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CHANGES IN SOME CLINICAL AND LABORATORY INDICES IN DOGS WITH EXPERIMENTAL *STAPHYLOCOCCUS AUREUS* SEPSIS

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Summary

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The study was performed in 6 clinically healthy dogs, experimentally infected via intravenous injection of 5 mL broth culture of a field *Staphylococcus aureus* strain (1.2×10^9 cells/mL). For a 28-day period, the dynamics of rectal temperature, heart and respiratory rates and some blood laboratory parameters (erythrocyte counts, haematocrit, haemoglobin, erythrocyte sedimentation rate, total and differential leukocyte counts, total protein, fibrinogen, bilirubin, urea, creatinine, pyruvate and lactate) were followed out.

It was observed that by the post infection hour 2, an increase in body temperature, tachycardia and tachypnea occurred. Also, leukopenia followed by increased leukocyte counts by the 24^{th} h with a left shift were noticed.

Statistically significant increases in the values of blood biochemical parameters were observed for fibrinogen and bilirubin while the concentrations of pyruvate decreased . The levels of total protein, creatinine, urea and lactate remained without significant deviations during the entire period of the survey.

Key words: dogs, sepsis, staphylococcal infections

INTRODUCTION

It is assumed that *Staphylococcus aureus* is responsible for 45% of the surgical infections in dogs. This agent is also involved in 15% of mixed infections in this species (Dow *et al.*, 1989). There is increasing evidence that *S. aureus* participates actively in the development of canine septic shock (Goodwin & Schaer, 1989; Opal & Cohen, 1999; Barton, 2001; Tello, 2002).

It is the main etiological agent in the development of several pathological processes – septic conditions in dogs and cats (Hardie *et al.*, 1986; Strand & Shulman, 1992), wound infections (West, 1995), abscesses (West, 1995; Brook, 2002), dermatites in humans and dogs (Dikov & Markova, 2000; Niemand & Suter, 2001), catheter-associated human and animal infections (Tan *et al.*, 2003).

From the other side, the rapidly developing resistance to antibiotics results in progressively increased incidence of staphylococcal infections (Dimitrova *et al.*, 2002; Alouf & Muller-Alouf, 2003; Urumova, 2004).

The precise diagnostics of staphylococcal infections is impeded by the nu-

merous manifestations which they show by themselves – fever or hypothermia, tachycardia, hypocapnia or tachypnea, leukocytosis or leukopenia and/or increase in band neutrophils (Tarello, 2001; Aird, 2003). Attempts for construction of clinical criteria in dogs are made by Purvis & Kirby (1994), Hardie (1995) and Hauptman *et al.* (1997).

The aim of the present study was to monitor the occurring changes in some clinical parameters characterizing the sepsis and the systemic inflammatory response syndrome (SIRS), as well as some haematological and biochemical parameters in systemic staphylococcal infections in dogs.

MATERIALS AND METHODS

Experimental animals

The experiments were performed on 6 clinically healthy mongrel dogs at the age of 6–7 years and body weight of 16 ± 2 kg, placed in individual cages with area of 1.5 m^2. Each animal had individual feeding bowls and free access to water. The animal were placed under equal rearing regimen. Prior to and during the experiment, they were given a balanced dry food for adult dogs – Canil-21% (Sosil Guyomarc, H, Sao Paolo, Brazil).

One week before the experiment, the dogs were treated against parasites with the combination praziquantel and abamectin (Prazimec-D, Biovet Co, Peshtera, Bulgaria) at a dose of 1 tablet per 10 kg.

Experimental design

The experimental infection was reproduced by inoculation of 5 mL 24 h broth culture of a field *S. aureus* strain with a density of 1.2×10^9 cfu/mL. The typization of the strain was done by the "Sceptor – Becton Dickinson Diagnostic" system in the Department of Hygiene, Microbiology, Infectious Diseases and Epidemiology at the Faculty of Medicine, Trakia University, Stara Zagora, Bulgaria. The colonies showed the characteristic morphology of staphylococci (2–5 mm).

