

Title: CHANGES IN SYSTEMIC AND RENAL PLASMA PROSTANOID CONCENTRATIONS ASSOCIATED WITH ALTERATIONS IN RENAL FUNCTION DURING HYPERDYNAMIC SEPSIS IN SHEEP

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Introduction: Alterations in eicosanoid activity during sepsis may play an important role in modifying intrarenal microcirculation. In the present study, we evaluated the renal hemodynamic and functional changes and their relationship to arterial and venous renal prostanoid concentrations during the time course of experimental hyperdynamic sepsis in awake sheep.

Methods: After institutional approval by the ethical committee, nine sheep weighing 27-36 kg were chronically instrumented and intravascular catheters placed in the aorta, the pulmonary artery, the jugular and renal veins, with a transit-time ultrasonic flow probe around the right renal artery, and with a urinary catheter in the bladder. On the next day the awake animals were given a continuous iv infusion of *E. coli* endotoxin (20 ng·kg⁻¹·min⁻¹) during 3 days. Intravascular crystalloids were infused to maintain pulmonary capillary wedge pressure. Concentrations of thromboxane B₂ (TxB₂) and 6-keto-PGF_{1α} in aortic and renal venous blood and urine were determined by a scintillation proximity assay.

Results: Two hours after the start of endotoxin infusion, animals showed a significant (*P*<0.001) and sustained 30% decrease in systemic arterial pressure and vascular resistance, associated with severe lactacidemia. After 12h of endotoxemia, 8 out of the 9 sheep died of irreversible metabolic acidosis (between 13-36h after start of endotoxin infusion). The 5 animals surviving more than 36h developed a typical hyperdynamic septic state with increased cardiac output (CO) and low systemic vascular resistances, whereas the 4 sheep dying between 13-20h did not increase their CO. To try to explain the early lethality of this latter group of 4 sheep, we compared the time course of their hemodynamic and biological variables with those of the 5 animals surviving more than 36h. There were no significant differences between both subgroups regarding systemic and pulmonary hemodynamics, gas exchange, or white blood cell count, whereas renal blood flow, urine output, plasma creatinine (Cl_{Cr}) and PAH (Cl_{PAH}) clearances, and both plasma and urinary TxB₂ and 6-keto-PGF_{1α} concentrations were significantly different during the first hours of endotoxemia (Fig. 1; all data mean ± SE). Low Cl_{Cr} and Cl_{PAH} values were significantly associated with elevated renal venous concentrations of 6-keto-PGF_{1α} (Fig. 2; 12-h data points) throughout the first 20-h endotoxemia period, and of TxB₂ (during the first 8h), but prostanoid concentrations were not correlated with renal blood flow or the markedly reduced fractional sodium excretion.

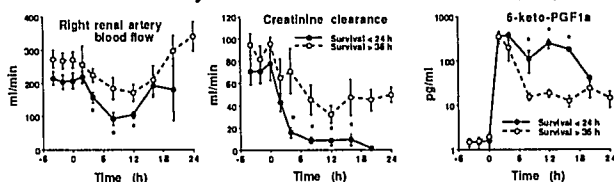


Fig. 1. * *P*<0.05 compared to other subgroup (unpaired *t*-test).

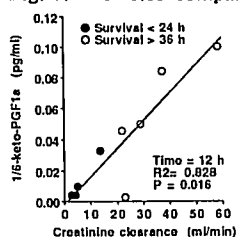


Fig. 2.

Conclusions: Our results indicate that standard hemodynamic and respiratory monitoring poorly predicts outcome of severe endotoxin shock in sheep, whereas the degree of acute renal failure (impairment of glomerular filtration) is associated with elevated renal venous plasma and urinary TxB₂ and 6-keto-PGF_{1α} levels and might be an early and sensitive marker of outcome.

