Understanding the metabolic response to sepsis

Introduction

Systemic inflammatory response syndrome (SIRS) is the response of the body to an infection or injury (e.g. pancreatitis, burns, multiple trauma or haemorrhagic shock) (*Table 1*). When SIRS occurs in the presence of a presumed or confirmed focus of infection, the term sepsis is used to describe the syndrome (Levy et al, 2003). Other terms such as severe sepsis and septic shock represent further categorization based on haemodynamic and biochemical parameters noted on presentation. These have important prognostic implications with worse respective outcomes (Brealey and Singer, 2000; Levy et al, 2003).

The SIRS response has multiple components and is characterized by the release of cellular, humoral and neuro-endocrine mediators, resulting in significant aberrations in metabolic function. While the purpose of the metabolic response is protective, it does in some instances lead to dysfunction of one or more organs, e.g. if sepsis is severe or prolonged (Pinsky et al, 1993; Pinsky, 2007).

Despite advances over the last two decades in our understanding of the physiological response to sepsis and its consequent metabolic derangements, multi-organ dysfunction syndrome (failure of two or more organ systems) continues to be associated with significant morbidity and a high mortality (Brealey and Singer, 2000) and attempts to modulate the inflammatory process have so far failed to prevent organ failure or shorten its duration (Brealey and Singer, 2000).

A greater appreciation and delineation of the pathophysiology and metabolic changes associated with SIRS is likely to afford the clinician a more judicious approach to current interventions commonly used in this setting including exogenous catecholamines (e.g. adrenaline and noradrenaline), endocrine system manipulation (e.g. steroids, insulin, thyroxine) and nutritional supplementation (total parenteral nutrition, enteral nutrition, glucose). This article will focus on the metabolic response and derangements commonly found in sepsis syndromes. The precise nature of the effect of key mediators involved will be discussed in the context of carbohydrate, fat and protein metabolism.

Miss Kaji Sritharan *is Specialist Registrar in General Surgery, Lister Hospital, Stevenage SG1 4AB, and*
Dr Mamoun Abu-Habsa *is Specialist Registrar in Intensive Care Medicine, Oxford Radcliffe Hospitals, Oxford*

Correspondence to: Miss K Sritharan

Triggers and mediators

Following an inciting stimulus, e.g. infection, trauma or other inflammatory condition, the host reacts by mounting a concerted systemic response. This results in activation of a complex cascade of events which includes increased activity within the anterior pituitary gland, leading to the increased production of a number of stress hormones (e.g. catecholamines, glucagon and corticoids), and a concurrent immune-mediated cytokine and endothelial response (Pinsky et al, 1993; Van den Berghe, 2000; Singer et al, 2004). In the initial phase of sepsis, the net metabolic effect is a state of catabolism within the peripheral tissues, resulting in an increase in the availability of substrate (glucose, amino acids and free fatty acids) essential for energy production. However, this comes at a cost as both muscle and adipose tissue are sacrificed in the process (Gauna et al, 2005).

The severity and length of the host response to sepsis is governed by a complex interplay between the various cellular, humoral and neuro-endocrine components and is related to the severity of the initial insult as well as to both the period of exposure to the insult (e.g. untreated infection, necrotic tissue, ongoing autoimmune dysfunction) and host factors (Pinsky et al, 1993; Brealey and Singer, 2000; Singer et al, 2004). Inflammation, in particular the pro-inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α, is thought to play a central role in the host response to sepsis, acting both to promote catabolism and as mediators of endothelial cellular dysfunction (Pinsky et al, 1993; Remick, 2007).

Table 1. Diagnosis of systemic inflammatory response syndrome requires the presence of two or more of the following criteria

Pyrexia >38°C or hypothermia <36°C
Tachycardia >90 beats per minute
Tachypnoea >20 breaths per minute or $PaCO_2$ <4.3kPa
White cell count >12 000 cells/μl or <4000 cells/μl

From Levy et al (2003)

Mitochondria: the power house of the cell

Adenosine triphosphate (ATP) molecules function as a rechargeable energy source for intracellular metabolism. High energy phosphate bonds within the molecule can be rapidly hydrolysed to generate energy essential for performing cellular functions, and formation of ATP through oxidative phosphorylation of adenosine diphosphate molecules is a key function of mitochondria. Mitochondria generate nearly 95% of the huge cellular ATP requirement, and this uses approximately 90% of the body's total oxygen consumption (Brealey and Singer, 2000; Singer, 2007).

However, even under normal physiological conditions, the system functions close to capacity, such that at any given time, the total pool of ATP is only ever sufficient to meet the body's energy requirement for just 1 minute (Sobotka and Soeters, 2008). In addition, mitochondria are also implicated in a number of other cellular processes, such as the initiation of apoptosis, intracellular calcium regulation, oxygen sensing, steroidogenesis and cell signalling (Costa et al, 2008; Jeong and Seol, 2008).