Clinical, haematological and blood biochemical parameters

During the experiment, the following clinical, haematological and blood biochemical parameters were followed out: rectal temperature (º C), heart rate (min^{-1}), respiratory rate (min^{-1}), locomotor activity, appetite and behaviour prior to and after *S. aureus* inoculation, haematocrit (L/L), erythrocyte counts (T/L), total leukocyte counts (G/L), erythrocyte sedimentation rate (ESR) (mm/h) and differential leukocyte counts – by routine methods; haemoglobin (g/L) – on an acid-base analyser (ABL-3, Radiometer, Denmark); total protein (g/L) – by the biuret method with commercial kit (Human Diagnostica GmbH, Germany); fibrinogen (g/L) and urea (mmol/L) – with commercial kits (Human Diagnostica GmbH, Germany); creatinine (μmol/L) – with a commercial kit (Bayer Co, Germany); total bilirubin (μmol/L) – by the dimethyl sulphoxide (DMSO) method (Biolabo, France); pyruvate (μmol/L) and lactate (mmol/L) - with commercial kits (Roche Diagnostics, Germany).

All animals included in the experiment were examined prior to application of the infective agent (hour 0), post infection hours 2, 6, 24, 48 and 72, and post infection days 14, 21 and 28.

Statistical analysis

The results were statistically processes by the one-way ANOVA at $P<0.05$ and the U-test of Mann-Whitney (StatMost for

Windows) and were presented as mean ± standard error of the mean. All comparisons of the parameters monitored after induction of the experimental infections were made vs the respective baseline values.

RESULTS

Clinical parameters

The experimental staphylococcal infection in dogs was manifested with depression as early as the 2nd hour after the inoculation of the agent, vomiting, lack of appetite, bristled hair, diarrhoeic stools by the 24th hour of the infection. By hour 72, in one of dogs, serous-purulent nasal discharge was observed. At later periods (days 7–14) of experimental infection, arthritic signs appeared in two animals in the tarsal and carpal joints respectively with apparent painfulness, increased local temperature and oedema of joints.

The experimental *S. aureus* infection was accompanied by increased body temperature to 40.28 ± 0.33 °C (at P<0.01) by hour 2 that persisted up to the 6th h of the i.v. inoculation of the agent (40.32 ± 0.28 °C, P<0.01 vs baseline values of 39.17 ± 0.11°C) (Fig. 1).

During the next periods, the rectal temperature values were close to initial ones.

As a result of developing infection, heart rate reached 153.00 ± 5.13 min^{-1} by hour 2 (P<0.001 vs 105 ± 2.77 min^{-1} by hour 0). The enhanced heart rate persisted by hours 6 and 24 as well, being 147.33± 3.34 and 135.67 ± 4.33 min^{-1} respectively (p<0.01). From the 48th hour to the 28th day, a tendency towards heart rate normalization to initial values was observed.

Respiratory rates increased together with changes in rectal temperature and

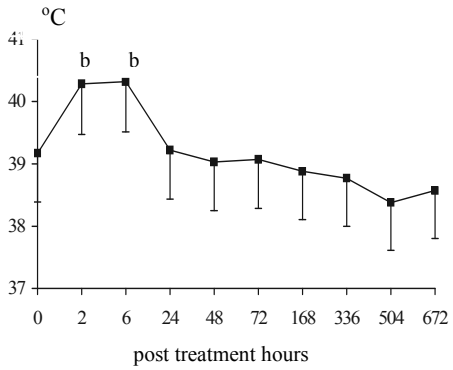

Fig. 1. Changes in rectal temperature in dogs (mean ± SEM; n=6) with experimental infection produced by i.v. injection of bacterial suspension of a field S. aureus strain (1.2 × 10^9 cells/mL) at a dose of 5 mL; [b] P < 0.01 vs hour 0.

