Commentary

Recently published papers: inflammation, elucidation, manipulation?

Justin Kirk-Bayley[1] and Richard Venn[2]

[1]Research registrar, Anaesthesia and Intensive Care, Worthing Hospital, West Sussex, UK
[2]Consultant, Anaesthesia and Intensive Care, Worthing Hospital, West Sussex, UK

Correspondence: Justin Kirk-Bayley, jkb@orange.net

Published online: 3 July 2003 *Critical Care* 2003, **7**:282-284 (DOI 10.1186/cc2347)
This article is online at http://ccforum.com/content/7/4/282

The search for *the* marker in sepsis and inflammation continues. Perhaps when we do find it we may be able to alter and influence the underlying pathophysiology of sepsis. Many reports from those who believe that this may lie in the hypothalamic–pituitary–adrenal axis have recently been published. Manglik and colleagues [1] looked into secondary adrenocortical insufficiency in patients who present with severe sepsis. Measuring maximal cortisol secretion after stimulation with adrenocorticotrophic hormone, those investigators found that 9% of their population failed an adrenocorticotrophic hormone stimulation test. Four per cent had previously undiagnosed pituitary disease and 5% were suffering from sepsis-related adrenal dysfunction. They used absolute cortisol levels and not delta cortisol to define adrenocortical insufficiency, but until we have an established definition for adrenocortical insufficiency in sepsis the studies will continue to yield disparate results.

Looking at reduced endogenous steroid levels in sepsis, Marx and coworkers [2] focused on the androgens dehydroepiandrosterone (DHEA) and its sulphated precursor (DHEAS) and looked at disparity between survivors and nonsurvivors from severe sepsis. The cortisol levels of survivors reached upper normal limits and decreased significantly toward late sepsis. However, nonsurvivors had persistently lower cortisol levels (but within the normal physiological range) throughout sepsis. DHEAS paralleled this in survivors, with normal early levels reducing in late sepsis, but in nonsurvivors levels were persistently low throughout and to a significant degree. Survivors had persistently elevated levels of DHEA as compared with nonsurvivors. Marx and coworkers showed that relative adrenocortical insufficiency extends to androgens, that DHEA and DHEAS changes do not parallel each other, and that DHEAS levels may even predict survival in severe sepsis, which APACHE (Acute Physiology and Chronic Health Evaluation) scores do not.

So will stress doses of hydrocortisone attenuate severe systemic inflammatory response syndrome after cardiac surgery with cardiopulmonary bypass? Kilger and coworkers [3] would suggest that in high-risk patients this is so. They found that severe systemic inflammatory response syndrome (serum interleukin-6 concentration >1000 pg/ml) was best predicted in their population by a bypass time in excess of 97 min and cardiac ejection fraction below 40%. Thus, by targeting their predefined high-risk patients to receive hydrocortisone, they showed recipients to have significantly lower interleukin-6 levels, reduced duration of ventilation and catecholamine support, and reduced duration of stay in the intensive care unit and the hospital. Nothing yet suggests a mortality benefit though.

Increased tissue factor is produced as part of the septic inflammatory process because the coagulation cascade is activated too. Carraway and coworkers [4] have already shown that pretreating baboons with active site-inactivated factor VII and tissue factor pathway inhibitor at the onset of sepsis attenuates organ injury and is protective for lung and kidney. They have now shown that similarly blocking tissue factor in established Gram-negative sepsis will attenuate this damage [5]. Using a baboon model again, they blocked coagulation cascade initiation using active site-inactivated factor VII at the time of first antibiotic therapy after inducing sepsis. This resulted in reduced acute lung injury, renal injury, metabolic acidosis and sepsis-induced coagulopathy. Can we manipulate this therapeutically in human sepsis? Time and more research will tell.

ARDS = acute respiratory distress syndrome; DHEA(S) = dehydroepiandrosterone (sulphate); NO = nitric oxide.

