Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

PMID: 31112383

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阿部 建彦
INTRODUCTION
集中治療領域では、“less intervention”が主流

・Lung-protective ventilation
・Fewer transfusion
・Less bed rest
・Fewer intubation
・Less sedation

ARDSに対するNMBの使用は、“Less is more”の精神に反する

Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome

- 4 ICUs in France, 56 patients
- P/F <150
- Cisatracurium 50mg bolus
  + 5mcg/kg/min 48hours
  - TOF 0になるように調整
- 120時間後の酸素化：NMB群で改善
- 人工呼吸器期間・死亡率は有意差ないも、NMB群で良い傾向

**Crit Care Med 2004; 32:113–119**
ACURASYS

- 20 ICUs in France, 340 pts.
  - 2006.3-2008.3
- P/F <150
- Cisatracurium 15mg bolus
  + 37.5mg/hr 48hours
- 90日死亡率：31.6% vs. 40.7%
- Barotrauma：5.1% vs. 11.7%

**Figure 2. Probability of Survival through Day 90, According to Study Group.**

*Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome*

NMB が ARDS の人工呼吸管理にもたらす影響

Before paralysis

Respiratory cycle

Patient

Pressure generated

Ventilator

Lung volume

Active expiration

Increased tidal volume secondary to increased respiratory drive due to:

↓ Arterial PO₂
Lung reflexes
Anxiety
Permissive hypercapnia

Dyssynchrony

↑ Lung volume

↑ Lung volume

↓ Lung volume

Ventilator-induced lung injury

Alveolus

O₂ molecules

Surfactant

Translocation of mediators from alveolar space to circulation

↑ Mediators (e.g., interleukin-8)

Barotrauma

↑ Injury due to ↑ pulmonary blood flow

↑ Alveolar-capillary permeability

Volutrauma

"Atelectrauma"

Biotrauma

↑ Mediators

Vital organs

Muscles

O₂ used for muscle contraction

Severely reduced venous PO₂

↓ Arterial PO₂

↓ Blood flow

↑ Mediators

To lungs

↓ Venous PO₂

V/Q 18:31/10

AUTHOR PLEASE NOTE:

Figure has been redrawn and type has been reset

Please check carefully

Slutsky Knoper and minions

Issue date

NMBがARDSの人工呼吸管理にもたらす影響

低O2・高CO2・反射・不安など
↓
呼吸努力が上昇→TV上昇

肺胞からサイトカインが血中に移動

筋収縮により酸素消費↑
NMBがARDSの人工呼吸管理にもたらす影響

NMBがARDSの人工呼吸管理にもたらす影響

- 人工呼吸器と同調
- VILI (baro-, volu-, atelec-, biotrauma)が減少
- サイトカインが減少
- 呼吸筋の仕事量減少、肺胞血流量の減少
- 換気血流比の改善
- 酸素化の改善
- NMBの抗炎症作用
- 臓器障害の進展を抑制

Reverse trigger
  呼吸時の吸気に関連して、横隔膜が収縮、患者の吸気が誘発される。結果として、過伸展・経肺圧上昇

Pendelluft
  自発呼吸の開始時に、肺内の胸膜圧の変化により腹側(non-dependent)から背側(dependent)に空気が移動。吸気時に腹側が虚脱、背側が過伸展する。

Ineffective efforts
  患者吸気がトリガされずに、呼気中に吸気が起こる

CHEST 2013;143: 927-938.


Mechanical Ventilation-Induced Reverse-Triggered Breaths

- ARDS 8症例のFlow, Paw, Pes or EAdiを測定
### Mechanical Ventilation-Induced Reverse-Triggered Breaths

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>RASS</th>
<th>Recording Time, s</th>
<th>Entrainment, s (% of Recording Time)</th>
<th>Ratio, % of Entrainment Time</th>
<th>PaO₂, mm Hg</th>
<th>PaCO₂, mm Hg</th>
<th>pH</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>−5</td>
<td>875</td>
<td>407 (46)</td>
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<td>60</td>
<td>46</td>
<td>7.41</td>
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<tr>
<td>2</td>
<td>−5</td>
<td>439</td>
<td>58 (13)</td>
<td>1:2</td>
<td>55</td>
<td>54</td>
<td>7.30</td>
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<td>3</td>
<td>−4</td>
<td>467</td>
<td>184 (39)</td>
<td>1:3</td>
<td>86</td>
<td>45</td>
<td>7.44</td>
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<tr>
<td>4</td>
<td>−5</td>
<td>1658</td>
<td>1,421 (86)</td>
<td>1:1</td>
<td>68</td>
<td>47</td>
<td>7.46</td>
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<tr>
<td>5</td>
<td>−5</td>
<td>1538</td>
<td>683 (44)</td>
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<td>92</td>
<td>30</td>
<td>7.45</td>
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<tr>
<td>6</td>
<td>−4</td>
<td>619</td>
<td>619 (100)</td>
<td>1:3</td>
<td>74</td>
<td>39</td>
<td>7.25</td>
</tr>
<tr>
<td>7</td>
<td>−4</td>
<td>365</td>
<td>43 (12)</td>
<td>1:1</td>
<td>78</td>
<td>46</td>
<td>7.41</td>
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<tr>
<td>8</td>
<td>−5</td>
<td>1295</td>
<td>246 (19)</td>
<td>1:2</td>
<td>63</td>
<td>48</td>
<td>7.43</td>
</tr>
</tbody>
</table>

**• Reverse trigger：12-100%で起こる**

**• 人工呼吸器の吸気に関連して、横隔膜が収縮・患者吸気が誘発 → TV増加・過伸展・barotrauma**
特に、高い吸気努力＆肺傷害ある患者⇒局所性肺傷害（pendelluft障害）

P_L↑ = Pa_W - P_PL↓

経肺圧 気道内压 胸膜圧

陰圧：背側＞胸膜側⇒背側肺領域に過伸展

19/04/09 「人工呼吸中の自発呼吸を考える」より
Spontaneous Effort Causes Occult Pendelluft during Mechanical Ventilation

Am J Respir Crit Care Med 2013; 188: 1420–27

1) The end of expiration
2) The early stage of inspiration
3) 4)

- 肺傷害モデルのブタでPendelluft現象を実証
- 自発呼吸時の陰圧は背側で大きい
- 吸気の始めに、腹側から背側に気体が移動
  → 腹側：虚脱
  背側：過伸展
Clusters of ineffective efforts during mechanical ventilation: impact on outcome

**Intensive Care Med. 2017;43 :184-191.**

- Ineffective efforts (IEs)とアウトカムとの関係
- 前向き観察研究
- 2010.1-2011.7, 110 pts., 4,456,537 breaths

IEs: 患者吸気がトリガされず呼気中に患者吸気が起こる → breath stacking、過伸展

- 42/110 pts.(38.2%)で出現
- ICU滞在日数・MV期間・院内死亡率上昇
ATS/ESICM/SCCMのガイドライン

NMBに関しては、情報が限定されているため評価せず

次回以降のガイドラインでは、NMBに対しての項目が記載されるだろう
成人ARDS患者において人工呼吸を実施する際、筋弛緩薬を使用するべきか

推奨
成人 ARDS 患者において人工呼吸を実施する際、限定的に筋弛緩薬の使用を提案する
（GRADE 2B、推奨の強さ「弱い推奨」/エビデンスの確信性「中」）

付帯事項
日常的に使用することを避ける。中等症以上の ARDS 患者 (PEEP ≥ 5cmH₂O で P/F 比 ≤ 200) で、発症早期に投与期間を 48 時間以内に限定して使用すべきである。本邦で使用できる筋弛緩薬では ICU 関連筋力低下のリスクが増す可能性がある。特にステロイドとの併用には留意すべきである。
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

JAMA. 2016;315(8):788-800.

