The American Journal of Surgery (2013) 205, 500-504

The American Journal of Surgery®

North Pacific Surgical Association

Reducing time on for extra-corporeal membrane oxygenation for adults with H1N1 pneumonia with the use of the Volume Diffusive Respirator

Andrew J. Michaels, M.D.[a,*], Jonathan G. Hill, M.D.[a], William B. Long, M.D.[a], Bernie P. Sperley, D.O.[a], Brian P. Young, M.D.[a], Paulene K. Park, M.D.[b], Peter T. Rycus, B.S.[b], Robert H. Bartlett, M.D.[b]

[a]*Legacy Emanuel Medical Center, Portland, OR, USA;* [b]*University of Michigan, Ann Arbor, MI, USA*

KEYWORDS:
Extracorporeal membrane oxygenation;
ARDS;
H1N1;
Volume Diffusive Respirator;
VDR;
ELSO

Abstract

BACKGROUND: The investigators compared a series of adult survivors of severe H1N1 pneumonia treated with extracorporeal membrane oxygenation (ECMO) with members of the Extracorporeal Life Support Organization registry for patients with H1N1 with regard to ventilator management while on ECMO.

METHODS: Adults who survived ECMO were compared regarding time on ECMO for those treated with the Volume Diffusive Respirator (VDR) or with conventional "lung rest." The VDR delivered 500 percussions/min, with tidal pressures of 24/12 cm H_2O and a fraction of inspired oxygen of .4 at 15 beats/min.

RESULTS: There were no differences between the study patients (n = 7) and the Extracorporeal Life Support Organization cohort (n = 150) regarding age, pre-ECMO ventilator days, pre-ECMO ratio of partial pressure of oxygen to fraction of inspired oxygen, or survival after lung recovery. Patients treated with VDR required ECMO support for a shorter duration (mean, 193.29 ± 35.71 vs 296.63 ± 18.17 hours; $P = .029$).

CONCLUSIONS: These data suggest that the VDR enhanced pulmonary recovery from severe H1N1 pneumonia in adults. Shorter times on ECMO may improve the risk/benefit and cost/benefit ratios associated with ECMO care.

At the extremes of lung failure, it becomes impossible to oxygenate and ventilate a patient. The ventilator itself can cause additional injury to the lung.[1–3] Various strategies of protective ventilation have become standards of care,[4,5] yet even these methods may fail to support a patient with the most severe manifestations of acute respiratory distress syndrome (ARDS). For many years, extracorporeal membrane oxygenation (ECMO) for adult ARDS was considered controversial because of early studies involving techniques that are no longer clinically relevant.[6,7] Recent reports have suggested that patients cared for at ECMO centers have improved survival from generic ARDS[8] and lung failure caused by the H1N1 virus.[9]

Current controversy regarding the routine use of ECMO for ARDS is focused on 2 primary criticisms. First, the

The authors declare no conflicts of interest.

* Corresponding author. Tel.: +1-503-413-2100; fax: +1-503-413-2178.

E-mail address: amichael@lhs.org

Manuscript received November 19, 2012; revised manuscript January 16, 2013

0002-9610/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjsurg.2013.01.024

efficacy of ECMO relative to aggressive use of the ventilator continues to be challenged.[10,11] Second, concerns about the cost and safety of ECMO remain barriers to more widespread adoption. Any strategy that enhances lung recovery and decreases the time a patient requires extracorporeal support reduces both the cost and the risk of ECMO and enhances the cost/benefit and risk/benefit ratios of the therapy.

At our center, we provide aggressive multifaceted care for patients with ARDS. We use lung-protective ventilation with the Volume Diffusive Respirator (VDR; Percussionaire Corporation, Sand Point, ID). During the autumn of 2009, we treated a number of adults with H1N1 pneumonia with ECMO. Although the basic tenet of ECMO support for ARDS is predicated on using the circuit to support respiration and minimizing the ventilator to "rest settings" to eliminate ventilator-induced lung injury (VILI),[12] we used the VDR with modest settings. These settings were chosen not to affect the gas exchange of oxygen or carbon dioxide but to facilitate pulmonary recovery through airway clearance of secretions, exudates, and blood; gentle alveolar recruitment: and restoration of functional residual capacity. We report a single-center series of adults who required ECMO for refractory hypoxemic ARDS due to pandemic (2009) H1N1 pneumonia in comparison with a cohort of similar patients reported to the H1N1 registry of the Extracorporeal Life Support Organization (ELSO).[13]

Methods

Our approach to the treatment of ARDS is based on a protocolized and evidence-based regimen focused on adequate oxygen delivery using the lowest possible levels of ventilator support.[14] Specifics of our current regimen for patients requiring ECMO support have been described.[15] Our center uses the full spectrum of ventilator modes, including airway pressure release ventilation and high-frequency ventilation. Our most advanced ventilator management uses the VDR-4 critical care ventilator, which is a high-frequency device that delivers pressure-controlled tidal ventilation and a simultaneous small-volume, high-frequency percussive component at a rate of 500 Hz (Fig. 1).

