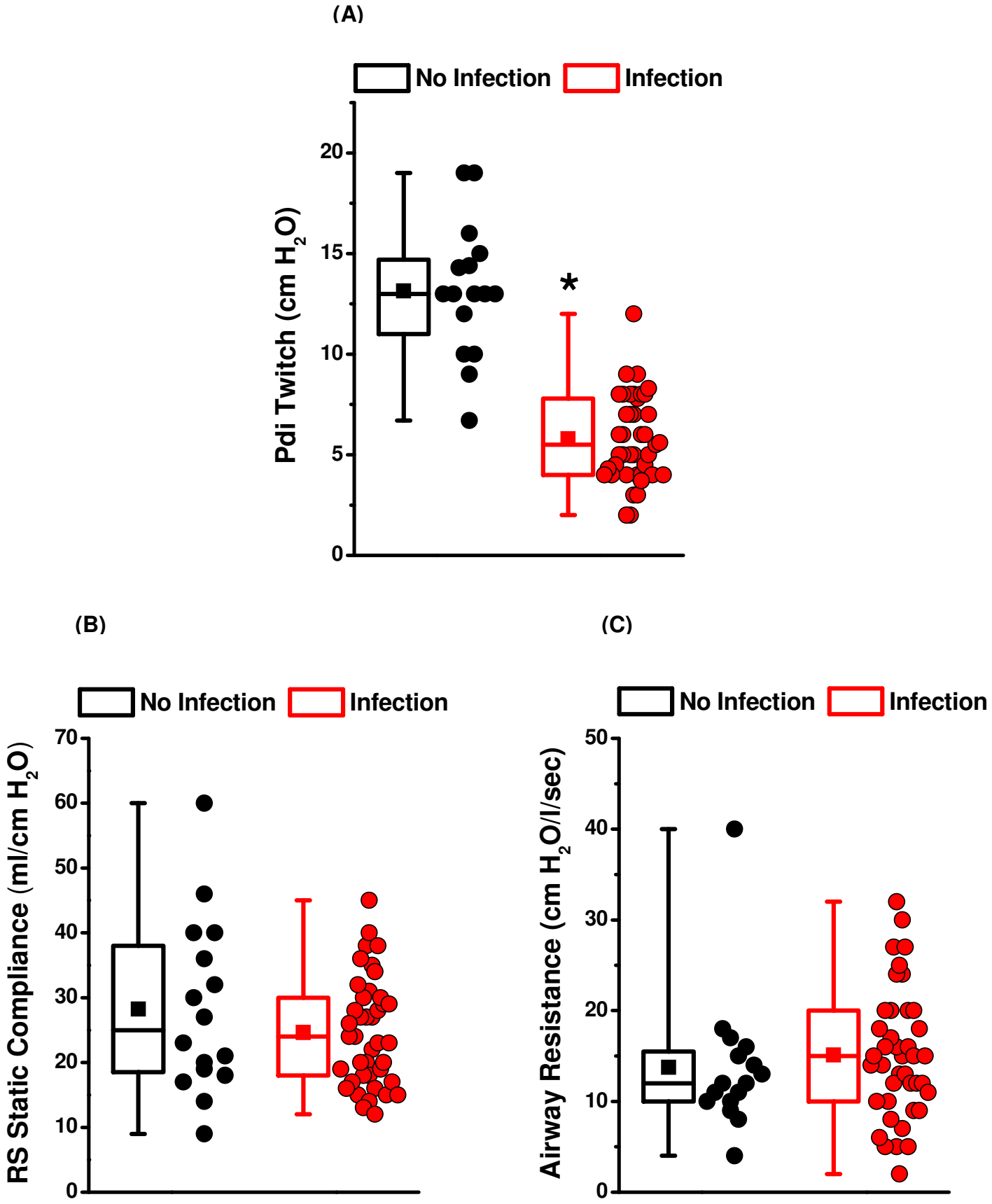
(A)
No Infection
Infection
Pdi Twitch (cm H2O)
20
15
10
5
0
*
(B)
No Infection
Infection
RS Static Compliance (ml/cm H2O)
70
60
50
40
30
20
10
0
(C)
No Infection
Infection
Airway Resistance (cm H2O/l/sec)
50
40
30
20
10
0

