the Massachusetts, New Hampshire, and Vermont Medical Societies, so the name was changed back to the *New England Journal of Medicine*.

The early pages of the *Journal* contain anecdotes of cases, new treatments of diseases, and reprints of lectures and talks given by eminent physicians in New England and Europe, as well as news of physicians in the area and even local meteorologic summaries and a long treatise in 1837 on the climate of Santa Cruz (now St. Croix).[2] This early archive includes the classic 1846 description by H.J. Bigelow of the first use of ether, "Insensibility during Surgical Operations Produced by Inhalation."[3] One finds everything from "On a New Method of Determining the Quantity of Urea in the Urine"[4] to "The Production and Management of Bees"[5] (both from 1854) and from "Salicylic Acid in Rheumatism"[6] to a grisly treatise on "Hanging as a Fine Art"[7] (both 1876). This unfiltered historical record of American medicine also contains a surprising number of entries in the early 19th century about "alleged malpractice." In the issue of April 13, 1865, the day before Abraham Lincoln was shot, one finds a report about the sudden death of a healthy, robust 19-year-old man. The physicians conscientiously review the difficult details, trying to understand whether this death was because of a congenital ventricular septal defect or rupture of the interventricular septum.[8]

From the first issue of the more recent archive on January 4, 1945, one sees examples of the evolution of modern medicine, such as in a scholarly article on the Waterhouse–Friderichsen syndrome, with attempts to understand the causative agent in this decimating physiological cascade.[9] In the same issue, there is a comprehensive review article on porphyrin metabolism, which begins by noting that the average physician sees the topic as "bewilderingly complex."[10] (Some things do not change.) In 1948, there is the early report with some hope about a terrible disease: "Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist, 4-Aminopteroyl-Glutamic Acid (Aminopterin)" by Sidney Farber et al.[11] The most widely cited review article appears in 1967 in five parts: "Fat Transport in Lipoproteins — An Integrated Approach to Mechanisms and Disorders" by Fredrickson et al.[12] In this era, there are the philosophical insights of Lewis Thomas, published as Notes of a Biology-Watcher, and the international perspective consisted primarily of John Lister's reports called By the London Post. The final volume in the *Journal*'s archive includes the news-making, research-changing report from the Physicians' Health Study on the use of aspirin to prevent myocardial infarction.[13] We hope that readers will find the new digital archive useful and informative.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

1. Warren J. Remarks on angina pectoris. N Engl J Med Surg 1812;1:1-11.
2. Tuckerman J. Observations on the climate, &c. of Santa Cruz. Boston Med Surg J 1837;16:357-64, 373-9, 395-402.
3. Bigelow HJ. Insensibility during surgical operations produced by inhalation. Boston Med Surg J 1846;35:309-17.
4. Draper JW. On a new method of determining the quantity of urea in the urine. Boston Med Surg J 1854;50:49-50.
5. The production and management of bees. Boston Med Surg J 1854;50:15-7.
6. Towle SK. Salicylic acid in acute rheumatism. Boston Med Surg J 1876;94:593-5.
7. Hanging as a fine art. Boston Med Surg J 1876;94:197-8.
8. Jackson JBS. Congenital interventricular opening of the heart in an adult of robust health; or rupture of the septum two months before death? Boston Med Surg J 1865;72:209-11.
9. D'Agati VC, Marangoni BA. The Waterhouse–Friderichsen syndrome. N Engl J Med 1945;232:1-7.
10. Welcker ML. The porphyrins. N Engl J Med 1945;232:11-9.
11. Farber S, Diamond LK, Mercer RD, Sylvester RF Jr, Wolff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). N Engl J Med 1948;238:787-93.
12. Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins — an integrated approach to mechanisms and disorders. N Engl J Med 1967;276:34-44, 94-103, 148-56, 215-25, 273-81.
13. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.

Neuromuscular Blocking Agents in ARDS

Arthur S. Slutsky, M.D.

In this issue of the *Journal*, Papazian and colleagues[1] present intriguing results of their study examining neuromuscular blockade in patients with severe, early acute respiratory distress syndrome (ARDS). The investigators randomly assigned 340 patients to receive the neuromuscular

blocking agent cisatracurium or placebo for a period of 48 hours. Both groups underwent mechanical ventilation according to a lung-protective strategy previously shown to decrease mortality.[2] Both the adjusted 90-day survival rate and time off the ventilator were greater in the cisatracurium group as compared with the placebo group.

ARDS is an inflammatory disease characterized by pulmonary edema, stiff lungs, and hypoxemia.[3] It affects approximately 140,000 patients annually in the United States and is associated with a mortality estimated at over 40%.[4] Despite intense research, there are no specific pharmacologic therapies proven to decrease this mortality.[5] The only confirmed therapy is a lung-protective strategy involving the use of relatively small tidal volumes with limitation of the end-inspiratory lung stretch.[2]

The study by Papazian and coworkers can be viewed as a step back from a developing paradigm in critical care. Over the past decade, reflecting increasing recognition of the iatrogenic consequences of many therapies, there has been a shift toward "less intervention." Lung-protective ventilation is an example of this minimalist philosophy, with a focus on less ventilation to protect the lung from ventilator-induced lung injury, rather than more ventilation to maintain normal blood gas levels. Other examples of the minimalist approach include the administration of fewer transfusions,[6] less bed rest,[7] fewer intubations,[8] and less sedation.[9] Until now, neuromuscular blocking agents have largely fallen under this "less-is-more" strategy. Although neuromuscular blocking agents are used in more than 25% of patients with ARDS, most authorities recommend minimizing their use, largely because of concerns about long-term muscle weakness.

The study by Papazian and colleagues makes us reevaluate this philosophy. Of course, their results need to be replicated, but assuming they are robust, it is interesting to speculate on the possible mechanisms conferring the beneficial effects. The two major causes of death in patients with ARDS are multiorgan failure[10] secondary to infection, sepsis, hemodynamic compromise, or ventilator-induced lung injury[11]; and severe hypoxemia.[10]

Neuromuscular blocking agents such as cisatracurium may affect these risk factors through interrelated mechanisms (Fig. 1). They may have a direct antiinflammatory effect, though this seems unlikely to be the mechanism of death, given the lack of effect on mortality of very potent antiinflammatory agents in previous studies.[5]

Neuromuscular blocking agents could decrease the oxygen consumption of respiratory and other muscles, reducing cardiac output, increasing the mixed venous partial pressure of oxygen, and increasing the partial pressure of arterial oxygen. In addition, ventilation–perfusion relationships may be improved (or worsened), depending on the distribution of lung injury and the effect that regional activation of respiratory muscles has on the distribution of ventilation and perfusion before paralysis. However, improved oxygenation is unlikely to be the major explanation for the positive results of Papazian and coworkers, since gas-exchange measurements were essentially the same in the two groups during the period of administration of the neuromuscular blocking agent.

By paralyzing respiratory muscles, neuromuscular blocking agents may indirectly minimize various manifestations of ventilator-induced lung injury,[12] including "atelectrauma" (injury due to repetitive opening and closing of lung units), barotrauma (gross air leaks), volutrauma (increased alveolar-capillary permeability due to overdistention of the lung), and biotrauma (release of mediators in the lung and translocation of these mediators into the systemic circulation). By preventing active expiration, neuromuscular blocking agents may allow positive end-expiratory pressures to be better controlled, resulting in decreased "atelectrauma." Optimal implementation of mechanical ventilation can be complex, owing to difficulty in synchronizing the breaths delivered by the ventilator and the patient's inherent respiratory drive. Pharmacologically paralyzing the patient and administering "controlled ventilation" prevents patient–ventilator dyssynchrony, including autotriggering, stops the patient from "fighting" the ventilator, and could minimize the risk of volutrauma and barotrauma.

