Intensive Care Med (1993) 19:155–160

Intensive Care Medicine

Corticosteroid by aerosol in septic pigs – effects on pulmonary function and oxygen transport

S. Walther, I. Jansson, S. Berg, L. Olsson Rex and S. Lennquist

Trauma Research Unit, Department of Surgery, University Hospital, Linköping, Sweden

Received: 4 May 1992; accepted: 13 November 1992

Abstract. *Objective:* To assess effects of nebulized corticosteroid on lung function in sepsis.
Design: Randomized, placebo-controlled, blinded study in septic pigs.
Setting: A trauma research laboratory.
Materials: 16 juvenile pigs, one excluded due to pulmonary hypertension at baseline.
Interventions: Mechanical ventilation and continuous light anesthesia. Brief infusion of live *Staph. aureus* (4×10^{10} cfu) followed by nebulization of beclomethasone dipropionate (BDP) 50 µg/kg ($n=8$) or placebo ($n=7$) 30 and 360 min after start of septic challenge.
Measurements and results: Vascular pressures, cardiac output, lung mechanics, gas exchange and oxygen transport variables were measured at regular intervals. An identical transient rise in mean pulmonary artery pressure was seen in both groups (mean ± SD: 48 ± 4 mmHg), followed by a gradual increase in pulmonary vascular resistance, reaching maximum at 4 h but significantly reduced by BDP compared to placebo ($p<0.01$, ANOVA). Mean systemic arterial pressure, arterial oxygen tension and lung compliance did not change significantly in the BDP group, but they all declined in the placebo-group ($p<0.01$ compared to baseline, $p<0.05-0.01$ between the groups). Oxygen delivery decreased significantly in the placebo group at 12 h ($p<0.05$). Oxygen extraction increased in both groups ($p<0.01$ compared to baseline), being significantly higher in the placebo group at 12 h ($p<0.05$).
Conclusion: Nebulized corticosteroid protects pulmonary function in sepsis, indicating a therapeutic role in the treatment of septic ARDS.

Key words: Sepsis – *Staph. aureus* – ARDS – Corticosteroid – Aerosol

This study was supported by the Swedish Medical Research Council (MFR Grant No. B90-17X-04987-12C) and by Glaxo Foundation, Sweden

Pulmonary autoinjury by activated immunocompetent cells trapped in the pulmonary microvasculature is considered an important pathogenetic mechanism in sepsis [1–5]. Neutrophils, eosinophils, lymphocytes and macrophages have all been incriminated as possible cellular mediators of septic lung injury [6]. Corticosteroids have a number of effects of potential benefit in this context, e.g. inhibition of complement activation [7] and interference with recruitment and activation of inflammmatory cells [8]. Substantial experimental data support the use of high-dose corticosteroid therapy (HDC) in sepsis [9–12]. Most clinical studies have, however, failed to show any benefit in terms of pulmonary morbidity or mortality of this therapy [13–17]. Moreover, there is data indicating a worse outcome among patients treated with HDC [16, 18]. This has led to the abandoning of HDC as a therapeutic adjunct in sepsis [19, 20], although the controversy still persists [21].

Nebulized corticosteroid has been used previously in experimental ARDS in order to achieve high concentrations of drug in proximity to the capillo-alveolar interface, with a minimum of systemic effects [22–24], a strategy which has proved useful in obstructive lung disease. Improved pulmonary function and increased survival was found in an open pilot study in pigs subjected to a Gram-positive septic insult and followed for 44 h [24]. The purpose of the present study was to further penetrate into the effects of nebulized corticosteroid in septic lung injury. Firstly, we wanted to validate previous observations using a blinded experimental design. Secondly, we wanted to characterize the early effects of nebulized corticosteroid in more detail, including the influence on oxygen delivery and uptake.

Material and methods

Sixteen adolescent pigs, mean ± SD 19.9 ± 1.5 kg were used. The experiments were approved by the ethics committee of the University Hospital of Linköping. After intramuscular premedication with azaperone (Stresnil, Leo, Helsingborg, Sweden) 4 mg/kg and atropine 1 mg, the animals were anesthetized with intravenous metomidate (Hypnodil,

Leo) 10 mg/kg. Instrumentation included tracheostomy, central venous, aortic and pulmonary artery catheters and a cystostomy. After the operation had finished, sedation was maintained with intermittent doses of pentobarbital (Mebumal Vet, ACO, Stockholm, Sweden) 1–4 mg/kg and analgesia was provided by a continuous infusion of meperidine (Pethidin, ACO) 1 mg/kg/h. The animals received continuous positive pressure ventilation with air (tidal volume: 20–25 ml/kg) establishing normocapnia or slight hypocapnia. Normothermia was maintained with heating pads. Balanced electrolyte solutions, 8–12 ml/kg/h, were infused. No antibiotics were given.

