A positive fluid balance does not deteriorate tissue metabolism during fluid resuscitation of sepsis

Jaromir Koci [1,2], Martin Oberreiter [3], Radek Hyspler [4], Alena Ticha [4], Martin Valis [1], Petr Lochman [3], Eduard Havel [2], Alexander Ferko [2]

1 Department of Emergency Medicine, University Hospital Hradec Kralove, Czech Republic
2 Department of Surgery, University Hospital Hradec Kralove, Czech Republic
3 Department of Field Surgery Hradec Kralove, University of Defence Brno, Czech Republic
4 Department of Gerontology and Metabolism, University Hospital Hradec Kralove, Czech Republic

Correspondence to: Jaromir Koci, MD.
Department of Emergency Medicine; University Hospital Hradec Kralove
500 05, Hradec Kralove, Czech Republic.
TEL: +420 495834114; FAX: +420 495832026; E-MAIL: jaromir.koci@email.cz

Submitted: 2011-02-23 Accepted: 2011-03-13 Published online: 2011-06-29

Key words: **microdialysis; sepsis; fluid resuscitation**

Neuroendocrinol Lett 2011; **32**(3):345–348 **PMID:** 21712791 NEL320311A11

Abstract

OBJECTIVE: Hypovolemia has occurs frequently in sepsis. Due to pathologically increased permeability of the capillaries, the fluid leaks to the interstitium. An adequate fluid therapy is the corner stone to achieve circulatory stabilization and sufficient tissue perfusion; on the other hand, according to the data from the literature a tissue swelling is associated with a risk of deteriorated function of the tissues. The study aimed to examine the effect of a positive fluid balance on muscular metabolism.

METHODS: The experimental study employed the model of sepsis in the domestical pig. Ten animals were randomly distributed into a control and a septic group. Sepsis was induced by intravenous administration of *E. coli*, followed by fluid resuscitation by crystaloids. Microdialysis samples were withdrawn at one-hour intervals for a period of 24 hours and values of lactate, pyruvate, glycerol, and glucose.

RESULTS: Pearson's method revealed positive correlations between the lactate/pyruvate ratio and cumulative fluid balance in the septic group ($R=0.292$, $p<0.001$) and negative correlations in the control group ($R=-0.279$, $p<0.05$). In both groups, however, there was a gradual significant decrease in glycerol values.

CONCLUSION: Fluid resuscitation results in positive fluid balance in both septic and control animals. This leads to circulatory stabilization of septic animals, but not a decrease in the anaerobic share of glycolysis. A positive fluid balance in control animals does not result in alteration of muscular aerobic glycolysis. Decreasing glycerol levels in both groups give evidence that a positive fluid balance does not exert a negative impact on cell metabolism.

ORIGINAL ARTICLE

INTRODUCTION

Intact and correctly functioning microcirculation is the principal precondition for an adequate supply of oxygen to the tissues. Microcirculation disorder is the key pathophysiological mechanism characteristic of organ dysfunction in sepsis (De Backer *et al.* 2002; Chierego *et al.* 2006; Trzeciak *et al.* 2005). Early fluid resuscitation ranks among the basic therapeutic steps in sepsis (Rivers *et al.* 2001). Fluid resuscitation aims to ensure sufficient perfusion pressure and to restore the supply of oxygen to the tissues. Excessive expansion of plasmatic volume is, however, in the terrain of pathological microvascular permeability associated with a risk of tissue oedema, which further deteriorates tissue distribution of oxygen (Matejovic *et al.* 2002; Singh *et al.* 2000).

Patient's monitoring is an important guide for correct and sufficiently effective resuscitation. Nevertheless, "central" monitoring (mean arterial pressure, central venous pressure, saturation of mixed venous blood etc.) does not precisely reflect the condition of the peripheral tissues and thus it cannot reveal occult tissue hypoxia (LeDoux *et al.* 2000). One of the methods which make it possible to study the metabolism in the interstitium of the skeletal muscle is microdialysis. Microdialysis is a method enabling continual examination of the changes in the concentrations of low-molecular substances in the v extracellular space of the tissues. This minimally invasive method makes it possible to examine the kinetics of selected analytes directly in the tissue. The method has been used in experiments since the 1970s, in clinical practice since the 1990s (Muller 2002; Rooyackers *et al.* 2004). In the experiment, microdialysis served to detect regional intestinal ischemia (Sommer *et al.* 2004; Ungerstedt *et al.* 2003), to map the metabolism of the jejunum, peritoneum, muscle and brain during cardiac arrest (Korth *et al.* 2003) or metabolic changes in the muscle, subcutaneous tissue, liver, and peritoneal cavity during hypoxia and reoxygenation (Klaus *et al.* 2003) and brain metabolism (Fiserova-Sustkova *et al.* 2009). Very few studies have dealt with microdialysis and metabolism in sepsis (de Boer *et al.* 1994; Klaus *et al.* 2003; Martikainen *et al.* 2005; Martinez *et al.* 2003). No study has been concerned with the metabolism of the muscle during fluid resuscitation of sepsis.

