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Permissive Hypercapnia in the Management of Congenital Diaphragmatic Hernia: Our Institutional Experience

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Abstract

BACKGROUND—Congenital diaphragmatic hernia (CDH) is a potentially lethal anomaly associated with pulmonary hypoplasia and persistent pulmonary hypertension. Permissive hypercapnia is a strategy designed to reduce lung injury from mechanical ventilation in infants. It has been shown to be a potentially superior method of ventilator management for patients with CDH. In 2001, the Divisions of Neonatology and Pediatric Surgery at the University of Virginia Children's Hospital established permissive hypercapnia as the management strategy for treatment of CDH. We hypothesized that permissive hypercapnia would be associated with improved outcomes in this patient population.

STUDY DESIGN—This retrospective review compares outcomes of infants treated for CDH in the extracorporeal membrane oxygenation (ECMO) era before and after initiation of permissive hypercapnia at a single institution. Outcomes were compared using univariate statistical analysis.

RESULTS—Ninety-one patients were available for analysis and were divided into 2 groups: 42 (Group 1) treated before and 49 (Group 2) treated after implementation of permissive hypercapnia. Survival was higher in Group 2 (85.8% vs 54.8%; p = 0.001; relative risk [RR] 3.17). Morbidity was lower in Group 2 and approached statistical significance (65.3% vs 83.3%; p = 0.052). Patients in Group 2 were repaired later, had a lower rate of ECMO use, and were extubated earlier. There was no difference in hospital stay.

CONCLUSIONS—The use of permissive hypercapnia for infants with CDH was associated with decreased mortality, a longer period of ventilation before repair with a shorter period of ventilation after repair, a lower rate of ECMO use, and no lengthening of hospital stay. Permissive hypercapnia remains the standard of care for ventilation of infants with CDH at our institution.

Congenital diaphragmatic hernia of the Bochdalek type (CDH) is a potentially lethal birth defect involving herniation of abdominal contents into the thoracic cavity through a defect in the diaphragm. Traditionally, it has been believed that extrinsic compression from abdominal contents on the developing lung results in pulmonary hypoplasia and persistent pulmonary hypertension.[1–3] Recent research, however, suggests that aberrations in pulmonary development itself may be causative in CDH. These studies suggest that the affected lung is intrinsically abnormal and may compromise the development of the

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diaphragm, resulting in a hernia.[4,5] CDH has an estimated incidence of 1:2,200 to 4,000 live births, with a historically expected survival of 50% to 80%.[2,3,6–9]

Management of an infant with CDH involves early intubation, appropriate ventilator management, treatment of pulmonary hypertension, and surgical correction of the diaphragm defect. Traditional methods of therapy involved an aggressive ventilator management strategy in which high peak inspiratory pressures (PIP), hyperoxygenation, and alkalization via hyperventilation and administration of sodium bicarbonate were used to maintain a postductal arterial oxygen pressure (PaO_2) of >90%, pH >7.2, and partial pressure of CO_2 ($PaCO_2$) within normal physiologic parameters.[1,6,7,10,11] The ventilatory pressures and volumes, and oxygenation required to achieve these goals, were recognized as causing lung trauma that was a significant source of morbidity and mortality in this population. Postmortem analysis of patients treated with aggressive ventilator management showed distinct evidence of barotrauma.[11] In 1985, Wung and colleagues[12] proposed a novel approach, now commonly recognized as “permissive hypercapnia” or “gentle ventilation,” to ventilator management in infants with persistence of fetal circulation (and pulmonary hypertension). It involved limiting the PIP and oxygenation levels in an effort to decrease barotrauma. The $PaCO_2$ was not a controlling parameter and was allowed to rise to a level as high as 60 mmHg. This strategy was later applied to CDH patients and has since demonstrated a potential survival benefit. In particular, as the treatment of CDH has shifted toward delayed rather than emergent repair, the appropriate ventilatory management of underlying pulmonary hypertension and hypoplasia has proven to be vital in maximizing pulmonary outcomes for these patients.[7,8] Although permissive hypercapnia has been a promising ventilator strategy for lung protection, its benefit for survival has not been definitively determined.[13]

