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Pilot Feasibility Study of Therapeutic Hypothermia for Moderate to Severe Acute Respiratory Distress Syndrome

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Abstract

Objectives—Prior studies suggest hypothermia may be beneficial in ARDS, but cooling causes shivering and increases metabolism. The objective of this study was to assess the feasibility of performing a randomized clinical trial (RCT) of hypothermia in patients with ARDS receiving treatment with neuromuscular blockade (NMB) because they cannot shiver.

Design—Retrospective study and pilot prospective open-label feasibility study.

Setting—Medical Intensive Care Unit.

Patients—Retrospective review of 58 patients with ARDS based on Berlin criteria and $P_aO_2:FiO_2$ (P:F)<150 who received NMB. Prospective hypothermia treatment in 8 ARDS patients with (P:F)<150 receiving NMB.

Intervention—Cooling to 34°–36°C for 48h.

Measurements and Main Results—Core temperature, hemodynamics, serum glucose and electrolytes, and P:F, were sequentially measured and medians (interquartile ranges) presented, and 28-day ventilator-free days (VFDs), and hospital mortality were calculated in historical controls and 8 cooled patients. Average patient core temperature was 36.7(36–37.3)°C and fever occurred during NMB in 30/58 retrospective patients. In the prospectively cooled patients core temperature reached target range 4h of initiating cooling, remained <36°C for 92% of the 48h

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cooling period without adverse events, and was lower than the controls (34.35(34–34.8)°C; $p<0.0001$). Compared with historical controls, the cooled patients tended to have lower hospital mortality (75% vs 53.4%; $p=0.26$), more VFDs (9(0–21.5) vs. 0(0–12); $p=0.16$) and higher day-3 P:F (255(160–270) vs. 171(120–214), $p=0.024$).

Conclusions—NMB alone does not cause hypothermia, but allowed ARDS patients to be effectively cooled. Results support conducting an RCT of hypothermia in ARDS and the feasibility of studying ARDS patients receiving NMB.

Keywords

Acute respiratory distress syndrome; therapeutic hypothermia; neuromuscular blockade

INTRODUCTION

The Acute Respiratory Distress Syndrome (ARDS) remains an important health problem with substantial mortality (1, 2) and morbidity (3–9). Despite advances in understanding of ARDS pathogenesis (10, 11), only three interventions have been shown to reduce mortality in Phase III RCTs: low tidal volume ventilation (12), NMB (13), and prone positioning (14) and mortality in moderate to severe ARDS remains >40% (15, 16). Other than NMB, pharmacologic therapies have been disappointing (17–20) and a role for extracorporeal membrane oxygenation (ECMO) in ARDS has not been well defined (21).

Several studies suggest that clinically relevant hypothermia suppresses signaling pathways that contribute to pulmonary endothelial dysfunction, including Mitogen-Activated Protein Kinases (MAPKs), Transient Receptor Vanilloid 4 (TRPV4) (22–24) and mitigates multiple animal models of acute lung injury (ALI) (25–32). A small, non-randomized concurrently controlled trial found hypothermia ($33.7\pm0.6^{\circ}\text{C}$ for $70\pm15\text{h}$) improved survival from 0/0 to 3/9 in moribund patients with septic shock and ARDS (33). That study preceded American-European Consensus Conference and Berlin definitions of ARDS and adoption of ARDSNet protocols for ventilation and fluid management, and mortality in both groups was much higher than current experience. A more recent retrospective review of post-cardiac arrest hypothermia showed that standard hypothermia treatment (core temperature $32^{\circ}\text{--}34^{\circ}\text{C}$) tended to be associated with improved pulmonary function (34).

While this evidence suggests that hypothermia would benefit ARDS patients, cooling in critically ill patients is complicated by shivering and its adverse metabolic consequences (35). The recent addition of NMB to ARDS management protocols (36) provides an opportunity to avoid the problem of shivering in an initial study of hypothermia in ARDS, since treatment with NMB would prevent shivering. This pilot study was designed to assess the feasibility and direct the design of a potential RCT of targeted temperature management in ARDS patients receiving NMB. We retrospectively analyzed body temperatures in ARDS patients receiving NMB. We then performed a pilot study of mild hypothermia to $34^{\circ}\text{--}36^{\circ}\text{C}$ for 48h in patients with ARDS receiving NMB to evaluate effectiveness and safety of cooling. Finally, we estimated effect size of hypothermia on potential outcome measures by comparing with historical controls.