If, despite and after the above measures, a patient cannot achieve an PaO_2:FiO_2 ratio (PF ratio) (ratio of the partial pressure of oxygen [PaO_2] to the fraction of inspired oxygen [FiO_2]) >100 on "safe" settings (ie, FiO_2 <80%, peak inspiratory pressure <40 cm H_2O, and tidal volume <6 to 8 cm^3/kg), the patient is considered for ECMO support. We follow the World Health Organization recommendation that the treatment of ARDS associated with the novel influenza A (H1N1) virus infection be based on evidence-based guidelines for sepsis-associated ARDS using low–tidal volume, lung-protective mechanical ventilation as the initial strategy. The protocol is designed to rapidly apply increasingly intense methods of pulmonary support and to identify patients who demonstrate failure to respond to ARDS Network[5] ventilation strategies, airway pressure release ventilation, and the VDR while they are in the early stages of the H1N1 pneumonia, before VILI and secondary complications ensue.

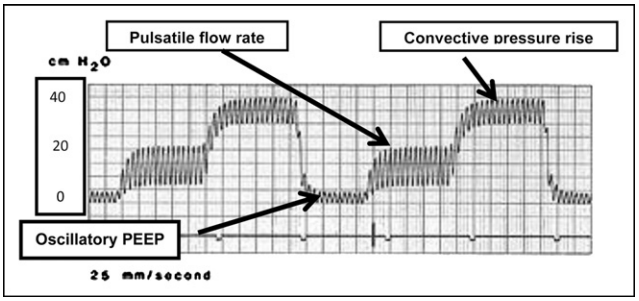

Figure 1 Time/pressure tracing of a single ventilatory cycle of the VDR. The frequency of percussive impulses is 500 beats/min. The oscillatory PEEP is the lowest pressure to which the pressure falls during exhalation and is analogous to PEEP. The pulsatile flow rate (or basic oscillatory equilibrium) is the inspiratory pressure, and the convective pressure rise (or accelerated equilibrium) is an additional increase in inspiratory pressure that may be added to each breath.

Once adequate ECMO support is instituted, the ventilator is set to low "recruitment" settings. All patients are maintained with the VDR. VDR settings during ECMO support consist of FiO_2 of 40%, pulsatile flow rate (inspiratory pressure) in the mid–20 cm H_2O range, an oscillatory positive end-expiratory pressure (PEEP) of 12 ± 2 cm H_2O, a rate of 15 cycles/min with an inspiratory/expiratory ratio of 1:1, and a percussive frequency of 500 beats/min. These lung-protective recruitment settings were not adjusted during the entirety of the ECMO course. As patients recover and "trials off" ECMO are initiated, a convective pressure rise and other adjustments are added to the ventilator management as clinically indicated.

When a patient begins to show evidence of pulmonary recovery, he or she is given a "trial off" consisting of a protocolized evaluation of a patient's native pulmonary function. The ventilator is set for optimal levels of pulsatile flow rate and oscillatory PEEP, and inspired oxygen is set at 100%. Then the ECMO circuit gas exchange is stopped while flows are maintained. At this point, there is no extracorporeal oxygenation or carbon dioxide removal. If the patient's hemodynamic status and gas exchange are adequate on the VDR, inspired oxygen on the ventilator is reduced to 50%. Patients are removed from ECMO support if their PaO_2/FiO_2 ratio is >200 with an FiO_2 of 50% and pressures <38 cm H_2O. Beyond these parameters, we do not use the ventilator to correct carbon dioxide in patients weaning from ECMO. If mild to moderate respiratory acidosis persists, it is managed with the addition of bicarbonate or tromethamine drips that are titrated for a pH >7.2.

Data are reported as numbers, percentages, and mean ± SEM. All data are derived from the ELSO H1N1 registry reported on January 13, 2011, and comparisons of mean

values were performed using *t* tests. *P* values <.05 were considered statistically significant.