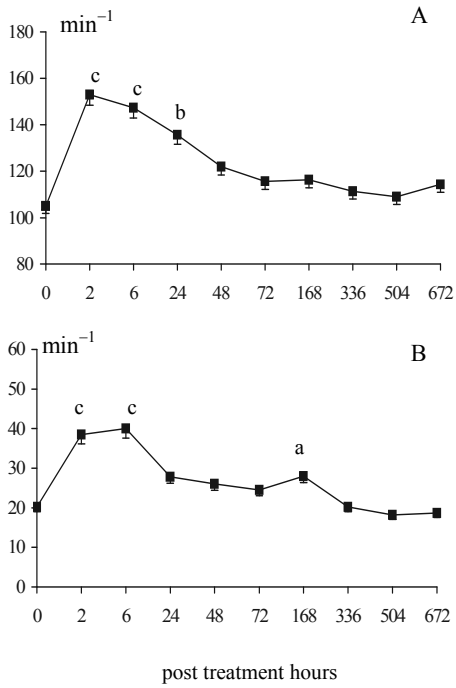

Fig. 2. Changes in heart rate (A) and respiratory rate (B) in dogs with experimental infection produced by i.v. injection injection of bacterial suspension of a field *S. aureus* strain (1.2 × 10^9 cells/mL) at a dose of 5 mL; [a] P < 0.05; [b] P < 0.01; [c] P < 0.001 vs hour 0.

heart rate (Fig. 2). By post infection hours 2 and 6, the values were statistically significantly higher than hour 0 (38.50 ± 1.98 min^{-1} and 40.00 ± 1.13 min^{-1} at P<0.001 vs 20.17 ± 1.35 min^{-1}). This trend was present to the 7th day when respiratory rate was 28.00 ± 2.85 min^{-1} (P<0.05). This parameter gradually returned to normal until the 28th day (18.67 ± 2.97 min^{-1}).

Blood laboratory parameters

The haematological changes during the course of the experimental staphylococcal infection in dogs are presented in Table 1.

The total erythrocyte counts decreased. The diminution was the best manifested, although statistically insignificantly, by post infection hour 6 – 5.33 ± 0.23 T/L vs baseline (5.82 ± 0.15 T/L) .

The haemoglobin content was reduced at the highest extent compared to baseline by post infection days 7, 14 and 21 – 120.33 ± 9.30 g/L (P<0.05); 119.67 ± 6.22 g/L (P<0.05) and 120.33 ± 5.60 g/L (P<0.05), respectively.

The haematocrit values were also decreased, being the lowest determined by day 14 (0.34 ± 0.02 L/L) (P<0.01). The differences were statistically significant vs hour 0 at all intervals between hour 48 and day 21.

The ESR tended to be enhanced up to day 28 (31.33 ± 17.29 mm/30 min) vs initial values of 5.67 ± 1.23 mm/30 min.

Total leukocyte counts decreased as early as the 2nd hour after the inoculation to 3.00 ± 1.51 G/L (P<0.05) vs 7.85± 0.63 G/L at baseline. Afterwards, the counts increased up to 12.80 ± 2.19 G/L by hour 24 of the experimental infection.

Lymphocyte percentages were reduced by the 2nd hour of the inoculation to 20.50 ± 6.02 % (P<0.05) vs baseline percentage of 33.17 ± 5.02 %. The lowest value occurred by post infection hour 6 – 6.67 ± 1.43 % (P<0.001). By hour 24 and 48, the values were also significantlt decreased: 14.17 ± 4.31 % (P<0.01) and 21.50 ± 2.58 %, (P<0.05), respectively.

Monocytes reached 4.00 ± 1.39 % (P<0.05) by hour 24 and 3.67 ± 1.41 % (P< 0.05) by day 7 vs baseline values of 0.67 ± 0.67 % .

Eosinopenia persisted to the 28th day (Table 1). The lowest value (1.83 ± 1.05 %) vs baseline of 8.00 ± 2.00% was measured by hour 6 (P<0.05).

A considerable increase in band neutrophils was observed, the peak values being those by post infection hours 6 (17.17 ± 1.11 %, P<0.001 vs 0.67 ± 0.43 %. at baseline). By hours 2, 24, 48, 72 and days 7 and 14, band neutrophil percentages persisted at levels, statistically significantly higher than the initial ones.

The changes in blood biochemical parameters are shown in Table 2.

After inoculation of the infective agent, blood total protein did not changed significantly.

The hyperfibrinogenaemia was considerable by post infection hours 24 and 48 – 4.23 ± 0.30 g/L (P<0.01) and 4.23 ± 0.22 g/L (P<0.01), respectively vs 2.77 ± 0.18 g/L at baseline. The peak value was attained by hour 72 – 4.58 ± 0.26 g/L (P<0.001). In subsequent periods, the values remained statistically significantly higher.

Creatinine values increased from 55.50 ± 14.25 µmol/L (prior to infection) to 135.33 ± 47.69 µmol/L by the 6th hour and 86.00 ± 19.55 µmol/L by hour 24. The differences were not statistically significant.