Moving away from direct involvement of the inflammation/coagulation process, Soliman and colleagues [6] looked at how the ionized portion of serum magnesium varies in the critically ill. They found that ionized magnesium level at presentation did not affect outcomes (two-thirds of their population had normal levels), but that the development of reduced levels of ionized magnesium while in intensive care was associated with higher mortality and more severe organ dysfunction. Sepsis was an independent risk factor for ionized hypomagnesaemia, but Soliman and colleagues postulated that prolonged disease and diuretic administration may also be contributory. It may be that low levels contribute to critical illness, or that just the converse is true. Which is true is unclear. What we need now is to discover how magnesium supplementation will alter these findings.

Inappropriate ventilatory strategies for patients with acute respiratory distress syndrome (ARDS) may have more consequences for the recipient than just lung abnormalities. Imai and colleagues [7] indicated that remote cellular damage also occurs and that this may contribute to the multiple organ dysfunction that often accompanies ARDS. They looked at end-organ epithelial cell apoptosis in a rabbit model of ARDS and at the effects of plasma on epithelial cells from recipients of the injurious ventilatory strategy, and analyzed samples from a previous trial into lung protective ventilation [8]. They showed that kidney and small intestine damage occurred when ventilation with high tidal volumes and low positive end-expiratory pressures were used, and that plasma from rabbits in this group would induce apoptosis in cells *in vitro*. The Fas–Fas ligand system is involved in cell apoptosis, and they found elevated levels of soluble Fas ligand in human patients who had not received a protective ventilatory strategy, which correlated well with elevations in creatinine levels. Choosing the right ventilation strategy for ARDS patients has more benefits than just lung protection, and therapeutic targeting of these factors that induce end organ apoptosis may be the next step.

Choosing the right ventilation strategy may not be the only way to avoid lung problems in patients with ARDS. Desirable strategies involve the prevention of over-distended alveoli and their de-recruitment. Thus, it is not unreasonable to consider that periodic endotracheal suctioning might undermine these benefits. Maggiore and colleagues [9] set out to find out whether this was so in patients with acute lung injury, and considered preventative measures. They found that closed suctioning systems reduced large lung volume falls and preserved positive end-expiratory pressure induced recruitment. Recruitment was augmented by performing recruitment manoeuvres at the time of suctioning. Repetitive shearing stresses on alveoli are injurious, and this study shows some ways to prevent this.

Using inhaled nitric oxide (NO) in patients with ARDS improves oxygenation, but it has not been proven to improve outcome. Why is this so? Gerlach and coworkers [10] looked at dose–response characteristics when long-term NO is used and found that these characteristics changed. Patients could become sensitized to NO, such that the number of responders to low NO doses increased and some became nonresponders at higher NO doses. It would seem that constant dose NO is not right for all patients throughout their treatment, and that there is more inter-patient and intra-patient NO dose–response variability than we had thought. Titrating doses at each step may improve long-term benefits from NO therapy.

With respect to inotropes, which one should we use? The debate continues. De Backer and colleagues [11] compared inotropes and their effects on the splanchnic circulation in sepsis. Dopamine was used and then substituted for either adrenaline (epinephrine) or noradrenaline (norepinephrine) to achieve or maintain adequate arterial pressures depending on shock severity. The three inotropes were comparable in moderate shock, and dopamine would actually appear to have modest benefits for splanchnic circulation. However, in more severe septic shock adrenaline impaired splanchnic circulation, and De Backer and colleagues suggested that it should be avoided in high doses in these patients. A larger, truly randomized trial should determine whether they are correct. However, if you use low dose dopamine in critically ill patients for renal protection, Holmes and Walley [12] tell us that the practice should be, "relegated to the place of high-tidal volume ventilation and liberal transfusion practices".

Competing interests

None declared.