After a 60 min period of stabilisation, sepsis was induced by a 20 min infusion of live *Staph. aureus* (Oxford strain S209, ATCC 6538P, AB Biodisk, Stockholm, Sweden), roughly 4×10^{10} cfu, through the central venous line.

Two inhalations of placebo solvent or beclomethasone dipropionate (BDP) 50 µg/kg (Becotide, Glaxo, Mölndal, Sweden) were given, the first 5–10 min after the end of the infusion of bacteria, and the second 6 h later. The aerosol was generated by a jet nebulizer (Aiolos inhaler, Aiolos Medicinsk Teknik AB; Karlstad, Sweden) automatically synchronized to the inspiratory phase of the ventilator. The driving pressure of the nebulizer was selected to generate a particle size distribution in which 85% of the nebulised drug mass comprised particles with a diameter < 10 µ. During nebulization, which took 20–30 min, the animal lay on its back. The aerosol was fed into the suction port of a double swivel tracheal connector (Portex, Hythe, England), attached to the tracheal cannula.

Heart rate, intravascular pressures and thermodilution cardiac output was measured at regular intervals. Lung/thorax compliance (C_L) was measured with a Lung Mechanics Calculator (Siemens Elema, Stockholm, Sweden). Blood gases were analyzed with an automated blood gas laboratory, ABL 2 (Radiometer A/S, Copenhagen, Denmark). Hemoglobin and oxygen saturation was measured with an OSM 2 analyzer (Radiometer A/S).

Measurements were made one hour after the end of the operation (baseline), after the septic challenge and the first BDP-inhalation (1 h), and subsequently at 2, 4, 6, 8, 10, and 12 h after baseline. Mean pulmonary arterial pressure (MPAP) was monitored during the septic insult and the maximum recorded.

The animals were killed at the end of the experiment, and lungs excised, weighed and desiccated for calculation of wet:dry weight ratio. Blood was cultured from a sample taken immediately before sacrifice.

Experimental groups

The animals were randomized to receive beclomethasone dipropionate 50 µg/kg (BDP-group, $n = 8$) or the equivalent volume (about 5 ml) of solvent (placebo-group, $n = 8$) from coded vials. The code was broken at the end of the series of experiments.

Calculations and statistics

Pulmonary vascular resistance (PVR) and oxygen transport variables indexed to body weight were calculated with standard formulas. As interanimal variations in baseline measurements of gas exchange and lung mechanics were considerable (PaO_2 108–129 mmHg, C_L 19–31 ml/cmH_2O) these data were analyzed comparing individual values at baseline and later points in time. All data are expressed as mean±SD. Analysis of variance and the protected least significant difference method was used to assess differences within and between groups. A probability of less than 0.05 was accepted as significant.

Results

All animals survived 12 h. One animal randomised to the placebo group was found to have pulmonary hypertension on baseline measurements (MPAP 33 mmHg), it collapsed during infusion of bacteria because of extreme pulmonary vasoconstriction (MPAP 80 mmHg). It was excluded from final analysis, although after resuscitation its 12 h response to sepsis not differed from the rest of the placebo group (MPAP 24 mmHg, PaO_2 −38 mmHg, C_L −7 ml/cmH_2O).

The initial pulmonary vascular response to the septic challenge with an almost 300% increase in MPAP was transient (Fig. 1). This pronounced but brief initial increase in pulmonary vascular resistance (PVR) could not be calculated because thermodilution cardiac output was impossible to assess with accuracy during infusion of bacteria. The decline in PVR, as reflected by a fall in MPAP, towards the end of the bacterial infusion was followed by a gradual rise in PVR reaching its maximum in both groups at 4 h. This increase was significantly smaller in the BDP-group ($p < 0.01$, at 4 h and $p < 0.05$ at 6 h, Fig. 1). The increase in PVR was compared to baseline significant in the placebo group from 2 h ($p < 0.01$). In the BDP-group PVR was significantly elevated compared with baseline at 4 ($p < 0.01$) and 10 h ($p < 0.05$). A significant decrease in MAP was recorded in