Table 4. Use of Adjunctive and Other Optimization Measures in Invasively Ventilated Patients With Acute Respiratory Distress Syndromea

<table>
<thead>
<tr>
<th>Patients of No. (%) [95% CI]</th>
<th>All (n = 2377)</th>
<th>Milda (n = 498)</th>
<th>Moderatea (n = 1150)</th>
<th>Severea (n = 729)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular blockade</td>
<td>516 (21.7)</td>
<td>34 (6.8)</td>
<td>208 (18.1)</td>
<td>274 (37.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>[20.1-23.4]</td>
<td>[4.8-9.4]</td>
<td>[15.9-20.4]</td>
<td>[34.1-41.2]</td>
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</tr>
<tr>
<td>Recruitment maneuvers</td>
<td>496 (20.9)</td>
<td>58 (11.7)</td>
<td>200 (17.4)</td>
<td>238 (32.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>[19.2-22.6]</td>
<td>[9.0-14.8]</td>
<td>[15.2-19.7]</td>
<td>[29.3-36.2]</td>
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<tr>
<td>Prone positioning</td>
<td>187 (7.9)</td>
<td>5 (1.0)</td>
<td>63 (5.5)</td>
<td>119 (16.3)</td>
<td>&lt;.001</td>
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<tr>
<td></td>
<td>[7.1-12.6]</td>
<td>[0.3-1.3]</td>
<td>[4.8-9.4]</td>
<td>[11.0-26.1]</td>
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</tr>
</tbody>
</table>

- 全体で21.7%
  - Mild: 6.8%, Moderate: 18.1%, Severe: 37.8%
- 重症症例でより多く使用されている

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n = 557)</th>
<th>Moderate (n = 1106)</th>
<th>Severe (n = 729)</th>
<th>P Valueb</th>
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</thead>
<tbody>
<tr>
<td>Esophageal pressure catheter</td>
<td>19 (0.8)</td>
<td>2 (0.4)</td>
<td>8 (0.7)</td>
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<td>[0.04-1.4]</td>
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<td>[0.3-1.3]</td>
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<tr>
<td>Tracheostomy</td>
<td>309 (13.0)</td>
<td>48 (9.6)</td>
<td>155 (13.5)</td>
<td>.034</td>
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<td>[11.6-14.4]</td>
<td>[7.1-12.6]</td>
<td>[11.6-15.6]</td>
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<tr>
<td>High-dose corticosteroidsc</td>
<td>425 (17.9)</td>
<td>61 (12.3)</td>
<td>194 (16.9)</td>
<td>&lt;.001</td>
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<tr>
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<td>[16.4-19.5]</td>
<td>[9.5-15.5]</td>
<td>[14.7-19.2]</td>
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<tr>
<td>Pulmonary artery catheter</td>
<td>107 (4.5)</td>
<td>9 (1.8)</td>
<td>53 (4.6)</td>
<td>.001</td>
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<td>[3.7-5.4]</td>
<td>[0.8-3.4]</td>
<td>[3.4-6.0]</td>
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</tr>
</tbody>
</table>
NMBの長期使用 → ICU-AWとの関連
Second, our sensitivity analyses found that studies limited to patients with severe sepsis or septic shock demonstrated the strongest association between NMBAs and neuromuscular dysfunction acquired in critical illness; inadequate reporting of patients with sepsis (as opposed to severe sepsis or septic shock) precluded this group from being included in this analysis. Both of the studies in the severe sepsis or septic shock sensitivity analysis evaluated for CIP. The first case series to describe CIP, published by Bolton et al (34) in 1984, implicated sepsis in its pathogenesis. Subsequent analyses that adjusted for confounders (13) also supported sepsis as an independent risk factor. Our analysis provides additional support that an association between NMBAs given to patients with sepsis and neuromuscular dysfunction acquired in critical illness exists, and consistent with prior work (9, 29), the association may be proportional to the severity of sepsis. Specifically, as demonstrated in Supplemental Figure 1 (Supplemental Digital Content 6, http://links.lww.com/CCM/B854; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/B855),
Neuromuscular Blockade and Skeletal Muscle Weakness in Critically Ill Patients

Am J Respir Crit Care Med 2012; 185: 911–7

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Study</th>
<th>Mean Age (yr)</th>
<th>Diagnosis</th>
<th>Mean APACHE Score (SD)</th>
<th>Design</th>
<th>Frequency of ICU-AW</th>
<th>Neuramocular Blocking Agent Used</th>
<th>Mean Length of Use of Neuramocular Blocking Agent (d)</th>
<th>Days Ventilated Prediagnosis of ICU-AW</th>
<th>Diagnostic Method for ICU-AW</th>
<th>Association with Neuromuscular Blocking Agent</th>
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<tr>
<td>Leijen et al.</td>
<td>1995</td>
<td>&lt;.75</td>
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<td>Prospective observational</td>
<td>29/50</td>
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<td>Vecuronium</td>
<td>Not reported</td>
<td>Not standardized</td>
<td>EP Testing</td>
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<td>Latronico et al.</td>
<td>1996</td>
<td>50.2</td>
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<td>Not recorded</td>
<td>Pancuronium or atracurium</td>
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<td>Clinical examination</td>
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<td>Kesler et al.</td>
<td>2009</td>
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<td>10/74</td>
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<td>2 patients</td>
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<td>Leatherman et al.</td>
<td>1996</td>
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<td>Behbehani et al.</td>
<td>1999</td>
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<td>Segredo et al.</td>
<td>1992</td>
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<td>Respiratory failure</td>
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<td>Garnacho-Montero et al.</td>
<td>1996–1999</td>
<td>62</td>
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<td>11/73</td>
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<td>Campollone et al.</td>
<td>1995–1995</td>
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<td>Liver transplantation</td>
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<td>&gt;7</td>
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<td>de Letter et al.</td>
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<td>Clinical examination</td>
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<td>Bednarik et al.</td>
<td>2000–2002</td>
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<td>Pimecuronium</td>
<td>Not reported</td>
<td>Not standardized</td>
<td>Clinical examination</td>
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</tbody>
</table>
ACURASYSの問題点

• 2006-2008年の研究  
  → ARDSの管理がここ10年で変わってきている

• NMB + Deep sedation vs. Deep sedation  
  → Light sedationの方がMV期間や死亡率が改善


• 両群はLow PEEPで設定  
  → 重症ARDSはPEEPを高めで管理
ACURASYSの問題点

・2日間の使用で、予後が18日以降で差が出る
・P/F<120で差が出る（<150では同等）
・NMBはVILIやbiotraumaを低下させるとなってい
るが、確証はされていない
  ・TV, Pplatには変化がない

NMB + Deep sedation vs. Light sedation with High PEEPでの検討が必要
Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

**ROSE trial**
- PETAL: Prevention and Early Treatment of Acute Lung Injury
- ROSE: Reevaluation of Systemic Early Neuromuscular Blockade
METHODS
P：中等度〜重症のARDS患者 (P/F < 150)

I：早期にCisatracuriumを48時間持続投与

C：通常の管理

O：90日死亡率
Patients

• 2016.1 – 2018.4
• 48 hospitals in U.S.
• 18歳以上
• 発症から48時間以内
• P/F < 150 (PEEP 8cmH2O以上)
• 胸水・無気肺・結節では説明できない両側浸潤影
• 心不全や輸液負荷では説明できない呼吸不全
Patients

Exclusion criteria

- 同意が取れない
- 登録前にNMBが投与されていた
- ECMOを導入されていた
- 慢性呼吸不全：PaCO2 > 60mmHg
- 自宅で呼吸器を使用（SAS除く）
- 肥満：1kg/cm以上
- 肝硬変：Child-Pugh 12-15
- 1年以内の骨髄移植
- MVが48時間以内と予想される
- 延命治療を希望しない
- 24時間以内に死亡が予測される