The potentially decreased oxygen consumption after administration of neuromuscular blocking agents could decrease the ventilatory demand (and thus the risk of ventilator-induced lung injury due to a higher minute ventilation).[13] The use of blocking agents would also minimize the increase in minute ventilation due to the height-

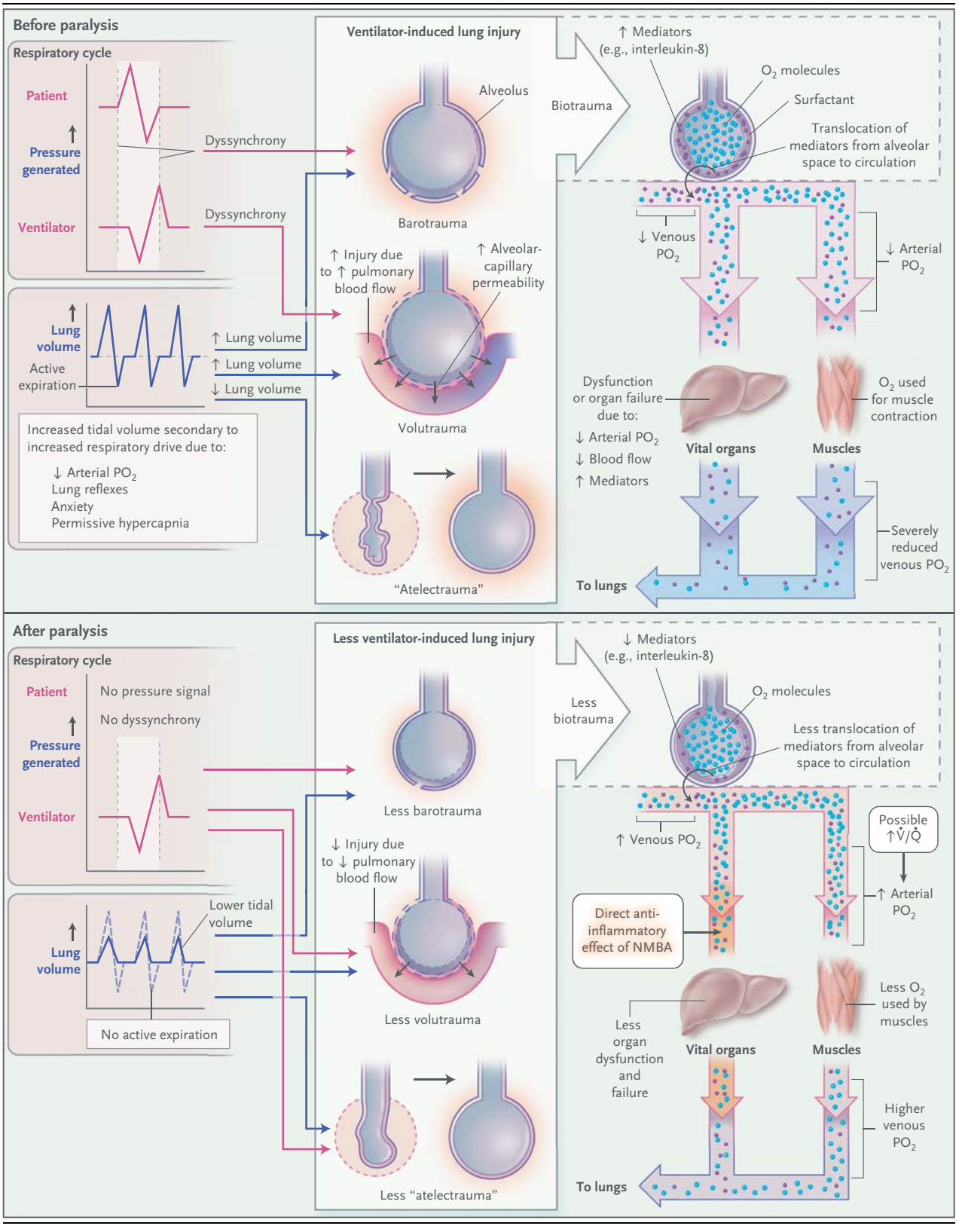

Figure 1 (facing page). Possible Mechanisms by Which Neuromuscular Blocking Agents (NMBAs) Might Lead to Improved Survival in Patients with the Acute Respiratory Distress Syndrome (ARDS).

Respiratory physiological features of a patient with ARDS are illustrated before (top) and after (bottom) paralysis induced with the use of NMBAs. Before paralysis, increased respiratory drive from multiple causes can lead to increased tidal volumes, active exhalation, and patient–ventilator asynchrony, all of which can potentially worsen various forms of ventilator-induced lung injury. In addition, muscle activation may divert blood flow away from vital organs and lead to a lower mixed venous partial pressure of oxygen (PO_2). These mechanisms may lead to increased organ dysfunction and ultimately death. After paralysis, the administered NMBAs prevent patient-initiated generation of high and low lung volumes and also prevent active expiration, allowing for better lung-protective ventilation and less ventilator-induced lung injury. Ventilator-induced lung injury may also be lessened by less pulmonary blood flow due to decreased oxygen consumption. NMBAs may also indirectly improve arterial oxygenation by decreasing blood flow to active muscle groups (because of decreased oxygen requirements) and by improving the distribution of ventilation relative to perfusion ($\dot{V}/\dot{Q}$). (Arterial PO_2 may also be decreased through this mechanism if $\dot{V}/\dot{Q}$ is worsened.) Finally, NMBAs may have a direct antiinflammatory effect. The relative effect of NMBAs on many of these mechanisms depends on the state of muscle activation before paralysis, which is dependent on a number of factors, including the patient's level of sedation.

ened respiratory drive associated with permissive hypercapnia, an approach often used as part of lung-protective strategies. Finally, the potential decrease in cardiac output (and decreased pulmonary blood flow) associated with reduced oxygen consumption could also mitigate ventilator-induced lung injury.[14]

These respiratory mechanisms could lead to a decrease in the release of pulmonary and systemic mediators (i.e., decreased biotrauma) and hence could minimize the development of organ dysfunction.[11] This hypothesis is in keeping with a previous study showing that administration of cisatracurium over a 48-hour period was associated with decreasing levels of interleukin-8 in bronchoalveolar-lavage fluid and decreasing levels of interleukin-6 and interleukin-8 in serum.[15] Ongoing cytokine release, related to the biotrauma mechanism, can occur for many days and might explain the time lag in the beneficial effects of neuromuscular blocking agents. In the study by Papazian and colleagues, the Kaplan–Meier curves for the cisatracurium group and the placebo group started to separate only after approximately 12 days regarding the probability of breathing without assistance and only after approximately 18 days regarding mortality, even though the study intervention was limited to the first 48 hours. Biotrauma has also been suggested to explain the decrease in mortality of the Acute Respiratory Distress Syndrome Network (ARDSNet) study involving the lung-protective strategy.[2]

It is unclear from the present study which of these (or other) mechanisms might explain the benefit from neuromuscular blockade. Variables commonly used to assess the propensity for ventilator-induced lung injury (e.g., plateau pressures and tidal volumes) did not differ significantly between the cisatracurium group and the placebo group, a result that argues against an effect on ventilator-induced lung injury as the major mechanism. Nonetheless, significantly more patients in the placebo group than in the cisatracurium group received open-label cisatracurium, presumably because they had a plateau pressure of more than 32 cm of water and were thus at greater risk for ventilator-induced lung injury. Most importantly, the placebo group had a significantly higher incidence of barotrauma, suggesting that abrogation of ventilator-induced lung injury may have been central to the beneficial effects.

This study raises many unanswered questions in addition to those concerning putative mechanisms of action. What is the optimal duration of use of neuromuscular blocking agents? Is the observed benefit specific to cisatracurium or shared within the drug class? Would very heavy sedation produce results similar to those reported? Why does the beneficial effect appear to be present only in patients with more severe hypoxemia? The answers to these and other questions will ultimately determine whether, how, and when neuromuscular blocking agents are used to improve the outcomes of patients with ARDS.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Keenan Research Center at the Li Ka Shing Knowledge Institute of St. Michael's Hospital, the Interdepartmental Division of Critical Care Medicine, and the Department of Medicine, University of Toronto — all in Toronto.

1. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
2. 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. N Engl J Med 2000;342:1301-8.
3. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-49.
4. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685-93.
5. Raghavendran K, Pryhuber GS, Chess PR, Davidson BA, Knight PR, Notter RH. Pharmacotherapy of acute lung injury and acute respiratory distress syndrome. Curr Med Chem 2008;15:1911-24.
6. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409-17. [Erratum, N Engl J Med 1999;340:1056.]
7. Kress JP. Clinical trials of early mobilization of critically ill patients. Crit Care Med 2009;37:Suppl:S442-S447.
8. Hill NS, Brennan J, Garpestad E, Nava S. Noninvasive ventilation in acute respiratory failure. Crit Care Med 2007;35:2402-7.
9. Wunsch H, Kress JP. A new era for sedation in ICU patients. JAMA 2009;301:542-4.
10. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and timing of death in patients with ARDS. Chest 2005;128:525-32.
11. Slutsky AS, Tremblay LN. Multiple system organ failure: is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 1998;157:1721-5.
12. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 2006;32:24-33.
13. Marini JJ. Early phase of lung-protective ventilation: a place for paralytics? Crit Care Med 2006;34:2851-3.
14. Broccard AF, Hotchkiss JR, Kuwayama N, et al. Consequences of vascular flow on lung injury induced by mechanical ventilation. Am J Respir Crit Care Med 1998;157:1935-42.
15. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006;34:2749-57.