In June 2001, the Divisions of Neonatology and Pediatric Surgery at the University of Virginia Children’s Hospital (UVACH) adopted a new guideline establishing permissive hypercapnia as the primary ventilation strategy for infants with CDH (Appendix 1, online only). Ventilatory pressures just high enough to produce chest rise are used with an emphasis to avoid PIP >25 and positive end-expiratory pressure > 5 cm H_2O. Fraction of inspired oxygen (FiO_2) is aggressively weaned to maintain preductal oxygen saturations between 90% and 95%. The pH is maintained within physiologic norms. $PaCO_2$ level is not a primary goal and is allowed to rise to as high as 70 mmHg as long as all other parameters are satisfied. High frequency oscillatory ventilation (HFOV), inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO) are used where appropriate according to the discretion of the treating physicians.

The purpose of this study was to evaluate the effectiveness of permissive hypercapnia in the management of infants with CDH at UVACH. Our primary hypothesis was that survival would be improved in this patient group with the introduction of permissive hypercapnia. A secondary hypothesis was that indicators of certain morbidities, particularly post-treatment respiratory insufficiency, would be improved.

METHODS

All patients with CDH admitted to the UVACH from May 1994 until October 2010 were enrolled in this retrospective chart review. The study was approved by the Institutional Review Board at the University of Virginia Health System. All patients with CDH were eligible for analysis, with exclusion criteria comprising lethal birth defects precluding definitive repair, delayed presentation outside the neonatal period, death at or immediately after birth or before treatment could be initiated, and lack of sufficient data in the chart to support statistical analyses.

In June 2001, a formal guideline establishing the use of permissive hypercapnia to treat patients with CDH was adopted by the Divisions of Neonatology and Pediatric Surgery at UVACH. Our patients were divided into 2 groups based on their chronological association with this guideline. Patients in Group 1 (1994 to 2001) received traditional hyperventilation, oxygenation, and alkalinization therapy before institution of permissive hypercapnia. Patients in Group 2 (2001 to 2010) were managed with permissive hypercapnia. Patients in Group 2 were initially placed on synchronized intermittent mandatory ventilation (SIMV) mode with a PIP only sufficient to produce a chest rise, 100% FiO_2, and minimal sedation. FiO_2 was then aggressively weaned to maintain preductal oxygen saturations of 90%. Inhaled nitric oxide was used as the initial adjunctive treatment for persistently low oxygen saturations. Arterial pH was maintained between 7.30 and 7.35. $PaCO_2$ was allowed to rise to 70 mmHg as long as the pH remained above 7.25. Sodium bicarbonate or HFOV were considered for persistent acidosis. By 1994, surgical repair of CDH was no longer undertaken on an emergent basis. However, the true elective nature of this operation was still in evolution at that time in our institution and may have resulted in earlier surgical intervention after presentation in the earlier years of our review than in subsequent years. Overall, operations were performed on an elective basis rather than emergently, with the exact timing based on consensus between the pediatric surgical and neonatal ICU treatment teams about the infant's stability and readiness for repair. ECMO was used in patients with severe or persistent oxygenation and/or ventilation compromise refractory to other treatments including HFOV and inhaled nitric oxide. Early in the time course of this study, if ECMO was required, repair of CDH was accomplished while the infant was on ECMO. More recently, there has been a preference for weaning from ECMO before repair is undertaken. No infant in our review was denied care or operation due to a perceived basis of critical lung hypoplasia.

Basic demographics, hospital admission and discharge, use of ECMO, in-hospital death, comorbidities including associated physical anomalies, and in-hospital complication data were entered into a secure, password-protected computer database. Descriptive analyses comparing demographic data between the 2 treatment groups were performed using univariate analysis, with statistical significance set at $p < 0.05$. Continuous variables are presented as mean ± SEM and compared using a 2-sample *t*-test for independent samples. Categorical variables were analyzed using chi-square or Fisher's exact test. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute).