Figure 2

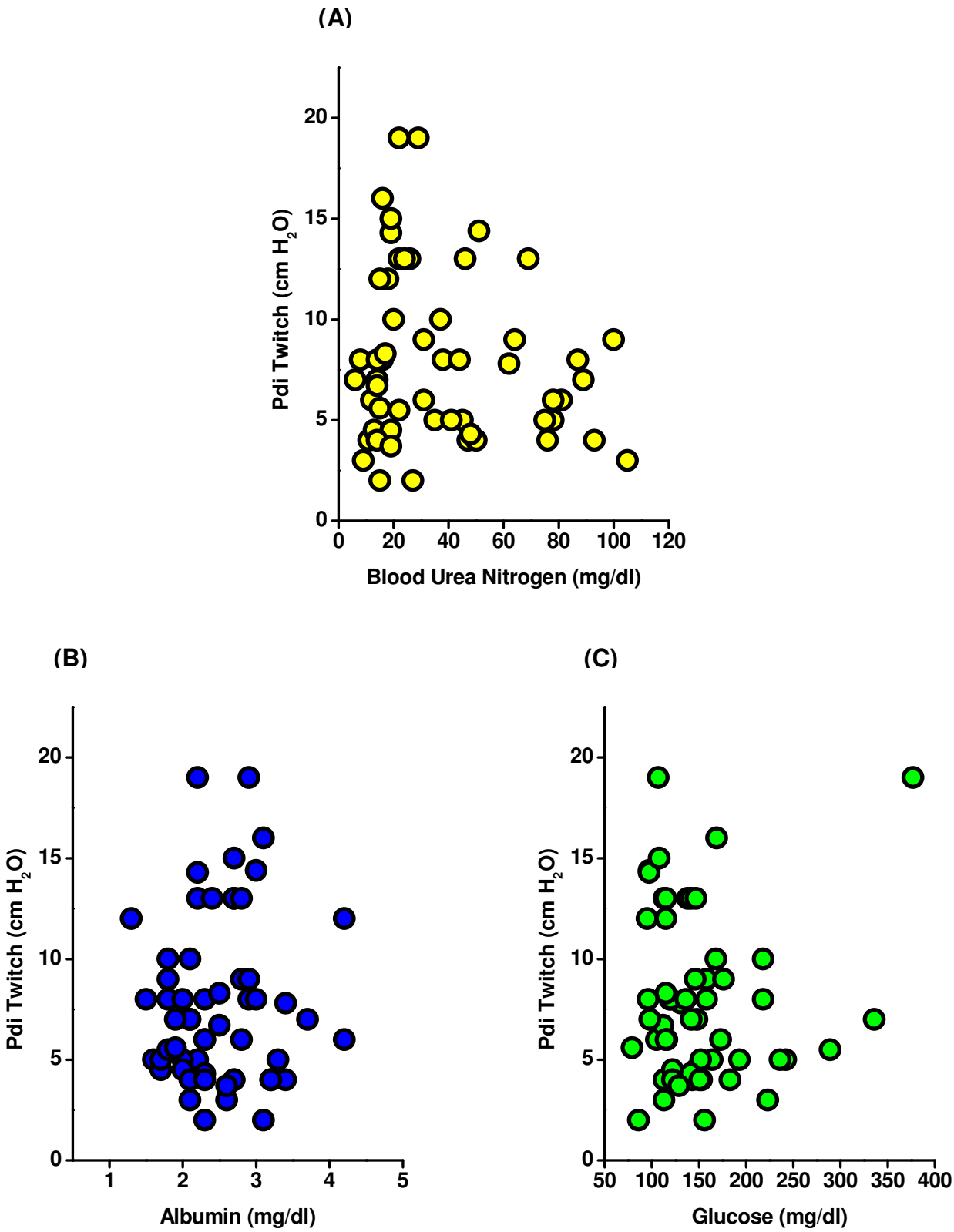
(A)
Pdi Twitch (cm H2O)
Blood Urea Nitrogen (mg/dl)
(B)
Albumin (mg/dl)
(C)
Glucose (mg/dl)