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TITLE: CYTOKINE ELEVATION IN CHILDREN WITH SEPSIS SYNDROME AND ARDS

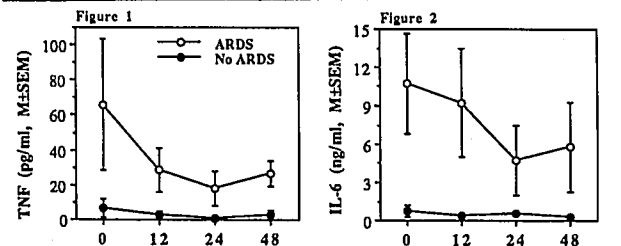
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ARDS is a major cause of morbidity and mortality in children with septic shock. Cytokines, proteins produced by monocytes and macrophages in response to infectious stimuli such as endotoxin (LPS), are thought to cause the cardiorespiratory signs and vital organ dysfunction characteristic of sepsis syndrome.^{1,2} They have additionally been implicated as mediators of the endothelial injury, increased pulmonary vascular and airways resistances and decreased surfactant production that are components in the pathogenesis of ARDS. The cytokines most prominent in these conditions are: tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6). In order to investigate the relationship of cytokines to ARDS, documented septic shock, the sepsis syndrome (the clinical findings of septic shock without identification of a microorganism³) and patient outcome, we determined plasma levels of TNF, IL-6, IL-1, and LPS in 29 critically ill children.

Study subjects were selected from children admitted with the presumptive diagnosis of sepsis to the pediatric intensive care unit at The Children's Hospital of Philadelphia. Criteria for diagnosis were based on those proposed by Bone et al.³ modified for the pediatric population. ARDS was diagnosed using the criteria of Murray.⁴ EDTA/plasma samples were collected at presentation (t=0) and at three subsequent time intervals (Table) in aprotinin-containing tubes and were chloroform extracted. Cytokine levels were determined by ELISA and LPS levels determined by limulus amoebocyte lysate assay. Comparisons (ANOVA) of plasma LPS and cytokines were made between 1) children with sepsis vs sepsis syndrome, 2) ARDS (ARDS) vs without ARDS (nARDS), 3) survivors vs nonsurvivors.

Twenty one children with culture proven septic shock (9 of 21 with ARDS) and 8 with sepsis syndrome (2 of 8 with ARDS, data unavailable for two) were studied. Children with ARDS had marked elevations of TNF (*p*<0.001, Fig. 1), IL-6 (*p*<0.001, Fig. 2), and IL-1 (*p*<0.01, Table). No differences between groups were noted for plasma LPS (Table). Similarly, cytokines distinguished between the 13 children who died and the 16 who survived (*p*<0.001 for TNF and IL-6, *p*=0.06 for IL-1). When children with sepsis were compared to those with sepsis syndrome, no overall difference nor differences at any time point, were noted for the cytokines or LPS.



TIME (hrs)	0	12	24	48	<i>p</i>
TNF (pg/ml)	65.9±11.3	28.4±40.3	18.0±29.5	26.3±21.0	<0.001
nARDS (n=15)	6.7±21.0	2.6±8.1	0.9±3.2	2.7±8.5	
IL-6 (ng/ml)	10.7±12.9	9.2±13.9	4.7±8.6	5.8±9.2	<0.001
nARDS (n=15)	0.8±1.7	0.4±0.7	0.5±0.7	0.2±0.5	
IL-1 (pg/ml)	316±495	172±398	21±21	34±62	<0.01
nARDS (n=7)	8±12	3±5	8±12	5±8	
LPS (ng/ml)	0.58±1.58	0.79±1.60	0.05±0.04	0.29±0.67	NS
nARDS (n=9)	0.79±1.35	0.03±0.01	0.45±1.12	0.51±0.75	

(Mean ± SD)

Conclusion: 1) Cytokines are elevated in children with septic shock and sepsis syndrome but levels do not distinguish between culture confirmed sepsis and sepsis syndrome; 2) Cytokines are elevated in children with ARDS when compared to those without lung injury and sepsis syndrome; 3) Cytokine elevation in ARDS is associated with increased mortality. (Supported by NIH grants RR-00240 and PO1-NS-17752 and the Nicholson Fund)

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