MATERIALS AND METHODS

Retrospective Analysis

Potential patients were identified by searching the University of Maryland Medical Center (UMMC) pharmacy database for Medical Intensive Care Unit (MICU) patients who received continuous cisatracurium infusions between 2012 and 2015. Charts and electronic records were analyzed for data to support diagnosis of moderate to severe ARDS based on Berlin criteria with $P_aO_2:FiO_2$ (P:F) ratio <150 based on simultaneous assessment of FiO_2 and P_aO_2 with PEEP ≥ 5 cm H_2O (37). The selected records were further reviewed for information about physiologic and clinical outcomes.

Prospective Cooling Pilot

The University of Maryland Baltimore Institutional Review Board approved the retrospective study, including waiver of consent, and approval for a pilot prospective study of eight subjects. Between October, 2015 and April, 2016, we screened consecutive patients 18 years of age admitted to the UMMC MICU or Critical Care Resuscitation Unit with a diagnosis of ARDS based on Berlin criteria with P:F ratio <150 measured with PEEP ≥ 5 cm H_2O (37) within 72h who had started NMB within 24h of consent. Exclusion criteria were active bleeding, refractory hypotension, pregnancy, unlikely to remain intubated or alive 48h, skin lesions that interfere with cooling, and ECMO treatment during the hospitalization. After consent was obtained from the patient's Legally Authorized Representative, a baseline blood sample was obtained and cooling was initiated using the UMMC therapeutic hypothermia protocol. A target temperature of 34° – $36^{\circ}C$ was arbitrarily selected based on a recent study of cardiac arrest survivors (38). Cooling was performed using the Arctic Sun™ system in two patients and Cincinnati Sub-Zero Blanketrol II cooling blankets in six. Temperature was measured from esophageal (7) or urinary (1) probes. After 48h at target temperature, patients were rewarmed by $0.33^{\circ}C/h$ until core temperature reached $37^{\circ}C$ and the cooling devices were removed. Patients received usual MICU care, including telemetry, protocolized ventilator management based on ARDSNet guidelines (12), management of sedation and NMB using the UMMC institutional protocol, blood glucose monitoring, and daily laboratory measurements for electrolytes, serum creatinine, and complete blood counts. Blood for serum was collected at enrollment and study days 1, 2, 3, and 7 and analyzed for interleukin (IL)-6, IL-10 and total transforming growth factor- β (TGF- β) in the University of Maryland Cytokine Core Laboratory using reagents from R&D Systems (Minneapolis, MN).

Outcomes

To facilitate comparison between cooled patients and historical controls, we defined day 0 as beginning 06:00 on the day NMB began; cooling started some time on day 0 and ended some time on day 2. Demographic information, comorbidities, and disease severity measures were recorded at baseline. Core temperature, mean airway pressure, PEEP, and FiO_2 were recorded every 2h. The highest and lowest serum glucose, potassium, and magnesium levels were recorded and 28-day ventilator-free days (VFDs), ICU-free days (ICU-FDs) and duration of NMB calculated. All arterial blood gas values obtained on days 0–3 were entered into the database for calculation of P:F ratio and oxygenation index (OI) and the mean of the

best and worst values for each day were used for analysis. Complications during the cooling period and subsequent ICU course were prospectively identified from discussions with the clinical team and examination of the medical records. Hypo- and hyperglycemia were defined as serum glucose <70 and >180, respectively. Electrolytes were considered abnormal if they fell out of the normal range for the UMMC clinical laboratory, 3.5–5.1 mmol/L for potassium and 1.6–2.5 mg/dL for magnesium.