From Palliation to Targeted Therapy in Myelofibrosis

Alessandro M. Vannucchi, M.D.

Myelofibrosis is a very debilitating chronic myeloproliferative neoplasm.[1] It may be primary or develop late in the course of essential thrombocythemia or polycythemia vera, the two most common and benign myeloproliferative neoplasms. Patients with myelofibrosis have shortened survival and a reduced quality of life. The current treatment is palliative and aimed at alleviating symptoms due to splenomegaly, controlling myeloproliferation, and improving anemia and other cytopenias.

In this issue of the *Journal*, Verstovsek et al. report on the results of a phase 1–2 trial of an oral Janus kinase 1 (JAK1) and Janus kinase 2 (JAK2) inhibitor, INCB018424, in advanced myelofibrosis.[2] The majority of the patients who received INCB018424 had prompt and durable improvement in constitutional symptoms and overall performance status. In more than half the patients, the size of the enlarged spleen was reduced by at least 50%, with a reduction of abdominal discomfort and gain in body weight. However, only 14% of the patients with anemia became transfusion-independent, and new-onset anemia developed in a similar proportion of patients. Thus, the results of this trial point to JAK1 and JAK2 inhibition as a new therapeutic intervention associated with meaningful clinical benefits in myelofibrosis. It is hoped that the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT) trials, two ongoing phase 3 studies involving either patients receiving placebo (COMFORT-I; ClinicalTrials.gov number, NCT00952289) or a control group of patients receiving "best-available therapy" (COMFORT-II; NCT00934544), will strengthen our enthusiasm. Furthermore, according to a preliminary report of a phase 2 trial (Study to Determine the Safety and Efficacy of INCB018424 in Patients with Polycythemia Vera or Essential Thrombocythemia; NCT00726232), the drug also could have considerable efficacy in advanced polycythemia vera or essential thrombocythemia that is refractory to hydroxyurea.[3]

Clinical development of JAK inhibitors for myeloproliferative neoplasms closely followed the discovery of a V617F point mutation in the *JAK2* gene in more than 90% of patients with polycythemia vera and 60% of patients with primary myelofibrosis or essential thrombocythemia.[4] The mutation results in constitutive kinase activity of JAK2, a member of a family of receptor-associated tyrosine kinases that transduce signals originating from numerous cytokine receptors (Fig. 1).[5] The same spectrum of signaling abnormalities and clinical phenotypes may be attributed

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators*

ABSTRACT

BACKGROUND

In patients undergoing mechanical ventilation for the acute respiratory distress syndrome (ARDS), neuromuscular blocking agents may improve oxygenation and decrease ventilator-induced lung injury but may also cause muscle weakness. We evaluated clinical outcomes after 2 days of therapy with neuromuscular blocking agents in patients with early, severe ARDS.

METHODS

In this multicenter, double-blind trial, 340 patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (178 patients) or placebo (162 patients). Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of less than 150, with a positive end-expiratory pressure of 5 cm or more of water and a tidal volume of 6 to 8 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died either before hospital discharge or within 90 days after study enrollment (i.e., the 90-day in-hospital mortality rate), adjusted for predefined covariates and baseline differences between groups with the use of a Cox model.

RESULTS

The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for both the baseline PaO_2:FIO_2 and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups.

CONCLUSIONS

In patients with severe ARDS, early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness. (Funded by Assistance Publique–Hôpitaux de Marseille and the Programme Hospitalier de Recherche Clinique Régional 2004-26 of the French Ministry of Health; ClinicalTrials.gov number, NCT00299650.)

From Assistance Publique–Hôpitaux de Marseille Unité de Recherche sur les Maladies Infectieuses et Tropicales Émergentes (URMITE), Centre National de la Recherche Scientifique–Unité Mixte de Recherche (CNRS-UMR) 6236 (L.P., J.-M.F., A.R.) and Faculté de Médecine (A.L.), Université de la Méditerranée Aix–Marseille II; Hôpital Sainte-Marguerite (C.P.-R.); Assistance Publique–Hôpitaux de Marseille (G. Perrin); Hôpital Ambroise Paré (J.-M.S.); and Centre d'Investigations Cliniques, Assistance Publique–Hôpitaux de Marseille, INSERM 9502 (S.M.) — all in Marseille; Hôpital Pontchaillou, Rennes (A.G.); Hôpital Saint Eloi, Montpellier (S.J.); Hôpital Font-Pré, Toulon (J.-M.A.); Hôpital Jean Minjoz, Besançon (D.P.); Hôpital Hôtel-Dieu, Clermont-Ferrand (J.-M.C.); Centre Hospitalier, Avignon (P.C.); Hôpital Caremeau, Nîmes (J.-Y.L.); Hôpital de la Croix-Rousse, Lyon (C.G.); and Hôpital de Cavale Blanche, Brest (G. Prat) — all in France. Address reprint requests to Dr. Papazian at Service de Réanimation Médicale, Hôpital Nord, Chemin des Bourrely, 13009 Marseille, France, or at laurent.papazian@ap-hm.fr.

*The ARDS et Curarisation Systematique (ACURASYS) study investigators are listed in the Appendix.

N Engl J Med 2010;363:1107-16.

The acute respiratory distress syndrome (ARDS) is characterized by hypoxemic respiratory failure; it affects both medical and surgical patients.[1] Despite rigorous physiological management,[2] in most studies, ARDS has been fatal in 40 to 60% of patients.[3-7]

Neuromuscular blocking agents are used in a large but highly variable proportion of patients with ARDS.[8-12] Current guidelines indicate that neuromuscular blocking agents are appropriate for facilitating mechanical ventilation when sedation alone is inadequate, most notably in patients with severe gas-exchange impairments.[10] In a four-center randomized, controlled trial of gas exchange in 56 patients with ARDS,[13] infusion of a neuromuscular blocking agent for a period of 48 hours was associated with improved oxygenation and a trend toward lower mortality in the intensive care unit (ICU) (46%, vs. 71% among patients who did not receive a blocking agent; P=0.06). However, this study was not designed or powered to evaluate mortality. Thus, the benefits and risks of adjunctive therapy with neuromuscular blocking agents in patients with ARDS who were receiving lung-protective mechanical ventilation[14] require further evaluation.

We conducted a multicenter, randomized, placebo-controlled, double-blind trial to determine whether a short period of treatment with the neuromuscular blocking agent cisatracurium besylate early in the course of severe ARDS would improve clinical outcomes.

Methods

Patients

Patients were enrolled from March 2006 through March 2008 at 20 ICUs in France (see the Appendix). Eligibility criteria were the receipt of endotracheal mechanical ventilation for acute hypoxemic respiratory failure and the presence of all of the following conditions for a period of no longer than 48 hours: ratio of the partial pressure of arterial oxygen (PaO_2, measured in millimeters of mercury) to the fraction of inspired oxygen (FIO_2, which is unitless) of less than 150 with the ventilator set to deliver a positive end-expiratory pressure of 5 cm of water or higher and a tidal volume of 6 to 8 ml per kilogram of predicted body weight, and bilateral pulmonary infiltrates that were consistent with edema. An additional eligibility criterion was the absence of clinical evidence of left atrial hypertension — that is, a pulmonary-capillary wedge pressure, if available, of less than 18 mm Hg. If the pulmonary-capillary wedge pressure was not available, echocardiography was performed if the patient had a history of, or risk factors for, ischemic heart disease or had crackles on auscultation. Exclusion criteria are listed in Figure 1.

The trial was monitored by an independent data and safety monitoring board. Randomization and blinding regarding the study-group assignments were performed according to Consolidated Standards for the Reporting of Trials (CONSORT) guidelines, as indicated in the Supplementary Appendix (available with the full text of this article at NEJM.org). The study protocol and statistical analysis plan (also available at NEJM.org) were approved for all centers by the ethics committee of the Marseille University Hospital (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale), according to French law. The study was conducted in accordance with the protocol and statistical analysis plan. Written informed consent was obtained from the patients or their proxies.

