

# Changes in plasma calcium during septic shock

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## SUMMARY

Previous studies have documented a decrease in plasma calcium occurring early after trauma, haemorrhage and cardiac arrest. Therefore, changes in plasma calcium in an ovine experimental model of septic shock due to intraperitoneal sepsis were investigated. Subjects were volume-loaded with Ringer's lactate solution. Plasma calcium and albumin were measured before and 24 h after surgical induction of sepsis. Subjects were divided into two groups according to the severity of shock. Group 1 ( $n = 8$ ) developed severe hyperdynamic sepsis with renal failure. Group 2 ( $n = 8$ ) showed no change in blood pressure, cardiac output or renal function.

Plasma calcium fell significantly in both groups, and was lower in Group 1 during sepsis (Group 1:  $2.36 \pm 0.19$  to  $1.84 \pm 0.14$  mmol l<sup>-1</sup>; Group 2:  $2.34 \pm 0.12$  to  $2.01 \pm 0.13$  mmol l<sup>-1</sup>; mean  $\pm$  SD; both  $P < 0.001$ ). Plasma albumin fell during sepsis, and the reduction was greater in Group 1. The plasma calcium, corrected for albumin, was still significantly reduced and was similar in each group during sepsis (Group 1:  $2.55 \pm 0.13$  to  $2.23 \pm 0.12$  mmol l<sup>-1</sup>; Group 2:  $2.50 \pm 0.08$  to  $2.27 \pm 0.09$  mmol l<sup>-1</sup>; both  $P < 0.001$ ).

In this large animal model of septic shock, which reproduces the important features of clinical sepsis, there were significant decrements in uncorrected and corrected plasma calcium 24 h after the surgical induction of intraperitoneal sepsis. These changes may contribute to the pathophysiology of this condition.

**Key words:** albumin, calcium, septic shock

## INTRODUCTION

A decrease in plasma calcium, both total and ionized, has been observed after trauma, haemorrhage and cardiac arrest.<sup>1-3</sup> This has been described both in experimental animals and in patients, but the pathophysiology and significance of these changes

remains unclear.<sup>4</sup> There is little information regarding plasma calcium changes in septic shock. It has been shown that the normal pressor response to intravenous calcium infusion is lost during experimental endotoxaemia;<sup>5</sup> however, acute changes in plasma calcium have not been documented in this condition.

Therefore changes in plasma calcium and albumin in an ovine model of septic shock as a result of intraperitoneal sepsis were investigated. This extensively studied experimental model closely resembles the haemodynamic and metabolic features of clinical sepsis.<sup>6,7</sup> Measurements were made before and 24 h after surgical induction of sepsis. Animals were classified according to the severity of shock.

## MATERIALS AND METHODS

This study conforms to the regulations of the Canadian Council on Animal Care and was approved by the Ethics Committee of the University of Western Ontario. The technique of surgical induction of peritonitis was modified from that of Wichterman *et al.*<sup>8</sup> as described previously.<sup>9</sup> In brief, 16 healthy sheep aged between 12 and 18 months and weighing between 45 and 50 kg underwent cannulation of the common carotid artery, and the pulmonary artery via the external jugular vein with a triple-lumen Swan Ganz catheter, under general anaesthesia. The bladder was catheterized per urethra. After recovery from anaesthesia, animals were volume-loaded with 3 l of Ringer-lactate solution intravenously (i.v.) over 24 h. After control haemodynamic measurements and blood and urine sampling, animals underwent a second general anaesthetic; peritonitis was induced by caecal ligation and puncture. Post-operatively all animals received 50 mg pethidine i.v., and were continued thereafter on an i.v. infusion of pethidine (50 mg 6 h<sup>-1</sup>). Infusion (i.v.) of Ringer-lactate solution, 125 ml h<sup>-1</sup>, continued for the duration of the experiment and the rate of additional fluid administration was adjusted to

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maintain pulmonary artery occlusion pressure at baseline values.

Animals were supervised continuously during the study, and if they showed any evidence of discomfort or distress, despite pethidine infusion, they were killed immediately by i.v. injection of pentobarbital.

