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BRIEF REPORT

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Hypercapnia in late-phase ALI/ARDS: providing spontaneous breathing using pumpless extracorporeal lung assist

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Abstract *Objective:* The fibroproliferative phase of late ALI/ARDS as described by Hudson and Hough (Clin Chest Med 27:671–677, 2006) is associated with pronounced reductions in pulmonary compliance and an accompanying hypercapnia complicating low tidal volume mechanical ventilation. We report the effects of extracorporeal CO_2 removal by means of a novel pumpless extracorporeal lung assist (p-ECLA) on tidal volumes, airway pressures, breathing patterns and sedation management in pneumonia patients during late-phase ARDS. *Design:* Retrospective analysis. *Setting:* Fourteen-bed university hospital ICU. *Patients:* Ten consecutive late-phase ALI/ARDS patients with low pulmonary compliance, and severe hypercapnia. *Intervention:* Gas exchange, tidal volumes, airway pressures, breathing patterns and sedation requirements before (baseline) and after (2–4 days) initiation of treatment with p-ECLA were analysed. Patients were ventilated in a pressure-controlled mode with PEEP adjusted to pre-defined oxygenation goals. *Measurements and main results:* Median reduction in pCO_2 was 50% following institution of p-ECLA. Extracorporeal CO_2 removal enabled significant reduction in tidal volumes (to below 4 ml/kg predicted body weight) and inspiratory plateau pressures [30 (28.5/32.3) cmH_2O, median 25, 75% percentiles]. Normalization of pCO_2 levels permitted significant reduction in the dosages of analgesics and sedatives. The proportion of assisted spontaneous breathing increased within 24 h of instituting p-ECLA. *Conclusion:* Elimination of CO_2 by p-ECLA therapy allowed reduction of ventilator-induced shear stress through ventilation with tidal volumes below 4 ml/kg predicted body weight in pneumonia patients with severely impaired pulmonary compliance during late-phase ARDS. p-ECLA treatment supported control of breathing pattern while sedation requirements were reduced and facilitated the implementation of assisted spontaneous breathing.

Keywords Late-phase ARDS · Hypercapnia · Low tidal volume ventilation · Ventilator-induced lung injury · Shear stress · Pumpless extracorporeal lung assist · Sedation · Assisted spontaneous breathing

Introduction

A prolonged course of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) with no recovery during the first week has been termed as late-phase ARDS [1]. It has been characterized by organization and collagen remodelling and pronounced reductions in pulmonary compliance [2]. In this subset of patients even low tidal volume ventilation may cause lung overdistension and attendant detrimental high inspiratory airway plateau pressures [3]. Furthermore, hypercapnia results in increased inspiratory flows and tidal volumes, and decreased breath-to-breath variability in tidal volumes complicating patient–ventilator interaction and prolonging weaning from mechanical ventilation [4, 5]. In fact, severe hypercapnia, tachypnoea and possible patient distress have been highlighted as reasons why low tidal volume ventilation strategies are not universally implemented in ALI/ARDS patients [6, 7].

To optimize plateau pressures and patient–ventilator interaction long-term ventilated patients with high CO_2-levels often receive high doses of analgesics and sedatives or muscle relaxants [8, 9]. All these factors may compromise weaning and sedation protocols [10] and negate the benefits of early spontaneous breathing [11, 12].

We hypothesized that extracorporeal CO_2 removal using a pumpless extracorporeal lung assist system (p-ECLA, NovaLung®) facilitates lung protective ventilation and the management of sedation in late-phase ALI/ARDS patients with severe hypercapnia.

Methods

We retrospectively analysed a consecutive series of postpneumonic late-phase ALI/ARDS patients [1, 2, 13] with pronounced impairment of pulmonary compliance and severe hypercapnia who were treated in a university-affiliated tertiary referral centre for severe ALI/ARDS in a 18 months period. We assessed the impact of extracorporeal CO_2 removal [14, 15] on airway pressures, tidal volumes, $PaCO_2$ levels, breathing pattern and use of sedatives.

