A Centrally Acting Antihypertensive, Clonidine, Sedates Patients Presenting With Acute Respiratory Distress Syndrome Evoked by Severe Acute Respiratory Syndrome-Coronavirus 2

To the Editor:

The severe acute respiratory syndrome-coronarovirus 2 pandemics overwhelmed the critical care units (CCUs) in Alsace, France. The disease evokes acute respiratory distress syndrome (ARDS) (1). Therefore, as much as ~20 patients *per diem* (d) presented in the emergency department (ED) of the Mulhouse Hospital ("Centre Hospitalier de Mulhouse" [CHM]) requiring endotracheal intubation (intubation) and controlled mechanical ventilation (CMV). To off-load the CCU of the CHM, a modular army field hospital ("Element Militaire de Réanimation": EMR, i.e. tents) was set up mid-March 2020. A sympatholytic, alpha-2 agonist, clonidine (Catapres, Catapressan; Boehringer Ingelheim, Paris, France) with sedative effects (2, 3) was used for cooperative sedation. This cheap, widely available drug does not depress the respiratory generator (4), shortens the duration of CMV (5) and the CCU length of stay (LOS) (6). We report on the sedation and ventilation method.

The patients (18–70 yr old, body mass index < 37, $n = 47$) presented with little comorbidities, positive testing to coronarovirus-2, ARDS, and no other organ failure: (1) patients transferred from the CCU of the CHM under conventional sedation (midazolam + sufentanil or propofol + sufentanil) for weaning and (2) moderate or severe ARDS (Pao_2/Fio_2 = P/F < 200 or 100, respectively) patients after intubation, conventional sedation, and paralysis and transferred directly from the ED to the EMR. Some mild ARDS deteriorated to severe ARDS after admission to the EMR. Our method is described in the last subset of patients. They present with a high neural drive, hyperthermia (38–40°C), and inflammation restricted to the lung (7) (*pulmonary* ARDS with a low prevalence of circulatory failure). This evokes patient's self-inflicted lung injury (P-SILI; tachypnea: increased respiratory rate [RR]; hyperpnea: increased tidal volume: [Vt]) requiring CMV (8) to avoid inflammation evoked by the spontaneous breathing (SB) itself (P-SILI), in addition to the inflammation evoked by the virus and ventilator-induced lung injury.

Given previous experiences (9–12), austere conditions, and the massive influx of patients, the priorities were as follows: 1) a high turn-over requiring early SB. Many patients could not be admitted to the CHM and were dispatched elsewhere; 2) simplicity: at odd with other's practice, no specialized prone positioning team was available; and 3) anesthetics shortage. Upon admission, after "normalized" volemia (iterative passive leg raising under echocardiographies) and absence of contraindications (sick sinus syndrome, atrio-ventricular block II/III, acute kidney injury), conventional sedation is switched to clonidine 1–2 μg/kg/hr (~23 vials/70 kg, i.e., up to 3,360 μg/d; –2 < Richmond Agitation-Sedation Scale [RASS] < 0). Rescue sedation (midazolam 3–5 mg IV as required) addresses the slow onset of sedation evoked by clonidine (3–4 hr) administered "without" loading dose to –2 < RASS < 0. Clonidine sedation is supplemented with haloperidol (up to 5 mg × 4) "if" needed. "More" importantly, increased RR and Vt are addressed: 1) iterative echocardiographies optimize the cardiac output (CO) and suppress systemic acidosis (13); 2) the normalized CO, and the sympatholysis evoked by clonidine, improve the microcirculation, as documented by iterative arterial and venous gases, diuresis, etc; and 3) temperature is normalized to ~35°C to lower oxygen consumption (Vo_2). Given the sub-zero °C temperature observed in Alsace, March 2020, and despite massive warming under the tents, the weather may have helped normalizing Vo_2, (4) clonidine suppresses agitation, pain, and a high neural drive. SB with mild permissive hypercapnia (40–50 mm Hg) is actively pursued "as soon as the factors of P-SILI are addressed" (above). As soon as SB is set, proning sequences are switched to the continuous "upright" position (14). Low level pressure support (PS) addresses the work of breathing caused by the circuit, valves, and endotracheal tube. As soon as SB is achieved, the positive end-expiratory pressure (PEEP) is easily reset to higher levels (plateau pressure ≤30 cm H_2O). Under SB, high PEEP allows one to achieve high arterial oxygen saturation greater than 96% and suppresses the hypoxic drive and tachypnea. The Fio_2 is lowered from 1 to 0.4 within 12–72 hour. Then, given a steady Fio_2 equals to 0.4, PEEP is lowered to ~10 cm H_2O within an additional 12–72 hour. Under clonidine infusion (–2 < RASS < 0), extubation of the trachea allows weaning. This method (cooperative sedation with clonidine, immediate P-SILI control, early SB-low PS-high PEEP, upright position) was used earlier (9, 10, 12, 13).

The absence of detailed results (length of intubation, CMV, SB, P/F, inflammatory markers, etc.) relates to the spartan conditions, minimal staffing with a priority to patients' care, without retrospective access to the "contaminated" files. Obviously, the observations need documentation: 1) easy implementation of CMV or SB (CMV: no major hypercapnia; SB: no tachypnea, hyperpnea, hypercapnia, high neural drive, inadvertent extubation, absence of agitation); 2) at variance with (15, 16), extubation of a clinically significant number of patients transferred directly from the ED to the EMR was achieved within ~2–10 d; and 3) massive anesthetic sparing. Iterative checking of volemia and absence of administration of opiates led to little hypotension/bradycardia.