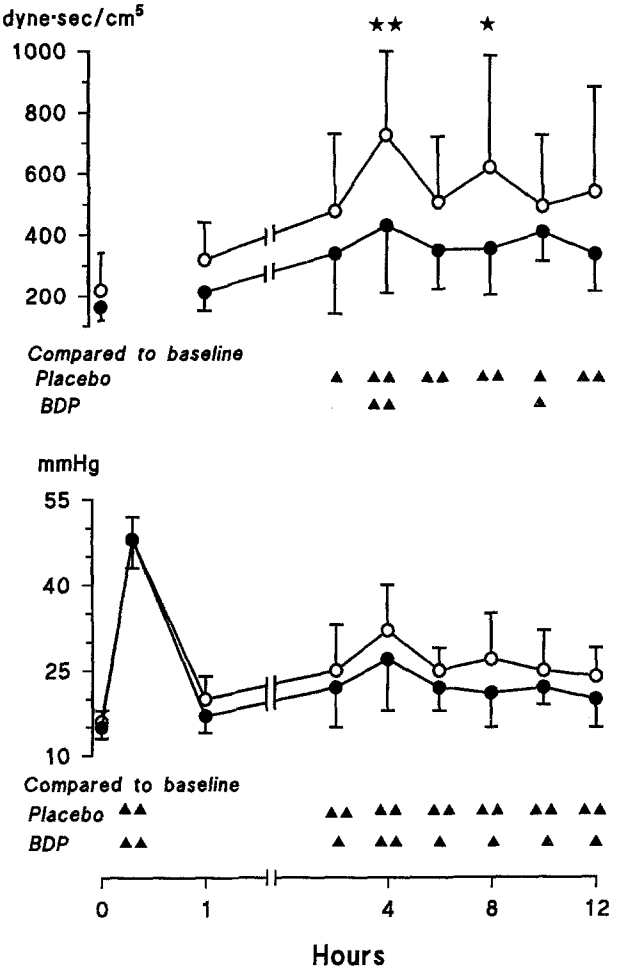

Fig. 1. Pulmonary vascular resistance, PVR (*top*), and mean pulmonary artery pressure (*bottom*). Peak PVR during the first hour was impossible to calculate accurately because stable thermodilution cardiac output could not be obtained due to extreme pulmonary vasoconstriction during the septic challenge. *Filled circles*, beclomethasone dipropionate group; *open circles*, placebo group. Mean±SD; $*p < 0.05$ and $**p < 0.01$ between groups, $\blacktriangle p < 0.05$ and $\blacktriangle\blacktriangle p < 0.01$ compared to baseline

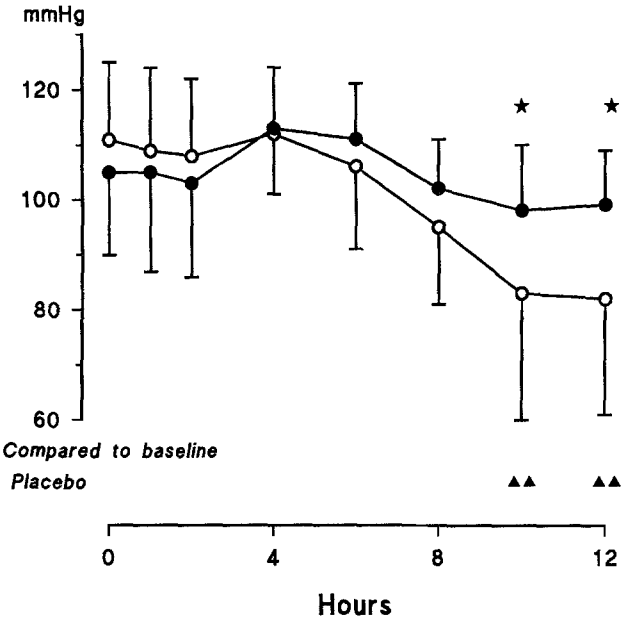

Fig. 2. Mean systemic artery pressure. Symbols as in Fig. 1

the placebo group, with significantly lower mean pressures than in the BDP group at the end of the experiment (Fig. 2). There were no significant differences within or between groups in cardiac filling pressures.

Arterial oxygen tension (PaO_2) did not change significantly with time in the BDP-group (Fig. 3). In the placebo group a significant decrease compared with baseline was seen from 3 h ($p < 0.05-0.01$). The difference between the groups at 12 h was statistically highly significant ($p < 0.01$). There were no significant changes within, or differences between the groups in arterial $PaCO_2$. C_L decreased gradually in both groups from 2 h of observation. The decrease was not significant compared to baseline in the BDP-group. A statistically highly significant fall was noticed in the placebo group ($p < 0.01$ at 12 h, Fig. 4). The differences between the groups was significant from 8 h ($p < 0.05-0.01$).