Upon transfer from outside hospitals all patients were ventilated in a pressure-controlled mode (biphasic positive airway pressure ventilation allowing assisted spontaneous breathing, BIPAP/ASB) to be aimed at a tidal volume of 6 ml/kg predicted body weight (PBW). Patients received standardized treatment including permissive hypercapnia, PEEP adjusted to oxygenation, intermittent prone positioning and reduction of extravascular lung water [16–18]. Sedation levels were assessed three times daily using the Ramsay Score with a target of 2–3 [19]. The depth of sedation was increased when hypercapnia was associated with tachypnoe > 40/min, high inspiratory flows, tidal volumes > 6 ml/kg PBW or poor patient–ventilator interaction. Triggers for putting patients on the p-ECLA device were inspiratory plateau pressures > 35 cm H_2O, a $pCO_2 > 80$ mmHg and/or respiratory acidosis with a pH < 7.2 [16]. We performed p-ECLA as described elsewhere [16, 20].

During the period of review we treated a total of 12 patients with p-ECLA. Two patients died due to refractory septic shock within 24 h of beginning p-ECLA. We did not include these two patients in the analysis as no data regarding the primary outcome measures were available.

Measurements

Ventilator settings, arterial blood gases, doses of analgesics and sedatives before (baseline) and after (1 h, 12 h, 2–4 days) initiation of treatment with p-ECLA were retrieved from an electronic patient data management system (PDMS). Ventilator settings were electronically sent to the PDMS every 10 min. The inspiratory plateau pressures (P_{plat}) were automatically computed from the ventilator on mandatory mechanical breaths. The ASB pressures were set to equal the P_{plat} minus PEEP (ΔP_{aw}). After beginning p-ECLA the primary goal was to reduce inspiratory plateau pressures below 32 cmH_2O even if tidal volumes resulted in less than 6 ml/kg PBW [16]. PEEP values were adjusted according to FiO_2. The mandatory rate was decreased when the spontaneous rate increased after reduction of sedation.

Statistics

For repeated measurements Friedman's two-way analysis of variance was used. Post hoc testing of values prior to p-ECLA and values at day 4 after p-ECLA implementation was performed by Wilcoxon-testing for paired samples; $P < 0.05$ (two-sided) was considered statistically significant. Data for continuous variables are given as median and 25th percentiles. Statistical analyses were performed using SPSS, Version 14, SPSS, Inc., Chicago, Illinois, USA.

Results

Ten patients with ALI/ARDS caused by pneumonia were included (Table 1). In three patients there was evidence of a pre-existing pulmonary fibrosis and in one patient a bronchiolitis obliterans and organizing pneumonia (BOOP) was demonstrated histologically. Nine of the ten patients had already been treated in another hospital for a median of 7 (2.25/13.25) days prior to transfer to our

hospital. Three of the patients (patients 6, 7 and 8 in Table 1) had ARDS due to a second infective hit [21] following drug-induced lung injury, immuno-suppression related aspergillosis [22] and pulmonary reinfection, respectively. These patients had also required significant periods of non-invasive ventilation and intensive respiratory therapy prior to intubation and mechanical ventilation. Median duration of ventilation prior to implementation of p-ECLA therapy was 11.5 (2.5/18.75) days. Duration of p-ECLA treatment ranged from 7 to 77—18.5 (8.8/60)—days. In the four patients who survived, the median duration of p-ECLA therapy was 38 (7.25/75) days.

Prior to p-ECLA, median semi-static lung compliance was 14.5 (11.6/19.7) ml/cmH_2O, median pCO_2 was 120 (81.9/154.5) mmHg and median pH was 7.06 (6.9/7.3). In seven patients p-ECLA was established during the first 24 h of ICU admission and in the three remaining patients between 7 and 12 days after admission. For extracorporeal gas exchange we placed a 5 mm (15F) cannula in the femoral artery and a 5.7 mm (17F) cannula in the femoral vein. In one patient dissection and temporary occlusion of the left deep femoral artery occurred during cannulation. In this patient cannulation of the right femoral artery was subsequently performed under angiographic control. Recanalization of the left deep femoral profound artery was in this case achieved through anticoagulation with heparin. No further intervention was necessary.