TABLE 1. Outcome as of May 1, 2020

Outcomes	
CCU length of stay (d), median (interquartile range)	14 (9–20)
Airlift to other hospitals	7 (5–8)
No airlift	15 (13–23)
Direct discharge to home, *n* (%)	21 (44.7)
On-going hospitalization, *n* (%)	
CCU	10 (21.3)
Ward	12 (25.5)
Death, *n* (%)	4 (8.5)

CCU = critical care unit.

Finally, 1) the low mortality ($n = 47$, ~8.5%; **Table 1**) does not compare with the mortality observed in young patients elsewhere (Seattle: 37% [17]; Wuhan: 38% [18]; New York: 76% [19]): our cohort is biased toward young patients with little comorbidities and single-organ failure (median: 62 yr old; range: 54–67); 2) dexmedetomidine presents advantages (U.S. Food and Drug Administration approval, IV preparation, shorter time to steady state cooperative sedation, no contraindication in the setting of acute kidney injury); and 3) patient's care was designed mid-March 2020, that is, before a switch emphasizing noninvasive ventilation.

Dr. Quintin holds U.S. Patent 8,03,697, April 22, 2014: Method for treating early severe diffuse acute respiratory distress syndrome. He is a retired anesthesiologist from Service de Santé des Armées (reserve list). Drs. Danguy des Deserts, Leroy, Quintin, and Escarnebt disclosed off-label product use clonidine. Dr. Leroy received funding from Actelion (employee). Dr. Escarment is a retired anesthesiologist from French Military Health Service. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Fabrice Petitjeans, MD, Jean-Yves Martinez, MD, MSc, Marc Danguy des Déserts, MD, Sandrine Leroy, MD, PhD, Luc Quintin, MD, PhD, Jacques Escarment, MD,
Critical Care, Hôpital d'Instruction des Armées Desgenettes, Lyon, France; and Élément Militaire de Réanimation, Centre Hospitalier, Mulhouse, and Epismart, Paris, France

REFERENCES

1. Huang C, Wang Y, Li X, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497–506
2. Onesti G, Bock KD, Heimsoth V, et al: Clonidine: A new antihypertensive agent. *Am J Cardiol* 1971; 28:74–83
3. Dollery CT, Davies DS, Draffan GH, et al: Clinical pharmacology and pharmacokinetics of clonidine. *Clin Pharmacol Ther* 1976; 19:11–17
4. Voituron N, Hilaire G, Quintin L: Dexmedetomidine and clonidine induce long-lasting activation of the respiratory rhythm generator of neonatal mice: Possible implication for critical care. *Respir Physiol Neurobiol* 2012; 180:132–140
5. Ruokonen E, Parviainen I, Jakob SM, et al; "Dexmedetomidine for Continuous Sedation" Investigators: Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. *Intensive Care Med* 2009; 35:282–290
6. Zhang Z, Chen K, Ni H, et al: Sedation of mechanically ventilated adults in intensive care unit: A network meta-analysis. *Sci Rep* 2017; 7:44979
7. Remy KE, Brakenridge SC, Francois B, et al: Immunotherapies for COVID-19: Lessons learned from sepsis. *Lancet Respir Med* 2020. In press
8. Carteaux G, Millán-Guilarte T, De Prost N, et al: Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: Role of tidal volume. *Crit Care Med* 2016; 44:282–290
9. Pichot C, Picoche A, Saboya-Steinbach MI, et al: Combination of clonidine sedation and spontaneous breathing-pressure support upon acute respiratory distress syndrome: A feasibility study in four patients. *Acta Anaesthesiol Belg* 2012; 63:127–133
10. Galland C, Ferrand FX, Cividjian A, et al: Swift recovery of severe hypoxemic pneumonia upon morbid obesity. *Acta Anaesthesiol Belg* 2014; 65:109–117
11. Petitjeans F, Pichot C, Ghignone M, et al: Early severe acute respiratory distress syndrome: What's going on? Part II: Controlled vs. spontaneous ventilation? *Anaesthesiol Intensive Ther* 2016; 48:339–351
12. Petitjeans F, Quintin L: Noninvasive failure in de novo acute hypoxemic respiratory failure: High positive end-expiratory pressure-low pressure support, i.e., "inverted settings"? *Crit Care Med* 2016; 44:e1153–e1154
13. Pichot C, Petitjeans F, Ghignone M, et al: Spontaneous ventilation-high PEEP upon severe ARDS: An erratum to further the analysis. *Med Hypotheses* 2013; 81:967
14. Dellamonica J, Lerolle N, Sargentini C, et al: Effect of different seated positions on lung volume and oxygenation in acute respiratory distress syndrome. *Intensive Care Med* 2013; 39:1121–1127
15. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
16. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
17. Bhatraju PK, Ghassemieh BJ, Nichols M, et al: Covid-19 in critically ill patients in the seattle region - case series. *N Engl J Med* 2020; 382:2012–2022
18. Yang X, Yu Y, Xu J, et al: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8:475–481
19. Richardson S, Hirsch JS, Narasimhan M, et al: Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; 323:2052–2059

DOI: 10.1097/CCM.0000000000004503