- 血管炎由来のびまん性肺胞出血
- TBSA >70%の熱傷
- TV 6ml/kgが適応できない
- Cisatracuriumに対するアレルギー
- 神経筋疾患の既往
- ICHの治療をしている
- ARDSの介入研究に登録済み
- ランダム化化前にP/F >200に改善
- 5日以上挿管されている
- 肺移植の待機患者
NMB群

• Deep sedation (RASS -4-5, SAS 5-6, RSS 1-2)
  ：割付後4時間以内に達成
• Cisatracurium
  ：15mg bolus + 37.5mg/hr 48hrs
• 末梢神経刺激による投与量の調整はなし
• NMBの早期終了
  ：FiO2 <0.4, PEEP <8 cmH20を12時間維持
コントロール群

• Light sedation
  - RASS：0, -1
  - SAS：3, 4
  - RSS：2, 3
• ルーティンのNMBの使用はしない
共通項目

呼吸器管理

• Low tidal volume 6ml/kg PBW：割付後2時間以内
• High PEEP strategy：割付後5日間
  • 酸素化悪化・低血圧・Pplat>30cmH2O・pH<7.15が予想されるときはPEEPを下げる事は可能
  • 気胸出現・barotraumaのリスクが高い患者には、PEEPは下げて対応

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>.30</th>
<th>.40</th>
<th>.50</th>
<th>.60</th>
<th>.70</th>
<th>.80</th>
<th>.90</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5-16</td>
<td>16-20</td>
<td>20</td>
<td>20</td>
<td>20-22</td>
<td>22</td>
<td>22.24</td>
</tr>
</tbody>
</table>

• 腹臥位療法は臨床医の判断に委ねる
共通項目

**NMB投与**

- 以下の時、Cisatracurium 20mgボーラスが可能
  - 鎮静薬・TV/PEEPを調整しても Pplat >30cmH2Oが10分以上続く場合
    - Pplatが2cmH2O以上低下すれば、再度NMB投与は可能、下がらないなら24時間は投与しない
- 48時間経過後、NMBの継続をするかは臨床医に委ねられる
- 比較しやすいようにNMBはCisatracurium換算
Trial design

✓ 筋弛緩薬の種類・投与量・投与期間は ACURASYS と同様

✓ コントロール群は Light sedation

✓ 両群とも Low TV ventilation + high PEEP protocol

✓ 輸液方法も Conservative fluid strategy を使用
End points

• Primary end point
  • 90日死亡率

• Secondary end point
  • SOFA score
  • 28日死亡率
  • ICU日数、MV日数
  • 3, 6, 12ヶ月後に身体機能や精神状態などを評価
  • Safety end point
Statistical analysis

• 死亡率：NMB群 27%, コントロール群 35%
• 検出力 90%、有意水準 0.05
  → 1408人
• Primary end point：Wald検定
• サブグループ解析：一般線形モデル
  ARDS重症度 (P/F 120)、ARDS期間 (登録〜割付の中央値)、登録前NMB使用率が多い病院、性別、人種、民族
Statistical analysis

• Adverse events: ポアソン回帰分析
  • Nonserious - 1, serious - 2
• 90日 / 1年死亡率: Z検定

• 全てIntension-to-treatで解析
• SAS version 9.4
RESULTS
Early Neuromuscular Blockade in ARDS

Figure 1. Patient Screening, Enrollment, and Follow-up.

Patients may have had more than one reason for exclusion. Two patients were randomly assigned twice to the control group. No patients were lost to follow-up. NMB denotes neuromuscular blockade, and P/O2:F/IO2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

1008 Underwent randomization
4848 Patients were assessed for eligibility
3840 Were excluded

- 658 Had P/F>200 at time of randomization
- 655 Were receiving continuous NMB at enrollment
- 394 Declined to participate or had surrogate who declined
- 384 Were not expected to survive 24 hr
- 307 Were withdrawn by physician
- 270 Did not have surrogate available
- 245 Had been receiving mechanical ventilation for >120 hr
- 237 Had severe chronic liver disease
- 209 Had inclusion criteria for >48 hr
- 245 Had been receiving mechanical ventilation for >120 hr
- 227 Had severe chronic liver disease
- 113 Were receiving extracorporeal membrane oxygenation treatment
- 114 Had body weight >1 kg/cm of height
- 109 Were expected to receive mechanical ventilation for <48 hr
- 561 Had other reason

502 Were assigned to the intervention group (cisatracurium)
506 Were assigned to the control group

86 Received any NMB in the first 48-hr intervention period
40 Received any NMB in the second 48-hr trial period

501 Were included in the primary analysis
505 Were included in the primary analysis

1 Was immediately withdrawn from the trial after randomization owing to ineligibility and did not receive cisatracurium
1 Was immediately withdrawn from the trial after randomization owing to ineligibility and did not receive NMB

488 Received cisatracurium in the first 48-hr intervention period
3 Did not receive cisatracurium in first 48-hr intervention period
3 Were withdrawn before administration of NMB
1 Was deemed too unstable by physician
2 Died before administration of NMB
1 Did not reach target sedation
6 Had other reasons

419 Did not receive any NMB in the second 48-hr trial period
Early Neuromuscular Blockade in ARDS

**Figure 1. Patient Screening, Enrollment, and Follow-up.**

Patients may have had more than one reason for exclusion. Two patients were randomly assigned twice to the control group. No patients were lost to follow-up. NMB denotes neuromuscular blockade, and $\text{PaO}_2$:F$\text{IO}_2$ the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

- **Underwent randomization**: 502
- **Patients were assessed for eligibility**: 484
- **Were excluded**: 384
  - Had $\text{PaO}_2$:F$\text{IO}_2$ > 200 mm Hg at time of randomization: 65
  - Were receiving continuous NMB at enrollment: 65
  - Declined to participate or had surrogate who declined: 39
  - Were not expected to survive 24 hr: 44
  - Were withdrawn by physician: 30
  - Did not have surrogate available: 27
  - Had been receiving mechanical ventilation for >120 hr: 24
  - Had severe chronic liver disease: 23
  - Had inclusion criteria for >48 hr: 20
  - Decided to withhold life-sustaining treatment: 15
  - Had body weight $>1$ kg/cm of height: 12
  - Were receiving extracorporeal membrane oxygenation: 11
  - Were expected to receive mechanical ventilation for <48 hr: 10
  - Had other reason: 5

- **Were assigned to the intervention group (cisatracurium)**: 502
- **Were assigned to the control group**: 506

- **Received cisatracurium in the first 48-hr intervention period**: 488
  - Did not receive cisatracurium in first 48-hr intervention period: 69
  - Were withdrawn before administration of NMB: 13
  - Was deemed too unstable by physician: 2
  - Died before administration of NMB: 1
  - Did not reach target sedation: 6
  - Had other reasons: 4
- **Did not receive any NMB in the second 48-hr trial period**: 419

- **Received any NMB in the first 48-hr intervention period**: 86
- **Received any NMB in the second 48-hr trial period**: 40

- **Were included in the primary analysis**: 501
- **Were included in the primary analysis**: 505