Detailed data concerning gas exchange and respiratory mechanics are provided in Table 2. Median gas flow through the membrane (sweep flow) was 7.8 (6.6/9) l/min and median p-ECLA blood flow was 1.2 (1.0/1.3) l/min within the first 4 days of the study. The PaO_2/FiO_2 ratios did not change significantly after initiation of p-ECLA; however, the FiO_2 could be reduced during the observation period. Median $PaCO_2$ was reduced by 50% within 12 h of starting p-ECLA. We observed a significant reduction of P_{plat} and ΔP_{aw} by reducing tidal volumes below 4 ml/kg PBW during p-ECLA therapy. The pulmonary compliance remained unchanged. The median pre-intervention infusion rates of fentanyl [8.9 (7.6/10.5) µg/kg per h] (Fig. 1) and midazolam [0.28 (0.17/0.51) mg/kg per h] (Fig. 2) were decreased significantly to 4.4 (2.7/7.1) and 0.19 (0.1/0.2) mg/kg per h, respectively within 4 days of p-ECLA treatment. But there was only a minor change in the depth of sedation: Ramsay score 6 (5/6) at baseline and 5 (4/6) by day 4 ($P > 0.05$). However, a corresponding and statistically significant increase in the proportion of spontaneous breathing (RR_{spon}) was observed. Norepinephrine administration was significantly reduced from 0.2 (0.06/0.7) µg/kg per min at baseline to 0.02 (0/0.13) at day 4 of p-ECLA treatment.

Discussion

We reported that extracorporeal CO_2 removal with a novel pumpless extracorporeal lung assist device facilitated normocapnic ventilation with tidal volumes of less than 4 ml/kg PBW. Reduction of tidal volumes resulted in a significant reduction of inspiratory plateau pressures and ΔP_{aw} reflecting improved lung protection in patients with late-phase ALI/ARDS [1]. Following initiation of p-ECLA we were able to significantly reduce doses of sedatives and analgesics and observed a parallel increase in the proportion of assisted spontaneous breathing.

Table 1 Clinical and demographic characteristics of patients

Patient no.	Gender	Age (years)	MV prior p-ECLA (days)	p-ECLA treatment (days)	ICU-LOS days after transfer	APACHE-II (admission)	SOFA (admission)	Reason for respiratory failure	S/NS	Cause of death
1	M	43	10	8	19	28	6	CAP, BOOP	S	
2	M	46	13	68	115	35	7	Aspiration pneumonia	S	
3	M	47	30	14	29	27	8	Metothrexat-induced lung fibrosis, pneumonia	NS	Pulmonary embolism
4	M	76	9	9	9	32	9	CAP	NS	MOF
5	F	60	14	57	57	31	11	Bleomycin-induced lung fibrosis, pneumonia	NS	Pulmonary bleeding
6	F	56	3	23	43	39	10	Invasive aspergillosis after renal transplantation	NS	MOF
7	F	53	0	13	13	18	4	Cyclophosphamid-induced lung fibrosis, pneumonia	NS	MOF
8	M	46	1	7	51	44	15	HAP	S	
9	F	47	17	77	349	30	15	HAP	S	
10	M	67	24	39	51	40	15	CAP	Ns	MOF

p-ECLA Pumpless extracorporeal lung assist, *ICU-LOS* intensive care unit length of stay, *APACHE-II* Acute Physiology and Chronic Health Evaluation score, *SOFA* Sequential Organ Failure Assessment score, outcome: *S* survivor, *NS* non-survivor, *CAP* community acquired pneumonia, *HAP* hospital acquired pneumonia, *MOF* multiple organ failure, *MV* mechanical ventilation

Table 2 Gas exchange and respiratory parameters before and after p-ECLA insertion