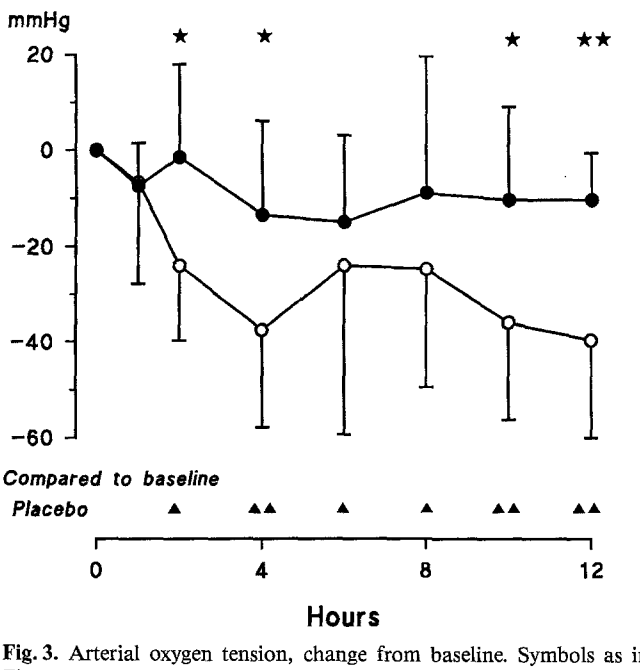

Fig. 3. Arterial oxygen tension, change from baseline. Symbols as in Fig. 1

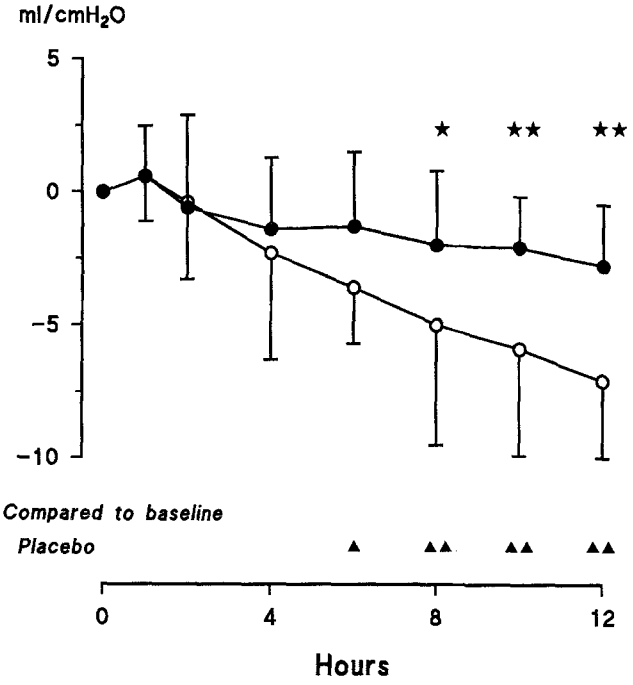

Fig. 4. Lung/thorax compliance, change from baseline. Symbols as in Fig. 1

Oxygen delivery decreased in both groups, the decline was most marked in the placebo group ($p < 0.05$ compared to baseline at 12 h, Fig. 5). Oxygen consumption increased 30%–35% in both groups and reached its highest value 11.4 ml O_2/min at 4 h, and remained thereafter essentially unchanged. The overall changes were too small to attain statistical significance (Fig. 5). Oxygen extraction ratio increased significantly ($p < 0.01$) from 34%±4% to 58%±3% in the BDP group and from 34%±8% to 70%±17% in the placebo group ($p < 0.05$ between groups at 12 h, Fig. 6).

The wet: dry weight ratio was increased in the placebo group compared with the BDP treated animals (6.88±0.90 compared with 5.29±0.58, $p < 0.05$). Both groups received similar amounts of crystalloid solutions (BDP-group 9.9±1.2 vs placebo group 10.2±1.4 ml/kg/h) during the study. All blood cultures obtained before sacrifice grew *Staph. aureus* S209.

Discussion

In the present study we used a Gram-positive septic challenge, which previously has been shown to induce pulmonary dysfunction with a greater than 50% mortality during a 44 h period of observation [24]. The pulmonary hemodynamic response to the infusion of staphylococci was biphasic. The initial threefold increase in MPAP is probably explained by an imbalance in eicosanoid production favoring the vasoconstrictor thromboxane A_2, which is produced in the pulmonary circulation in response to live *Staph. aureus* [25] as well as staphylococcal