Study Treatment

Cisatracurium besylate (150-mg formulation, GlaxoSmithKline) and placebo were prepared in identical separate 30-ml vials for intravenous infusion. Peripheral-nerve stimulators were not permitted. The Ramsay sedation scale was used to adapt sedative requirements. The scale assigns the conscious state a score of 1 (anxious, agitated, or restless) to 6 (no response on glabellar tap). Once the assigned Ramsay sedation score was 6 and the ventilator settings were adjusted (Table 1), a 3-ml rapid intravenous infusion of 15 mg of cisatracurium besylate or placebo was administered, followed by a continuous infusion of 37.5 mg per hour for 48 hours. This regimen was based on the results of two studies of a total of 92 patients monitored for paralysis.[13,15]

Ventilation and Weaning Protocol

The volume assist–control mode of ventilation was used, with a tidal volume of 6 to 8 ml per kilogram of predicted body weight (Table 1). The goal was a saturation of peripheral blood oxygen (SpO_2) as measured by means of pulse oximetry of 88 to 95% or a PaO_2 of 55 to 80 mm Hg. To achieve this goal, FIO_2 and the positive end-expiratory pres-

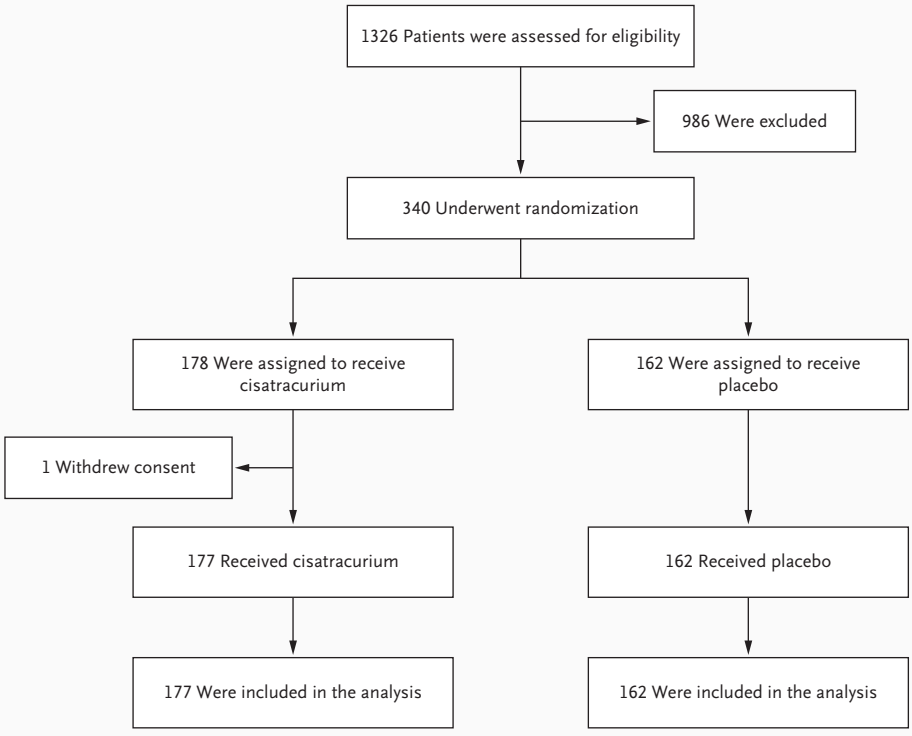

Figure 1. Randomization and Follow-up of the Patients, According to Study Group.

For the 986 patients who were assessed for eligibility but excluded, the reasons for exclusion were as follows: age younger than 18 years (19 patients, 1.9%), lack of consent (185 patients, 18.8%), continuous infusion of a neuromuscular blocking agent at enrollment (42 patients, 4.3%), known pregnancy (19 patients, 1.9%), enrollment in another trial within the previous 30 days, (57 patients, 5.8%), increased intracranial pressure (18 patients, 1.8%), severe chronic respiratory disease requiring long-term oxygen therapy or mechanical ventilation at home (95 patients, 9.6%), actual body weight exceeding 1 kg per centimeter of height, (20 patients, 2.0%), severe chronic liver disease (Child–Pugh class C) (82 patients, 8.3%), bone marrow transplantation or chemotherapy-induced neutropenia (97 patients, 9.8%), pneumothorax (18 patients, 1.8%), expected duration of mechanical ventilation of less than 48 hours (15 patients, 1.5%), decision to withhold life-sustaining treatment (168 patients, 17.0%), other reason (103 patients, 10.4%), and time window missed (48 patients, 4.9%).

sure were adjusted as in the Prospective, Randomized, Multi-Center Trial of 12 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARMA).[14]

An open-label, rapid, intravenous injection of 20 mg of cisatracurium was allowed in both groups if the end-inspiratory plateau pressure remained greater than 32 cm of water for at least 10 minutes despite the administration of increasing doses of sedatives and decreasing tidal volume and positive end-expiratory pressure (if tolerated). If this rapid, intravenous injection resulted in a decrease of the end-inspiratory plateau pressure by less than 2 cm of water, a second injection of 20 mg of cisatracurium was allowed. If after the injection, the end-inspiratory plateau pressure did not decrease or decreased by less than 2 cm of water, cisatracurium was not administered again during the following 24-hour period.

ORGAN OR SYSTEM FAILURE

Patients were monitored daily for 28 days for signs of failure of nonpulmonary organs or systems.[14] Circulatory failure was defined as systolic blood pressure of 90 mm Hg or less or the need for vasopressor therapy. Coagulation failure was defined as a platelet count of 80,000 or less per cubic millimeter. Hepatic failure was defined as a serum bilirubin level of 2 mg per deciliter (34 μmol per liter) or higher. Renal failure was defined as a serum creatinine level of 2 mg per deciliter (177 μmol

Table 1. Summary of the Ventilation Procedure.*

Variable
Ventilator mode: volume assist–control
Initial tidal volume: 6–8 ml/kg of predicted body weight
Plateau pressure: ≤32 cm of water
Oxygenation goal: PaO_2 of 55–80 mm Hg or SpO_2 of 88–95%
Permitted combinations of FiO_2 and PEEP, respectively (cm of water): 0.3 and 5, 0.4 and 5, 0.4 and 8, 0.5 and 8, 0.5 and 10, 0.6 and 10, 0.7 and 10, 0.7 and 12, 0.7 and 14, 0.8 and 14, 0.9 and 14, 0.9 and 16, 0.9 and 18, 1.0 and 18, 1.0 and 20, 1.0 and 22, and 1.0 and 24
pH goal: 7.20–7.45
Procedure when oxygenation goal not achieved despite adjustments to FiO_2 and PEEP: use inhaled nitric oxide, almitrine mesylate, prone positioning, or any combination thereof
Procedure when plateau pressure is >32 cm of water for at least 10 min (in the following order, as needed): increase sedation, reduce tidal volume to 4 ml/kg, decrease PEEP by decrements of 2 cm of water, and perform injection of cisatracurium in a bolus of 20 mg (not to be given again if plateau pressure decreased by <2 cm of water because further doses would probably be futile, but permitted if the drug had its intended effect)
Procedure to correct hypercapnia when pH is <7.20 (in the following order, as needed): connect Y-piece directly to endotracheal tube, increase respiratory rate to a maximum of 35 cycles per min, and increase tidal volume to a maximum of 8 ml/kg
Weaning attempt: starting on day 3, if FiO_2 ≤0.6
Goals during weaning procedure: SpO_2 ≥88% and respiratory rate 26–35 cycles per min
Weaning procedure: decrease PEEP over 20–30 min to 5 cm of water
Pressure-support ventilation levels used during weaning procedure: 20, 15, 10, and 5 cm of water
If weaning procedure fails at a pressure-support ventilation level of 20 cm of water, switch to volume assist–control mode of ventilation
After at least 2 hr of successful pressure-support ventilation at a level of 5 cm of water, disconnect patient from the ventilator

* FiO_2 denotes fraction of inspired oxygen, PaO_2 partial pressure of arterial oxygen, PEEP positive end-expiratory pressure, and SpO_2 saturation of peripheral blood oxygen, as measured by means of pulse oximetry.

per liter) or higher. The number of days without organ or system failure was calculated by subtracting the number of days with organ failure from 28 days or from the number of days until death, if death occurred before day 28. Organs and systems were considered to be free of failure after hospital discharge. There was no recommendation regarding volume-resuscitation goals.