		Day 1			Day 2	Day 3	Day 4
		Prior p-ECLA	6 h post p-ECLA	12 h post p-ECLA			
FiO_2	mmHg	1.0 (1.0/1.0)	0.78 (0.66/1.0)	0.88 (0.66/1.0)	0.83 (0.66/1.0)	0.80 (0.55/0.95)	0.73 (0.66/0.94)*#
PaO_2/FiO_2	mmHg	121.5 (79.3/178.3)	87.5 (74.3/174)	87 (73/139.3)	124.9 (85.8/229.7)	108.5 (80.3/247)	91.5 (78.5/145.5)
$PaCO_2$	mmHg	120 (81.9/154.5)	58.7 (50.5/68.8)	60.3 (52.5/69)	54.8 (45.9/64.5)	56.1 (52.1/61)	53.4 (48.2/58.4)*#
pH		7.06 (6.9/7.3)	7.39 (7.15/7.54)	7.38 (8.18/7.48)	7.34 (7.29/7.44)	7.41 (7.27/7.45)	7.37 (7.3/7.43)*#
Vt	ml/kg PBW	5.2 (4.4/5.9)	4.0 (3.1/4.6)	3.5 (3.1/4.2)	3.5 (2.7/4.1)	3.4 (2.6/4.1)	3.0 (1.8/3.7)*#
RR total	Breath/min	22 (17.5/24)	18 (15.8/26.3)	18 (15/21.5)	23.5 (18.8/27.5)	26 (18.5/36)	19 (17/30.3)*#
RR BIPAP	Breath/min	20 (16/22)	16 (14/17)	15 (10/17)	13 (10/14)	13 (7/14)	13 (10/14)*#
RR spontan	% total RR	2.1 (0/32.8)	33.6 (7.8/55)	32.5 (0/82)	51 (20.5/62.3)	50.8 (4/73.9)	49 (4/55)*#
Insp. plateau pressure	cmH_2O	39 (34.8/43.3)	32 (29.3/35.3)	31.5 (28.8/33.5)	31.5 (30.3/34.3)	31 (28.5/32.3)	30 (28.5/32.3)*#
PEEP	cmH_2O	14 (12.75/17.0)	15 (13.5/16.25)	16 (13.5/17.0)	16 (13.75/17.0)	15.5 (13.5/16.25)	16 (13.25/16.5)
ΔP_{aw}	cmH_2O	25 (19.8/27.5)	17.5 (13.8/21.8)	15 (13/19.5)	16 (14.8/18.5)	16 (11.8/21)	14 (11.8/16.8)*#
Compl. Plat.	ml/cmH_2O	14.5 (11.6/19.7)	14.5 (12.2/17.3)	16.2 (11.4/22.5)	16 (10.3/18.3)	17.8 (6.9/21.6)	13.9 (7/20.7)

p-ECLA Pumpless extracorporeal lung assist, *Vt* tidal volume per kg predicted body weight, *PIP* inspiratory plateau pressure of biphasic positive pressure ventilation (BIPAP), ΔP_{aw} reflects inspiratory pressure minus applied PEEP for mandatory and assisted spontaneous breath, *Compl. Plat* semi-static compliance calculated by (tidal volume)/(plateau pressure minus applied PEEP), *spont RF* frequency of spontaneous respiratory breath in % of total respiratory frequency

* Post hoc testing by Wilcoxon-test for paired observations, values prior to p-ECLA (pumpless extracorporeal lung assist) treatment and values at day 4 after implementation of p-ECLA were compared, $P < 0.05$

Friedman's two-way analysis of variance was used for repeated measurements, $P < 0.05$

It has been shown that low stretch ventilation with low tidal volumes (4–6 ml/kg, PBW) reduces ARDS mortality [23, 24]. However, in patients with severely impaired lung compliance low tidal volume ventilation with 4–6 ml/kg PBW may still represent overexpansion of the lung. Extracorporeal CO_2 elimination may have the potential to reduce inspiratory plateau pressures, ΔP_{aw}, and ultimately ventilator-induced lung injury [25, 26] by enabling ventilation with tidal volumes of less than 4 ml/kg PBW.

We noted a non-significant trend towards a reduced PaO_2/FiO_2 ratio after institution of p-ECLA, while FiO_2 could be reduced. It has been discussed that tidal volumes below 4 ml/kg PBW may result in alveolar derecruitment

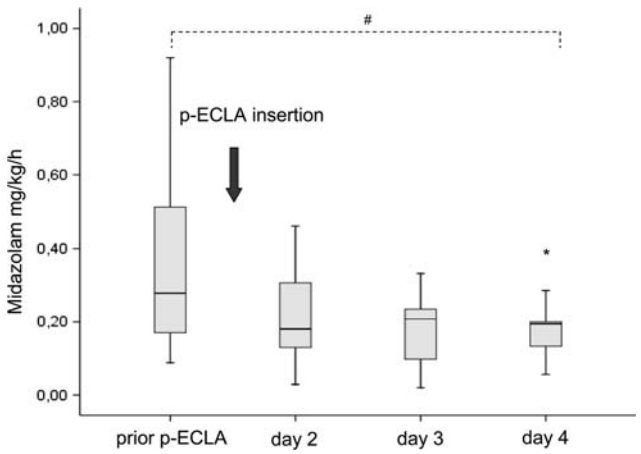

Fig. 1 Cumulative daily dosage of Midazolam (mg/kg per h) before and during p-ECLA (pumpless extracorporeal lung assist); # Friedman's two-way analysis of variance was used for repeated measurements, $P < 0.05$; * post hoc testing by Wilcoxon-test for paired observations, cumulative dosage of midazolam prior p-ECLA and on day 4 after p-ECLA implementation were compared, $P < 0.01$