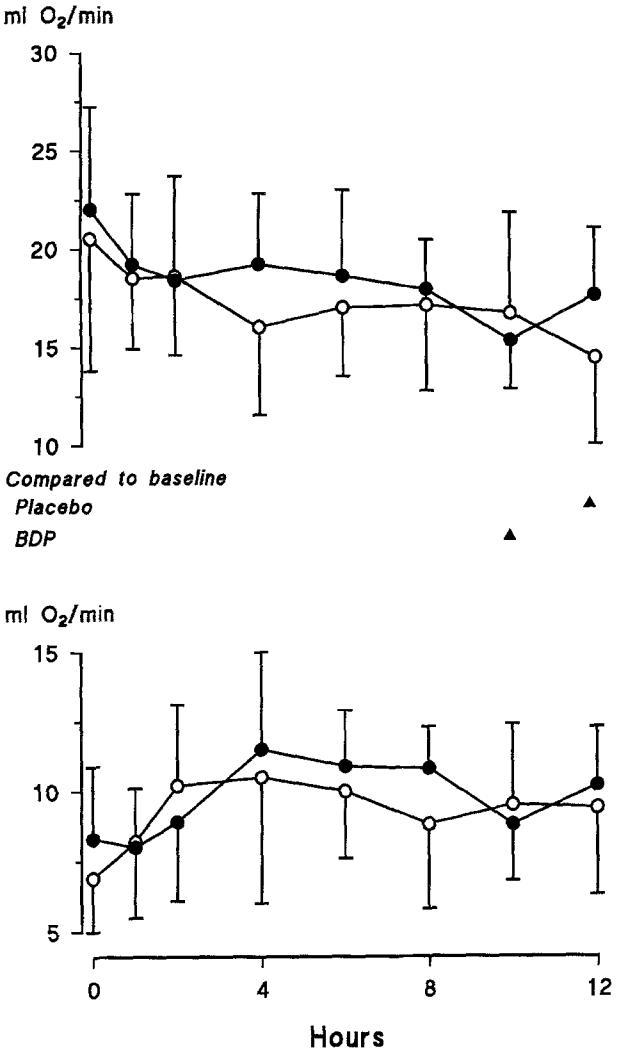

Fig. 5. Oxygen delivery (*top*) and consumption (*bottom*). Symbols as n Fig. 1

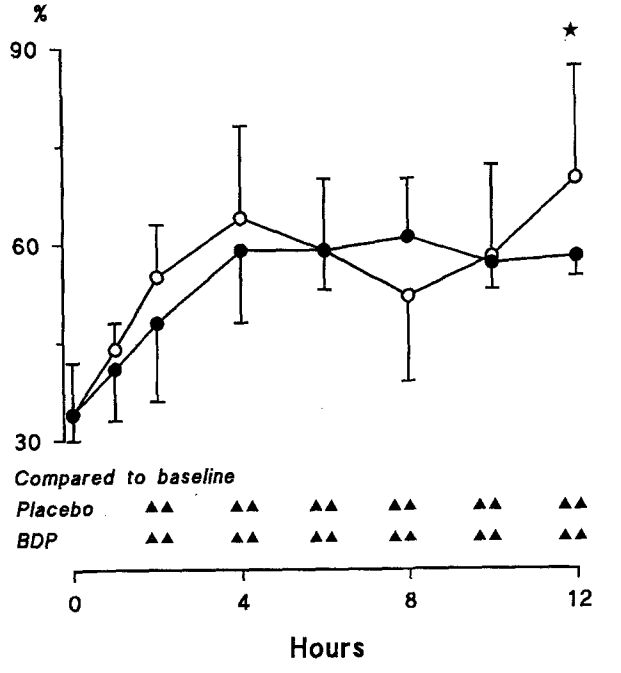

Fig. 6. Oxygen extraction ratio. Symbols as in Fig. 1

exotoxin [26]. The gradually evolving pulmonary hypertension, which could be attributed to an increased microvascular opening pressure secondary to endothelial and interstitial swelling [27], was significantly reduced by administration of BDP. The septic challenge caused a pronounced deterioration in gas exchange with a fall in PaO_2 among placebo treated animals. The decrease occured in spite of ventilatory support, which others have found to prevent alterations in gas exchange in endotoxemia [28]. Administration of BDP slowed the fall in PaO_2. Nebulized BDP reduced the fall in C_L noted in the placebo treated group, which has been shown to coincide with an increase in lung lymph flow in endotoxemic sheep [29] indicating an association with accumulation of interstitial fluid in the lung. This accords with the lower wet:dry weight ratio in the BDP group.

Systemic blood pressure was maintained among BDP treated pigs, whereas a decrease was observed in the placebo group. Septic injury to the pulmonary vascular endothelium could explain part of the systemic circulatory dysregulation encountered in sepsis, as the endothelium is rich in enzymes that take up and convert vasoactive substances [30]. Although speculative, the better preserved systemic blood pressure in the BDP group could reflect a better maintained metabolic function in the pulmonary circulation.