Statistical Analysis

We summarized the temperature response in each control as mean of temperature measurements during NMB and in each of the prospectively cooled patient as mean of temperature measurements during cooling beginning with the first temperature <36°C. We compared the medians of the temperature responses in the two groups with a Wilcoxon Rank-Sum test. The distributions of temperature over time between 32° and 39°C were compared visually by constructing histograms in half-degree increments for the two groups. Since the number of relevant temperature measurements differed among individuals, we compared the means of all temperature measurements in the two groups during NMB and cooling, respectively, using a mixed model repeated measures (MMRM) analysis (39) with first-order autoregressive correlation and group as the only independent variable. Two primary sets of analyses were performed, one comparing cooled patients with all 58 controls and one comparing cooled patients with a subset of matched controls. Two controls were matched to each cooled patients based on enrollment APACHE II score and P:F ratio, underlying cause, age, BMI, and gender, in that order by two of the authors (JDH and CBS) who were blind to outcome. When controls were similar to cases except for pneumonia as the underlying cause, we accepted non-pneumonia sepsis as sufficiently similar. Statistical analysis was performed using the SAS version 9.3 statistical software package (SAS Institute, Cary, NC). Quantitative data are presented as median (interquartile range). Comparisons between cooled patients and all 58 controls were tested using the Wilcoxon-Mann-Whitney test for quantitative variables and Fisher's Exact test for dichotomous data. Comparisons between cooled patients and matched controls were tested using the Friedman test for quantitative data and the Cochran-Mantel-Haenszel chi-square test for matched dichotomous variables. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

Retrospective analysis of core temperatures during NMB in ARDS patients

Retrospective analysis of UMMC MICU patients between 2012–2015 identified 148 patients who received continuous infusion of cisatracurium, of whom 113 met criteria for moderate to severe ARDS (Figure 1A). Thirty-six patients were excluded because they did not survive 48h from start of NMB. Thirteen more were excluded because they received ECMO, 1 because of lung transplant, and 5 because their medical records were incomplete.

Fifty-eight patients with moderate to severe ARDS who received continuous infusion of cisatracurium were included in the retrospective study (Table 1). The 32 men and 26 women were 49(38–57) years old. The group had high disease severity with APACHE II scores 23.5(19.75–30) and severe oxygenation defect with P:F ratio 91(75–110) and OI 24(15.8–

34.6). The underlying causes of ARDS were pneumonia (22), non-pulmonary sepsis (30), non-septic shock (1), blood product transfusion (4), and hemophagocytic lymphohistiocytosis (1). These patients had 0(0–12) VFDs and 0(0–6) ICU-FDs. ICU and hospital mortality were 51.7% and 53.5%, respectively. Duration of cisatracurium infusion was 57.5(29.75–82) hours.

Core temperature was measured centrally from esophageal probes in 34 control patients or urinary catheter in 1, rectally in 11, orally in 3, axillary in 7, and unspecified in 2. Core temperature was 36.9(36.2–37.8)°C at initiation of cisatracurium. The mean of temperature measurements during cisatracurium infusion was 36.6(36–37.3)°C (Figure 1B). Core temperature was <36°C for 6h during NMB in 22 of the 58 controls, 17 of whom were receiving continuous renal replacement therapy (CRRT) (Figure 1C). Of those not receiving CRRT, only one had core temperature <35°C. Fever (>38°C) occurred in 30 of 58 (52%) patients receiving cisatracurium, indicating that NMB alone was insufficient to block fever or induce hypothermia, but may have allowed hypothermia when combined with CRRT.

Effectiveness of surface cooling in ARDS Patients treated with NMB

We performed an open-label pilot study of therapeutic hypothermia (core temperature 34°–36°C for 48h) in patients with ARDS and P:F<150 who were receiving cisatracurium (Table 2). The 6 men and 2 women were 55.5(46–59) years old and were similar to the historical controls at pre-cisatracurium baseline (Table 1). At enrollment median APACHE II score was 30(24–32.75), P:F ratio was 86.5(63–104) and OI was 19(16.4–26.3). ARDS was caused by pneumonia in all 8 subjects and was a complication of influenza infection in 4. Core temperature at enrollment was 37(36.1–38.0)°C. Patient #8 was receiving CRRT and was already at target temperature at enrollment but required external cooling for part of the 48h treatment period.