Results

Between October 2009 and January 2010, 15 patients with H1N1 pneumonia were treated with ECMO at Legacy Emanuel Health Center (LEH) in Portland, Oregon. Twelve of these were adults (aged >17 years; range, 26 to 59 years), 7 recovered lung function and were weaned from ECMO, and 6 survived to discharge. One patient died after recovery from cerebral hypoxia incurred before the initiation of ECMO support. The LEH patients (n = 7) were compared with the ELSO cohort of adults who recovered (n = 135) and who survived to discharge (n = 118).

The surviving patients in the LEH series were 34.0 ± 2.45 years old, and 50% were men. Before the initiation of ECMO, they had been ventilated for 3.70 ± 1.6 days and had a mean PaO_2/FiO_2 ratio of 58.9 ± 5.5. There were no significant differences in these measures between the LEH patients and the ELSO cohort (Table 1).

LEH patients who recovered lung function and were weaned from ECMO spent 193.3 ± 35.7 hours on ECMO. This time is significantly shorter than the duration of ECMO for the ELSO patients, which was 296.6 ± 18.2 hours (*P* = .029). The mean post-ECMO PaO_2/FiO_2 ratio measured within 24 hours of weaning from ECMO was 310.2 ± 26.2 in the surviving LEH patients. In both the LEH and ELSO cohorts, 86% of those who recovered to wean from ECMO survived to discharge.

Comments

The H1N1 pandemic generated a worldwide resurgence of interest in ECMO after the nearly simultaneous publication of a large clinical series describing the role of ECMO for H1N1 in the Southern Hemisphere[16] and a prospective randomized trial reporting the benefit of referral to an ECMO center for adults with ARDS.[8] The 2009 novel H1N1 influenza pandemic provided a large cohort of acutely ill, otherwise healthy patients with profound and isolated viral ARDS. The experience of the Australian and New Zealand investigators stimulated our center to increase both ECMO and advanced ventilation capabilities. Our most advanced ventilator was the VDR-4.

The VDR is a pneumatically powered, pressure-limited ventilator that delivers tidal breaths with a superimposed high-frequency, sub–tidal volume percussive component (high-frequency percussive ventilation [HFPV]). Typically, the tidal portion is provided at a rate of 15 cycles/min, and the inspiratory/expiratory ratio is 1:1. The high-frequency percussive aspect is provided by the ventilator and a flow interrupter called a Phasitron (Percussionaire Corporation) that delivers tiny (approximately 30 cm^3) percussive bursts of air at frequencies of 500 beats/min (range, 50 to 900 beats/min). Fig. 1 illustrates a typical waveform in which the end-expiratory pressure is labeled the "oscillatory PEEP," the inspiratory pressure is called the "pulsatile flow rate," and an optional additional pressure increase is called the "convective pressure rise."

In animal models of aspiration and inhalation injury, HFPV has been shown to improve both oxygenation and carbon dioxide clearance while decreasing histologic evidence of lung injury and chemical evidence of inflammation.[17–20] Clinical studies in burn and trauma patients have demonstrated improved oxygen indices, PaO_2/FiO_2 ratios, ventilation, and compliance relative to conventional ventilation modes in both retrospective observational reviews[21–26] and prospective, randomized trials.[27,28]

The mechanisms by which HFPV improves oxygenation, recruits atelectatic segments, and mobilizes secretions without increasing VILI involve both the tidal respirations and the high-frequency, low-volume percussions. Specifics of VDR ventilation are related to longitudinal dispersion, bulk flow, pendelluft, and laminar flow for the high-frequency components and a general increase in mean airway pressure without increasing peak pressures for the low-frequency tidal breaths. HFPV has been most widely adopted in burn care, for which the clearance of thick secretions and debris is critical. Application to the dense consolidation of profound H1N1 pneumonia (Fig. 2) was a natural extension of our experiences with ARDS in pediatric, septic, burn, and trauma patients.