RESULTS

A total of 103 patients with CDH were identified at UVACH during the study period. Ultimately, 91 patients met criteria for statistical analysis. Patients were excluded from analysis because of death before surgical intervention (including stillbirth, other lethal anomalies, nonresponse to medical support) (n = 6), presentation outside the neonatal period (n = 4), inadequate data in the chart for statistical analysis (n = 1), and 1 patient with pentalogy of Cantrell was excluded because the diaphragmatic hernia only entered the pericardium and did not result in pulmonary hypoplasia. A total of 42 patients were in Group 1 and 49 in Group 2. Average birth weight was slightly higher in Group 2 and approached statistical significance. The 2 groups were statistically similar in terms of sex, gestational age, rate of prenatal diagnosis, right-sided CDH, and the use of a diaphragmatic patch for repair (Table 1).

Overall mortality rates were 42.9% in Group 1 and 14.3% in Group 2. Decreased mortality in Group 2 was also demonstrated for patients who had other congenital anomalies (Table 2). There was no statistical difference in mortality rates for patients with recurrent CDH or ECMO requirements. There were 5 total cases of recurrent CDH during the study: 2 in

Group 1 with 1 mortality, and 3 in Group 2 with no mortalities (p = 0.4). Mortality rates for infants receiving ECMO were 53.8% in Group 1 and 50.8% in Group 2. Most patients in the study died due to severe pulmonary hypertension (n = 10). Other causes for mortality were cerebral intraparenchymal hemorrhage (n = 4), sepsis (n = 2), multisystem failure (n = 2), withdrawal of care due to associated anomalies (n =2), pulmonary hemorrhage (n =1), heart failure (n =1), mechanical ECMO failure (n = 1), withdrawal of support by family members for reasons unclear during chart review (n = 1), and an acute decompensation of unclear etiology (n = 1).

Overall rates of morbidity (all kinds) were lower in Group 2 and approached statistical significance (Table 3). Morbidity rates were 83.3% and 65.3% in Groups 1 and 2, respectively. There was no difference in recurrent CDH between the 2 groups. Rates of home oxygen requirement after repair as well as manifestations of persistent pulmonary disease, such as bronchopulmonary dysplasia and asthma, were also similar. Likewise, there was no difference between the 2 groups in terms of neurologic, bleeding, infectious, cardiac, gastrointestinal, or renal complication rates. There was a significant (p = 0.003) difference in the rates of additional or replacement tube thoracostomy between the 2 groups: 35.7% of patients in Group 1 required a replacement or additional chest tube compared with 10.2% in Group 2.

Rates of HFOV between the 2 groups were similar but rates of inhaled nitric oxide use were statistically higher in Group 2. ECMO use was statistically lower in Group 2 (28.6%) compared with Group 1 (61.9%). Total days on ECMO were similar, with a mean of 15.2 days in Group 1 vs 13.2 days in Group 2. Overall, patients spent a similar number of days intubated after repair. However, there was a single patient in Group 2 who was intubated for a total of 424 days. With this patient excluded, Group 2 had a statistically shorter intubation period after repair. On average, repair was offered on day of life 5.9 in Group 1 and on day of life 9 in Group 2. There was no statistical difference between preoperative ventilation days between survivors and mortalities in each group (Table 4). There was no difference in overall hospital stay between the 2 groups.

DISCUSSION

Our study demonstrates a significant decrease in overall mortality after the introduction of permissive hypercapnia as the primary ventilator management strategy for infants with CDH. A recent Cochrane review, although not limited to CDH management, indicated that there is not enough evidence to support the use of permissive hypercapnia over normocapnia as a superior ventilatory management strategy.[13] However, our positive results are similar to those at other institutions that have adopted permissive hypercapnia for the management of CDH,[6,7,11,14–16] A strong trend toward lower overall morbidity was also identified but was not statistically significant in our study. Overall, our 2 groups were statistically similar, so theoretically there should be no difference in outcomes attributable to demographic differences between the 2 groups. However, the average birth weight in Group 2 was higher, approaching statistical significance. It is unclear what effect, if any, this slight increase in birth weight would have in terms of overall morbidity and mortality. It is reasonable to believe that larger infants may have a survival advantage. Indeed, Sola and colleauges[17] demonstrated a survival benefit in CDH patients with a birth weight greater than 3 kg.