Haemodynamic parameters measured were mean arterial pressure, central venous pressure, pulmonary artery pressure, pulmonary artery occlusion pressure, and thermodilution cardiac output. Plasma creatinine, sodium, potassium, calcium, phosphate and albumin were measured by standard techniques. Plasma calcium was corrected for plasma albumin using the formula:

$$\text{adjusted plasma Ca} = \text{measured Ca} + 0.02 \times (40 - \text{plasma albumin}) \quad (1)$$

For analysis, for each variable, the values included were those at baseline (pre-sepsis), and at the termination of the study (24 h post-operatively). As appropriate, paired or unpaired Student's *t*-tests, corrected for multiple comparisons, were used to assess the significance of changes with time, and the significance of between-group differences. Values for  $P < 0.05$  were taken to be significant. All results are shown as Mean  $\pm$  SD.

## RESULTS

As in the studies performed to establish and validate this experimental model,<sup>6,7,9</sup> a polymicrobial peritonitis and bacteraemia developed; organisms grown on blood culture included *E.coli*, *Serratia*, *Enterobacter*, *Pseudomonas* and *Bacteroides* species.

Pulmonary artery occlusion pressure was main-

tained in the range 10–20 mmHg during the study (mean  $13.7 \pm 2.2$  mmHg). In Group 1 (severe sepsis,  $n = 8$ ), there was a small but significant fall with time in blood pressure, a 50% reduction in systemic vascular resistance index, an increase in pulmonary artery pressure, and a reduction in creatinine clearance and fractional sodium excretion. In Group 2 (moderate sepsis,  $n = 8$ ), these parameters did not alter significantly (Table 1). Plasma calcium fell significantly in both groups, and was lower in Group 1 during sepsis (Group 1:  $2.36 \pm 0.19$  to  $1.84 \pm 0.14$  mmol l<sup>-1</sup>,  $P < 0.001$ ; Group 2:  $2.34 \pm 0.12$  to  $2.01 \pm 0.13$  mmol l<sup>-1</sup>;  $P < 0.001$ . Group 1 vs. Group 2 at 24 h,  $P < 0.05$ .) (Fig. 1). The fall in plasma albumin was greater in Group 1:  $30.3 \pm 3.7$  to  $20.8 \pm 5.0$  g l<sup>-1</sup>,  $P < 0.001$ ; Group 2:  $32.1 \pm 3.9$  to  $27.0 \pm 3.0$  g l<sup>-1</sup>,  $P < 0.001$ . Group 1 vs. Group 2 at 24 h,  $P < 0.05$  (Fig. 2).

The plasma calcium, corrected for plasma albumin, was similar in each group during sepsis, although still significantly reduced (Group 1;  $2.55 \pm 0.13$  to  $2.23 \pm 0.12$  mmol l<sup>-1</sup>,  $P < 0.01$ . Group 2;  $2.50 \pm 0.08$  to  $2.27 \pm 0.09$  mmol l<sup>-1</sup>,  $P < 0.05$ ) (Fig. 3).

## DISCUSSION

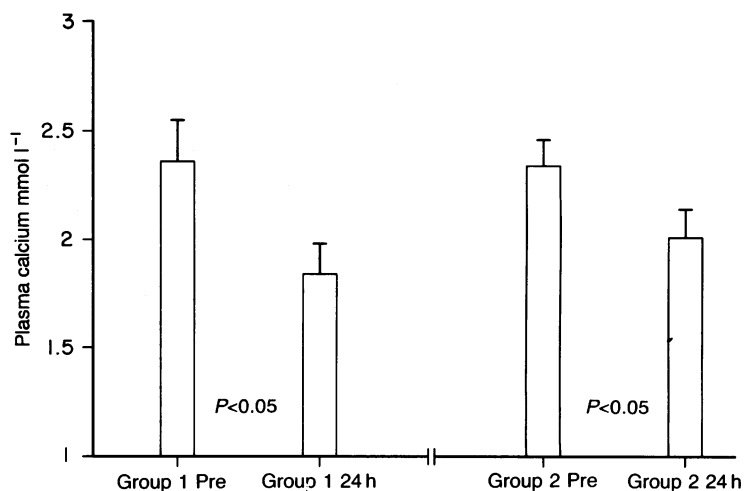
Studies of electrolyte changes in clinical septic shock are complicated by lack of pre-sepsis baseline parameters, problems in assessing the stage and severity of the shock syndrome, and the multiple treatments required. The experimental model of sepsis utilized in this study overcomes these difficulties, and reproduces the state of volume-loaded, hyperdynamic and vasodilated septic shock typically seen in clinical practice.<sup>6,7,9</sup> As part of a detailed investigation of neuroendocrine function and the