The current standards for ventilator management for adult ARDS patients on venovenous ECMO recommend "lung rest"[29] during ECMO support. The rationale for this approach is that the lung itself is unable to provide essential oxygenation and/or ventilation functions, and to persist with aggressive ventilation increases the risk for VILI without any benefit. Venovenous ECMO itself does not treat ARDS or its causes. It merely provides gas exchange while the initiating source is identified and treated if the lungs are

Table 1 Characteristics of the study populations

Variable	n	Mean	SEM	*P* (2 tailed)
Age (y)				
LEH	7	34.03	2.45	NS
ELSO	150	33.69	.98	
Days of ventilation before ECMO				
LEH	7	3.70	1.63	NS
ELSO	150	4.72	.47	
PaO_2/FiO_2 ratio in the 24 h before ECMO				
LEH	7	58.86	5.52	NS
ELSO	134	70.39	6.92	
Hours spent on ECMO				
LEH	7	193.29	35.71	.029
ELSO	150	296.63	18.17	
Survival				
LEH	7	.86	.143	NS
ELSO	150	.87	.027	

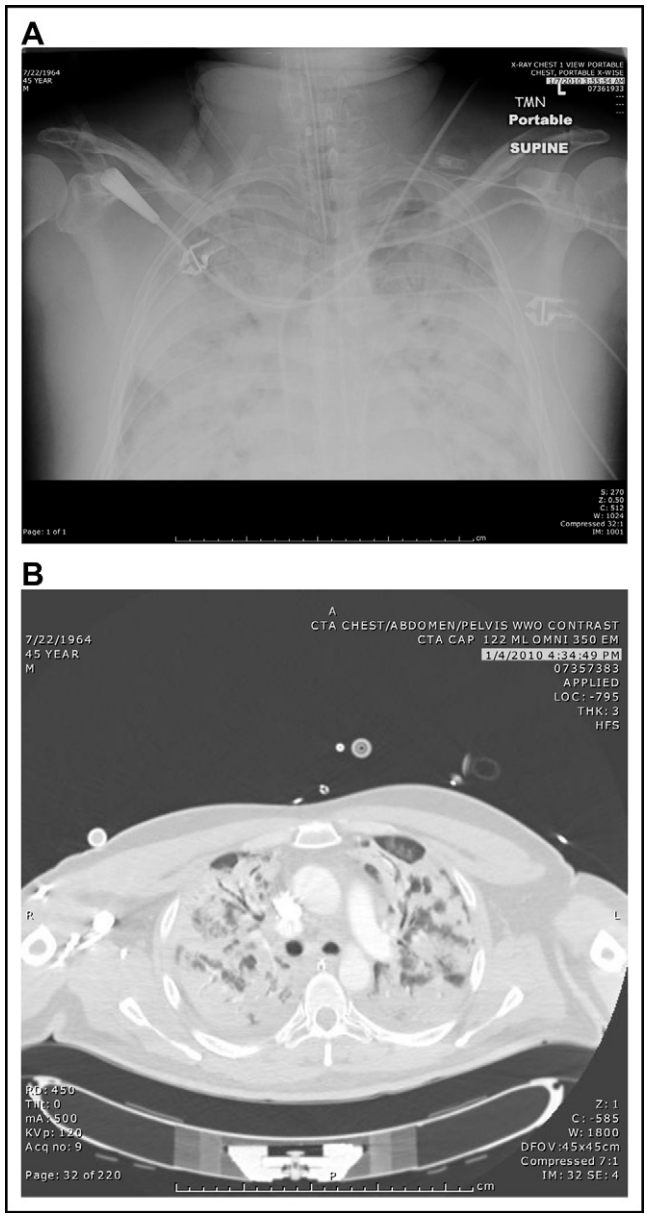

Figure 2 (A) Plain chest x-ray demonstrates the profound consolidation of advanced H1N1 pneumonia in a patient several days after the initiation of ECMO. (B) Computed tomographic scan at the level of the corina of a patient with advanced H1N1 pneumonia demonstrates the dense panpulmonic. The patient had no secondary bacterial infection and survived.

to heal. The standards for "lung rest" involve reducing the ventilator pressure and decreasing inspired oxygen. ELSO recommends that this involve a pressure control mode, PEEP of 10 to 15 cm H_2O, peak airway pressures of PEEP + 10 cm H_2O, an FiO_2 of 30%, and a respiratory rate of 10 beats/min. The settings we chose as "rest settings" on the VDR closely reflect the above recommendations (pressures of 24/12 cm H_2O, a rate of 15 cycles/min with an inspiratory/expiratory ratio of 1:1, and FiO_2 of 40%), with the exception that we used the VDR and a superimposed percussive rate of 500 beats/min. The addition of the percussive component was designed to gradually recruit available functional residual capacity, limit secondary atelectasis, mobilize secretions, and facilitate lung recovery.