The extension analyzing global oxygen transport and consumption variables was motivated by improved maintenance of systemic blood pressure observed earlier in pigs receiving BDP [24]. The duration of this study, which was determined as a result of effects of BDP on pulmonary function and mortality within 12 h in previous work, was long enough to track effects on systemic hemodynamics. It was, however, too short to allow for a definite analysis of the effects of BDP on oxygen utilization. Both groups were capable of increasing oxygen extraction substantially, the reserve capacity probably being less in the placebo group in which extraction was significantly higher than in the BDP group at the end of the experiment.

Intrapulmonary corticosteroid administration in sepsis has been studied previously [22–24], with the aim of reducing systemic effects of the therapy. Intratracheal and inhaled nebulized budesonide administration initiated before sepsis was associated with prolonged survival and normalized hematocrit in rats [22]. Similar plasma concentrations of budesonide was, however, seen following intravenous and intratracheal administration, suggesting essentially similar systemic effects irrespective of administration route. Prophylactic treatment with nebulized group III corticosteroid liposomes either 2 h or 15 min before endotoxemia in pigs reduced some aspects of pulmonary dysfunction without affecting endogenous cortisol secretion [23]. Earlier preliminary work showed increased survival and reduced pulmonary dysfunction in septic pigs treated with nebulized BDP 10 μg/kg every 6 h for 44 h with no detectable BDP in blood [24]. The positive pulmonary action of BDP, although in a higher dosage, was confirmed in this blinded and placebo-controlled study. We could, however, not detect any further improvement in response to the increased dosage.

Beclomethasone-dipropionate (BDP), has been used in the treatment of obstructive lung disease since 1972. The total dose used in the present set up, about 2000 μg, is 3–4 times higher/kg bodyweight than the high dose used in obstructive lung disease [31] and the interval between doses was as in current clinical practice. Intravenously administered BDP is roughly 25 times as potent a systemic glucocorticoid as hydrocortisone, but it is an extremely effective topical anti-inflammatory agent, thought to be about 5000 times more so than hydrocortisone [32]. Because the drug is partly metabolised by esterases in the lung [33], the favorable ratio between topical and systemic activity increases further when BDP is given directly into the lungs. In view of this, it is unlikely that BDP exerts its hemodynamic and pulmonary effects in the present study only after absorption into the blood stream. The pharmacodynamic data also suggest that the effects were attained with a minimum of systemic side effects.

The short interval between septic insult and start of aerosol therapy makes extrapolation of the results to a clinical context difficult. BDP was, however, administered after the peak pulmonary vascular response, which suggest positive actions of the corticosteroid on already initiated pathophysiologic processes. To be able to analyze the significance of nebulized corticosteroid in clinical sepsis, further studies with delayed therapy are necessary. If, although speculative, actions of nebulized corticosteroid are mediated by reduced accumulation and activation of immunocompetent cells in the lung, delayed therapy should perhaps be combined with interventions aimed at already present secondary mediators produced by sequestered cells [34, 35].

To conclude, the positive pulmonary and hemodynamic actions of nebulized corticosteroid given 30 and 360 min after initial septic challenge indicate that this treatment modality deserves further analysis as a therapeutic adjunct of value in ARDS.

Acknowledgements. This work was supported by grants from the Swedish Medical Research Council (MFR Grant No. B90-17X-04987-12C). The inhalers were donated by Aiolos Medicinsk Teknik. Beclomethasone dipropionate was kindly supplied by Glaxo. We thank Gunilla Willén, Elisabeth Palmquist, Mats Gunnarsson and Mats Johansson for excellent technical assistance.