Figure 3

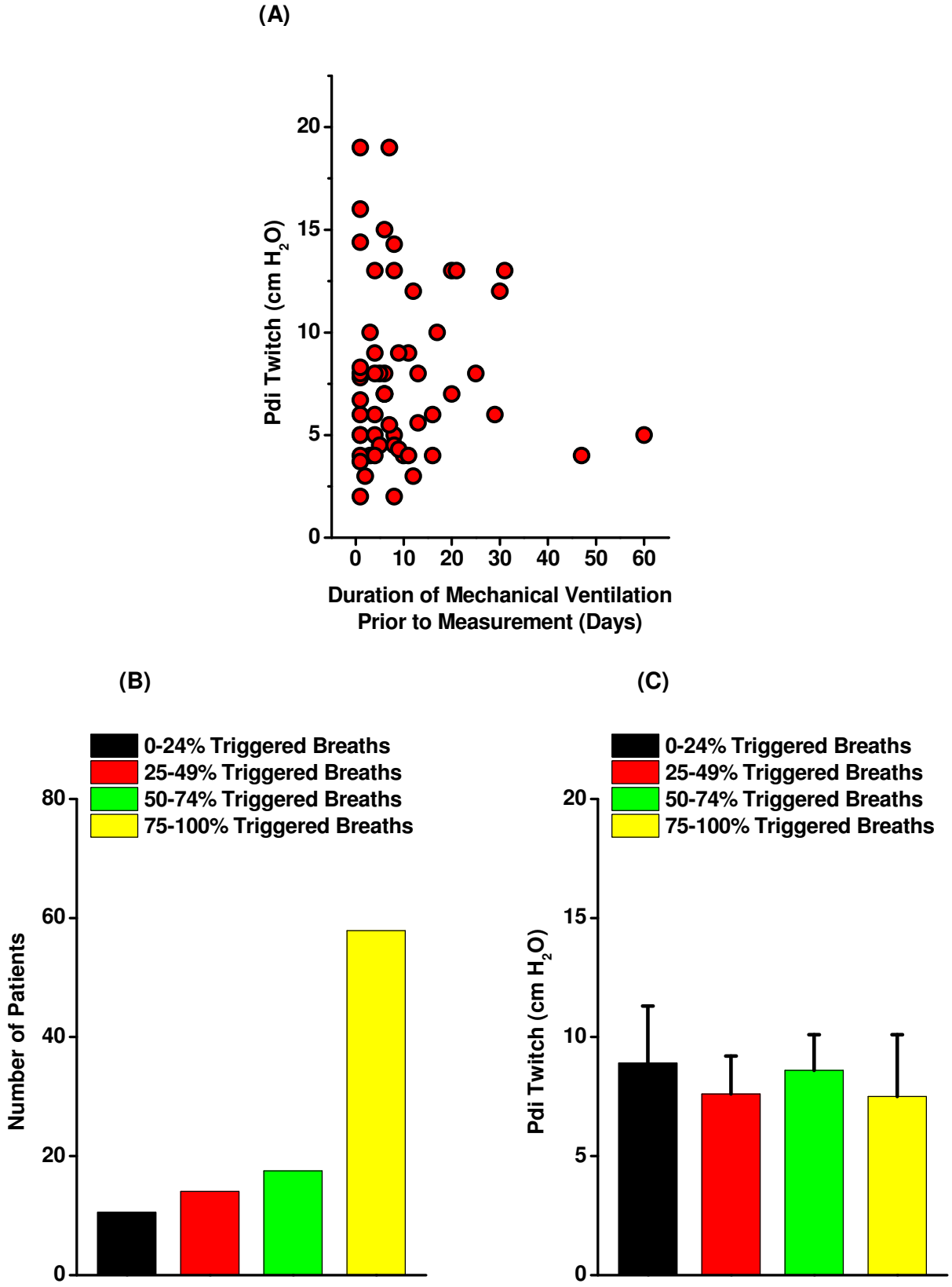
(A)
Pdi Twitch (cm H_2O)
0
5
10
15
20
0
10
20
30
40
50
60
Duration of Mechanical Ventilation
Prior to Measurement (Days)
(B)
0-24% Triggered Breaths
25-49% Triggered Breaths
50-74% Triggered Breaths
75-100% Triggered Breaths
Number of Patients
0
20
40
60
80
(C)
0-24% Triggered Breaths
25-49% Triggered Breaths
50-74% Triggered Breaths
75-100% Triggered Breaths
Pdi Twitch (cm H_2O)
0
5
10
15
20