In sepsis, energy generation initially increases to meet the increased metabolic requirements of the body. The prime objective of the initial catabolic phase of SIRS is to provide the essential substrate required to meet the increases in cellular energy demand. The increases in intracellular metabolism can be up to 200%, accompanied by a substantial increase in oxygen consumption (Moriyama et al, 1999; Singer et al, 2004). Clinical studies have shown that septic patients who are able to raise their cardiac output and oxygen delivery to meet the increases in meta-

bolic demand have significantly better outcomes than those who cannot (Shoemaker et al, 2000). Pharmacological manipulation of the cardiovascular system to achieve oxygen delivery parameters associated with improved outcome have so far failed to show benefit in the critically ill population (Hayes et al, 1994).

As the SIRS response evolves, and particularly if prolonged, mitochondria may enter a phase of dysfunction or 'hibernation' where oxidative phosphorylation is impaired and energy production reduced. This is evidenced by rapid falls in tissue ATP levels (Singer, 2007) (*Figure 1*). This has in part been attributed to direct damage to the mitochondrion and in part to the hormonal downregulation of genes expressing mitochondrial proteins and a decrease in anterior pituitary activity (Gauna et al, 2005). Although mitochondria appear to have receptors for glucocorticoids and thyroid hormones (Psarra and Sekeris, 2008), the effect of these hormones on mitochondrial function is not well understood. Onset of this phase of mitochondrial dysfunction can be hours or days from the initial insult or the first measurable evidence of sepsis. Some authors have suggested that this may represent a period of protective cellular hibernation to aid recovery (Singer, 2007), although there is also evidence linking these changes in mitochondrial function to the sequelae of organ failure.

Many patients proceed to the anabolic or recovery phase (*Figure 1*) without clinical or biochemical evidence of organ dysfunction (Singer, 2007) and this is likely to depend on the severity of the acute illness, timing and type of resuscitative intervention and the patient population affected (Brealey and Singer, 2000; Pinsky, 2007; Vincent, 2007). Recovery following sepsis can, at least in part, be seen to rely on the regeneration of sufficient healthy mitochondria to enable normal metabolic processes to proceed. This is supported by histological data derived from patients dying of sepsis-induced multiple organ failure, where skeletal muscle, cardiac muscle and liver biopsies taken soon after death demonstrated marked mitochondrial damage (Vanhorebeek et al, 2005; Singer, 2007).

The focus of conventional critical care practice is thus to provide patients who sustain organ failure with appropriate support when predetermined dysfunction thresholds are reached (e.g. haemofiltration for acidosis or hyperkalaemia which occurs secondary to renal failure) until signs of organ recovery appear.

Glucose metabolism

Glucose formation is arguably the single most important metabolic goal of the stress response. Shock and sepsis commonly result in hyperglycaemia often in association with normal or heightened insulin levels. This ensures a high flow of glucose to the predominantly glucose-consuming cells which may not necessarily have active mitochondrial respiration, e.g. white blood cells, macrophages and compromised or injured tissues (Andersen et al, 2004).

Subnormal biological response to insulin has been described as insulin resistance and is attributed to increased secretion of stress hormones (cortisol, catecholamines, glucagon and growth hormone) and direct cytokine effects on tissues which collectively act as counter-regulators to the biological response to insulin, thereby promoting catabolism (Singer et al, 2004).

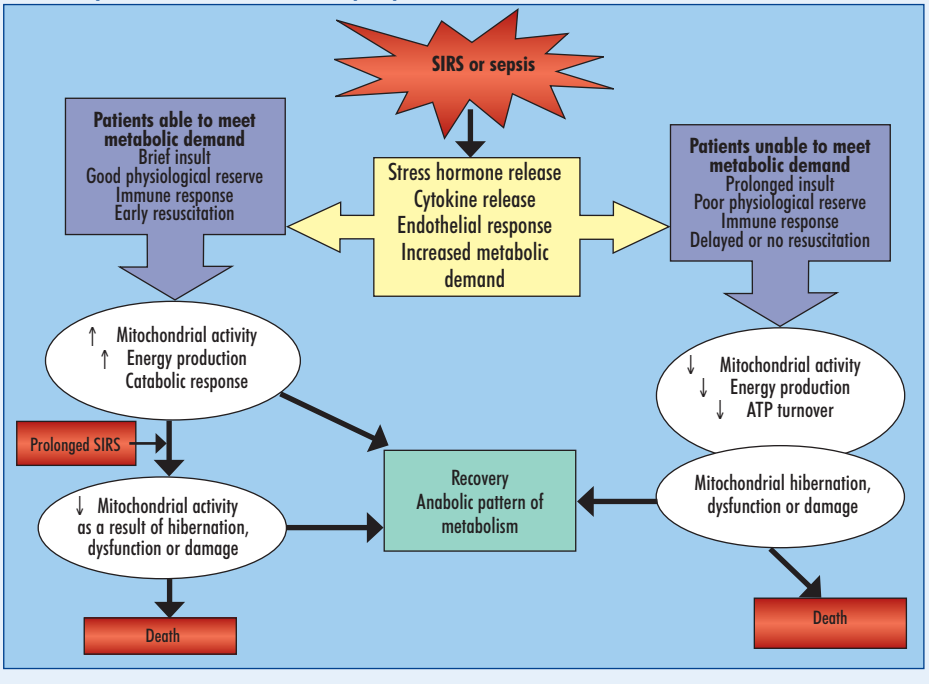
Hepatic glycogen breakdown (glycogenolysis) provides the first supply source of glucose, this can last for 12–24 hours in starvation but stores are consumed far quicker in critical illness (Andersen et al, 2004). Hence, a key effect of the stress response is increased hepatic glucose production (gluconeogenesis) which in itself is an energy-consuming process but one that provides substrate for glucose-dependant cells (brain, inflammatory and injured cells). The precursors for this process can be amino acids, lactate and glycerol (from adipose tissue); lactate, being a byproduct of anaerobic glucose metabolism, is quantitatively the most abundant in a hypermetabolic state (Sobotka and Soeters, 2008).