Under aerobic conditions, the final product of glucose metabolism is 36 molecules of ATP and pyruvate, which is subsequently metabolized in the Krebs cycle. Under anaerobic conditions, 2 molecules of ATP are formed and pyruvate is metabolized in the tissues by lactate dehydrogenase to produce lactate. The tissue-specific lactate/pyruvate ratio thus serves as the indicator of cell hypoxia (Duke 1999; Fink 2002; Klaus *et al.* 2003). Degradation of the phospholipids of the cell membrane occurs in hypoxia or ischemia of most tissues. Glycerol as the final product of this degradation serves as a sensitive indicator of cell death (destruction of the cell wall) (Muller *et al.* 2002).

The study aimed to determine the influence of a positive fluid balance on the metabolism of the skeletal muscle during the fluid resuscitation of sepsis.

METHODS

It was an experimental study using the domestical pig (*S. scrofa* f. domestica). Ten animals were randomly divided into a control (n=5) and a septic (n=5) group. After twelve-hour fasting, the animal was premedicated with subcutaneous administration of ketamine in a dose of 4 mg/kg (Narkamon 4% Zentiva, Czech Republic) and atropine, 0.025 mg/kg (Atropin Biotika 0.5 mg inj. Hoechst-Biotika, Slovak Republic). A peripheral venous entry was made, and then the animal was put to general anaesthesia by administering thiopental in a dose of 200 mg intravenously (Thiopental ICN, ICN Czech Republic). It was followed by orotracheal intubation and artificial ventilation (Siemens-Elema 900B (Siemens, Sweden), FiO_2, 0.4, breath volume, 12 ml/kg, breath frequency, 16/min. Analgosedation was maintained by continual administration of sufentanil (Sufentanil Torrex, Torrex, USA) intravenously to achieve no interferece with the ventilator. Then a central venous catheter was introduced via the right jugular vein, a Swan-Ganz catheter (Edwards Life Science, USA) via the left jugular vein, a arterial catheter to the right femoral artery, a microdialysis catheter CMA-60 (CMA, Sweden) into the femoral muscle. The microdialysis catheter was perfused with saline in a rate of 200 µl/hour. Subsequently epicystostomy was performed. After instrumentation the animal was left alone for a period necessary for stabilization of its condition. Sepsis was initiated by intravenous administration of a bolus of a suspension of *E. coli* (concentration, 10^9/ml) to manifest pulmonary hypertension or systemic hypotension. The control group received saline in the same amount. Continual infusion of suspension was followed in the rate 1 ml/hour. At the same time, fluid resuscitation with Hartman solution began at a rate of 20 ml/kg/hour. Physiological functions, parameters of invasive hemodynamics were measured at one-hour intervals. Microdialysis samples were withdrawn at one-hour intervals. Microdialyzates served to determine the levels of glucose, glycerol, lactate, and pyruvate (an analyzer ISCUS, CMA Sweden). Cumulative fluid balance was also examined. After 24 hours the animal was killed by intravenous administration of the euthanasic agent B 61. The protocol of the experiment was approved by the Committee for the Work with Laboratory Animals at the Faculty of Military Health Service, University of Defence, Hradec Králové.

Statistics

Statistical analysis was carried out by means of the programme SigmaStat 3.1. (Systat Software, USA).

RESULTS

No significant difference was found in the mean cumulative fluid balance, the septic group, 8472 ml, the control group, 6770 ml (p=0.721). With the use of the Pearson method of linear regression, a positive correlation was found between cumulative fluid balance and lactate/pyruvate ratio in the septic group (R=0.292, $p<0.001$, Figure 1), and on the other hand, a negative correlation in the control group (R=–0.279, $p<0.05$, Figure 2). In both groups a significant continual decrease in glycerol levels ($p<0.05$) was observed.

DISCUSSION

Dysfunction of microcirculation was identified as the principal pathophysiological mechanism of sepsis. There occurs a reduction in the number of perfused capillaries, dysfunction of the endothelial cells (contraction) with their increased permeability, increased activity of polymorphonuclears and their adhesion to the endothelium and microthrombotizations (Vincent *et al.* 2005). Intravascular fluid increasingly leaks into the interstitium, which participates in the development of hypovolemia and deterioration of tissue hypoperfusion. Early fluid resuscitation is a cornerstone of therapy of sepsis (Rivers *et al.* 2001). Fluid resuscitation aims to ensure sufficient perfusion pressure and to restore the supply of oxygen to the tissues. However, excessive expansion of plasmatic volume is in the terrain of pathological microvascular permeability associated with a risk of the development of tissue oedema, which further deteriorates the tissue distribution of oxygen (Matějovič *et al.* 2002).