References

1. Repine JE, Beehler CJ (1991) Neutrophils and the adult respiratory distress syndrome: two interlocking perspectives in 1991. Am Rev Respir Dis 144:251–252
2. Weiland JE, Davis WB, Holter JF, Mohammed JR, Dorinsky PM, Gadek JE (1986) Lung neutrophils in the adult respiratory distress syndrome. Clinical and pathophysiologic significance. Am Rev Respir Dis 133:218–225
3. Regel G, Dwenger A, Seidel J, Nerlich ML, Sturm J, Tscherne H (1987) Die Bedeutung der neutrophilen Granulozyten bei der Entstehung des posttraumatischen Lungenversagens. Unfallchirurg 90:99–106
4. Hällgren R, Borg T, Venge P, Modig J (1984) Signs of neutrophil an eosinophil activation in adult respiratory distress syndrome. Crit Care Med 12:14–18
5. Warner AE, Molina RM, Brain JD (1987) Uptake of bloodborne bacteria by pulmonary macrophages and consequent inflammatory responses in sheep. Am Rev Respir Dis 136:683–690
6. Modig J (1990) ARDS – Current concepts and therapy. In: Aasen AO, Risberg B (eds) Surgical pathophysiology. Harwood, Chur, Switzerland, pp 241–266
7. Packard BD, Weiler JM (1983) Steroids inhibit activation of the alternative-amplification pathway of complement. Infect Immun 40:1011–1014
8. Fauci AS, Dale DC, Balow J (1976) Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med 84:304–315
9. Brigham KL, Bowers RE, McKeen CR (1981) Methylprednisolone prevention of increased lung vascular permeability following endotoxaemia in sheep. J Clint Invest 67:1003–1110
10. Demling RH, Smith M, Gunther R, Wandzilak T (1981) Endotoxin-induced lung injury in unanaesthetized sheep. Effect of methylprednisolone. Circ Shock 8:351–360
11. Hinshaw LB, Beller-Todd BK, Archer LT (1982) Current management of the septic shock patient: experimental basis for treatment. Circ Shock 9:543–553
12. Borg T, Gerdin B, Modig J (1985) Prophylactic and delayed treatment with high-dose methylprednisolone in a porcine model of early ARDS induced by endotoxaemia. Acta Anaesthesiol Scand 29:831–845
13. The Veterans Administration Systemic Sepsis Cooperative Study Group (1987) Effect of high-dose corticosteroid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 317:659–665
14. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, Kariman K, Higgins S, Bradley R, Metz CA, Harris TR, Brigham KL (1987) High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 317:1565–1570
15. Schein RMH, Bergman R, Marcial EH, Schultz D, Duncan RC, Arnold PI, Sprung CL (1987) Complement activation and corticosteroid therapy in the development of the adult respiratory distress syndrome. Chest 91:850–854
16. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, The Methylprednisolone Severe Sepsis Study Group (1987) Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest 92:1032–1036
17. Luce JM, Montgomery AB, Marks JD, Turner JM, Murray JF (1988) Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 138:62–68
18. Weigelt JA, Norcross JF, Borman KR (1985) Early steroid therapy for respiratory failure. Arch Surg 120:536–540
19. Sprung L, Schein MH, Long WM (1989) Corticosteroids and nonsteroidal anti-inflammatory agents in the sepsis syndrome. In: Reinhart K, Eyrich K (eds) Sepsis – an interdisciplinary challenge. Springer, Berlin, pp 87–96
20. Bone RC, Brown RC (1990) Therapy of septic shock: new strategies. In: Vincent JL (ed) Update in intensive care and emergency medicine 10. Springer, Berlin, pp 121–127
21. Sjölin J (1991) High-dose corticosteroid therapy in human septic shock: has the jury reached a correct verdict? Circ Shock 35:139–151
22. Ottoson J, Dawidsson IJA, Svensjö E, Brattsand R, Dahlbäck M (1987) Intravenous versus intrapulmonary administration of corticosteroids in combination with fluid infusion in experimental septic shock. Acta Chir Scand 153:507–512
23. Forsgren PE, Modig JA, Dahlbäck CMO, Axelsson BI (1990) Prophylactic treatment with aerosolized corticosteroid liposome in a porcine model of early ARDS induced by endotoxemia. Acta Chir Scand 156:423–431
24. Walther S, Jansson I, Gunnarsson M, Lennquist S (1991) Nebulized corticosteroid improves pulmonary function and outcome in experimental porcine septicemia. Acta Anaesthesiol Scand 35:635–641
25. Shoemaker SA, Heffner JE, Canham EM, Tate RM, Morris HG, McCurtry IF, Repine JE (1984) *Staphylococcus aureus* and human platelets cause pulmonary hypertension and thromboxane genera-

tion in isolated saline-perfused rabbit lung. Am Rev Respir Dis 129:92–95
26. Seeger W, Bauer M, Bhakdi S (1984) Staphylococcal α-toxin elicits hypertension in isolated rabbit lungs: evidence for thromboxane formation and the role of extracellular calcium. J Clin Invest 74:849–858
27. Hales C (1986) Pulmonary vasoreactivity in acute lung injury. In: Kazemi H, Hyman AL, Kadowitz PJ (eds) Acute lung injury. PSG, Littleton, Mass, pp 81–92
28. Borg T, Modig J (1987) Intermittent and continuous positive-pressure ventilation in the prophylaxis of endotoxin-induced lung insufficiency. A study in pigs. Acta Anaesthesiol Scand 31:67–72
29. Esbenshade AM, Newman JH, Lams PM, Jolles H, Brigham KL (1982) Respiratory failure after endotoxin infusion in sheep: lung mechanics and lung fluid balance. J Appl Physiol 53:967–976
30. Gillis CN, Catravas JD (1982) Altered removal of vasoactive substances in the injured lung: detection of lung microvascular injury. Ann NY Acad Sci 384:458–474
31. Smith MJ, Hodson ME (1983) High-dose beclomethasone inhaler in the treatment of asthma. Lancet I:265–268
32. Harris DM (1975) Some properties of beclomethasone dipropionate and related steroid in man. Postgrad Med J 51 [Suppl 4]:20–25
33. Martin LE, Harrison C, Tanner RJ (1975) Metabolism of beclomethasone dipropionate by animals and man. Postgrad Med J 51 [Suppl 4]:11–20
34. Jepson S, Herlevsen P, Knudsen P, Bud MI, Klausen N-E (1992) Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. Crit Care Med 20:918–923
35. Bone RC (1992) Phospholipids and their inhibitors: A critical evaluation of their role in the treatment of sepsis. Crit Care Med 20:884–890