DATA COLLECTION

During the 24-hour period before randomization, we recorded data on demographic characteristics, physiological variables, relevant interventions performed in the ICU, radiographic findings, coexisting conditions, and medications. Data on ventilator settings, physiological variables, radiographic findings, and relevant therapeutic interventions were also recorded just before starting the study-drug infusion and again at 24, 48, 72, and 96 hours. Physiological variables were also measured daily between 6 a.m. and 10 a.m. until day 90 or until hospital discharge of a patient who could breath spontaneously.

Opioid doses were converted to morphine equivalents. The equivalencies were as follows: 0.01 mg of sufentanil=10 mg of morphine=0.1 mg of fentanyl=0.1 mg of remifentanil.[16]

Barotrauma was defined as newly developed pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele larger than 2 cm in diameter. Muscle strength was evaluated with the use of the Medical Research Council (MRC) scale, a previously validated scale that assesses three muscle groups in each arm and leg. The score for each muscle group can range from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60.[17] The definition of ICU-acquired paresis was an MRC score of less than 48.[17]

STUDY OUTCOMES

Primary Outcome

The primary outcome was the proportion of patients who died before hospital discharge and within 90 days after study enrollment (the 90-day mortality). Patients who were outside the hospital (including those in other types of health care facilities) and who were able to breathe spontaneously at day 90 were considered to have been discharged home. Because we anticipated that there would be an imbalance in at least one key risk factor at baseline, the primary outcome was derived from a Cox regression model in which we adjusted for such imbalance. We also report the crude mortality at day 90.

Secondary Outcomes

Secondary outcomes were the day-28 mortality, the numbers of days outside the ICU between day 1 and day 28 and between day 1 and day 90, the number of days without organ or system failure between day 1 and day 28, the rate of barotrauma, the rate of ICU-acquired paresis, the MRC scores on day 28 and at the time of ICU discharge, and the numbers of ventilator-free days (days since successful weaning from mechanical ventilation) between day 1 and day 28 and between day 1 and day 90. It was required that the patient breathe spontaneously,

without the aid of a ventilator, for a period of at least 48 hours for weaning from the ventilator to be considered successful. The number of ventilator-free days was considered to be zero for patients who were weaned from mechanical ventilation but who died before day 28 or day 90.[18]

STATISTICAL ANALYSIS

Assumptions for the sample-size calculation were based on our previous studies[13,15] that used the same inclusion criteria and on the European epidemiologic study Acute Lung Injury Verification (ALIVE).[4] Assuming a 50% mortality at 90 days in the placebo group, we calculated that 340 patients would need to be enrolled to detect a 15% absolute reduction in the 90-day mortality in the cisatracurium group as compared with the placebo group, with 80% statistical power and a two-sided alpha value of 0.05. No interim analysis was performed.

We assessed the differences between the groups using Student's t-test, the Wilcoxon test, the chi-square test, or Fisher's exact test, as appropriate. All reported P values are two-sided and have not been adjusted for multiple comparisons. Kaplan–Meier curves were plotted to assess the time from enrollment to death and the time to disconnection from the ventilator for a period of at least 48 hours.

The primary analysis consisted of evaluating the effect of cisatracurium on the primary outcome (i.e., 90-day mortality), with adjustment by means of a Cox multivariate proportional-hazards model that included two predefined covariates: the baseline Simplified Acute Physiology Score (SAPS) II and the baseline plateau pressure.[19] SAPS II is calculated from 12 physiological measurements during a 24-hour period, information about previous health status, and some information obtained at admission. This score ranges from 0 to 163, with higher scores indicating more severe disease. We planned to include all the variables for which there was an imbalance between the two groups at baseline, but the only imbalanced variable was the PaO_2:FIO_2 ratio. Therefore, we also conducted an analysis based on the baseline PaO_2:FIO_2 ratio, in which the two thirds of patients with a ratio below 120 (indicating hypoxemia) were compared with the third with a higher ratio. A total of 12 secondary analyses of prespecified outcomes were performed, and results of 9 of these are reported. Only one post hoc analysis was conducted; the results are reported.

RESULTS

BASELINE CHARACTERISTICS

We enrolled 340 patients, of whom 178 were randomly assigned to cisatracurium and 162 to placebo. We excluded 986 patients (Fig. 1). One patient in the cisatracurium group withdrew consent before treatment was started, and data for this patient were therefore not included in the analysis. The median time from the diagnosis of ARDS to study inclusion was 16 hours (interquartile range, 6 to 29) in the study population and did not differ significantly between the cisatracurium group (median, 18 hours; interquartile range, 6 to 31) and the placebo group (median, 15 hours; interquartile range, 7 to 27; P=0.45). The median time from initiation of mechanical ventilation to study inclusion did not differ significantly between the cisatracurium group (22 hours; interquartile range, 9 to 41) and the placebo group (21 hours; interquartile range, 10 to 42; P=0.91). The only significant difference between the two groups at baseline was a lower mean PaO_2:FIO_2 value in the cisatracurium group (P=0.03) (Table 2, and Table 1 in the Supplementary Appendix).

OUTCOMES

Primary Outcome

The Cox regression model yielded a hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, of 0.68 (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for the baseline PaO_2:FIO_2, SAPS II, and plateau pressure (Fig. 2). The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08).

Secondary Prespecified Outcomes

The beneficial effect of cisatracurium on the 90-day survival rate was confined to the two thirds of patients presenting with a PaO_2:FIO_2 ratio of less than 120. Among these patients, the 90-day mortality was 30.8% in the cisatracurium group and 44.6% in the control group (P=0.04) (Fig. 2 in the Supplementary Appendix). The absolute difference in 28-day mortality (mortality in the cisatracurium group minus mortality in the placebo group) was −9.6 percentage points (95% CI, −19.2 to −0.2; P=0.05) (Table 3).

The cisatracurium group had significantly more ventilator-free days than the placebo group during

Table 2. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic†	Cisatracurium (N=177)	Placebo N=162)	P Value
Age — yr	58±16	58±15	0.70
Tidal volume — ml/kg of predicted body weight	6.55±1.12	6.48±0.92	0.52
Minute ventilation — liters/min	10.0±2.5	10.1±2.2	0.83
PEEP applied — cm of water	9.2±3.2	9.2±3.5	0.87
Plateau pressure — cm of water	25.0±5.1	24.4±4.7	0.32
Respiratory-system compliance — ml/cm of water	31.5±11.6	31.9±10.7	0.71
FIO_2	0.79±0.19	0.77±0.20	0.33
PaO_2:FIO_2‡	106±36	115±41	0.03
pH	7.31±0.10	7.32±0.10	0.11
PaO_2 — mm Hg	80±24	85±28	0.09
$PaCO_2$ — mm Hg	47±11	47±11	0.62
Prone position or inhaled nitric oxide or almitrine mesylate — no. (%)	33 (18.6)	23 (14.2)	0.31
SAPS II§	50±16	47±14	0.15
Nonfatal condition according to McCabe–Jackson score — no. (%)¶	133 (75.1)	125 (77.2)	0.66
Main reason for ICU admission — no. (%)			
Medical	129 (72.9)	113 (69.8)	0.52
Surgical, emergency	27 (15.3)	31 (19.1)	0.34
Surgical, scheduled	21 (11.9)	18 (11.1)	0.83
Corticosteroids for septic shock — no. (%)	70 (39.5)	73 (45.1)	0.30
Direct lung injury — no. (%)	142 (80.2)	123 (75.9)	0.34

* Plus–minus values are means ±SD. FIO_2 denotes fraction of inspired oxygen, ICU intensive care unit, $PaCO_2$ partial pressure of arterial carbon dioxide, PEEP positive end-expiratory pressure, and SpO_2 saturation of peripheral oxygen as measured by means of pulse oximetry.
† All variables listed except age, nonfatal condition according to McCabe–Jackson score, and main reason for ICU admission were inclusion criteria.
‡ Partial pressure of arterial oxygen (PaO_2) was measured in millimeters of mercury.
§ The Simplified Acute Physiology Score (SAPS) II is calculated from 12 physiological measurements during a 24-hour period, information about previous health status, and some information obtained at admission. Scores can range from 0 to 163, with higher scores indicating more severe disease.
¶ Possible McCabe–Jackson scores for medical condition are 1 (nonfatal), 2 (ultimately fatal), and 3 (fatal).

the first 28 and 90 days (Table 3, and Fig. 3 in the Supplementary Appendix). The Cox regression model yielded an adjusted hazard ratio for weaning from mechanical ventilation by day 90, in the cisatracurium group as compared with the placebo group, of 1.41 (95% CI, 1.08 to 1.83; P=0.01). The cisatracurium group had more days free of failure of organs, other than the lungs, during the first 28 days (15.8±9.9 days, vs. 12.2±11.1 days in the placebo group; P=0.01). There were nearly significant between-group differences in the numbers of days without coagulation abnormalities, hepatic failure, and renal failure (Table 3). No patient required dialysis after hospital discharge during the first 28 days. Significantly more days were spent outside the ICU between day 1 and day 90 in the cisatracurium group.