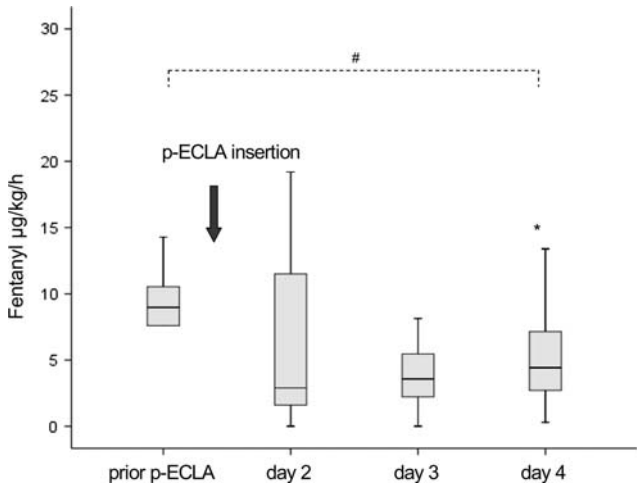

Fig. 2 Cumulative daily dosage of Fentanyl (µg/kg per h) before and during p-ECLA (pumpless extracorporeal lung assist); # Friedman's two-way analysis of variance was used for repeated measurements $P < 0.05$; * post hoc testing by Wilcoxon-test for paired observations, cumulative dosage of fentanyl prior p-ECLA and on day 4 after p-ECLA implementation were compared, $P < 0.01$

if insufficient PEEP levels are applied [27]. On the other hand this might have been caused by a decrease in a CO_2 dependent cardiac output.

Depth of sedation is adversely related to duration of ventilation, length of ICU stay and outcome [10, 28]. Our patients with hypercapnic respiratory drive had high cumulative doses of analgesics and sedatives (Figs. 1, 2) and deep sedation [Ramsay score 6 (5/6)] prior to p-ECLA. Although p-ECLA treatment resulted in a reduction of sedation requirements, we could not observe significant changes in the depth of sedation. This may indicate that dosages prior to p-ECLA were associated with accumulation and reflects a common problem in late-phase ALI/ARDS patients with hypercapnia—namely that high doses of sedation are required in order to achieve an acceptable level of patient–ventilator interaction. However, we observed that reduction of sedatives and analgesics resulted in an increase of spontaneous breathing in the context of a normocapnic respiratory drive.

Our study has a number of limitations. Data concerning breath-to-breath variability in tidal volumes in order to better estimate to what extent extracorporeal CO_2 elimination effects this parameter were not available.

Experiences with the treatment of patients with multiple organ failure and coagulation disorders with a p-ECLA device are limited. The indication of p-ECLA treatment in our cohort was an individual decision with respect to the protracted deleterious mechanical ventilation.

Two patients who died during p-ECLA therapy within the first 24 h were in profound septic shock with massive instable hemodynamics at the time of starting p-ECLA therapy. In both cases p-ECLA was being used as an attempted rescue therapy of profound respiratory acidosis and catecholamine insensitivity. However, there are no data available to substantiate the value of p-ECLA therapy in such cases.

Conclusions

In this study p-ECLA treatment allowed ventilation with tidal volumes below 4 ml/kg PBW in patients with significantly impaired pulmonary compliance. Pulmonary shear stress was reduced and normal pCO_2 and pH could be maintained. We also reported a reduction in sedation requirements and a corresponding increase in assisted spontaneous breathing without the synchronization problems frequently seen in hypercapnic patients. Prospective randomized trials are required to determine whether these observations hold true in larger patient groups and whether there is a beneficial impact on outcome.