Target temperature was reached by 11(5.25–15.5) hours after initiation of cisatracurium and by 4(2.25–9) hours after cooling device placement. Once target core temperature was achieved, it was maintained between 34° and 36°C for 76% and between 33° and 36°C for 92% of the cooling period. The median of the mean core temperatures during cooling for the 8 subjects was lower than median of the mean core temperatures during NMB in the 58 controls (34.35(34–34.8)°C vs. 36.7(36–37.3)°C; $p<0.0001$) (Fig. 1B). The histograms, conveying the distribution of all core temperature measurements in the two groups shows a partial overlap (Fig. 1C). The overall mean of the distribution for the cooled group (34.4°C) was lower than the mean of the distribution in the control group (36.7°C) in the MMRM analysis ($p<0.0001$). Core temperature was >36°C for 78% of the NMB infusion time for the historical controls compared with 2.5% of the cooling period for the prospectively cooled patients. We did not attempt to suppress fever after completion of the 48h cooling period. Two patients had fever in the 24h following cooling (Supplemental Table S1). The average temperatures during NMB in the controls with and without CRRT were 36.2°C and 37.2°C, respectively.

Safety of hypothermia in ARDS patients treated with NMB

All patients tolerated hypothermia without serious adverse events (SAEs). Two patients in the cooling group died following cooling (Table 2). Patient #5, a 60 year old man with hypertension and diabetes mellitus, presented with pneumonia, septic shock, and the poorest oxygenation in the cooling group. After completing the cooling protocol he had fatal asystolic arrest during prone to supine positioning. The other death occurred in patient #6, who had ARDS as a complication of newly diagnosed acute myelocytic leukemia, had improvement in OI from 20.7 to 7.3 by day-3, but died on study day-14 from septic shock.

The cooled patients and historical controls had similar frequencies of significant bleeding that was treated with at least 2 units of blood products (1/8 vs. 8/58) and symptomatic bradycardia (0/8 vs. 1/58) during the cooling/NMB period and VAP (1/8 vs. 7/58) (Table 3). Abnormalities in serum glucose, potassium, and magnesium were similar between the groups. Hypokalemia occurred in five patients during cooling and only one the following day. One cooled patient, 13 of 58 controls, and 5 of 16 matched controls received CRRT prior to starting cisatracurium. Of the patients not already on CRRT at the start of cisatracurium infusion, cooled patients tended to receive RRT more frequently during the cooling period than the 58 controls (4 of 7 vs. 14 of 45; $p=0.21$).

Comparing physiologic and clinical outcomes with historical controls

Because the cooled patients tended to have higher APACHE II scores (30.0 vs. 23.5; $p=0.15$) and lower P:F ratios (86.5 vs. 91.0; $p=0.4$) at enrollment and higher incidence of pneumonia as underlying cause of ARDS (100% vs. 38%), we compared cooled patients with all 58 controls and with 16 matched controls (Table 4). ICU and hospital mortality was 25% in the cooled group, 68.8% and 75%, respectively in the 16 matched controls ($p=0.061$ and 0.027), and 51.7% and 53.4% in all 58 controls ($p=0.26$ and 0.26). The distribution of VFDs was bimodal in the cooled patients; 4 patients had 0 VFDs and four had 18–22 VFDs. Two of the four with 0 VFDs died without liberating from the ventilator and two others, who had pre-existing cardiomyopathy and left ventricular ejection fraction $<30\%$, required mechanical ventilation for 29 and 43 days. Cooled patients had more VFDs (9(0–21.5)) and ICU-FDs (5.5(0–17.5)) than matched controls (0(0–0) VFDs, $p=0.009$) and 0(0–0) ICU-FDs, $p=0.014$) and tended to have more VFDs (0(0–12), $p=0.16$) (Figure 1D) and ICU-FDs (0(0–6), $p=0.058$) than the 58 controls (Supplemental Figure S1A).

Day-3 P:F ratios were higher in the cooled patients than the 58 controls (255(160–270) vs. 171(120–214), $p=0.024$) and tended to be higher than matched controls (175(75–231), $p=0.16$). Day-3 OI values were similar in the cooled patients and the 58 controls (9.8(4.7–11.5) vs. 11.1(8.4–19), $p=0.14$) and matched controls (12.1(8.5–31.3), $p=0.16$) (Supplemental Figure S1B, C). One cooled patient and 8 of 58 controls, but none of the matched controls, died before study day-3 and were not included in the analysis of P:F ratio and OI.

The cooled patients (5/8 vs. 12/58) were more likely to receive prone positioning than the 58 controls (12 of 58) or the matched controls (3 of 16), but mortality, VFDs, ICU-FDs, day 3

P:F ratio, and day-3 OI were similar in controls who were prone and those who were not prone (Table 4).