**Table 1.** Haemodynamic and renal function variables in Group 1 (severe sepsis) and Group 2 (moderate sepsis), \* $P < 0.05$  vs. baseline

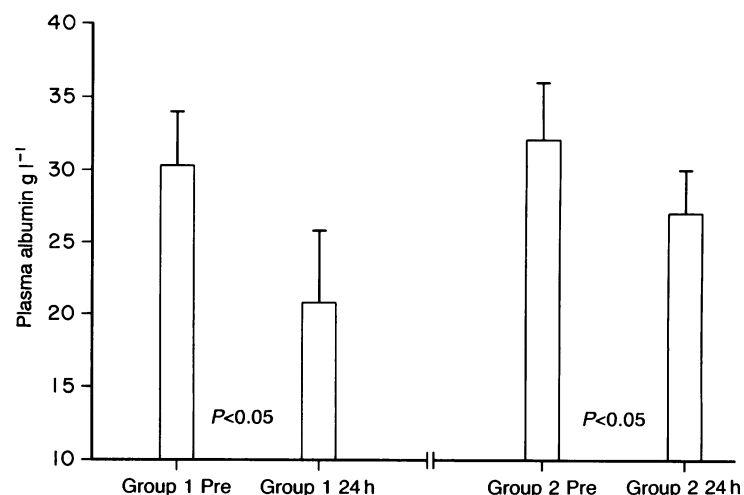
		Group 1		Group 2	
		Baseline	24 h	Baseline	24 h
Mean arterial pressure	mmHg	108 $\pm$ 5	90 $\pm$ 3*	96 $\pm$ 4	100 $\pm$ 6
Systemic vascular resistance	dyne s <sup>-1</sup> cm <sup>-5</sup> m <sup>-2</sup>	2183 $\pm$ 243	1038 $\pm$ 107*	2026 $\pm$ 244	1677 $\pm$ 179
Pulmonary artery pressure	mmHg	16 $\pm$ 1.3	22 $\pm$ 1.1*	18 $\pm$ 1.8	21 $\pm$ 1
Creatinine clearance	ml min <sup>-1</sup>	142 $\pm$ 15	43 $\pm$ 8*	152 $\pm$ 30	123 $\pm$ 14
Fractional sodium excretion	%	2.9 $\pm$ 0.5	0.5 $\pm$ 0.2*	2.6 $\pm$ 0.5	2.0 $\pm$ 0.7

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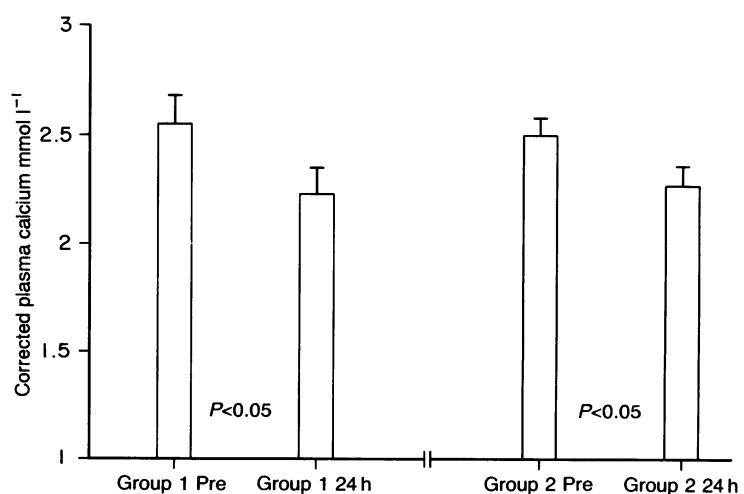
**Fig. 1.** Plasma calcium before and 24 h after surgical induction of sepsis in Group 1 (severe sepsis) and Group 2 (moderate sepsis).