References

1. Manglik S, Flores E, Lubarsky L, Fernandez F, Chhibber VL, Tayek JA: **Glucocorticoid insufficiency in patients who present to the hospital with severe sepsis: a prospective clinical trial.** *Crit Care Med* 2003, **31:**1668-1675.
2. Marx C, Petros S, Bornstein SR, Weise M, Wendt M, Menschikowski M, Engelmann L, Hoffken G: **Adrenocortical hormones in survivors and nonsurvivors of severe sepsis: diverse time course of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, and cortisol.** *Crit Care Med* 2003, **31:**1382-1388.
3. Kilger E, Weis F, Briegel J, Frey L, Goetz AE, Reuter D, Nagy A, Schuetz A, Lamm P, Knoll A, Peter K: **Stress doses of hydrocortisone reduce severe systemic inflammatory response syndrome and improve early outcome in a risk group of patients after cardiac surgery.** *Crit Care Med* 2003, **31:**1068-1074.
4. Welty-Wolf KE, Carraway MS, Miller DL, Ortel TL, Ezban M, Ghio AJ, Idell S, Piantadosi CA: **Coagulation blockade prevents sepsis-induced respiratory and renal failure in baboons.** *Am J Respir Crit Care Med* 2001, **164:**1988-1996.
5. Carraway MS, Welty-Wolf KE, Miller DL, Ortel TL, Idell S, Ghio AJ, Petersen LC, Piantadosi CA: **Blockade of tissue factor: treatment for organ injury in established sepsis.** *Am J Respir Crit Care Med* 2003, **167:**1200-1209.
6. Soliman HM, Mercan D, Lobo SS, Melot C, Vincent JL: **Development of ionized hypomagnesemia is associated with higher mortality rates.** *Crit Care Med* 2003, **31:**1082-1087.
7. Imai Y, Parodo J, Kajikawa O, de Perrot M, Fischer S, Edwards V, Cutz E, Liu M, Keshavjee S, Martin TR, Marshall JC, Ranieri VM, Slutsky AS: **Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experi-**

mental model of acute respiratory distress syndrome. *JAMA* 2003, **289:**2104-2112.
8. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: **Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial.** *JAMA* 1999, **282:**54-61.
9. Maggiore SM, Lellouche F, Pigeot J, Taille S, Deye N, Durrmeyer X, Richard JC, Mancebo J, Lemaire F, Brochard L: **Prevention of endotracheal suctioning-induced alveolar derecruitment in acute lung injury.** *Am J Respir Crit Care Med* 2003, **167:**1215-1224.
10. Gerlach H, Keh D, Semmerow A, Busch T, Lewandowski K, Pappert DM, Rossaint R, Falke KJ: **Dose–response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study.** *Am J Respir Crit Care Med* 2003, **167:**1008-1015.
11. De Backer D, Creteur J, Silva E, Vincent JL: **Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best?** *Crit Care Med* 2003, **31:**1659-1667.
12. Holmes CL, Walley KR: **Bad medicine: low-dose dopamine in the ICU.** *Chest* 2003, **123:**1266-1275.

Appendix

As well as the references cited in the text, I also recommend the following.

Dreyfuss D, Ricard JD, Saumon G: **On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury.** *Am J Respir Crit Care Med* 2003, **167**:1467-1471.

Ferrand E, Lemaire F, Regnier B, Kuteifan K, Badet M, Asfar P, Jaber S, Chagnon JL, Renault A, Robert R, Pochard F, Herve C, Brun-Buisson C, Duvaldestin P; French RESSENTI Group: **Discrepancies between perceptions by physicians and nursing staff of intensive care unit end-of-life decisions.** *Am J Respir Crit Care Med* 2003, **167**:1310-1315.

Meade MO, Granton JT, Matte-Martyn A, McRae K, Weaver B, Cripps P, Keshavjee SH: **A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation.** *Am J Respir Crit Care Med* 2003, **167**:1483-1489.

Shimizu S, Gabazza EC, Taguchi O, Yasui H, Taguchi Y, Hayashi T, Ido M, Shimizu T, Nakagaki T, Kobayashi H, Fukudome K, Tsuneyoshi N, D'Alessandro-Gabazza CN, Izumizaki M, Iwase M, Homma I, Adachi Y, Suzuki K: **Activated protein C inhibits the expression of platelet-derived growth factor in the lung.** *Am J Respir Crit Care Med* 2003, **167**:1416-1426.

Spragg RG, Lewis JF, Wurst W, Hafner D, Baughman RP, Wewers MD, Marsh JJ: **Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant.** *Am J Respir Crit Care Med* 2003, **167**:1562-1566.

Weinert CR, Gross CR, Marinelli WA: **Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals.** *Am J Respir Crit Care Med* 2003, **167**:1304-1309.