ECMO is an important treatment modality for severe pulmonary hypertension and CDH. Patients in our permissive hypercapnia group had a lower rate of ECMO use than previously treated patients. A similar trend was noted in a report by Wilson and associates.[11] The quoted mortality rates in the literature for patients treated with ECMO range from 32% to 60%.[7,8,18,19] We identified similar mortality rates on ECMO for both groups. Although

some studies have demonstrated a potential survival benefit, we were unable to demonstrate a survival benefit attributable to ECMO treatment based on ventilator management before or after its initiation.[11] Boloker and coworkers[7] also noted equal mortality on ECMO in their study of patients treated with permissive hypercapnia vs normocapnia. Interestingly, pre-ECMO $PaCO_2$ less than 60 mmHg has been found to be a predictor of ECMO survival, and elevated $PaCO_2$ may serve as a marker for potentially nonsurvivable pulmonary hypoplasia.[20] However, no infant was denied treatment in our series on the basis of any proposed criteria indicating nonsurvivable pulmonary hypoplasia.

It is important to recognize the effects of hypercapnia on cerebral perfusion. Hypercapnia causes cerebral vasodilatation and therefore increases cerebral blood flow in preterm infants.[21] Studies have suggested that the rate of intraventricular hemorrhage (IVH) is directly proportional to the $PaCO_2$ and that the incidence of IVH is increased with large variations in $PaCO_2$.[21,22] Therefore, one might expect to observe an increased rate of IVH or other neurologic complications in patients with permissive hypercapnia. However, this generally has not been demonstrated in the literature.[21] A prospective study by Danzer and colleagues[23] demonstrated some degree of neurologic impairment in approximately 50% of CDH patients. We found no statistical significance in the rates of IVH or other adverse neurologic outcomes between our 2 groups. These results are consistent with those noted by Hagen and coauthors.[24] It is noteworthy that two of these studies were performed in very low birth weight infants and specifically excluded patients with congenital anomalies.

Multiple ventilator modalities exist for the management of patients with CDH, and much attention has been paid to the effect these modalities have on the development of chronic lung disease.[25,26] Retrospective studies have demonstrated that 30% to 56% of CDH patients display symptoms of chronic lung disease long-term.[27] However, a randomized trial by Mariani and associates[28] demonstrated no difference between rates of chronic lung disease between preterm infants who received either permissive hypercapnia or normocapnia. One study by Valfre and colleagues[29] found that the degree of pulmonary hypertension in hospitalized neonates has no effect on postdischarge outcomes. Our study suggests that there may be no difference in chronic lung disease between patients treated with permissive hypercapnia and those treated with more traditional aggressive ventilation strategies. Rates of HFOV were similar between the 2 groups. The need for HFOV as the initial ventilatory modality for infants with CDH has been implicated as a risk factor for development of chronic lung disease.[27] Rates of inhaled nitric oxide use were statistically lower in our permissive hypercapnia group than in the normocapnia group; however, this may be unreliable due to a lack of consistency in the reporting of inhaled nitric oxide use.

CDH repair at our institution typically involves ipsilateral thoracostomy tube placement. Routine thoracostomy tube use has been implicated in increased mortality rates for CDH patients. This phenomenon is thought to result from gross hyperinflation of the ipsilateral lung immediately after repair, resulting in mechanical trauma as well as a decreased ability of the ipsilateral lung to deflate with exhalation.[7] Bagolan and coworkers[6] noted a decrease in preoperative thoracostomy tube placement for pneumothorax for patients treated with permissive hypercapnia. Our study was not designed to evaluate this association, but we did demonstrate a decrease in the rate of spontaneous pneumothorax requiring either primary placement or replacement (if after surgical repair) of a thoracostomy tube. This may be an effect of decreased peak pressures and associated barotrauma with use of permissive hypercapnia. Perhaps the decrease in damage associated with permissive hypercapnia is greater than any potential damage caused by the thoracostomy tube.