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### Table 1. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group (N=501)</th>
<th>Control Group (N=505)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age — yr</strong></td>
<td>56.6±14.7</td>
<td>55.1±15.9</td>
</tr>
<tr>
<td><strong>Female sex — no. (%)†</strong></td>
<td>210 (41.9)</td>
<td>236 (46.7)</td>
</tr>
<tr>
<td><strong>White race — no. (%)†</strong></td>
<td>361 (72.1)</td>
<td>344 (68.1)</td>
</tr>
<tr>
<td><strong>Shock at baseline — no. (%)</strong></td>
<td>276 (55.1)</td>
<td>309 (61.2)</td>
</tr>
<tr>
<td><strong>Median time from enrollment to randomization (IQR) — hr</strong></td>
<td>8.2 (4.0–16.4)</td>
<td>6.8 (3.3–14.5)</td>
</tr>
<tr>
<td><strong>Neuromuscular blockade use between meeting inclusion criteria and randomization — no./total no. (%)</strong></td>
<td>55/484 (11.4)</td>
<td>50/484 (10.3)</td>
</tr>
<tr>
<td><strong>Primary cause of lung injury — no. (%)</strong></td>
<td>292 (58.3)</td>
<td>301 (59.6)</td>
</tr>
<tr>
<td></td>
<td>91 (18.2)</td>
<td>75 (14.9)</td>
</tr>
<tr>
<td></td>
<td>68 (13.6)</td>
<td>71 (14.1)</td>
</tr>
<tr>
<td></td>
<td>50 (10.0)</td>
<td>58 (11.5)</td>
</tr>
<tr>
<td><strong>Assessments and measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>APACHE III score‡</strong></td>
<td>103.9±30.1</td>
<td>104.9±30.1</td>
</tr>
<tr>
<td><strong>Total SOFA score§</strong></td>
<td>8.7±3.6</td>
<td>8.8±3.6</td>
</tr>
<tr>
<td><strong>Tidal volume — ml/kg of predicted body weight¶</strong></td>
<td>6.3±0.9</td>
<td>6.3±0.9</td>
</tr>
<tr>
<td><strong>FiO2∥</strong></td>
<td>0.8±0.2</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td><strong>Inspiratory plateau pressure — cm of water</strong></td>
<td>25.5±6.0</td>
<td>25.7±6.1</td>
</tr>
<tr>
<td><strong>PEEP — cm of water††</strong></td>
<td>12.6±3.6</td>
<td>12.5±3.6</td>
</tr>
<tr>
<td><strong>Pao2:Fio2 — mm Hg‡‡</strong></td>
<td>98.7±27.9</td>
<td>99.5±27.9</td>
</tr>
<tr>
<td><strong>Imputed Pao2:Fio2 — mm Hg§§</strong></td>
<td>94.8±26.7</td>
<td>93.2±28.9</td>
</tr>
</tbody>
</table>

---

*Plus–minus values are means ±SD. There were no significant differences between the groups except for time from inclusion in the trial to randomization (P=0.047) and shock at baseline (P=0.05). Percentages may not total 100 because of rounding. IQR denotes interquartile range.

†Sex and race were determined by the coordinators on the basis of hospital records or information from the next of kin.

‡Acute Physiology, Age, and Chronic Health Evaluation (APACHE III) scores range from 0 to 299, with higher scores indicating more severe illness.

The APACHE III score was assessed in 455 patients in the intervention group and 459 in the control group.

§Sequential Organ Failure Assessment (SOFA) scores were measured in 5 organ systems (respiratory, cardiovascular, hematologic, gastrointestinal, and renal; the neurologic system was not assessed), with each organ scored from 0 to 4, resulting in an aggregated score that ranges from 0 to 20, with higher scores indicating greater dysfunction.

The SOFA score was not assessed in 1 patient in the control group.

¶The tidal volume was assessed in 445 patients in the intervention group and 443 in the control group.

∥The fraction of inspired oxygen (FiO2) was assessed in 469 patients in the intervention group and 474 in the control group.

**The inspiratory plateau pressure was assessed in 274 patients in the intervention group and 266 in the control group.

††The positive end-expiratory pressure (PEEP) was assessed in 492 patients in the intervention group and 495 in the control group.

‡‡The ratio of the partial pressure of arterial oxygen (Pao2) to FiO2 was assessed in 452 patients in the intervention group and 460 in the control group. The FiO2 value reflects the value that was recorded closest to the time of randomization within the 24 hours before randomization.

§§If an arterial blood gas analysis was not available at randomization, the Pao2:FiO2 could be inferred from the oxygen saturation as measured by pulse oximetry. The imputed Pao2:FiO2 was calculated in 49 patients in the intervention group and 45 patients in the control group.

---

- 約70%が白人
- コントロール群でショックが多い：55.1% vs. 62.2%
- NMB群で登録から割付までの時間が長い：8.2hr vs. 6.8hr
- 全体の中央値は7.6hr (3.7-15.6)
- 原因の60%は肺炎
- P/F 100、FiO2 0.8、PEEP 12
筋弛緩

**NMB群**
- 488 (97.4%) が cisatracurium を投与
- 割付から 1.9 ± 1.4 時間後に投与
- 投与期間：47.8hr (43.8-48.0)
- 状態改善による早期中止：74 (14.8%)

**コントロール群**
- 86 (17.0%) が cisatracurium を投与 (最初の 48 時間)
- 投与量：38mg (14-200)
筋弛緩

投与期間

<table>
<thead>
<tr>
<th></th>
<th>-48hr</th>
<th>48-96hr</th>
<th>&gt;96hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMB群</td>
<td>97.4%</td>
<td>16.0%</td>
<td>12.7%</td>
</tr>
<tr>
<td>コントロール群</td>
<td>17.0%</td>
<td>7.9%</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

![NMB Bar Chart](image-url)
NMB 群
• Deep sedation
• RASS -4,-5 / RSS 5,6 / SAS 1,2

コントロール群
• Light sedation
• RASS 0,-1 / RSS 2,3 / SAS 3,4

### Study Results

<table>
<thead>
<tr>
<th>Study day</th>
<th>Richmond Agitation-Sedation Score</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Intervention: -3.2 ± 7.0 (407)</td>
<td>Control: -2.6 ± 1.8 (406)</td>
</tr>
<tr>
<td>Day 1</td>
<td>Intervention: -4.8 ± 0.8 (395)</td>
<td>Control: -2.7 ± 1.9 (402)</td>
</tr>
<tr>
<td>Day 2</td>
<td>Intervention: -4.6 ± 5.1 (376)</td>
<td>Control: -2.3 ± 2.0 (372)</td>
</tr>
<tr>
<td>Day 3</td>
<td>Intervention: -2.9 ± 2.0 (361)</td>
<td>Control: -2.2 ± 2.0 (349)</td>
</tr>
<tr>
<td>Day 4</td>
<td>Intervention: -2.7 ± 5.6 (341)</td>
<td>Control: -2.0 ± 2.0 (332)</td>
</tr>
<tr>
<td>Day 5</td>
<td>Intervention: -2.2 ± 2.0 (326)</td>
<td>Control: -1.8 ± 2.0 (310)</td>
</tr>
<tr>
<td>Day 6</td>
<td>Intervention: -2.0 ± 2.0 (302)</td>
<td>Control: -1.6 ± 2.0 (291)</td>
</tr>
<tr>
<td>Day 7</td>
<td>Intervention: -1.6 ± 2.1 (280)</td>
<td>Control: -1.5 ± 1.9 (257)</td>
</tr>
</tbody>
</table>
Table S18. Use of adjunctive therapies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Control</th>
<th>Day 0-2 Difference (95% CI)</th>
<th>Intervention</th>
<th>Control</th>
<th>Day 0-28 Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any rescue therapy</td>
<td>93 (18.6)</td>
<td>90 (17.8)</td>
<td>0.7 (-4.0, 5.5)</td>
<td>130 (25.9)</td>
<td>125 (24.8)</td>
<td>1.2 (-4.2, 6.6)</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>68 (13.6)</td>
<td>60 (11.9)</td>
<td>1.7 (-2.4, 5.8)</td>
<td>84 (16.8)</td>
<td>75 (14.9)</td>
<td>1.9 (-2.6, 6.4)</td>
</tr>
<tr>
<td>Inhaled epoprostenol</td>
<td>16 (3.2)</td>
<td>17 (3.4)</td>
<td>-0.2 (-2.4, 2.0)</td>
<td>26 (5.2)</td>
<td>27 (5.3)</td>
<td>-0.2 (-2.9, 2.6)</td>
</tr>
<tr>
<td>Recruitment maneuvers</td>
<td>14 (2.8)</td>
<td>16 (3.2)</td>
<td>-0.4 (-2.5, 1.7)</td>
<td>29 (5.8)</td>
<td>30 (5.9)</td>
<td>-0.2 (-3.1, 2.8)</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>4 (0.8)</td>
<td>12 (2.4)</td>
<td>-1.6 (-3.1, 0.0)</td>
<td>7 (1.4)</td>
<td>17 (3.4)</td>
<td>-2.0 (-3.8, -0.1)</td>
</tr>
<tr>
<td>ECMO</td>
<td>2 (0.4)</td>
<td>3 (0.6)</td>
<td>-0.2 (-1.1, 0.7)</td>
<td>3 (0.6)</td>
<td>10 (2.0)</td>
<td>-1.4 (-2.8, 0.0)</td>
</tr>
</tbody>
</table>