Pneumothorax occurred in a larger proportion of patients in the placebo group (11.7%, vs. 4.0% in the cisatracurium group; P=0.01) and tended to develop earlier in the placebo group (Fig. 4 in the Supplementary Appendix). During the 48-hour period of study-drug infusion, pneumothorax occurred in one patient (0.6%) in the cisatracurium group as compared with eight patients (4.9%) in the placebo group (P=0.03). The plateau pressures and minute ventilations for the nine patients are presented in Table 5 in the Supplementary Appendix. Before the development of pneumothorax, none of these patients had an elevated plateau pressure necessitating changes in the mechanical-ventilation settings, changes in the sedation regimen, or open-label administration of cisatracurium.

The incidence of ICU-acquired paresis, as evaluated on the basis of the MRC score on day 28 or at the time of ICU discharge, did not differ significantly between the two groups (Table 3).

Secondary Post Hoc Outcome

Corticosteroids were used during the ICU stay in 189 patients. There was no significant effect of cisatracurium use on the 90-day mortality in the subgroup of patients given corticosteroids (Fig. 6 in the Supplementary Appendix).

VENTILATOR SETTINGS AND LUNG FUNCTION

Ventilator settings and lung-function variables during the first week are given in Table 7 in the Supplementary Appendix. On day 7, the PaO_2:FIO_2 ratio was higher, and the $PaCO_2$ value lower, in the cisatracurium group than in the placebo group.

COINTERVENTIONS

During the ICU stay, there were no significant between-group differences in the incidence of cointerventions. A total of 42% of patients in the cisatracurium group and 48% in the placebo group were treated with the use of prone positioning, inhaled nitric oxide, intravenous almitrine mesylate, or a combination of these (Table 8 in the Supplementary Appendix). The criteria for using these interventions were the same in the two groups.

Open-label cisatracurium was given more frequently in the placebo group than in the cisatracurium group during the first 48 hours after enrollment. However, the two groups did not differ significantly with respect to the number of patients given at least one open-label cisatracurium bolus during the entire ICU stay after enrollment (Table 8 in the Supplementary Appendix). The required dose of sedatives or analgesics was similar in the two groups during the first week of the study (Table 9 in the Supplementary Appendix).

SAFETY

Bradycardia developed during the cisatracurium infusion in one patient. No other side effects were reported.

DISCUSSION

Treatment with the neuromuscular blocking agent cisatracurium for 48 hours early in the course of severe ARDS improved the adjusted 90-day survival rate, increased the numbers of ventilator-free days and days outside the ICU, and decreased the incidence of barotrauma during the first 90 days. It did not significantly improve the overall 90-day mortality.

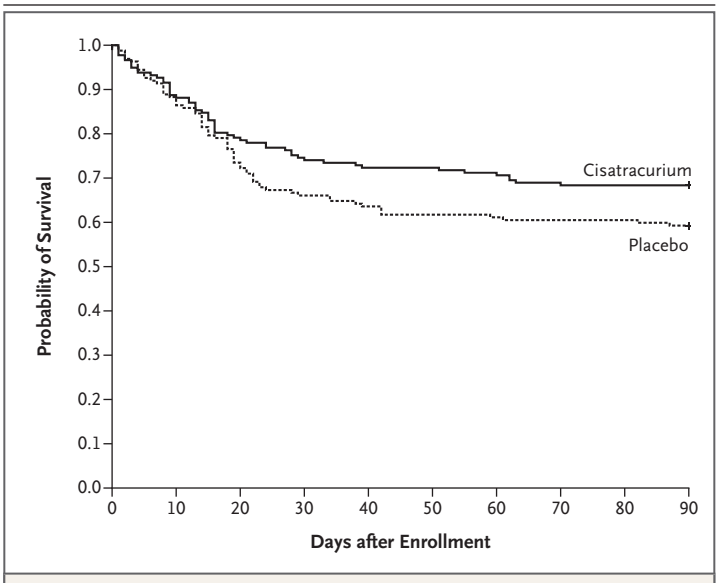

Figure 2. Probability of Survival through Day 90, According to Study Group.

Strengths of this trial include the methods used to minimize bias (blinded randomization assignments, a well-defined study protocol, complete follow-up, and intention-to-treat analyses). The recruitment of a large number of patients from 20 multidisciplinary ICUs where international standards of care are followed suggests that our data can be generalized to other ICUs.

Limitations of the trial include the fact that our results were obtained for cisatracurium besylate and may not apply to other neuromuscular blocking agents. Furthermore, we did not assess the use of a neuromuscular blocking agent late in the course of ARDS or use on the basis of plateau-pressure or transpulmonary-pressure measurements.[20] Another limitation is the absence of data on conditions known to antagonize or potentiate neuromuscular blockade. However, any condition that increases the duration of neuromuscular blockade would have adversely affected the patients receiving the neuromuscular blocking agent, in particular by increasing the duration of mechanical ventilation.

The sample-size calculation was based on our two previous studies performed in four ICUs[13,15] that used the same inclusion criteria as were used in the current trial and on the European epidemiologic study ALIVE.[4] However, the mortality in the placebo group in this study (40.7%) is lower than

Table 3. Secondary Outcomes, According to Study Group.*

Outcome	Cisatracurium (N=177)	Placebo (N=162)	Relative Risk with Cisatracurium (95% CI)	P Value
Death — no. (% [95% CI])				
At 28 days	42 (23.7 [18.1–30.5])	54 (33.3 [26.5–40.9])	0.71 (0.51–1.00)	0.05
In the ICU	52 (29.4 [23.2–36.5])	63 (38.9 [31.7–46.6])	0.76 (0.56–1.02)	0.06
In the hospital	57 (32.2 [25.8–39.4])	67 (41.4 [34.1–49.1])	0.78 (0.59–1.03)	0.08
No. of ventilator-free days†				
From day 1 to day 28	10.6±9.7	8.5±9.4		0.04
From day 1 to day 90	53.1±35.8	44.6±37.5		0.03
No. of days without organ failure, from day 1 to day 28				
No cardiovascular failure	18.3±9.4	16.6±10.4		0.12
No coagulation abnormalities	22.6±8.9	20.5±9.9		0.05
No hepatic failure	21.3±9.6	19.1±10.6		0.05
No renal failure	20.5±10.1	18.1±11.6		0.05
None of the four	15.8±9.9	12.2±11.1		0.01
No. of days outside the ICU				
From day 1 to day 28	6.9±8.2	5.7±7.8		0.16
From day 1 to day 90	47.7±33.5	39.5±35.6		0.03
Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)	22.3 (15.8–30.5)	18.8 (12.2–27.8)		0.52
Barotrauma — no. (% [95% CI])‡	9 (5.1 [2.7–9.4])	19 (11.7 [7.6–17.6])	0.43 (0.20–0.93)	0.03
Pneumothorax — no. (% [95% CI])	7 (4.0 [2.0–8.0])	19 (11.7 [7.6–17.6])	0.34 (0.15–0.78)	0.01
MRC score — median (IQR)§				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94
Patients without ICU-acquired paresis¶				
By day 28 — no./total no. (% [95% CI])	68/96 (70.8 [61.1–79.0])	52/77 (67.5 [56.5–77.0])		0.64
By ICU discharge — no./total no. (% [95% CI])	72/112 (64.3 [55.1–72.6])	61/89 (68.5 [58.3–77.3])		0.51

* Plus–minus values are means ±SD. ICU denotes intensive care unit, and IQR interquartile range.
† The number of ventilator-free days was defined as the number of days since successful weaning from mechanical ventilation after a period of spontaneous breathing lasting at least 48 consecutive hours.
‡ Barotrauma was defined as any new pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele larger than 2 cm in diameter.
§ The Medical Research Council (MRC) scale is a previously validated scale that assesses strength in three muscle groups in each arm and leg. The score for each muscle group can range from 0 (paralysis) to 5 (normal strength), with the overall score ranging from 0 to 60.[17]
¶ ICU-acquired paresis was defined as an overall MRC score of less than 48.

that in the control groups in the earlier studies. Given the observed mortality in our placebo group, the current study was underpowered. Indeed, 885 patients would have been needed to be enrolled to achieve 80% statistical power with a two-sided alpha value of 0.05.