Figure 4

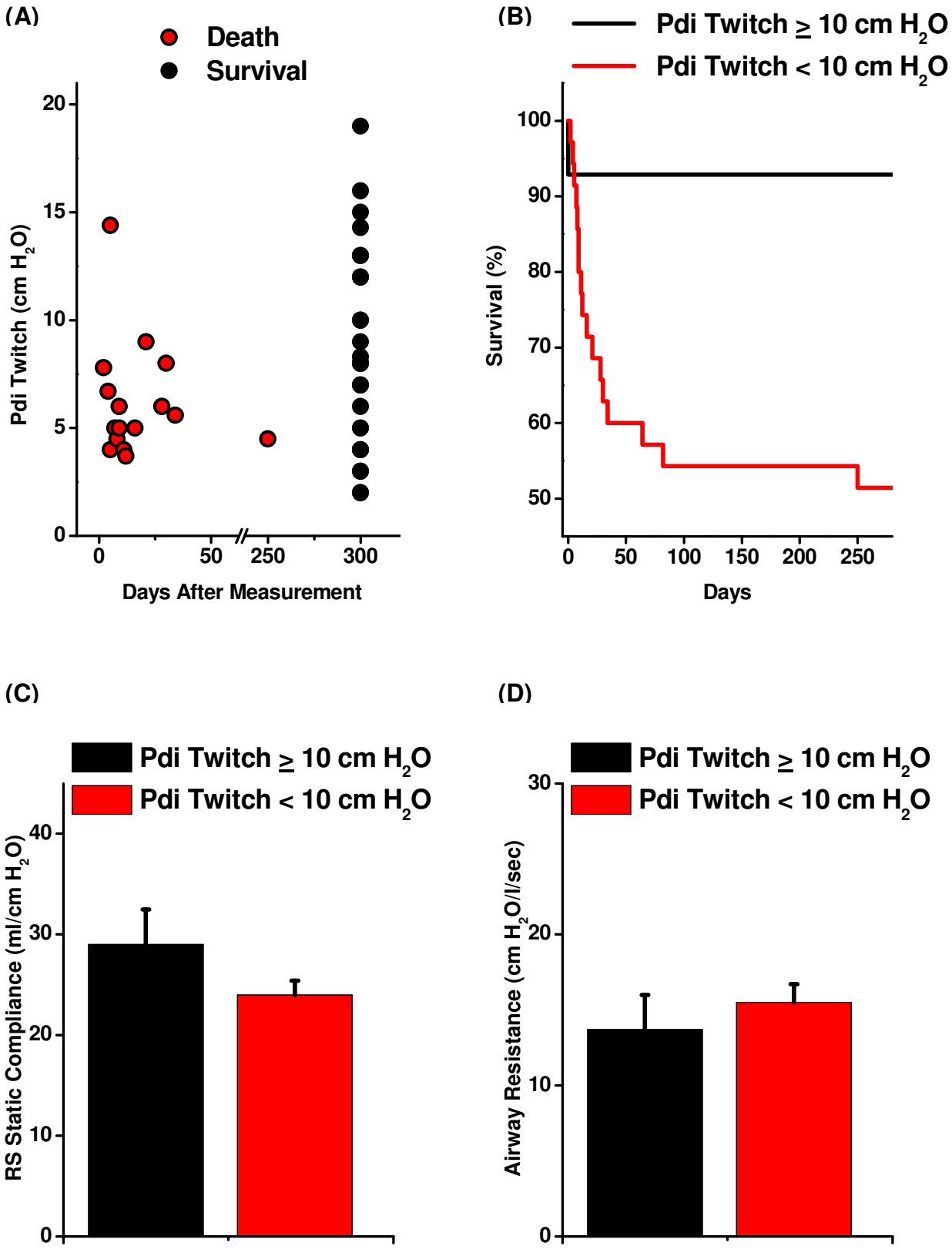
(A)
Death
Survival
Pdi Twitch (cm H2O)
Days After Measurement
(B)
Pdi Twitch ≥ 10 cm H2O
Pdi Twitch < 10 cm H2O
Survival (%)
Days
(C)
Pdi Twitch ≥ 10 cm H2O
Pdi Twitch < 10 cm H2O
RS Static Compliance (ml/cm H2O)
(D)
Pdi Twitch ≥ 10 cm H2O
Pdi Twitch < 10 cm H2O
Airway Resistance (cm H2O/l/sec)