Blood pyruvate tended to decreased during the entire 28-day experimental period. The lowest values occurred by hour 2 (22.33 ± 8.08 µmol/L, P < 0.05),

Table 1. Haematological parameters (mean ± SEM) in dogs with experimental infection produced by i.v. injection of bacterial suspension of a field *Staphylococcus aureus* strain (1.2 × 10^9 cells/mL) at a dose of 5 mL (n = 6)

Parameters	Prior to infection	After infection								
		hour 2	hour 6	hour 24	hour 48	hour 72	day 7	day 14	day 21	day 28
Erythrocytes, T/L	5.82 ± 0.15	5.47 ± 0.19	5.83 ± 0.23	5.58 ± 0.22	5.58 ± 0.34	5.64 ± 0.39	5.49 ± 0.33	5.57 ± 0.25	5.59 ± 0.40	5.97 ± 0.43
Haemoglobin, g/L	142.33 ± 6.97	138.50 ± 8.09	132.67 ± 6.08	133.00 ± 5.26	131.17 ± 6.66	126.67 ± 7.0	120.33 ±9.30 a	119.67 ± 6.22 a	120.33 ± 5.60 a	126.67 ± 6.68
Haematocrit, L/L	0.43 ± 0.02	0.41 ± 0.02	0.38 ± 0.02 a	0.38 ± 0.02 a	0.37 ± 0.02 a	0.35 ±0.05 a	0.36 ± 0.02 a	0.34 ± 0.02 b	0.35 ± 0.02 a	0.38 ± 0.02
ESR mm/30 min	5.67 ± 1.23	5.83 ± 1.90	8.67 ± 2.50	13.67 ± 5.51	14.17 ± 6.27	15.33 ±5.43	14.67 ± 2.82	24.67 ± 9.65	22.67 ± 14.50	31.33 ± 17.29
Leukocytes, G/L	7.85 ± 0.63	3.00 ± 1.51 a	9.60 ± 1.79	12.80 ± 2.19	11.50 ± 1.20	11.05 ± 1.45	7.50 ± 0.68	8.38 ± 1.96	9.28 ± 1.72	7.47 ± 0.54
Band neutrophils, %	0.67 ± 0.42	4.67 ± 1.33 c	17.17 ± 1.11 c	11.00 ± 0.89 c	6.00 ± 045 c	5.17 ±0.83 b	4.67 ± 1.69 b	5.00 ± 0.86 b	2.50 ± 0.62	2.00 ± 0.86
Segmented neutrophils, %	56.00 ± 5.18	48.00 ± 11.29	72.67 ± 1.20	67.33 ± 5.44	63.50 ± 2.00	57.00 ± 7.51	60.17 ± 3.76	57.33 ± 7.13	52.83 ± 7.27	49.33 ± 4.86
Eosinophils, %	8.00 ± 2.00	8.67 ± 3.70	1.83 ± 1.05 a	3.50 ± 2.00	6.67 ± 1.61	6.17 ± 1.87	3.17 ± 1.22	3.33 ± 1.52	3.33 ± 1.52	4.00 ± 1.63
Lymphocytes, %	33.17 ± 5.02	20.50 ± 6.02 a	6.67 ± 1.43 c	14.17 ± 4.31 b	21.50 ±2.58 a	29.33 ± 8.86	28.33 ± 3.84	29.50 ± 5.62	49.67 ± 7.56	38.33 ± 6.50
Monocytes, %	0.67 ± 0.67	0.00 ± 0.00	1.67 ± 0.80	4.00 ± 1.39 a	2.33 ± 0.76	2.33 ± 0.61	3.67 ± 1.41 a	2.33 ± 1.20	1.33 ± 0.84	1.67 ± 0.61

a P< 0.05; b P< 0.01; c P< 0.001 vs hour 0.