Finally, all our patients had severe ARDS. Additional work is needed to determine whether the use of neuromuscular blocking agents for only 24 hours is beneficial in selected patients. In our general analysis, which was prespecified but with post hoc determination of the threshold value for classifying subgroups, we found that the beneficial effect of the neuromuscular blocking agent on survival was confined to the two thirds of patients with a PaO_2:FIO_2 ratio below 120.

The mechanisms underlying the beneficial effect of neuromuscular blocking agents remain speculative. A brief period of paralysis early in the course of ARDS may facilitate lung-protective mechanical ventilation by improving patient–ventilator synchrony and allowing for the accurate adjustment of tidal volume and pressure levels, thereby limiting the risk of both asynchrony-related alveolar collapse and regional alveolar-pressure increases with overdistention. Another possible mechanism of the benefit involves a decrease in lung or systemic inflammation.[15]

The main safety concern with the use of a neuromuscular blocking agent is muscle weakness; the risk varies among agents.[21,22] Steroidal compounds (vecuronium, pancuronium, and rocuronium) may carry the highest risk of myopathy,[23] although myopathy has also been reported with benzylisoquinolines, including cisatracurium besylate.[24,25] Muscle weakness was not increased significantly by the use of the neuromuscular blocking agent in our study. The short duration of use of the neuromuscular blocking agent probably explains this result.

In conclusion, this multicenter trial provides evidence that the administration of a neuromuscular blocking agent early in the course of severe ARDS managed with low-tidal-volume ventilation may improve outcomes. Future studies are needed to replicate and expand these findings before they can be widely adopted in clinical practice.

Supported by the Assistance Publique–Hôpitaux de Marseille and a grant from the Ministère de la Santé (Programme Hospitalier de Recherche Clinique Régional 2004-26). GlaxoSmithKline France provided the study drugs.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Kahena Amichi, Daniel Pulina, François Voillet, Patrick Sudour, Teodora Iordanova, Jean-Charles Reynier, Mohamed Fathallah, Karine Barrau, Pascal Auquier, Yann Lebras, Nathalie Boggi, Ammar Zerrar, Cécile Roché-Thiaux, Fabienne Brégeon, Didier Dreyfuss, Marie-Josée Bonavita, Marie-Dominique Chollet, Didier Sanchez, and Antoinette Wolfe.

APPENDIX

The ARDS et Curarisation Systematique (ACURASYS) study investigators are as follows (all in France): **Marseille:** *Hôpital Nord* — J. Albanese, V. Blaso, M. Leone, F. Antonini, P. Visintini; *Hôpital Sainte-Marguerite, Réanimation des Urgences* — G. Perrin, D. Blayac, B. Eon, P. Michelet, P. Saux, D. Lambert, V. Fulachier; *Hôpital Sainte-Marguerite, Réanimation Médicale* — J.M. Forel, A. Roch, C. Guervilly, J. Allardet-Servent, D. Demory, N. Embriaco, M. Gainnier, L. Papazian; *Hôpital Ambroise Paré* — J.M. Seghboyan, N. Beni Chougrane, R. Soundaravelou, A. Piera, M. Bonnetty. **Paris:** *Hôpital Saint-Louis* — E. Azoulay. **Besançon:** *Hôpital Jean Minjoz* — D. Perez, G. Capellier, P. Midez, C. Patry, E. Laurent, E. Belle, J.C. Navellou. **Clermont-Ferrand:** *Hôpital Hôtel-Dieu* — J.M. Constantin, S. Cayot-Constantin, R. Guerin. **Avignon:** *Centre Hospitalier* — P. Courant, T. Signouret, K. Pavaday, P. Garcia, L. Delapierre, K. Debbat. **Toulon:** *Hôpital Font-Pré* — J.M. Arnal, J. Durand-Gasselin, G. Corno, A. Orlando, I. Granier, S.Y. Donati. **Rennes:** *Hôpital Pontchaillou* — A. Gacouin, Y. Le Tulzo, S. Lavoue, C. Camus. **Nîmes:** *Hôpital Caremeau* — C. Gervais, C. Bengler, C. Arich, J.Y. Lefrant, P. Poupard, L. Muller, P. Joubert, R. Cohendy, G. Saissi, P. Barbaste. **Lyon:** *Hôpital de la Croix-Rousse* — C. Guérin, F. Bayle, J.C. Richard, J.M. Badet. **Bordeaux:** *Hôpital Pellegrin* — G. Hilbert, H. Bruno, E. Rosier, W. Pujol, H.N. Bui. **Montpellier:** *Hôpital Saint-Eloi* — S. Jaber, B. Jung, M. Sebbane, G. Chanques. **Brest:** *Hôpital La Cavale Blanche* — G. Prat, E. L'Her, J.M. Tonnelier. **Aix-en-Provence:** *Centre Hospitalier du Pays d'Aix* — O. Baldesi, C. Leroy, L. Rodriguez, J.L. Le Grand, B. Garrigues. **Nice:** *Hôpital de l'Archet* — G. Bernardin, J. Dellamonica. **Grenoble:** *Hôpital Sud* — C. Schwebel, J.F. Timsit, R. Hamidfar, L. Hammer, G. Dessertaine, C. De Couchon, A. Bonadona. **Saint-Etienne:** *Hôpital Bellevue* — F. Zeni, D. Thevenet, C. Venet, S. Guyomarc'h.

REFERENCES

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-49.
2. Malhotra A. Low-tidal-volume ventilation in the acute respiratory distress syndrome. N Engl J Med 2007;357:1113-20.
3. Bernard GR. Acute respiratory distress syndrome: a historical perspective. Am J Respir Crit Care Med 2005;172:798-806.
4. Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units: results from the ALIVE study. Intensive Care Med 2004;30:51-61.
5. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002; 287:345-55.
6. Esteban A, Ferguson ND, Meade MO, et al. Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med 2008;177:170-7.
7. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685-93.
8. Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN. Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure: a national survey. JAMA 1991;266:2870-5.
9. Mehta S, Burry L, Fischer S, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. Crit Care Med 2006;34:374-80.
10. Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2002;30: 142-56.
11. Samuelson KA, Larsson S, Lundberg D, Fridlund B. Intensive care sedation of mechanically ventilated patients: a national Swedish survey. Intensive Crit Care Nurs 2003;19:350-62.
12. Vender JS, Szokol JW, Murphy GS, Nitsun M. Sedation, analgesia, and neuromuscular blockade in sepsis: an evidence-based review. Crit Care Med 2004;32: Suppl:S554-S561.
13. Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 2004;32:113-9.

14. 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. N Engl J Med 2000;342:1301-8.
15. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006;34:2749-57.
16. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman J, Limbird L, eds. The pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill, 1996:521-55.
17. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288:2859-67.
18. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med 2002;30:1772-7.
19. Hager DN, Krishnan JA, Hayden DL, Brower RG. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 2005;172:1241-5.
20. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008;359:2095-104.
21. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 1992;327:524-8.
22. Murray MJ, Coursin DB, Scuderi PE, et al. Double-blind, randomized, multicenter study of doxacurium vs. pancuronium in intensive care unit patients who require neuromuscular-blocking agents. Crit Care Med 1995;23:450-8.
23. Testelmans D, Maes K, Wouters P, et al. Rocuronium exacerbates mechanical ventilation-induced diaphragm dysfunction in rats. Crit Care Med 2006;34:3018-23.
24. Davis NA, Rodgers JE, Gonzalez ER, Fowler AA III. Prolonged weakness after cisatracurium infusion: a case report. Crit Care Med 1998;26:1290-2.
25. Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. Am J Respir Crit Care Med 1996;153:1686-90.

CORRESPONDENCE

Neuromuscular Blockers and ARDS

TO THE EDITOR: In the study reported on by Papazian et al. (Sept. 16 issue),[1] patients with the acute respiratory distress syndrome (ARDS) treated early with cisatracurium had improved 90-day survival and an increased number of ventilator-free days. We are concerned about a number of methodologic limitations that detract from the reliability of the findings. First, considering that patients who are not paralyzed can trigger the ventilator and paralyzed patients cannot, adequate blinding of study-group assignments among caregivers would seem to have been nearly impossible. Furthermore, patient–ventilator dyssynchrony was not formally monitored, nor were strategies to deal with it prespecified.[2] Lacking that, it is conceivable that inadequate management of dyssynchrony in the placebo group could have predisposed to worse outcomes. Finally, the Medical Research Council (MRC) scale method used to evaluate muscle weakness was limited to 28 days (or to discharge from the intensive care unit [ICU]), a duration that may be too brief to recognize muscle weakness in patients who require prolonged mechanical ventilation, particularly if they are slow to awaken.[3]

John W. Devlin, Pharm.D.
Northeastern University
Boston, MA
j.devlin@neu.edu

Erik Garpestad, M.D.
Nicholas S. Hill, M.D.
Tufts Medical Center
Boston, MA

No potential conflict of interest relevant to this letter was reported.

1. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
2. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 2006;32:24-33.
3. Sharshar T, Bastuji-Garin S, Stevens RD, et al. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. Crit Care Med 2009;37:3047-53.

TO THE EDITOR: In the study by Papazian and colleagues, there was no clear explanation for the observed increase in survival in the group treated with paralytic agents.[1] Since the effectiveness of the neuromuscular blocking agent was not assessed with train-of-four stimulation, how can the reader be sure that there was adequate blockade? There are reports of tachyphylaxis[2] and resistance to neuromuscular blockers,[3] mainly in critically ill patients. Thus, it is possible that the benefits observed were due to possible effects of cisatracurium independent of muscle blockade.

Dimitri Gusmão, M.D.
Hospital Universitário Professor Edgar Santos
Salvador, Brazil
dimitrigusmao@gmail.com

No potential conflict of interest relevant to this letter was reported.

THIS WEEK'S LETTERS

1. Slutsky AS. Neuromuscular blocking agents in ARDS. N Engl J Med 2010;363:1176-80.
2. Haddad S. Tachyphylaxis to cisatracurium — case reports and literature review. Middle East J Anesthesiol 2008;19:1079-92.
3. Tschida SJ, Graupe KJ, Hoey LL, Vance-Bryan K. Resistance to nondepolarizing neuromuscular blocking agents. Pharmacotherapy 1996;16:409-18.

TO THE EDITOR: Papazian and colleagues performed a randomized, controlled trial of early short-term neuromuscular blockade in patients with ARDS. Although the primary end point was 90-day mortality, the study provides data on neuromuscular blockade as a risk factor for ICU-acquired paresis; muscle strength was assessed with the use of the sum of the scores on the MRC manual muscle-testing scale. Strength was assessed on day 28 and on the day of discharge, rather than on day 7 after awakening as originally described.[1] Regardless, these results challenge the view that neuromuscular blockade per se (rather than resultant immobility) causes ICU-acquired paresis.

We would be interested to learn whether any measures of physical activity and limb mobility, or of muscle bulk, were recorded during the ICU stay. Further, was there an increased incidence of ICU-acquired paresis in the subgroup of patients who received systemic glucocorticoids? Although the arbitrary cutoff MRC score of 48 (on a scale of 0 to 60, with higher scores indicating better muscle strength) was legitimately used to define ICU-acquired paresis, it might thus be that the spread of raw score data would be revealing. This observation could add weight to a synergistic model of the cause of ICU-acquired paresis.

Zudin Puthucheary, M.R.C.P.
University College London
London, United Kingdom
zudin.puthucheary.09@ucl.ac.uk

Nicholas Hart, M.R.C.P., Ph.D.
Kings College London
London, United Kingdom

Hugh Montgomery, F.R.C.P., Ph.D.
University College London
London, United Kingdom

No potential conflict of interest relevant to this letter was reported.

1. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288:2859-67.

THE AUTHORS REPLY: Devlin et al. suggest that blinding was not feasible because patients who received placebo would have been able to trigger the ventilator. All patients in both groups had a Ramsay score of 6 (no response on glabellar tap) before starting placebo or cisatracurium. Sedation was increased in patients with inspiratory efforts in response to glabellar tap (before starting placebo or cisatracurium). It is unlikely that patients with no response to glabellar tap can trigger the ventilator. Moreover, there was no difference between the two groups with regard to the respiratory rate during the first 2 days of the study. However, we cannot rule out that patients who received placebo had subclinical inspiratory efforts. The second comment by Devlin et al. is in contradiction to the first: if asynchrony had been monitored, blinding would not have been feasible. However, whether subclinical inspiratory efforts may contribute to an explanation of the results of the ARDS et Curarisation Systematique (ACURASYS) trial (ClinicalTrials.gov number, NCT00299650) would be an interesting topic for future studies. Concerning the timing of assessment of muscle weakness, the evaluation was done on day 28 — that is, later during the hospital stay than in the study cited by Devlin et al. Given the absence of any difference between the two groups on day 28 or at ICU discharge, a delayed difference after ventilator weaning and ICU discharge is very unlikely.

With regard to the comments by Gusmão: we chose the dosage regimen that abolished all responses to train-of-four stimulation in the 2 patients (of 92 included patients) who required the highest dosage regimen in our previously published studies.[1,2] Given the high dosage used, it is unlikely that a substantial number of patients had persistent muscle activity. Assessment of neuromuscular blockade is, however, valuable in the clinical setting, especially in patients with acute renal failure, to avoid sustained paralysis after discontinuation of neuromuscular blocking agents. We agree with the comment by Gusmão that cisatracurium may also exert beneficial effects that are not related to paralysis. Unfortunately, physical activity was not evaluated during the ICU stay. We performed a new analysis to determine the proportion of patients with ICU-acquired paresis among glucocorticoid-treated patients. We found that 36.6% of the patients

who received glucocorticoids had an ICU-acquired paresis, whereas 30% of the patients who did not receive glucocorticoids had an MRC score of less than 48 (P=0.32).

Laurent Papazian, M.D., Ph.D.
Jean-Marie Forel, M.D.
Antoine Roch, M.D., Ph.D.
Université de la Méditerranée Aix–Marseille II
Marseille, France
laurent.papazian@ap-hm.fr

Since publication of their article, the authors report no further potential conflict of interest.

1. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006; 34:2749-57.
2. Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 2004; 32:113-9.

Intensive Blood-Pressure Control in Hypertensive Chronic Kidney Disease

TO THE EDITOR: Appel and coworkers of the African-American Study of Kidney Disease and Hypertension (AASK) Collaborative Research Group (Sept. 2 issue)[1] report that in black patients with hypertensive renal disease, intensive blood-pressure control did not reduce the incidence of renal outcomes (worsening kidney function, end-stage renal disease [ESRD], or death) as compared with standard blood-pressure control. This finding, which is in contrast to that of observational studies, in which the relationship between blood pressure and the advancement of kidney disease is of a progressive nature,[2] will probably affect future hypertension guidelines in patients with kidney disease.

Although it was acknowledged in the Discussion section of their article, the authors downplay their own finding of major misclassification of standard office readings of blood pressure. A previous study involving AASK participants showed that more than two thirds of patients with standard office readings of controlled blood pressure actually had significant nocturnal hypertension.[3] In essence, this finding invalidates most of the conclusions derived from AASK office blood-pressure data, including the present conclusions. It shows how published literature may be deceiving when the measurement used does not reflect the reality that nocturnal hypertension (a form of masked hypertension) is the major determinant of outcome.[4,5]

Michael Bursztyn, M.D.
Hadassah–Hebrew University Medical Center
Jerusalem, Israel

Iddo Z. Ben-Dov, M.D., Ph.D.
Rockefeller University
New York, NY
iben@rockefeller.edu

No potential conflict of interest relevant to this letter was reported.

1. Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 2010;363:918-29.
2. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Stamler J. End-stage renal disease in African-American and white men: 16-year MRFIT findings. JAMA 1997;277:1293-8.
3. Pogue V, Rahman M, Lipkowitz M, et al. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension 2009;53:20-7.
4. Davidson MB, Hix JK, Vidt DG, Brotman DJ. Association of impaired diurnal blood pressure variation with a subsequent decline in glomerular filtration rate. Arch Intern Med 2006;166: 846-52. [Erratum, Arch Intern Med 2006;166:1619.]
5. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: unique aspects of blood pressure during sleep. Hypertension 2007;49:1235-41.

TO THE EDITOR: Appel et al. report on the differential effects of intensive blood-pressure control on the progression of kidney disease according to the presence or absence of proteinuria. Although the results were intriguing, a potential explanation for the findings may be the difference in disease progression among patients with chronic kidney disease with and without proteinuria as well as the study design.[1] This difference is evidenced by the authors' results showing a much higher rate of the primary outcome in both groups among patients with proteinuria. Furthermore, although the overall duration of the study