Figure 5

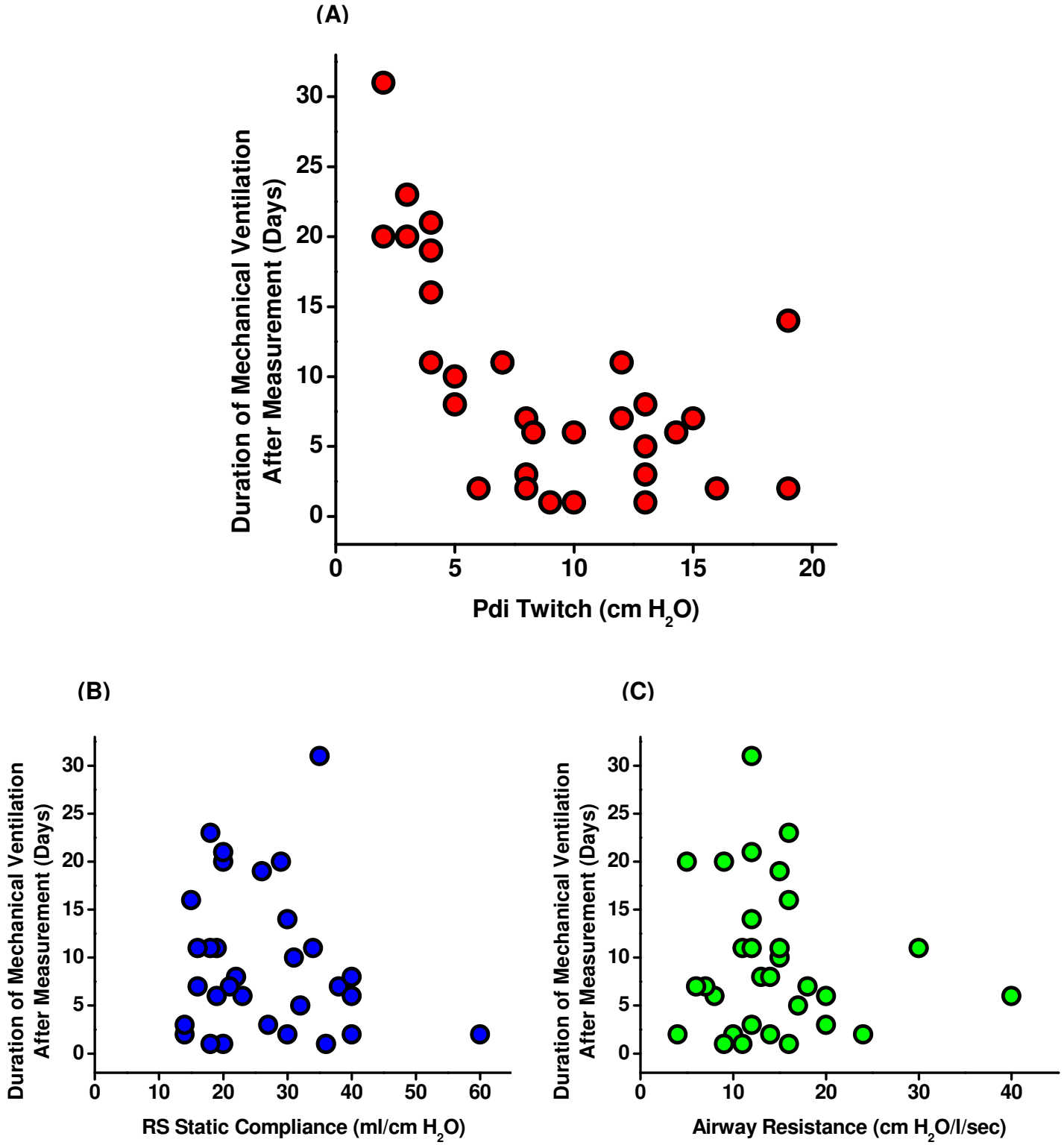
(A)
Duration of Mechanical Ventilation After Measurement (Days)
Pdi Twitch (cm H2O)
(B)
RS Static Compliance (ml/cm H2O)
(C)
Airway Resistance (cm H2O/l/sec)

Figure 6

Additional files provided with this submission:

Additional file 1: Additional File 1 Methods Figure Legends.docx, 14K
http://ccforum.com/imedia/9574869471022538/supp1.docx
Additional file 2: Additional File 2 TABLE S1.docx, 29K
http://ccforum.com/imedia/2408928211022537/supp2.docx
Additional file 3: Additional File 3 FIGURE S1 PEEP.docx, 27K
http://ccforum.com/imedia/1810848336102253/supp3.docx
Additional file 4: Additional File 4 FIGURE S2 HYDROCORTISONE.docx, 26K
http://ccforum.com/imedia/3242892731022537/supp4.docx