- 腹臥位：15%前後
- リクルートメント手技：5%前後
- ECMO：1%未満
酸素化・人工呼吸器

NMB群

• PEEP: -0.9 (-1.5 to -0.4)
• MV: -0.7 (-1.2 to -0.4)
• FiO2: -0.04 (-0.06 to -0.02)
• Driving pressure: 0.7 (0.0 to 1.3)

P/Fは両群とも差がない
ARDS期間：早期 vs. 晩期
酸素化の改善に差はない
プロトコール遵守率

Table S8. Additional measures of 'on protocol' compliance

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>Intervention (N=501)</th>
<th>Control (N=505)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On target tidal volume * - % (No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>88.2 (n=457)</td>
<td>86.7 (n=428)</td>
<td>1.5 (-2.9, 5.9)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>88.5 (n=425)</td>
<td>85.9 (n=377)</td>
<td>2.5 (-2.1, 7.2)</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>88.0 (n=366)</td>
<td>83.5 (n=303)</td>
<td>4.5 (-0.9, 9.8)</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>83.6 (n=304)</td>
<td>83.6 (n=262)</td>
<td>-0.0 (-6.2, 6.1)</td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>81.7 (n=164)</td>
<td>78.4 (n=148)</td>
<td>3.3 (-5.6, 12.2)</td>
<td></td>
</tr>
<tr>
<td>On target plateau pressure ◊ - % (No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>87.4 (n=382)</td>
<td>83.4 (n=331)</td>
<td>4.1 (-1.2, 9.3)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>89.1 (n=348)</td>
<td>84.8 (n=297)</td>
<td>4.2 (-1.0, 9.5)</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>91.5 (n=282)</td>
<td>86.4 (n=221)</td>
<td>5.1 (-0.5, 10.6)</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>92.8 (n=223)</td>
<td>85.9 (n=184)</td>
<td>7.0 (0.9, 13.0)</td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>92.2 (n=113)</td>
<td>89.2 (n=93)</td>
<td>3.0 (-5.2, 11.1)</td>
<td></td>
</tr>
</tbody>
</table>

- TV < 6.5ml/kg PBW
- Pplat < 30cnH2O
- 80-90%の患者で守られている
水分バランス

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>Intervention (N=501)</th>
<th>Control (N=505)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid balance - mL (No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1136 [-109 - 2487] (n=964)</td>
<td>1310 [65-2716] (n=478)</td>
<td>956 [-208-2315] (n=486)</td>
<td>273 (-26, 572)</td>
</tr>
<tr>
<td>Day 2</td>
<td>327 [-951 - 1456] (n=918)</td>
<td>377 [-786 - 1532] (n=461)</td>
<td>304 [-1029 – 1383] (n=457)</td>
<td>116 (-153, 388)</td>
</tr>
<tr>
<td>Day 3</td>
<td>-242 [-1432 - 728] (n=889)</td>
<td>-355 [-1478 – 700] (n=452)</td>
<td>-169 [-1353 – 810] (n=537)</td>
<td>-81 (-368, 206)</td>
</tr>
<tr>
<td>Day 4</td>
<td>-455 [-1539 - 620] (n=858)</td>
<td>-576 [-1701 – 428] (n=438)</td>
<td>-214 [-1387 – 970] (n=420)</td>
<td>-369 (-623, -116)</td>
</tr>
<tr>
<td>Day 7</td>
<td>-301 [-1359 - 561] (n=7360)</td>
<td>-330 [-1395 – 532] (n=375)</td>
<td>-274 [-1270 – 590] (n=361)</td>
<td>13 (-236, 262)</td>
</tr>
<tr>
<td>Cumulative fluid balance - mL (No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>2712 [611 - 5206] (n=970)</td>
<td>2678 [835 - 5569] (n=482)</td>
<td>2795 [365-4866] (n=488)</td>
<td>360 (-219, 939)</td>
</tr>
<tr>
<td>Day 2</td>
<td>2984 [-110 - 6206] (n=924)</td>
<td>3133 [33 - 6691] (n=463)</td>
<td>2741 [-319 – 5759] (n=461)</td>
<td>445 (-270, 1161)</td>
</tr>
<tr>
<td>Day 3</td>
<td>2260 [-1289 - 6255] (n=897)</td>
<td>2533 [-1074 – 6892] (n=455)</td>
<td>2014 [-1406 – 5768] (n=442)</td>
<td>482 (-362, 1326)</td>
</tr>
<tr>
<td>Day 4</td>
<td>1795 [-2103 - 6182] (n=872)</td>
<td>1804 [-2132 – 5992] (n=442)</td>
<td>1751 [-2083 – 6629] (n=430)</td>
<td>7 (-847, 1006)</td>
</tr>
<tr>
<td>Day 7</td>
<td>198 [-4389 - 5261] (n=778)</td>
<td>168 [-4297 – 5017] (n=395)</td>
<td>231 [-4568 – 5790] (n=383)</td>
<td>-33 (-1173, 1106)</td>
</tr>
</tbody>
</table>

- 両群に差はなし
- Day1,2でプラスバランスだが、その後はマイナスへ
Primary end point

Figure 3. Patients Who Survived to Hospital Discharge and Were Discharged Home during the First 90 Days after Randomization.

The period of hospitalization included transfer to other health care facilities.
サブグループ解析でもほぼ同様の結果
- ARDS重症度（P/F 120）
- 割付までの時間（中央値）
- 登録前NMB使用率での病院の層別化
- 医師による取り下げ率での病院の層別化
- 性別
- 人種
- 民族 P=0.015

図S2. 分子曲線、PaO_2/FI_2 < 120と≥120 mmHg
PaO_2/FI_2は酸素分圧と酸素分量の割合を示し、PaO_2/FI_2はmmHgを示します。
データはKaplan-Meier生存分析から得られ、死亡を Napoleon に定義した（見方方法）。分析分界値は120と≥120 mmHgで、先のサブグループ解析とACURASYS研究で同様に設定しました。治療分与間の相互作用は見られませんでした（p=0.76、見方S9）。
Secondary end points

<table>
<thead>
<tr>
<th>Table 2. End Points.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Primary end point: in-hospital death by day 90 — no. (%)†</td>
</tr>
<tr>
<td>Secondary end points</td>
</tr>
<tr>
<td>In-hospital death by day 28 — no. (%)</td>
</tr>
<tr>
<td>Days free of ventilation at day 28‡</td>
</tr>
<tr>
<td>Days not in ICU at day 28</td>
</tr>
<tr>
<td>Days not in hospital at day 28‡</td>
</tr>
</tbody>
</table>