Patients with CDH have been shown to have a high rate of associated complications, particularly gastroesophageal reflux disease, and require frequent invasive procedures.[30]

However, our study was designed primarily to identify mortality and morbidity with respect to ventilator management in this group of infants. Alterations in ventilator management without alterations to fundamental aspects of definitive repair or other critical care parameters might be unlikely to demonstrate statistical differences in morbidity for nonpulmonary organ systems. We found no difference in the rates of cardiac complications, gastroesophageal reflux disease, small bowel obstruction, acute kidney injury, or hematologic or infectious complications between the 2 groups. We found no difference in the rates of Nissen fundoplication or gastrostomy tube placement between the 2 groups. Specifically, other authors have also found no difference in gastroesophageal reflux disease or infection rates for patients treated with permissive hypercapnia vs normocapnia.[29]

Patients in the permissive hypercapnia group were generally extubated 14 days sooner after definitive repair. This decrease in postoperative intubation time has also been identified in previous studies.[7] However, other authors have not identified a decrease in the overall length of time of intubation.[28] Our treatment guideline also calls for elective or semielective repair rather than urgent repair. We believe that the combination of these 2 factors resulted in no statistical difference between total hospital days in these 2 groups.

In order to determine what role, if any, the length of time of ventilatory and medical management before operation may have in terms of mortality outcomes, we compared preoperative ventilation days for survivors vs mortalities within each group. Ultimately, we found no statistical difference between the numbers of days a patient was ventilated before surgery that related to survival. However, we did note an interesting trend. In both Groups 1 and 2, the patients who ultimately died from their illness were ventilated twice as long before operation than their surviving counterparts. One study noted that patients with more severe pulmonary hypertension, as evidenced by a high pulmonary artery-to-systemic artery ratio, underwent surgery much later than patients with low pulmonary artery-to-systemic artery ratios.[31] Perhaps our patients with more severe pulmonary hypertension (who would be more likely to die) took longer to stabilize before intervention than those with less severe pulmonary hypertension.

We recognize certain potential shortcomings of this report. First, as a retrospective study, the quality of the information available is of vital importance. During the study period, our institution used no less than 3 separate medical record systems and we must recognize the possibility of data loss, specifically with regard to daily progress notes or laboratory data before implementation of an electronic medical record system. Secondly, inadequate follow-up for some patients may affect outcomes reporting. Finally, this study does not account for changes in outcomes as a result of the overall advances in neonatology care as a whole over the study period.

CONCLUSIONS

The goal of permissive hypercapnia in the care of infants with CDH is to reduce lung injury that results from aggressive ventilation and oxygenation. Hypercarbia is a secondary effect that is allowed, if necessary, by this strategy of more gentle ventilation, therefore, the term *permissive hypercapnia*. Perhaps the term *gentle ventilation* is more appropriate because this reflects the primary goal of the strategy. Our study demonstrates a survival benefit to infants treated for CDH at UVACH since the institution of permissive hypercapnia. Permissive hypercapnia will remain the standard of care for all CDH patients treated at our institution and we endorse it as a strategy to be embraced at other institutions as well.

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Abbreviations and Acronyms

CDH	congenital diaphragmatic hernia
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
HFOV	high frequency oscillatory ventilation
IVH	intraventricular hemorrhage
$PaCO_2$	partial pressure of carbon dioxide
PIP	peak inspiratory pressure
UVACH	University of Virginia Children's Hospital

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Appendix

UVACH Guideline for Permissive Hypercapnia in the Treatment of Infants with Congenital Diaphragmatic Hernia

Ventilation

Patients will initially be ventilated with synchronized intermittent mandatory ventilation and 100% oxygen with pressure not to exceed that required to produce chest rise. A major attempt will be made to avoid PIP > 25 and PEEP > 5 cm H_2O.

Oxygenation

After the first few hours from birth (for example, 6 hours), FiO_2 will be adjusted to maintain preductal saturations of 90%. FiO_2 will be weaned for saturations >95% and increased only if saturations are persistently <90%. PaO_2 of 40 to 60 mmHg will be acceptable. Pre- and postductal saturations will be measured, but adjustments will be made for preductal values only, unless there is evidence of postductal compromise.

Acid-base

pH will be maintained in the normal range (7.30 to 7.35). $PaCO_2$ will be permitted to rise to 70 mmHg as long as pH remains >7.25. If pH is consistently < 7.25, HCO_3, Tham, or HFOV might be considered.

Nitric oxide

It would be reasonable to start NO if high FiO_2 requirements persist.

Sedation

Paralysis will be avoided if possible. Patients will be lightly sedated with a midazolam drip as necessary.

Perfusion/hydration

Mean arterial blood pressure will be supported with dopamine or volume expansion as necessary. Fluids will be maintained at approximately 100 mL/kg and adjusted as necessary.