Table 2. Blood biochemical parameters (mean ± SEM) in dogs with experimental infection produced by I.V. injection of bacterial suspension of a field *Staphylococcus aureus* strain ($1.2 \cdot 10^9$ cells/mL) as a dose of 5 mL (n = 6)

Parameters	Prior to infection	After infection							
		hour 2	hour 6	hour 24	hour 48	hour 72	day 7	day 14	day 21	day 28
Total protein, g/L	72.83 ± 2.61	71.00 ± 5.73	74.33 ± 4.30	76.33 ± 2.94	69.83 ± 4.47	72.17 ± 4.48	79.17 ± 6.80	81.17 ± 4.80	75.67 ± 4.75	75.00 ± 6.54
Fibrinogen, g/L	2.77 ± 0.18	2.72 ± 0.18	3.07 ± 0.19	4.23 ± 0.30 b	4.23 ± 0.22 b	4.58 ± 0.26 c	4.23 ± 0.42 b	3.55 ± 0.26 a	3.95 ± 0.50 a	5.55 ± 0.05 c
Creatinine, mmol/L	55.50 ± 14.25	70.33 ± 16.65	135.33 ± 47.69	86.00 ± 19.53	58.50 ± 13.81	36.50 ± 8.28	45.83 ± 9.10	34.00 ± 3.84	69.83 ± 22.35	80.00 ± 11.71
Урея, mmol/L	3.96 ± 0.34	4.66 ± 0.36	4.05 ± 0.53	9.52 ± 5.53	8.87 ± 3.18	6.41 ± 2.13	3.15 ± 0.26	4.01 ± 0.69	3.31 ± 0.16	4.12 ± 0.47
Пируват, mmol/L	59.67 ± 12.62	22.33 ± 8.08 a	14.00 ± 3.39 b	25.33 ± 4.65 a	35.17 ± 13.39	25.20 ± 7.91 a	22.83 ± 8.48 b	22.67 ± 3.82 b	45.75 ± 14.37	55.75 ± 18.79
Лактат, mmol/L	4.05 ± 1.24	4.97 ± 1.16	4.01 ± 0.63	3.55 ± 0.33	2.14 ± 0.36	1.68 ± 0.27	2.87 ± 0.34	3.59 ± 0.48	2.85 ± 0.58	2.93 ± 0.61
Белтрубин, mmol/L	4.62 ± 1.39	23.75 ± 7.85	21.33 ± 12.36	24.58 ± 10.71	20.63 ± 10.34	28.17 ± 8.74	16.43 ± 7.39	36.84 ± 10.60 a	29.73 ± 12.89	9.22 ± 2.93

a $P < 0.05$; b $P < 0.01$; c $P < 0.001$ vs hour 0.

hour 6 (14.00 ± 3.39 mmol/L, P<0.01) and hour 24 (25.33 ± 4.65 μmol/L, P<0.05). Another decrease in pyruvate was determined by the 72nd hour, the 7th and the 14th day – 25.20 ± 7.31 mmol/L (P<0.05), 22.83 ± 8.48 μmol/L (P<0.05) and 22.67 ± 5.82 μmol/L (P<0.01), respectively.

Reduced lactate concentrations observed by hours 48 and 72: 2.14 ± 0.36 mmol/L and 1.68 ± 0.27 mmol/L, respectively were not statistically significant.

Bilirubin levels increased as early as the 2nd hour of inoculation. Peak concentrations were attained by the 14th day – 36.84 ±10.60 μmol/L (P<0.05 vs baseline of 4.62 ± 1.39 μmol/L) .

DISCUSSION

The experimental staphylococcal sepsis in dogs developed with clear local and generalized changes of host organism. Unlike sepsis cause by Gram-negative microorganisms that was accompanied by considerable metabolic changes, in Gram-positive sepsis they were minimum as reported by other investigators (Garrido *et al.*, 2004). This was conformed by our results too.

Despite the statement about the active involvement of staphylococci in septic shock (Barton, 2001;Tello, 2002), the evaluation of changes in parameters, determined in our experiment allowed us to believe that the severity of staphylococcal infection was a moderate one.

The elevated rectal temperature by post infection hour 2 could be explained by triggering of the endogenous mechanism, related to the release of proinflammatory mediators such as interleukin-1 (IL-1) and tumour necrotizing factor (TNF-α). The hyperthermia is among the generalized signs of the developing systemic inflammatory response syndrome and sepsis (Kirby, 1995; Tashev *et al.*, 2003). The tachycardia and polypnea characteristic for the so-called "hyperdynamic septic state" (Dimitrova *et al.*, 2002; Bruins *et al.*, 2003) are related to it too. Nevertheless, its impact on red blood picture was not significant. The values of haemoglobin, haematocrit and erythrocyte counts began to decrease by the 7th day of the experimental infection. These changes could be considered as milder compared to those of teh same parameters in severe sepsis and with connection to the developing multiple organ dysfunction syndrome (MODS), accompanied by impaired liver and renal functions (Aird, 2003).

