

## SHORT REPORT

## Carbon monoxide concentrations in paediatric sepsis syndrome

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Plasma carbon monoxide (CO) concentrations were measured in 12 patients with sepsis syndrome. CO concentrations were found to be significantly increased in patients compared with those in 30 normal controls. Patients with septic shock had significantly higher plasma CO concentrations than those without shock. Results suggest that CO might play an important role in paediatric sepsis syndrome.

Despite widespread investigation and medical advances, the mortality of sepsis syndrome remains high, and how sepsis syndrome leads to septic shock, multiorgan dysfunction syndrome, and death is still not entirely understood. Recently, biomedical interest in endogenous carbon monoxide (CO) has grown rapidly as overproduction of CO has been proposed to induce excessive vascular relaxation, and hence a fall in blood pressure by activating guanylyl cyclase and increasing cellular concentrations of cyclic guanosine monophosphate (cGMP), similar to nitric oxide (NO).<sup>1</sup> Therefore, we wished to determine whether there is increased production of CO in a group of paediatric patients with sepsis syndrome.

## PATIENTS AND METHODS

## Patients

This study was conducted in the Department of Pediatrics, Research Institute of Surgery, Daping Hospital, Third Military Medical University, Chongqing, China. Children between 3 months and 8 years with a clinical diagnosis of sepsis were eligible for study entry when they met the Bone criteria for sepsis syndrome modified for the paediatric population.<sup>2</sup> Inclusion criteria were: temperature  $<36^{\circ}\text{C}$  or  $>38.5^{\circ}\text{C}$ , tachycardia ( $>90\%$  centile for age), tachypnoea ( $>90\%$  centile for age), WBC  $>10.0 \times 10^9$  or  $<0.4 \times 10^9$ , and evidence of organ

dysfunction/hypoperfusion. Relevant data were collected to determine disease severity by the mean paediatric risk of mortality (PRISM) score.<sup>3</sup> The diagnosis of septic shock was made when the patients had hypotension (systolic blood pressure lower than  $\text{age} \times 2 + 60$  mm Hg) or poor capillary refill ( $>3$  seconds) in addition to the sepsis syndrome. Thirty age matched healthy children served as control subjects.

## Methods

Blood samples were taken at the time of hospital admission. Informed parental consent from both subjects and controls was obtained. CO concentration was measured using the simple, sensitive spectrophotometric method described by Chalmers.<sup>4</sup> Nitrite/nitrate ( $\text{NO}_2^-/\text{NO}_3^-$ ) concentration has been confirmed to be a good indicator for NO production. The classic method described by Hegesh and Shiloah was used, modified slightly in our laboratory.<sup>5</sup>

## Statistical analysis

All data were presented as mean (SD) or median (range) for descriptive purposes. The Kruskal-Wallis test, and the Spearman rank correlation coefficient were used. Significance was accepted at  $p < 0.05$ .

## RESULTS

Between January 1996 and December 1998, a total of 12 patients were eligible and enrolled for admission to the study. The median age of the study subjects was 1.5 years (range 3 months to 8 years), with a male:female ratio of 1.4:1. The median age of the control subjects was 2.5 years (range 3 month to 12 years), with a male:female ratio of 1.5:1. There were no significant differences between the patients with sepsis and control subjects in age and sex ( $p > 0.05$ ).

Table 1 shows the clinical data of the patients. Five patients (41.7%) had culture positive bacterial sepsis, and all patients except one had received antibiotics before the culture samples

Table 1 Clinical data of the patients with sepsis syndrome

No.	Age	Sex	Major diagnosis	Admission leucocyte count ( $\times 10^9$ )	PRISM score	Septic shock	CO conc. ( $\mu\text{g/l}$ )	NO conc. ( $\mu\text{mol/l}$ )
1	8 y	F	<i>Bacillus dysenteriae</i>	21.8	28	Yes	5.31	76.06
2	3 y	F	Culture negative	12.6	7	No	2.52	27.79
3	2 y	M	Culture negative	18.9	3	No	2.26	25.89
4	1 y	M	Culture negative	4.0	1	No	1.35	22.76
5	3 y	F	Culture negative	19.2	0	No	1.11	20.47
6	4 y	M	Culture negative	15.6	12	Yes	3.23	59.30
7	3 mth	M	<i>Neisseria meningitidis</i>	13.2	9	No	2.53	31.51
8	1 y	M	Culture negative	10.1	2	No	1.93	22.95
9	5 mth	M	Culture negative	10.2	17	Yes	3.27	48.72
10	1 y	F	<i>Staphylococcus aureus</i>	13.5	5	No	2.91	41.22
11	2 y	M	<i>Staphylococcus aureus</i>	12.8	4	No	2.63	34.90
12	1 y	F	<i>Pseudomonas aeruginosa</i>	11.5	5	No	2.69	30.01

were taken. The mean PRISM score was 7.75 (range 0–28). Three patients developed septic shock.

Significantly increased plasma CO concentrations (2.65 (1.10) v 1.50 (1.12)  $\mu\text{g/l}$ ,  $p < 0.05$ ) and NO concentrations (36.80 (17.52) v 21.20 (5.25)  $\mu\text{mol/l}$ ,  $p < 0.05$ ) were found in the patients with sepsis compared with the control subjects. Moreover, plasma CO concentrations were statistically higher in the three patients with septic shock than in the nine patients with sepsis but without shock (3.94 (1.19) v 2.21 (0.62)  $\mu\text{g/l}$ ,  $p < 0.05$ ). Similarly, plasma NO concentrations were significantly higher in the patients with septic shock than those without septic shock (61.36 (13.78) v 28.61 (6.60)  $\mu\text{mol/l}$ ,  $p < 0.05$ ). In addition, the increased plasma CO concentrations were significantly related to the NO concentrations ( $r_s = 0.98$ ,  $p < 0.05$ ).

## DISCUSSION

During the 1990s, CO was recognised as a new messenger which might be part of a complex cascade of mediators participating in the pathogenesis of sepsis syndrome. CO shares many chemical and biological properties with NO. Endogenously produced CO may modulate blood vessel tone by activation of guanylyl cyclase, resulting in significantly increased production of cGMP. Recent studies have suggested that CO may contribute to regulation of vascular tone under basal conditions. However, the marked increase in haem oxygenase (HO) activity stimulated by endotoxin suggests that overproduction of CO may contribute to the reduction in vascular tone during endotoxic shock. Carboxyhaemoglobin has been proposed as a marker of stress in critically ill surgical patients. In 1999, Moncure *et al* showed significantly increased carboxyhaemoglobin concentrations during stress, sepsis, and shock.<sup>6</sup> Our present study provides the first evidence that plasma CO concentrations are significantly increased in

paediatric patients with sepsis syndrome, and that increased plasma CO concentrations are higher in patients with septic shock than those with sepsis but without shock.

The present study also suggests that increased plasma CO concentrations are correlated with increased NO concentrations in children with sepsis. In addition to NO, CO may be another endogenously produced mediator which plays an important role in the pathogenesis of sepsis and septic shock. The clinical importance of CO concentrations and the possible use of drugs to modulate CO in the course of sepsis need further investigation.

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