A positive fluid balance in healthy volunteers was demonstrated to result in deterioration of the pulmonary function 24 hours after infusion administration (Holte *et al.* 2003). Also the liberal fluid strategy in major abdominal interventions is associated, in contrast to the restrictive strategy, with a higher occurrence of the paralysis of gut, deterioration of ventilatory functions, and a longer stay at the intensive-care unit (Holte *et al.* 2007; Nisanevich *et al.* 2005). In spite of the fact that fluid resuscitation is the principal treatment of sepsis, no study has hitherto dealt with tissue metabolism in connection with positive fluid balance. The role of tissue (cellular) metabolism during sepsis has remained controversial. Nevertheless, it has been demonstrated that the reduction of blood flow results in oxygen deficit and thus in anaerobic metabolism. Sepsis is also characterized by a disorder in cell utilization of oxygen, the so-called cytopathic hypoxia (Fink 2002) and a primarily increased production of lactate as the so-called non-ischemic hyperlactemia. Disorders in microcirculation and direct influence of toxin result in cell death, which is manifested as an organ dysfunction. In sepsis there exists an elevation in the serum levels of creatine kinase as a marker of destruction of muscular cells and clinically the development of myopathy of critically ill patients may occur. The present experiment has demonstrated that with an increasing cumulative fluid balance (and thus a growing tissue swelling) in the septic group the lactate/pyruvate ratio is increased, and anaerobic metabolism thus continues to take place. This may be due to the effect of a positive fluid balance and penetration of the fluid into the interstitium, but more likely due to the effect of a septic insult, because in the control group even with a comparable positive

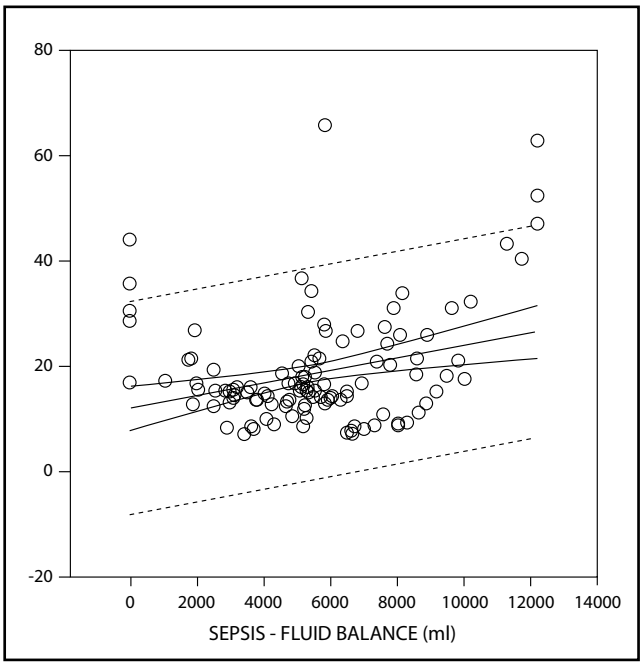

Fig. 1. Fluid balance vs. L/P ration in septic animals.

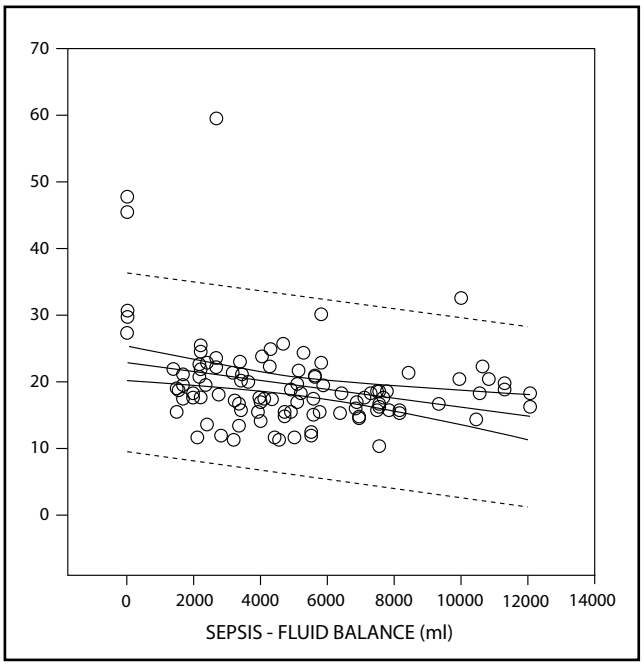

Fig. 2. Fluid balance vs. L/P ration in control animals.

fluid balance this phenomenon does not develop. It can be inferred from the decreasing glycerol level in the microdialysate that the interstitial oedema induced in the experiment does not result in cell destruction. Fluid therapy by crystalloids used in the present experiment results in a positive fluid balance also in the animals of the control group without sepsis. In the experimental group of animals the given rate achieved hemodynamic stability without using catecholamines, hemodynamic alteration being the precondition for the diagnosis of sepsis after inoculation of the bacterial culture to animal blood.

The results of the experimental study confirm the effectiveness of volume resuscitation using crystalloids to achieve hemodynamic stability in sepsis for the price of a positive fluid balance. The results do not allow think about deteriorated metabolism of the muscular tissue because of an interstitial swelling. Interstitial oedema did not result in the destruction of muscular cells and volume resuscitation protected muscular cells from destruction due to sepsis within the first 24 hours.

ACKNOWLEDGEMENT

Founded by Research Project MZO 00179906.

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