Numerous other series of ECMO for adult H1N1 have been published. Our patient time on ECMO of 193 hours (8 days; range, 3 to 15 days) compares favorably with the reports of the Italian[30] (9 days; range, 7 to 15 days), Japanese[31] (9 days; range, 6.5 to 12.5 days), Australian and New Zealand[15] (10 days; range, 7 to 15 days), Canadian[32] (15 days; range, 14 to 15 days), Swedish[33] (16 days; range, 9.5 to 30.5 days), Chinese[34] (18 days; range, 2.8 to 90 days), and French[35] (23 days; range, 3 to 47 days) groups. The complexity of these cases and the small number of patients in each series limit the validity of any strong conclusions, as many variables may explain the differences. Nevertheless, the patients treated with the VDR who survived ECMO for H1N1 pneumonia in the autumn of 2009 required fewer days to recover lung function than the patients in the ELSO registry, none of whom received VDR ventilation while on ECMO.

Retrospective comparisons of treatment by different providers in different centers are fraught with limitations. This study is somewhat unusual in that the patients were remarkably similar; all had ARDS from the H1N1 virus, and all were treated within a short period of time. The ELSO H1N1 registry provides a large data set with which to compare both processes and outcomes for a homogenous population with different treatment protocols. It is possible that factors other than the choice of ventilator for patients on ECMO differ between patients treated at LEH and the ELSO cohort, but the only differences apparent in the registry are the choice of ventilator management and the time these patients were on ECMO.

With regard to cost/benefit and risk/benefit evaluations of the value of ECMO for adult ARDS, the debates are fueled by both difficult analyses and emotion. The benefit side of the equation has been in constant controversy since the 1970s. Many observational series and randomized controlled trials, especially in the era of modern technologies and techniques, are demonstrating a clinical role for ECMO in the treatment of refractory hypoxemic ARDS. The most significant ECMO-associated risks as reported by ELSO are for bleeding and cerebral injury. Any strategy that reduces the time a patient must be anticoagulated would be expected to reduce these risks. The cost analyses[8,27,36–38] are varied because of population and practice differences but are similar in their conclusions that ECMO adds only a modest cost to the care of severely compromised young patients who have the potential to recover many years of productive life without disability. The implication of our observation that the VDR may reduce the time necessary to recover from profound H1N1 ARDS in adults requiring ECMO has the potential to favorably affect both the risk/benefit and cost/benefit ratios by simply decreasing the left side of the equation. To determine if this strategy has clinical benefit will require the application of

prospective studies in the lab and in the intensive care unit under rigorous protocol.