Serum mediators before and during hypothermia

Serum levels of IL-6, IL-10 and TGF β were analyzed. There was no clear temporal relationship between cytokine expression and cooling (Supplemental Table S2). Samples from the historical controls were not available for analysis of mediators.

DISCUSSION

We confirmed that cisatracurium alone does not cause hypothermia in our historical controls whose median of the average body temperatures was 36.7(36–37.3)°C and incidence of fever was 52% during NMB. We then showed in an open-label pilot study that surface cooling was effective and well-tolerated without serious adverse events. Target temperature was reached within 4(2.25–9) hours of cooling device placement, maintained below 36°C for 92% of the intended cooling period using either cooling blankets or the Arctic Sun™ System, and significantly different from historical controls. These results demonstrate the feasibility of studying hypothermia in patients receiving NMB for moderate to severe ARDS.

The 53.4% hospital mortality and 0(0–12) VFDs in the controls was substantially worse than previously reported (13, 14) and reflects the extensive comorbidities in our patient population. The prospectively cooled patients also had many co-morbidities (Table 1), which contributed to the bimodal VFD and ICU-FD data. Nonetheless, the prospectively cooled patients had better outcomes compared with matched controls, including more VFDs and ICU-FDs and improved post-cooling oxygenation on day-3.

Several factors in this small study may have contributed to the improved outcome in the cooled patients compared with historical controls. The omission of day-3 oxygenation values from patient #5 who died before day-3 might have changed the group results for the remaining patients, but a similar proportion of the controls (8 of 58) also died prior to day-3. Since our retrospective analysis period began after publication of the ACURASYS trial (13) but before the PROSEVA trial (14), only 12 of 58 controls were prone compared with 5 of 8 cooled patients. In the PROSEVA trial prone patients had lower 28-day and 90-day mortality (16.0% and 23.6%) and more VFDs (14) than our controls. The overall hospital mortality of our 58 controls, 53.4%, was higher than either the ACURASYS or PROSEVA trials. There were no large differences in outcomes between our controls who were prone and those who were not prone. The cooled patients had better day-3 P:F ratios and tended to have better OIs than the prone controls, and both deaths in the cooled patients occurred despite proning. These data suggest that differences in outcome between the cooled patients and historical controls cannot be fully explained by differences in proportion of patients prone.

ARDS was caused by pneumonia in all 8 cooled patients but only 20 of 58 controls; non-pulmonary sepsis was associated with modestly higher mortality than pneumonia in the controls (50% vs. 60%). The male:female ratio was higher in cooled patients, but ARDS-related mortality is usually higher in men (40). Influenza may be a self-limited cause of

ARDS and half of the cooled patients had influenza contribute to their acute illness; whereas, the number of historical controls is uncertain since influenza testing was not uniformly performed. Taken with the caveat that there were some important differences between the cooled patients and historical controls, these results provide encouragement to proceed with an RCT of hypothermia for ARDS. Importantly, our small prospective trial of hypothermia to 34°–36°C in ARDS patients receiving NMB did not find any of the serious adverse effects previously associated with hypothermia (38) and suggest the possibility of benefit.

The current study provided important information that can inform the planning of a Phase IIb RCT of hypothermia for ARDS. Patients with comorbidities that worsen prognosis for survival (e.g., newly diagnosed hematologic malignancy) or liberating from mechanical ventilation (e.g. cardiomyopathy) independent of ARDS should be excluded; (2) If patients receiving CRRT are included, there should be a protocolized provision for maintaining normothermia for those in control group; (3) serum potassium levels should be monitored during the cooling period.

CONCLUSIONS

We have shown that cooling to core temperature 34°–36°C is feasible and well tolerated, and supports conducting an initial RCT of hypothermia in ARDS patients treated with NMB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Li G, Malinchoc M, Cartin-Ceba R, et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. *Am J Respir Crit Care Med*. 2011; 183(1): 59–66. [PubMed: 20693377]
2. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005; 353(16):1685–1693. [PubMed: 16236739]
3. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003; 348(8):683–693. [PubMed: 12594312]
4. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011; 364(14):1293–1304. [PubMed: 21470008]
5. McHugh LG, Milberg JA, Whitcomb ME, et al. Recovery of function in survivors of the acute respiratory distress syndrome. *Am J Resp Clin Care Med*. 1994; 150(1):90–94.
6. Fan E, Dowdy DW, Colantuoni E, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med*. 2014; 42(4):849–859. [PubMed: 24247473]
7. Needham DM, Wozniak AW, Hough CL, et al. Risk factors for physical impairment after acute lung injury in a national, multicenter study. *Am J Respir Crit Care Med*. 2014; 189(10):1214–1224. [PubMed: 24716641]

8. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, et al. Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med*. 2012; 185(5):517–524. [PubMed: 22161158]
9. Bienvenu OJ, Gellar J, Althouse BM, et al. Post-traumatic stress disorder symptoms after acute lung injury: a 2-year prospective longitudinal study. *Psychological Med*. 2013; 43(12):2657–2671.
10. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000; 342(18): 1334–1349. [PubMed: 10793167]
11. Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med*. 1998; 157(6 Pt 1):1721–1725. [PubMed: 9620897]
12. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000; 342(18): 1301–1308. [PubMed: 10793162]
13. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010; 363(12):1107–1116. [PubMed: 20843245]
14. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013; 368(23):2159–2168. [PubMed: 23688302]
15. Phua J, Badia JR, Adhikari NK, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *Am J Respir Crit Care Med*. 2009; 179(3):220–227. [PubMed: 19011152]
16. Villar J, Blanco J, Kacmarek RM. Current incidence and outcome of the acute respiratory distress syndrome. *Curr Opin Crit Care*. 2016; 22(1):1–6. [PubMed: 26645551]
17. Ruan SY, Lin HH, Huang CT, et al. Exploring the heterogeneity of effects of corticosteroids on acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care*. 2014; 18(2):R63. [PubMed: 24708846]
18. Boyle AJ, MacSweeney R, McAuley DF. Pharmacological treatments in ARDS; a state-of-the-art update. *BMC Med*. 2013; 11:166. [PubMed: 23957905]
19. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest*. 2012; 122(8):2731–2740. [PubMed: 22850883]
20. Spieth PM, Zhang H. Pharmacological therapies for acute respiratory distress syndrome. *Current Opinion Crit Care*. 2014; 20(1):113–121.
21. Tulman DB, Stawicki SP, Whitson BA, et al. Veno-venous ECMO: a synopsis of nine key potential challenges, considerations, and controversies. *BMC Anesthesiol*. 2014; 14:65. [PubMed: 25110462]
22. Corwin D, Shah NG, Ramarathnam A, et al. Hypothermia and trpv4 channel inhibition mitigates thrombin-induced permeability. *Am J Respir Crit Care Med*. 2016; 193:A1358.
23. Yang D, Xie P, Guo S, et al. Induction of MAPK phosphatase-1 by hypothermia inhibits TNF- α -induced endothelial barrier dysfunction and apoptosis. *Cardiovasc Res*. 2010; 85(3):520–529. [PubMed: 19793766]
24. Li J, Beiser DG, Wang H, et al. Therapeutic hypothermia cardioprotection in murine hemorrhagic shock/resuscitation differentially affects p38 α /p38 γ , Akt, and HspB1. *J Trauma*. 2011; 71(5):1262–1270. [PubMed: 22071928]
25. Lim CM, Kim MS, Ahn JJ, et al. Hypothermia protects against endotoxin-induced acute lung injury in rats. *Intensive Care Med*. 2003; 29(3):453–459. [PubMed: 12624664]
26. Chin JY, Koh Y, Kim MJ, et al. The effects of hypothermia on endotoxin-primed lung. *Anesth Analg*. 2007; 104(5):1171–1178. [PubMed: 17456669]
27. Jo YH, Kim K, Rhee JE, et al. Therapeutic hypothermia attenuates acute lung injury in paraquat intoxication in rats. *Resuscitation*. 2011; 82(4):487–491. [PubMed: 21236547]
28. Kim K, Kim W, Rhee JE, et al. Induced hypothermia attenuates the acute lung injury in hemorrhagic shock. *J Trauma*. 2010; 68(2):373–381. [PubMed: 19996791]
29. Lim CM, Hong SB, Koh Y, et al. Hypothermia attenuates vascular manifestations of ventilator-induced lung injury in rats. *Lung*. 2003; 181(1):23–34. [PubMed: 12879337]