**Fig. 2.** Plasma albumin before and 24 h after surgical induction of sepsis in Group 1 (severe sepsis) and Group 2 (moderate sepsis).



**Fig. 3.** Plasma calcium, adjusted for plasma albumin, before and 24 h after surgical induction of sepsis in Group 1 (severe sepsis) and Group 2 (moderate sepsis).



pathogenesis of acute renal failure in sepsis, plasma calcium and albumin were measured, and significant changes observed.

In these studies, plasma calcium was reduced 24 h after surgical induction of sepsis. While this fall

was less marked when adjusted for the plasma calcium, it was still significant. It should be noted that this occurred despite the administration of large volumes of Ringer-lactate solution (125 ml h<sup>-1</sup>). This solution contains 2 mmol l<sup>-1</sup> of calcium as

calcium chloride, which is entirely ionized. It seems likely that even greater reductions in plasma calcium would have been seen if non-calcium containing fluids had been used for volume replacement.

It is known that the plasma total calcium concentration falls acutely in patients suffering from major trauma and/or haemorrhagic shock.<sup>1,2</sup> This is not dependent on citrate infused during transfusion.<sup>10</sup> There is an equivalent, or even greater, fall in ionized calcium, and infusion of colloids such as albumin may disguise this decrease, by a disproportionate effect on total calcium concentration.<sup>10</sup> Similar data are available for patients who are resuscitated from cardiorespiratory arrest.<sup>3,4</sup> In haemorrhagic shock, the hypocalcaemia may persist after resuscitation for up to 6 days, in the absence of supplementation.<sup>10</sup> It has been suggested that in these patients, hypocalcaemia may be associated with depression of myocardial performance and vascular contractility.<sup>11</sup> Beneficial effects of calcium supplementation on cardiocirculatory function have been described in patients with traumatic, haemorrhagic and cardiogenic shock.<sup>1,2,10-12</sup>

McCaig & Parratt<sup>5</sup> have shown that in cats infused with endotoxin, there is markedly reduced myocardial and vascular responsiveness to infusions of calcium chloride. Before infusion of endotoxin, calcium infusion produced a pressor response of 24 mmHg; however, no pressor effect was seen after endotoxin. This was ascribed to damage to receptor-operated calcium channels.<sup>13</sup> It seems likely that this phenomenon may aggravate the adverse haemodynamic consequences of a fall in plasma calcium during sepsis.

Increased uptake of calcium by skeletal muscle during sepsis has been demonstrated in rats using the caecal ligation and puncture model.<sup>14</sup> However, it was not clear whether this was accompanied by, or responsible for, any change in plasma calcium. It should be recalled that the extracellular calcium concentration is normally of the order of 16 000 times higher than the intracellular concentration.<sup>15</sup> Although it has been suggested that this calcium influx may act as a trigger to catabolism of skeletal muscle in sepsis, this has not been proved conclusively.<sup>14</sup> However, it may well be involved in the increased glucose uptake by skeletal muscle seen in sepsis, which in turn may contribute to hypoglycaemia and increased lactate production.<sup>16</sup>

In septic shock, the combination of a reduced plasma calcium, and decreased myocardial and vascular sensitivity to calcium, would be predicted to contribute to circulatory compromise, which could

be at least partly reversible by calcium infusion. Many emergency units and intensive therapy units now have the capacity to measure plasma ionized calcium. The authors' clinical experience using such a procedure suggests that in critically ill patients, including those with septic shock, the incidence of hypocalcaemia, and the benefits of calcium supplementation, have been underestimated.

## ACKNOWLEDGEMENTS

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