• 28日死亡率
• 28日でのVFD/IFD/HFD
• SOFA score

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>NMB</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.3 ± 1.6 (488)</td>
<td>2.5 ± 1.6 (496)</td>
</tr>
<tr>
<td>Day 1</td>
<td>2.8 ± 1.5 (468)</td>
<td>2.5 ± 1.5 (464)</td>
</tr>
<tr>
<td>Day 2</td>
<td>2.4 ± 1.5 (458)</td>
<td>2.1 ± 1.6 (442)</td>
</tr>
<tr>
<td>Day 3</td>
<td>2.0 ± 1.5 (434)</td>
<td>1.8 ± 1.5 (445)</td>
</tr>
<tr>
<td>Day 4</td>
<td>1.6 ± 1.5 (417)</td>
<td>1.5 ± 1.5 (386)</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.1 ± 1.3 (321)</td>
<td>1.4 ± 1.4 (297)</td>
</tr>
</tbody>
</table>
### Safety end points

#### In-hospital recall of paralysis

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients (%)</td>
<td>9 (1.8)</td>
<td>10 (2.0)</td>
<td>-0.2 (-1.9 to 1.5)</td>
</tr>
<tr>
<td>Among patients who received neuromuscular blockade — no./total no. (%)</td>
<td>9/487 (1.8)</td>
<td>2/129 (1.6)</td>
<td>0.3 (-2.1 to 2.7)</td>
</tr>
</tbody>
</table>

#### MRC score§

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>46.7±14.4</td>
<td>49.5±12.3</td>
<td>-2.8 (-6.1 to 0.6)</td>
</tr>
<tr>
<td>Day 28</td>
<td>45.7±13.9</td>
<td>49.8±10.6</td>
<td>-4.1 (-9.0 to 0.9)</td>
</tr>
</tbody>
</table>

#### ICU-acquired weakness — no./total no. (%)∥

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>50/122 (41.0)</td>
<td>41/131 (31.3)</td>
<td>-9.7 (-21.5 to 2.1)</td>
</tr>
<tr>
<td>Day 28</td>
<td>22/47 (46.8)</td>
<td>14/51 (27.5)</td>
<td>-19.4 (-38.2 to -0.6)</td>
</tr>
<tr>
<td>Any time through day 28</td>
<td>107/226 (47.3)</td>
<td>89/228 (39.0)</td>
<td>-7.3 (-15.7 to 1.1)</td>
</tr>
</tbody>
</table>

#### Serious adverse events — no. of events**

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>35</td>
<td>22</td>
<td>0.09</td>
</tr>
<tr>
<td>Serious cardiovascular adverse events</td>
<td>14</td>
<td>4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

#### Atrial fibrillation or SVT during ICU stay — no. (%) 

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>101 (20.2)</td>
<td>99 (19.6)</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

#### Barotrauma — no. (%)

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (4.0)</td>
<td>32 (6.3)</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

#### Pneumothorax on days 0 through 2 — no. (%)

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (1.6)</td>
<td>10 (2.0)</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

#### Pneumothorax on days 0 through 7 — no. (%)

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Between-Group Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (2.8)</td>
<td>25 (5.0)</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>
### Safety end points

<table>
<thead>
<tr>
<th>Safety end points</th>
<th>In-hospital recall of paralysis</th>
<th>MRC score§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients (%)</td>
<td>9 (1.8)</td>
<td>46.7±14.4</td>
</tr>
<tr>
<td>Among patients who received neuromuscular blockade — no./total no. (%)</td>
<td>9/487 (1.8)</td>
<td>49.5±12.3</td>
</tr>
</tbody>
</table>

- **MRC score** on Day 7:
  - **Intervention Group**: 46.7±14.4
  - **Control Group**: 49.5±12.3
  - **Between-Group Difference**: −2.8 (−6.1 to 0.6)¶

### In-hospital end points

- **Primary end point**: in-hospital death by day 90 — no. (%)
  - **Intervention Group**: 213 (42.5±2.2)
  - **Control Group**: 216 (42.8±2.2)
  - **Between-Group Difference**: −0.3 (−6.4 to 5.9)

### Secondary end points

- **In-hospital death by day 28 — no. (%)**
  - **Intervention Group**: 184 (36.7)
  - **Control Group**: 187 (37.0)
  - **Between-Group Difference**: −0.3 (−6.3 to 5.7)

- **Days free of ventilation at day 28‡**
  - **Intervention Group**: 9.6±10.4
  - **Control Group**: 9.9±10.9
  - **Between-Group Difference**: −0.3 (−1.7 to 1.0)

- **Days not in ICU at day 28**
  - **Intervention Group**: 9.0±9.4
  - **Control Group**: 9.4±9.8
  - **Between-Group Difference**: −0.4 (−1.6 to 0.8)

- **Days not in hospital at day 28‡**
  - **Intervention Group**: 5.7±7.8
  - **Control Group**: 5.9±8.1
  - **Between-Group Difference**: −0.2 (−1.1 to 0.8)

### Safety end points

- **In-hospital recall of paralysis**
  - **Total no. of patients (%)**
    - **Intervention Group**: 9 (1.8)
    - **Control Group**: 10 (2.0)
  - **Between-Group Difference**: −0.2 (−1.9 to 1.5)

- **Atrial fibrillation or SVT during ICU stay — no. (%)**
  - **Intervention Group**: 101 (20.2)
  - **Control Group**: 99 (19.6)
  - **Between-Group Difference**: 0.6 (−2.1 to 2.7)

- **ICU-acquired weakness — no./total no. (%)**
  - **Day 7**: 50/122 (41.0)
  - **Day 28**: 22/47 (46.8)
  - **Any time through day 28**: 107/226 (47.3)

- **Serious adverse events — no. of events**
  - **Intervention Group**: 35
  - **Control Group**: 22
  - **Between-Group Difference**: 0.09

- **Serious cardiovascular adverse events — no. of events**
  - **Intervention Group**: 14
  - **Control Group**: 4
  - **Between-Group Difference**: 0.02

- **Barotrauma — no. (%)**
  - **Intervention Group**: 20 (4.0)
  - **Control Group**: 32 (6.3)
  - **Between-Group Difference**: 0.12

- **Pneumothorax on days 0 through 2 — no. (%)**
  - **Intervention Group**: 8 (1.6)
  - **Control Group**: 10 (2.0)
  - **Between-Group Difference**: 0.81

- **Pneumothorax on days 0 through 7 — no. (%)**
  - **Intervention Group**: 14 (2.8)
  - **Control Group**: 25 (5.0)
  - **Between-Group Difference**: 0.10

---

*Unless otherwise indicated, plus–minus values are means ±SD. ICU denotes intensive care unit, and SVT supraventricular tachycardia.*

† Included are all deaths that occurred after randomization in any health care facility before discharge home until day 90 of the trial. Patients in a health care facility at day 91 were considered to be alive. The plus–minus values in this category are standard errors.

‡ If in-hospital death occurred before day 29, the days free of ventilation and the days not in the hospital at day 28 were considered to be zero.

§ The Medical Research Council (MRC) scale was used to assess muscle strength in 6 muscle groups on each side of the body, for a total of 12 muscle groups. The score for each muscle group can range from 0 (no movement observed) to 5 (muscle contracts normally against full resistance), with the overall score ranging from 0 to 60.

¶ The between-group difference is the difference in MRC score.

∥ ICU-acquired weakness was defined as an MRC score of less than 48 if all 12 muscle groups were assessed, or a mean muscle-group score of less than 4 when at least 7 of the 12 muscle groups were assessed.