S. Walther
Anestesikliniken
Lasarettet
S-601 82 Norrköping
Sweden

Announcements

Intensive Care Medicine

14th International Symposium on Current Problems in Emergency and Intensive Care Medicine 1993

This meeting will be held from May 12–15, 1993 at the Halle Münsterland in Münster, Germany. For further information, please contact: Univ.-Prof. Dr. Dr. h. c. P. Lawin, FCCM, Klinik und Poliklinik für Anästhesiologie und operative Intensivmedizin, Westfälische Wilhelms-Universität Münster, Albert-Schweitzer-Str. 33, W-4400 Münster, Germany. Phone: (0)251-837252/53, Fax: 49-251-88704

7th Continuing Education Meeting of the Victorian Branches of ANZICS abd CACCN

This meeting of the Australian and New Zealand Intensive Care Society (ANZICS) and the Confederation of Australian Critical Care Nurses (CACCN) will be held on May 28–29, 1993 at the World Trade Center in Melbourne. *Topics include:* Tonometry and tissue perfusion; New strategies for mechanical ventilation; Best ventilator management for ARDS in the 1990's; QALYS and Gut in critically ill patients. *For further information please contact:* Dr. Ch. Corke, Geelong Hospital, P.O. Box 281, Geelong, Victoria, Australia 3220. Phone: +61 5226.7765; Fax: +61 5229.9971.

Perioperative Cardiac Care – A Joint Anesthesiology-Cardiology Symposium

This symposium will be held in Eilat, Israel, from June 2–4, 1993. The *topics* will include all aspects of perioperative management of the patient with heart disease undergoing surgery, including: Preoperative assessment of the vascular patient; Choosing the ideal ionotropic agent; Effect of thoracic epidural anesthesia on cardiac ischemia; ACE inhibition during anesthesia. *For further information please contact:* Prof. Azriel Perel, Chairman, Department of Anesthesiology, Sheba Medical Center, Tel-Hashomer, Israel 52621. Phone: 972-3-5302754; Fax: 972-3-5302490.

6th World Congress on Intensive and Critical Care Medicine

This congress will be held from 14–18 June 1993 in Madrid, Spain. *For further information please contact:* Prof. A. Esteban, President of the Congress, Secretaria Tecnica Congrhisa, Av. Velaszquez 90-5°, E-26008, Madrid, Spain. Tel.: 34-1-5762580; Fax: 34-1-5773874.

International Satellite Symposium on Acute Renal Failure with Special Emphasis on Sepsis

This symposium sponsored by the International Commission on Acute Renal Failure will be held from 20–23 June 1993 in Halkidiki, Greece. *Topics will include:* new insights in the pathogenesis, infections and ARF, ARF in intensive care units, multiple organ failure, endotoxins, cytokines, endothelins, prostanoids, proteases, and their role in ARF, antiendoxins and growth factors, calcium antagonists in the management of ARF, CAVHD and plasmapheresis. *For further information please contact:* Dr. E. Alexopoulos, MD, Dept. of Nephrology, Hippokration General Hosp., 50 Papanastasiou Str, Thessaloniki, Greece. Tel: 031-828595; Fax: 0030-31-818254.

Fourth Annual Meeting of the European Society of Computing and Technology in Anaesthesia and Intensive Care (ESTAIC)

This meeting will be held on October 6–9, 1993 in Goldegg Castle, Salzburg, Austria. *For further information please contact:* Peter Schwab, Mensch & Arbeit Veranstaltungsorganisation GmbH, Keltenweg 22, A-5020 Salzburg, Austria. Phone: +43 662 436215; Fax: +43 662 436716.

3rd International Symposium. Nosocomial Infection Control in Intensive Care. Septicemia – Current Problems and Future Trends

This symposium will be held on October 28–30, 1993 in Freiburg, FRG. *For further information please contact:* Prof. Dr. K. Geiger, Department of Anesthesia, University of Freiburg, Hugstetterstrasse 55, W-7800 Freiburg, Germany. Phone: 761-2702306; Fax: 761-2702396.