The changes in total and differential leukocyte counts consist in several primary alterations due to exotoxins (haemolysins, leukocidins, enterotoxins), superficial proteins (protein A), enzymes and bacterial products released by staphylococci (Petrovski *et al.*, 1990): a) development of leukopenia on the 2nd hour of agent inoculation followed by a tendency towards increase in total leukocyte counts by hour 24 that persisted to the 21st day of the experimental infection; b) left shift beginning from the 2nd hour and present until the 14th day and c) significantly reduced lymphocyte percentages between hours 2 and 48 (lymphopenia). At the same time, sepsis is related to activation of circulating monocytes (Spittler *et al.*, 2000). These changes are characteristic not only for sepsis, but for the systemic inflammatory response syndrome (SIRS) too (Hauptman *et al.*, 1997; Spittler *et al.*, 2000).

The changes in total protein and protein fractions were minor that could be explained by the fact, that in numerous animals with signs of inflammatory process, liver protein synthesis could be un-

changed or even increased. In most studies, hypoalbuminaemia was common only in severe and chronic illness (O'Leary *et al.*, 2003). Regardless of this statement, the cholestasis due to the effect of teichoic acid, produced by Gram-positive bacteria and the subsequent reduced activity of Na/K ATP-ase pump result in bilirubinaemia along with unaltered liver enzyme activities (Strassburg, 2003).

Significant changes in blood biochemical parameters were those in fibrinogen, creatinine and bilirubin levels. The hyperfibrinogenaemia is a manifestation of the systemic response to infection (Borissov, 1988; Dinev, 2002), because fibrinogen is a positive acute phase protein, i.e an element of SIRS.

The changes in creatinine concentration, confirmed the hypothesis that this parameter changed only on the background of a severe sepsis and septic shock (Popa & Caulkins, 2000). The same was valid for changes in blood urea that were not statistically significant, probably because of the short period for development of infection due to the intravenous inoculation of the agent (Dikov & Markova, 2000).

Although that Gram-negative sepsis was almost always accompanied by a lactic acidosis (Levy *et al.*, 2000; Aird, 2003; Bruins *et al.*, 2003), pyruvate concentrations were statistically significantly reduced whereas those of lactate exhibited the same tendency, but without statistically significance. A hypermetabolic and hyperdynamic sepsis in compensated protein and carbohydrate metabolism is relatively rarely observed (Bruins *et al.*, 2003). Even in septic shock however, 52 % of dogs are hypoglycaemic, 36 % are normoglycaemic and 12 % are hyperglycaemic. It was assumed that this was due to the developing insulin resistance (Kogika *et al.*, 2001). In a state of sepsis, glucose is among the most important energetic substrates for lymphoid, nervous and muscle tissue. The increase in lactate levels in these instances is reflecting the lower oxygenation of glucose in tissues despite the increased blood supply (Bruins *et al.*, 2003). Sometimes (Bruins *et al.*, 2003) the liver spends more lactate than is synthesized or released from both visceral tissues and muscles. The energy needs for synthesis of purine, pyrimidine and ribose bases participating in nucleic acid structure, as well as for activation of monocytes and lymphocytes also increase.

In conclusion, the experimental acute bacterial infection with non-lethal doses of Staphylococcus aureus in dogs resulted in clinical changes manifested by fever, tachycardia, tachypnea, transient leukopenia followed by a left shift, lymphopenia, increased fibrinogen and bilirubin concentrations and reduced pyruvate levels. During the entire experimental period, the erythrocyte counts, total protein and lactate concentrations were not considerably changed.

CONCLUSIONS

The present experimental design allowed us to assume that the course of the staphylococcal infection was moderate. The causative agent is probably influenced by some serum-dependent avirulent factors, causing its rapid inactivation after their entrering the circulation.

There is a clear evidence that the systemic inflammatory response syndrome develops by the 2nd hour after the inoculation of the microbial agent. Because of the single introduction of the bacterial agent in our experiment however, this general inflammation was probably brief and did not pass into the subsequent phase, i.e. the

development of the multiple organ dysfunction syndrome.

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