Surgery

Operations will be performed electively, rather than emergently, and will sometimes be performed in the neonatal ICU (NICU), with adequate operating room and anesthesia support. If the patient is transported to the operating room for surgery, an attempt will be made to use the NICU ventilator in the operating room.

ECMO

ECMO will be used either pre- or postoperatively if the management strategies described above are unable to achieve satisfactory blood gases. Oxygenation index (OI) will not be useful with this new strategy because the OI will be low due to the low mean arterial pressure. A reasonable approach might be to consider ECMO for infants who cannot maintain preductal saturations >85% or postductal pO_2 > 30 mmHg or who show evidence of inadequate oxygen delivery using the above described management strategy. Usually, this will have included a trial of HFOV and nitric oxide.

Table 1

Patient Demographics Before (Group 1) and After (Group 2) Permissive Hypercapnia

Demographic	Group 1 (n = 42)	Group 2 (n = 49)	p Value
Male, %	61.9	67.3	0.59
Female, %	38.1	32.7	0.59
Gestational age, wk, mean ± SEM	36.4 ± 0.4	37.2 ± 0.4	0.17
Birth weight, g, mean ± SEM	2,655.2 ± 122.0	2,969.1 ± 98.9	0.05
Prenatal diagnosis, %	45.2	63.3	0.09
Right-sided CDH, %	23.8	16.3	0.37
Diaphragmatic patch, %	59.5	49	0.31

CDH, congenital diaphragmatic hernia.

Table 2

Mortality Before (Group 1) and After (Group 2) Permissive Hypercapnia

Mortality	Group 1 (n = 42)	Group 2 (n = 49)	p Value
Mortality, %	42.9	14.3	0.002 *
Mortality (anomalies), %	41.2	5.9	0.02 *
ECMO mortality, %	53.8	50	0.82

* Denotes statistical significance, $p < 0.05$.

ECMO, extracorporeal membrane oxygenation.

Table 3

Morbidity Before (Group 1) and After (Group 2) Permissive Hypercapnia

Morbidity	Group 1 (n = 42)	Group 2 (n = 49)	p Value
Morbidity (overall), %	83.3	65.3	0.052
Neurologic, %	45.2	26.5	0.06
Cardiac, %	2.4	2.0	1.0
Repeat tube thoracostomy, %	35.7	10.2	0.003*
O_2 requirement at discharge, %	21.4	22.4	0.94
Persistent pulmonary disease, %	14.3	10.2	0.56
Recurrent CDH, %	4.76	6.1	1.0
Gastrointestinal (all), %	19.1	20.4	0.87
Nissen, %	9.5	4.1	0.41
Gastrostomy, %	16.7	12.2	0.54
Nissen + Gastrostomy, %	9.5	4.1	0.41
Hematologic, %	19.1	6.1	0.10
Infection, %	14.3	20.4	0.44
Renal, %	7.1	0	0.09
ECMO, %	61.9	28.6	0.001*
Days on ECMO, mean ± SEM	15.2 ± 1.6	13.2 ± 2.7	0.49
iNO†, n (%)	12/37 (32.4)	27/46 (58.7)	0.02*
HFOV†, n (%)	26/37 (70.2)	34/45 (75.6)	0.59
Timing of repair, d, mean ± SEM	5.9 ± 1.01	9 ± 0.93	0.03*
Days intubated after repair, mean ± SEM	25 ± 3.9	19.9 ± 9.1	0.61
Days intubated after repair (modified), mean ± SEM	26 ± 3.9	11 ± 1.5	0.002*
Hospital stay, d, mean ± SEM	50.9 ± 7.9	42.2 ± 9.2	0.48

*Denotes statistical significance, $p < 0.05$.

†Variation in group size secondary to unobtainable chart data.

CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; HFOV, high frequency oscillatory ventilation; iNO, inhaled nitric oxide.

Table 4

Comparison of Preoperative Ventilation Days for Survivors vs. Mortalities per Group

Group	Survivors	Mortalities	p Value
Group 1, d, mean ± SEM	3.1 ± 0.6	7.9 ± 2.3	0.06
Group 2, d, mean ± SEM	7.3 ± 0.9	14.6 ± 3.4	0.09