References

1. Schmidt GA, Hall JB (2005) Management of the ventilated patient. In: Hall JB, Schmidt GA, Wood LDH (eds) Principles of critical care. McGraw-Hill Professional, New York, p 519
2. Hudson LD, Hough CL (2006) Therapy for late-phase acute respiratory distress syndrome. Clin Chest Med 27:671–677
3. Hager DN, Krishnan JA, Hayden DL, Brower RG, ARDS Clinical Trials Network (2005) Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 172:1241–1245
4. Wysocki M, Cracco C, Teixeira A, Mercat A, Diehl JL, Lefort Y, Derenne JP, Similowski T (2006) Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation. Crit Care Med 34:2076–2083
5. Fiamma MN, Straus C, Thibault S, Wysocki M, Baconnier P, Similowski T (2007) Effects of hypercapnia and hypocapnia on ventilatory variability and the chaotic dynamics of ventilatory flow in humans. Am J Physiol Regul Integr Comp Physiol 292:R1985–R1993
6. Ferguson ND, Frutos-Vivar F, Esteban A, Anzueto A, Alia I, Brower RG, Stewart TE, Apezteguia C, Gonzalez M, Soto L, Abroug F, Brochard L (2005) Airway pressures, tidal volumes, and mortality in patients with acute respiratory distress syndrome. Crit Care Med 33:21–30
7. Weinert CR, Gross CR, Marinelli WA (2003) Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals. Am J Respir Crit Care Med 167:1304–1309
8. Arroliga A, Frutos-Vivar F, Hall J, Esteban A, Apezteguia C, Soto L, Anzueto A (2005) Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest 128:496–506
9. Vinayak AG, Gehlbach B, Pohlman AS, Hall JB, Kress JP (2006) The relationship between sedative infusion requirements and permissive hypercapnia in critically ill mechanically ventilated patients. Crit Care Med 34:1668–1673
10. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW (2008) Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial). A randomised controlled trial. Lancet 371:126–134
11. Putensen C, Mutz NJ, Putensen Himmer G, Zinserling J (1999) Spontaneous breathing during ventilatory support improves ventilation–perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 159:1241–1248
12. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, Mutz N (2001) Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 164:43–49

13. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R (1994) The American–European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
14. Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX, Butz B, Birnbaum D, Taeger K, Schlitt HJ (2006) A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med 34:1372–1377
15. Bein T, Scherer MN, Philipp A, Weber F, Woertgen C (2005) Pumpless extracorporeal lung assist (pECLA) in patients with acute respiratory distress syndrome and severe brain injury. J Trauma 58:1294–1297
16. Deja M, Hommel M, Weber-Carstens S, Moss M, von Dossow V, Sander M, Pille C, Spies C (2008) Evidence-based therapy of severe acute respiratory distress syndrome: an algorithm-guided approach. J Int Med Res 36:211–221
17. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL (2008) Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 34:17–60 Erratum: 34:783–785
18. Lewandowski K, Rossaint R, Pappert D, Gerlach H, Slama KJ, Weidemann H, Frey DJ, Hoffmann O, Keske U, Falke KJ (1997) High survival rate in 122 ARDS patients managed according to a clinical algorithm including extracorporeal membrane oxygenation. Intensive Care Med 23:819–835
19. Ramsay MA, Savege TM, Simpson BR, Goodwin R (1974) Controlled sedation with alphaxalone–alphadolone. Br Med J 2:656–659
20. Fischer S, Simon AR, Welte T, Hoeper MM, Meyer A, Tessmann R, Gohrbandt B, Gottlieb J, Haverich A, Strueber M (2006) Bridge to lung transplantation with the novel pumpless interventional lung assist device novalung. J Thorac Cardiovasc Surg 131:719–723
21. Steinberg J, Halter J, Schiller H, Gatto L, Nieman G (2005) The development of acute respiratory distress syndrome after gut ischemia/reperfusion injury followed by fecal peritonitis in pigs: a clinically relevant model. Shock 23:129–137
22. Lin SJ, Schranz J, Teutsch SM (2001) Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 32:358–366
23. The Acute Respiratory Distress Syndrome Network (2000) 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 342:1301–1308
24. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
25. Hirsch J, Hansen KC, Sapru A, Frank JA, Chalkley RJ, Fang X, Trinidad JC, Baker P, Burlingame AL, Matthay MA (2007) Impact of low and high tidal volumes on the rat alveolar epithelial type II cell proteome. Am J Respir Crit Care Med 175:1006–1013
26. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61
27. Dembinski R, Hochhausen N, Terbeck S, Uhlig S, Dassow C, Schneider M, Schachtrupp A, Henzler D, Rossaint R, Kuhlen R (2007) Pumpless extracorporeal lung assist for protective mechanical ventilation in experimental lung injury. Crit Care Med 35:2359–2366
28. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342:1471–1477