30. Slack D, Corwin D, Shah NG, et al. Therapeutic Hypothermia Attenuates Pulmonary Vascular Permeability and Inflammation in a Mouse Model of Ventilator-Induced Lung Injury. *Am J Respir Crit Care Med*. 2016; 193:A5225.
31. Beurskens CJ, Aslami H, Kuipers MT, et al. Induced hypothermia is protective in a rat model of pneumococcal pneumonia associated with increased adenosine triphosphate availability and turnover*. *Crit Care Med*. 2012; 40(3):919–926. [PubMed: 22036856]
32. Peng CK, Huang KL, Wu CP, et al. The role of mild hypothermia in air embolism-induced acute lung injury. *Anesth Analg*. 2010; 110(5):1336–1342. [PubMed: 20418297]
33. Villar J, Slutsky AS. Effects of induced hypothermia in patients with septic adult respiratory distress syndrome. *Resuscitation*. 1993; 26(2):183–192. [PubMed: 8290813]
34. Karnatovskaia LV, Festic E, Freeman WD, et al. Effect of therapeutic hypothermia on gas exchange and respiratory mechanics: a retrospective cohort study. *Ther Hypotherm Temp Manag*. 2014; 4(2):88–95.
35. Shah NG, Cowan MJ, Pickering E, et al. Nonpharmacologic approach to minimizing shivering during surface cooling: a proof of principle study. *Journal of critical care*. 2012; 27(6):746 e741–748.
36. Guerin C, Mancebo J. Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: yes. *Intensive Care Med*. 2015; 41(12):2195–2197. [PubMed: 26399890]
37. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012; 38(10):1573–1582. [PubMed: 22926653]
38. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013; 369(23):2197–2206. [PubMed: 24237006]
39. Fitzmaurice, GM., Laird, NM., Ware, JH. *Applied Longitudinal Analysis*. 2nd. Hoboken, NJ: Wiley; 2011.
40. Cochi SE, Kempker JA, Annangi S, et al. Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013. *Ann Am Thorac Soc*. 2016; 13(10):1742–1751. [PubMed: 27403914]

Figure 1.

A. CONSORT flow diagram of retrospective chart review for patients with ARDS receiving NMB. B. Mean of all temperature measurements during NMB in controls and during hypothermia treatment period in cooled patients. Medians (indicated) were compared by Wilcoxon Rank-Sum test and p value is displayed. C. Temporal distribution of core temperature during NMB in controls and during the hypothermia treatment period in cooled patient. The difference in the means of all temperatures in the two groups was compared using a mixed model repeated measures (MMRM) analysis (39) and the p value is displayed. D. Box plots of 28-day VFDs for the cooled patients, all 58 controls, and the 16 matched controls. The 25th percentile values for VFDs was 0 for all three groups. Median values for

VFDs for all 58 controls and the matched controls was 0. The 75th percentile values for VFD for the matched controls was 0. The p-values for each comparison are indicated.

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Table 1Demographic information for Cooled Subjects and Controls¹

Parameter	All controls	Matched Controls	Cooled patients
Number	58	16	8
Age	49(38–57)	56(42–59)	55.5(46–59)
% male	55	50	75
% White (not Hispanic)	62	69	37.5
% AA	34	19	25
% Asian	2	6	12.5
% Hispanic	2	6	25
BMI	32(26–39.25)	35(29.75–42.25)	31.5(29–44)
APACHE II	23.5(19.75–30)	30(23.75–32)	30(24–32.75)
P:F ratio	91(75–110)	80(73–129)	86.5(63–104)
FiO2	100(77.5–100)	100(90–100)	80(72.5–97.5)
PEEP (cm H ₂ O)	15(12–18)	16(12–20)	14(12–16)
Number on VC or PRVC/PC/APRV/HFOV ³	38/17/2/1	10/5/1/0	4/3/1/0
Measured Respiratory rate (bpm)	25(20–30)	26(20–33)	23(18–25)
Measured Tidal volume (ml)	420(350–470)	350(300–430)	420(380–460)
OI	23.3(15.8–34.6)	28(19.2–41.4)	19(16.4–26.3)
% pneumonia	38	31	100
% non-pulmonary sepsis	52	69	0
% shock (not septic)	2	0	0
% hemorrhage	6	0	0
% other	2	0	0
Number started on RRT during study ²	14/45	5/11	4/7

¹ Medians (interquartile ranges) shown for demographic and pre-NMB baseline characteristics.² Number started on RRT during study/number not receiving RRT prior to start of cisatracurium.³ Number of subjects on Volume Control (VC) or Pressure Regulated Volume Control (PRVC), Pressure Control (PC), Airway Pressure Release Ventilation (APRV) or High Frequency Oscillator Ventilation (HFOV).