**A list of all adverse events is provided in Table S24 in the Supplementary Appendix. Participants may have had more than 1 adverse event.**
Safety end points

• 両群とも死亡率は高いが、cisatracuriumが関連する死亡は1例のみ
• 金縛りの頻度は低い
• NMB群で6日目までの身体活動度は低い
• MRC/ICU-AWも差はないが、半数以上が週1の筋力評価ができていない
• 心血管イベントはNMB群で多い
• Barotrauma・気胸は両群で変わらず
### Table S21. Outcomes at 3 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L *</td>
<td>0.66 ± 0.41 (n=207)</td>
<td>0.73 ± 0.39 (n=194)</td>
<td>0.0 (-0.1, 0.1)</td>
</tr>
<tr>
<td>Difficulty in a daily activity - no./available records (%)</td>
<td>168/212 (79.2)</td>
<td>154/196 (78.6)</td>
<td>0.7 (-7.3, 8.6)</td>
</tr>
<tr>
<td>Disability Score †</td>
<td>3.3 ± 2.7 (n=212)</td>
<td>3.0 ± 2.7 (n=196)</td>
<td>0.3 (-0.3, 0.8)</td>
</tr>
<tr>
<td>Self-rated Health ‡</td>
<td>3.4 ± 1.1 (n=164)</td>
<td>3.3 ± 1.0 (n=158)</td>
<td>0.1 (-0.1, 0.3)</td>
</tr>
<tr>
<td>Pain Interference §</td>
<td>2.6 ± 1.4 (n=162)</td>
<td>2.6 ± 1.4 (n=157)</td>
<td>0.0 (-0.3, 0.3)</td>
</tr>
<tr>
<td>PTSS - no. (%) ^</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MoCA blind *</td>
<td>22.2 ± 5.2 (n=154)</td>
<td>22.8 ± 4.8 (n=133)</td>
<td>-0.6 (-1.7, 0.6)</td>
</tr>
<tr>
<td>AD8 scores #</td>
<td>3.1 ± 2.8 (n=45)</td>
<td>2.5 ± 2.6 (n=37)</td>
<td>0.6 (-0.6, 1.8)</td>
</tr>
<tr>
<td><strong>Other outcomes - no./available records (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of residence % home</td>
<td>173/212 (81.6)</td>
<td>161/195 (82.6)</td>
<td>-1.0 (-8.4, 6.5)</td>
</tr>
<tr>
<td>Hospital readmission</td>
<td>69/211 (32.7)</td>
<td>63/195 (32.3)</td>
<td>0.4 (-8.7, 9.5)</td>
</tr>
<tr>
<td>ER visit</td>
<td>46/211 (21.8)</td>
<td>32/195 (16.4)</td>
<td>5.4 (-2.2, 13.0)</td>
</tr>
<tr>
<td>Return to work - no./available records (%)</td>
<td>32/212 (15.1)</td>
<td>34/196 (17.3)</td>
<td>-2.3 (-9.4, 4.9)</td>
</tr>
<tr>
<td>Significant change in work duties</td>
<td>77/119 (64.7)</td>
<td>68/107 (63.6)</td>
<td>1.2 (-11.4, 13.7)</td>
</tr>
<tr>
<td><strong>Impact on daily activities - no. (%)</strong></td>
<td>(n=246)</td>
<td>(n=238)</td>
<td></td>
</tr>
<tr>
<td>Eating</td>
<td>45 (18.3)</td>
<td>36 (15.1)</td>
<td>3.2 (-3.5, 9.8)</td>
</tr>
<tr>
<td>Getting in or out of bed</td>
<td>93 (37.8)</td>
<td>84 (35.3)</td>
<td>2.5 (-6.1, 11.1)</td>
</tr>
<tr>
<td>Using the toilet</td>
<td>82 (33.3)</td>
<td>66 (27.7)</td>
<td>5.6 (-2.6, 13.8)</td>
</tr>
<tr>
<td>Preparing a hot meal</td>
<td>67 (27.2)</td>
<td>66 (27.7)</td>
<td>-0.5 (-8.5, 7.5)</td>
</tr>
<tr>
<td>Making phone calls</td>
<td>43 (17.5)</td>
<td>37 (15.5)</td>
<td>1.9 (-4.7, 8.5)</td>
</tr>
<tr>
<td>Taking medications</td>
<td>49 (19.9)</td>
<td>44 (18.5)</td>
<td>1.4 (-5.6, 8.4)</td>
</tr>
<tr>
<td>Managing money</td>
<td>40 (16.3)</td>
<td>46 (19.3)</td>
<td>-3.1 (-9.9, 3.7)</td>
</tr>
<tr>
<td>Shopping for groceries</td>
<td>97 (39.4)</td>
<td>87 (36.6)</td>
<td>2.9 (-5.8, 11.5)</td>
</tr>
<tr>
<td>Stooping, kneeling or crouching</td>
<td>154 (62.6)</td>
<td>158 (66.4)</td>
<td>-3.8 (-12.3, 4.7)</td>
</tr>
<tr>
<td>Lifting/carrying weights &gt;10 pounds</td>
<td>145 (58.9)</td>
<td>139 (58.4)</td>
<td></td>
</tr>
</tbody>
</table>
DISCCUSION
本研究では...

- プロトコールの遵守率が高い
  - コントロール群のNMB使用が最小限
  - 呼吸器設定
  - 輸液方法

- サブグループ解析も同様の結果
  - 重症度
  - Onset time
  - Trial siteをNMB使用の有無での分別
90日死亡率が改善しなかった理由
両群ともHigh PEEPで設定
Moderate-severe ARDSに対するARDSの有用性
JAMA 2010;303:865-73.

NMB自体の効果が薄れた

コントロール群は浅い鎮静レベルで管理
浅鎮静での管理で予後が改善

NMB群は深鎮静の影響で低血圧・徐脈が多い
90日死亡率が改善しなかった理由

・腹臥位管理：15.8% vs. 30% (ACURASYS)
  16時間以上の腹臥位による管理で予後を改善


一般的な割合だが、ACURASYSで腹臥位が多い

発症〜登録までの時間(中央値)
  ：7.6hr vs. 16hr (ACURASYS)

→早期に死亡してしまう症例が含まれた可能性
→早期に改善する予後のいいARDSが含まれた可能性
Rapidly Improving ARDS in Therapeutic Randomized Controlled Trials

• ARDS networkの6研究を用いて2次解析
• riARDS：登録初日で抜管 or P/F >300

6 studies, 4361 patients
✓ 458(10.5%)がriARDS
✓ 予後も良好
  60日死亡率
  ：10.2% vs.26.3%

### TABLE 2 ] Outcomes of Patients With Rapidly Improving ARDS vs ARDS > 1 Day

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rapidly Improving ARDS (n = 265)</th>
<th>ARDS &gt; 1 Day (n = 1,644)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-d mortality</td>
<td>27 (10.2)</td>
<td>433 (26.3)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>27 (24-27)</td>
<td>18 (0-23)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>ICU-free days</td>
<td>24 (21-26)</td>
<td>16 (0-21)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Nonpulmonary organ failure-free days</td>
<td>25 (4-27)</td>
<td>15 (0-25)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Table S10. Day 90 mortality percentage stratified by duration of ARDS prior to randomization

<table>
<thead>
<tr>
<th>ARDS to randomization time</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; median (N=503)</td>
<td>40.5 ± 3.2 (232)</td>
<td>44.6 ± 3.0 (271)</td>
<td>-4.1 (-12.8, 4.5)</td>
<td></td>
</tr>
<tr>
<td>&gt; median (N=503)</td>
<td>44.2 ± 3.0 (269)</td>
<td>40.6 ± 3.2 (234)</td>
<td>3.6 (-5.0, 12.3)</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
<td>-7.8 (-20.0, 4.5)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Limitation

- Exclusion of patients who had prior NMB use = NMB use before enrollment
  → Clinical staff judged NMB to be effective in severe ARDS cases and decided not to use it during the study period.