References

1. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev 2007;13: CD003844. http://dx.doi.org/10.1002/14651858.CD003844.pub3.
2. Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. Chest 2007;131:554–62.
3. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307: 2526–33.
4. Girard TD, Bernard GR. Mechanical ventilation in ARDS: a state-of-the-art review. Chest 2007;131:921–9.
5. Brower RG, Lanken PN, MacIntyre N, et al, National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327–36.
6. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979;242:2193–6.
7. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295–305.
8. Peek GJ, Mugford M, Tiruvoipati R, et al, CESAR Trial Collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351–63.
9. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). JAMA 2011;306:1659–68.
10. Checkley W. Extracorporeal membrane oxygenation as a first-line treatment strategy for ARDS: is the evidence sufficiently strong? JAMA 2011;306:1703–4.
11. Collins SR, Randal S, Blank RS. Approaches to refractory hypoxemia in acute respiratory distress syndrome: current understanding, evidence, and debate. Respir Care 2011;56:1573–82.
12. Van Meurs K, Lally KP, Peek G, et al. ECMO: extracorporeal cardiopulmonary support in critical care. 3rd ed. Ann Arbor, MI: Extracorporeal Life Support Organization; 2005.
13. Extracorporeal Life Support Organization. H1N1 ECOM Registry. Available at: http://ww.elso.med.umich.edu/H1N1Registry.html. Accessed March 12, 2013.
14. Michaels AJ, Wanek SM, Dreifuss BA, et al. A protocolized approach to pulmonary failure and the role of intermittent prone positioning. J Trauma 2002;52:1037–47.
15. Michaels AJ, Hill JG, Long WB, et al. Adult refractory hypoxemic ARDS treated with ECMO: the role of a regional referral center. Am J Surg 2013;205:492–99.
16. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. JAMA 2009;302:1888–95.
17. Freitag L, Long WM, Kim CS, et al. Removal of excessive bronchial secretions by asymmetric high-frequency oscillations. J Appl Physiol 1989;67:614–9.
18. Wang D, Zwischenberger JB, Savage C, et al. High frequency percussive ventilation with systemic heparin improves short-term survival in a LD100 sheep model of acute respiratory distress syndrome. J Burn Care Res 2006;27:463–71.
19. Schmalstieg FC, Keeney SE, Rudloff HE, et al. Arteriovenous CO_2 removal improves survival compared to high frequency percussive and low tidal volume ventilation in a smoke/burn sheep acute respiratory distress syndrome model. Ann Surg 2007;246:512–21.
20. Allardet-Servent J, Bregeon F, Delpierre S, et al. High-frequency percussive ventilation attenuates lung injury in a rabbit model of gastric juice aspiration. Intensive Care Med 2008;34:91–100.
21. Cioffi Jr WG, Rue III LW, Graves TA, et al. Prophylactic use of high-frequency percussive ventilation in patients with inhalation injury. Ann Surg 1991;213:575–82.
22. Rue III LW, Cioffi WG, Mason AD, et al. Improved survival of burned patients with inhalation injury. Arch Surg 1993;128:772–8.
23. Allan PF, Osborn EC, Chung KK, et al. High-frequency percussive ventilation revisited. J Burn Care Res 2010;31:510–20.
24. Eastman A, Holland D, Higgins J, et al. High-frequency percussive ventilation improves oxygenation in trauma patients with acute respiratory distress syndrome: a retrospective review. Am J Surg 2006;192: 191–5.
25. Velmahos GC, Chan LS, Tatevossian R, et al. High-frequency percussive ventilation improves oxygenation in patients with ARDS. Chest 1999;116:440–6.
26. Hall JJ, Hunt JL, Arnoldo BD, et al. Use of high frequency percussive ventilation in inhalation injuries. J Burn Care Res 2007;28: 396–400.
27. Reper P, Wibaux O, Van Laeke P, et al. High frequency percussive and conventional ventilation after smoke inhalation: a randomized study. Burns 2002;28:503–8.
28. Carman B, Cahill T, Warden G, et al. A prospective, randomized comparison of the Volume Diffusive Respirator vs conventional ventilation for ventilation of burned children. 2001 ABA paper. J Burn Care Rehabil 2002;23:444–8.
29. Annich G, Lynch W, MacLaren G, et al. ECMO: extracorporeal cardiopulmonary support in critical care. 4th ed. Ann Arbor, MI: Extracorporeal Life Support Organization; 2012.
30. Patroniti N, Zangrillo A, Pappalardo F, et al. The Italian ECMO network experience during the 2009 influenza A (H1N1) pandemic: preparation for severe respiratory emergency outbreaks. Intensive Care Med 2011;37:1447–57.
31. Takeda S, Kotani T, Nakagawa S, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) severe respiratory failure in Japan. J Anesth 2012;26:650–7.
32. Freed DH, Henzler D, White CW, et al. Extracorporeal lung support for patients who had severe respiratory failure secondary to influenza A (H1N1) 2009 infection in Canada. Can J Anaesth 2010;57:240–7.
33. Holzgraefe B, Broomé M, Kalzén H, et al. Extracorporeal membrane oxygenation for pandemic H1N1 2009 respiratory failure. Minerva Anestesiol 2010;76:1043–51.
34. Hou X, Guo L, Zhan Q, et al. Extracorporeal membrane oxygenation for critically ill patients with 2009 influenza A (H1N1)-related acute respiratory distress syndrome: preliminary experience from a single center. Artif Organs 2012;36:780–6.
35. Beurtheret S, Mastroianni C, Pozzi M, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome: single-centre experience with 1-year follow-up. Eur J Cardiothorac Surg 2012;41:691–5.
36. Hemmila MR, Rowe SA, Boules TN, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. Ann Surg 2004;240:595–605.
37. Mishra V, Svennevig JL, Bugge JF, et al. Cost of extracorporeal membrane oxygenation: evidence from the Rikshospitalet University Hospital, Oslo, Norway. Eur J Cardiothorac Surg 2010;37:339–42.
38. Tiruvoipati R, Botha J, Peek G. Effectiveness of extracorporeal membrane oxygenation when conventional ventilation fails: valuable option or vague remedy? J Crit Care 2012;27:192–8.