Table 2

Demographic and Baseline Information in the cooled Subjects

Patient	Age	Gender	Ethnicity	BMI	APACHE2	P:F ratio OI	Proned	Survived	Underlying disease
1	45	M	White	29	33	100/13.9	No	Yes	Pneumonia
2	63	F	AA ¹	22	29	63/23.8	Yes	Yes	NSCLC ² , pneumonia
3	56	M	White	41	34	81/24.7	Yes	Yes	Cardiomyopathy, pneumonia
4	27	M	AA	50	23	142/16.2	No	Yes	Influenza, asthma, pneumonia
5	60	M	Asian	32	19	49/53.1	Yes	No	Pneumonia, septic shock
6	55	M	Hispanic	31	32	63/17.3	No	Yes	Renal Transplant, cardiomyopathy, pneumonia
7	56	F	Hispanic	45	27	92/20.7	Yes	No	AML ³ , pneumonia
8	50	M	White	29	31	105/17	Yes	Yes	Liver/renal failure, pneumonia

¹ African American² Non-small cell lung cancer³ Acute myelocytic leukemia

Table 3Complications in Cooled Patients and Controls[/]

Complication	All controls	Matched Controls	Cooled patients
Total Number of patients	58	16	8
VAP	7	1	0
Bradycardia (day 0–2)	1	0	0
Bleeding (day 0–2)	8	3	0
Hyperglycemia (day 0–2)	37	11	3
Hyperglycemia (day 3)	23	7	3
Hypoglycemia (day 0–2)	9	3	0
Hypoglycemia (day 3)	5	1	0
Hyperkalemia (day 0–2)	11	3	0
Hyperkalemia (day 3)	4	2	0
Hypokalemia (day 0–2)	25	5	5
Hypokalemia (day 3)	12	3	1
Hypermagnesemia (day 0–2)	15	7	3
Hypermagnesemia (day 3)	13	4	2
Hypomagnesemia (day 0–2)	7	1	0
Hypomagnesemia (day 3)	2	1	0

[/]Numbers of patients having the complication are listed.

Table 4

Outcome Differences between Cooled Patients and Controls

Outcome Measure	Cooled patients	Matched Controls (p vs. cooled)	All controls (p vs. cooled)	Proned controls (p vs. cooled)	Unproned controls (p vs. proned)
Number	8	16	58	12	46
ICU mortality	25%	68.75% (0.061)	51.7% (0.26)	50% (0.37)	52.2% (1.0)
Hospital mortality	25%	75% (0.027)	53.4% (0.26)	50% (0.37)	54.4% (1.0)
Number febrile D0	2	10 (0.11)	37 (0.007)	8 (0.17)	29 (0.35)
Number febrile D1	0	5 (0.056)	19 (0.18)	5 (0.055)	14 (0.29)
Number febrile D2	1	5 (0.62)	15 (0.67)	4 (0.60)	11 (0.27)
Number febrile D3	2	5 (1.0)	19 (1.0)	5 (0.64)	14 (0.29)
VFDs	9 (0–21.5) ^f	0 (0–0) (0.009)	0 (0–12) (0.16)	3 (0–16.5) (0.46)	0 (0–12) (0.32)
ICU-FDs	5.5 (0–17.5)	0 (0–0) (0.014)	0 (0–6) (0.058)	0 (0–16) (0.43)	0 (0–2) (0.25)
Number surviving 3 days	6	16	50	10	40
Day 3 P:F	255 (160–270)	175 (75–231) (0.16)	171 (120–214) (0.024)	175 (134–182) (0.032)	163 (115–220) (0.69)
Day 3 OI	9.8 (4.7–11.5)	12.1 (8.5–31.3) (0.16)	11.1 (8.4–19) (0.14)	11.3 (8.9–19.8) (0.19)	11.1 (7.25–18.4) (0.80)

^f Medians (interquartile ranges) shown.