**Table S11.** Day 90 mortality percentage stratified by hospital tercile for prior NMB use

<table>
<thead>
<tr>
<th>Tercile</th>
<th># hospitals; patients</th>
<th>Exclusion rate</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>16; 443</td>
<td>9.2%</td>
<td>38.1 ± 3.3 (223)</td>
<td>40.0 ± 3.3 (220)</td>
<td>-1.9 (-11.0, 7.2)</td>
</tr>
<tr>
<td>#2</td>
<td>16; 375</td>
<td>25.7%</td>
<td>50.3 ± 3.7 (185)</td>
<td>45.8 ± 3.6 (190)</td>
<td>0.045 (-5.6, 14.6)</td>
</tr>
<tr>
<td>#3</td>
<td>16; 188</td>
<td>61.1%</td>
<td>37.6 ± 5.0 (93)</td>
<td>43.2 ± 5.1 (95)</td>
<td>-5.5 (-19.5, 8.5)</td>
</tr>
</tbody>
</table>

Interaction P-Value: 0.47

Analysis was conducted for hospitals with low exclusion rates.

→ Result was similar to the Primary end point.
Limitation

• 呼吸器との非同調を評価していない
  → NMB使用することで本質的には同調できる

• 医療者は盲検化されていない
  → 短期での筋力評価・活動性評価・合併症の短期的な評価に影響した可能性
CONCLUSION
・Moderate〜severe ARDS (P/F < 150) に対して

・早期にcisatracuriumを持続投与することは

・高PEEP・浅鎮静で管理するのと比べて

・90日死亡率は低下させない
Early Paralytic Agents for ARDS? Yes, No, and Sometimes

Arthur S. Slutsky, C.M., M.D., and Jesús Villar, M.D., Ph.D.

• ACURASYSが広まらない理由
  • 介入群の死亡率が低下する理由が明確でない
  • 2日間の投与で、死亡率が18日目から差が出る
  • VILIやbiotraumaが減るとされるが、確証はなし
  • NMB投与によるICU-AWの懸念

Figure 2. Probability of Survival through Day 90, According to Study Group.
Table 1. Comparisons of the ACURASYS and ROSE Trials.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACURASYS Trial</th>
<th>ROSE Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of centers (location)</td>
<td>20 ICUs (Europe)</td>
<td>48 hospitals (United States)</td>
</tr>
<tr>
<td>No. of patients (intervention group vs. control group)</td>
<td>340 (178 vs. 162)</td>
<td>1006 (501 vs. 505)</td>
</tr>
<tr>
<td>Trial design for group assignment</td>
<td>Double blind</td>
<td>Unblinded</td>
</tr>
<tr>
<td>ARDS definition</td>
<td>American–European consensus</td>
<td>Berlin criteria</td>
</tr>
<tr>
<td>Criteria for moderate-to-severe ARDS</td>
<td>Pa(\text{O}_2):F(\text{I}_2) &lt;150 mm Hg with PEEP (\geq 5) cm of water</td>
<td>Pa(\text{O}_2):F(\text{I}_2) &lt;150 mm Hg with PEEP (\geq 8) cm of water</td>
</tr>
<tr>
<td>Median time from ARDS diagnosis to trial inclusion (IQR) — hr</td>
<td>16 (6–29)</td>
<td>8 (4–16)</td>
</tr>
<tr>
<td>Intervention vs. control strategies</td>
<td>Cisatracurium infusion plus deep sedation</td>
<td>Cisatracurium infusion plus deep sedation vs. light sedation</td>
</tr>
<tr>
<td>Mechanical-ventilation approach</td>
<td>Lung-protective ventilation with low PEEP</td>
<td>Lung-protective ventilation with high PEEP</td>
</tr>
<tr>
<td>Monitoring of patient–ventilator dyssynchrony</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>ICU-acquired paresis and long-term outcomes</td>
<td>No difference between groups</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Pneumothorax more frequent in the control group (11.7% vs. 4%)</td>
<td>Rates of overall barotrauma did not differ between groups</td>
</tr>
</tbody>
</table>

*Shown are comparisons between the ARDS et Curarisation Systematique (ACURASYS) and Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trials, which assessed the use of neuromuscular blocking agents in patients with moderate-to-severe acute respiratory distress syndrome (ARDS). ICU denotes intensive care unit, IQR interquartile range, Pa\(\text{O}_2\):F\(\text{I}_2\) the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and PEEP positive end-expiratory pressure.
Asynchronies during mechanical ventilation are associated with mortality

Intensive Care Med 2015; 41:633–41

• 人工呼吸器中の非同調の割合を調査
• 前向き観察研究
• 50症例、7027hr、8,731,981サイクル
• Asynchrony Index (AI)：10%以上で高頻度

Table 2 Relationship between AI and duration of MV, reintubation, tracheostomy, and ICU and hospital mortality by comparing patients AI ≤ 10 % vs AI > 10 %

<table>
<thead>
<tr>
<th></th>
<th>AI ≤ 10 % (n = 44)</th>
<th>AI &gt; 10 % (n = 6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of MV (days)</td>
<td>6 [5.0; 15.0]</td>
<td>16 [9.7; 20.0]</td>
<td>0.061</td>
</tr>
<tr>
<td>Reintubation</td>
<td>9 (20 %)</td>
<td>0 (0 %)</td>
<td>0.57</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>14 (32 %)</td>
<td>2 (33 %)</td>
<td>0.999</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>6 (14 %)</td>
<td>4 (67 %)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>10 (23 %)</td>
<td>4 (67 %)</td>
<td>0.044*</td>
</tr>
</tbody>
</table>
非同調は、人工呼吸器期間や死亡率を上昇させる。

Reverse trigger
  • Breath stacking → Over distension → VIDD, WOB上昇

Pes/EAdiがないと認識するのは難しい
• ARDSでどのくらい起こるかは不明（3-30%）
• 深鎮静にしていても起こる

ACURASYSのコントロール群は、深鎮静下でもbreath stacking・VILIが起こり、死亡率が悪化したと思われる。
この研究が意味するところ

• Moderate〜severe ARDSにルーティンにNMBは使用しない

• Breath stackingによりVILIを起こしそう、吸気努力が強く経肺圧が高い場合は、NMBを考慮する

• 人工呼吸器との非同調は、思っている以上にアウトカムに影響する

• 画一的なものではなく、個々の状況を鑑みARDSの状態に応じて、治療戦略を考える

• NMBの安全面は示された
私見

• P/F <150 ARDSにルーティンにNMBは使用しない
• 非同調をなくすように呼吸器を調整
• NMBを考慮するとき
  • 吸気努力が強い場合
    → Pes/EAdiをモニタリングしながら
  • レスキューとして
    → Pplatを下げる、酸素化を改善する
• 腹臥位療法を行う場合
  → 事故抜管などの管理面でも
NMB使用するとき

• メリット
  • lung-protective (経肺圧を下げる)、同調性、VILI減少

• デメリット
  • 深鎮静、せん妄、VIDD、ICU-AW、角膜損傷・褥瘡、回路外れによるトラブル

• 早期・短期間の使用にとどめる

• （末梢神経刺激装置でのモニタリング）
• （アミノステロイド系は使用しない）
Infusions of rocuronium and cisatracurium exert different effects on rat diaphragm function

- IMVで管理されているラット
- CisatracuriumとRocuroniumの横隔膜に対する影響
- 24時間持続投与（生食、Rocuro、Cisatra low, high）

![Bar chart showing calpain activity in the diaphragm.](image)

ロクロニウムの投与で横隔膜障害の可能性を示唆
私見

・CisatracuriumとRocuronium問題
・Rocuronium (アミノステロイド系)はICU-AWの可能性があるにしても、生死を分ける状況では致し方ない

・腹臥位・Pes/EAdi・NMBを組み合わせた研究に期待