Interestingly, glucose administration does not suppress the enhanced hepatic glucose production and lipolysis in septic and traumatized patients. However, insulin therapy (maintaining blood glucose <110 mg/dl) has been shown to reduce morbidity and mortality among critically ill patients in the surgical intensive care unit, suggesting either a beneficial role for insulin or an association between excessive gluconeogenesis or hyperglycaemia and adverse outcome (Langouche et al, 2005).

Protein metabolism

Increased skeletal protein breakdown (proteolysis) and inhibition of protein synthesis are an important feature of the stress response (Frost and Lang, 1998; Lang et al, 2007). Although this provides crucial substrate, it contributes substantially to morbidity and mortality associated with sepsis or severe acute injury (Frost and Lang, 1998).

Figure 1. Potential patient pathways in sepsis or systemic inflammatory response syndrome (SIRS) and contributory factors. ATP = adenosine triphosphate.



The amino acids released during proteolysis provide a primary energy source for cells such as enterocytes, neutrophils and injured tissues (glutamine) as well as providing a substrate for gluconeogenesis (Andersen et al, 2004) and are used by the liver in the synthesis of acute phase proteins.

Under normal physiological conditions, the liver synthesizes predominantly constitutive hepatic proteins, such as prealbumin, albumin or transferrin. In sepsis, this synthesis shifts from constitutive hepatic proteins to acute phase proteins, such as haptoglobin, α2-macroglobulin, α1-acid glycoprotein, procalcitonin, complement factors and C-reactive protein. This so-called acute phase response forms an important part of the immune response to sepsis and is largely mediated by IL-6 (Lang et al, 2007; Remick, 2007).

The most important mediators of proteolysis are the glucocorticoid hormones. Other factors such as the degree of SIRS-induced insulin resistance within tissues and acidosis are also thought to play a role, although the mechanisms through which this acts remain unclear (Langouche et al, 2005). In any case, continuation of the catabolic phase or absence of nutritional support to address the consequent negative nitrogen balance or provide alternative substrate can result in a daily loss of up to 1 kg of muscle tissue (Sobotka and Soeters, 2008).

In a critical care patient on respiratory support, this can impede weaning and subsequent rehabilitation. However, while nutritional support may address the total body negative nitrogen balance and to some extent reduce muscle loss, net muscle gain can only be achieved in the later anabolic phase of illness, provided appropriate rehabilitative activity is undertaken (Sobotka and Soeters, 2008). Shifting of protein synthesis from acute phase proteins to constitutive proteins is a commonly used and useful marker of recovery.

Lipid metabolism

Following major trauma and sepsis, patients have enhanced lipolysis and an increase in free as well as very low density lipoprotein fatty acids (Andersen et al, 2004). This is thought to be related to a combination of the stress response as well as immune-mediated insulin resistance within adipose tissue and the liver (Singer et al, 2004).

The substantial fatty acid release from adipose tissue provides a major energy source through fat oxidation and as a substrate for gluconeogenesis in the liver but this can exceed energy requirements. Remaining fatty acids are re-esterfied to triglycerides. In such circumstances, fatty infiltration of the liver and muscle tissue can develop and this is particularly pronounced in diabetic septic patients or if inappropriate continuous glucose infusions are substituting for nutritional supplementation (e.g. >4 mg/kg/min in an adult) (Sobotka and Soeters, 2008). While free fatty acids are essential for normal state metabolism, evidence suggests a metabolic consequence of sepsis is an inability to use free fatty acids as a metabolic substrate (Andersen et al, 2004).

Conclusions

SIRS is a frequently encountered phenomenon which can occur as a result of infective or non-infective insult. The body's response to SIRS is complex leading to significant metabolic perturbations.

A greater understanding of the mechanisms underlying the multiple facets of the metabolic response to sepsis will allow the clinician to more accurately tailor therapy to meet the body's physiological and nutritional requirements with the aim of improving outcome. A detailed analysis of how patient pathways can be influenced through early resuscitation to prevent cellular dysfunction and the merits of such strategies is beyond the scope of this article. **BJHM**

Conflict of interest: none.

KEY POINTS

- The metabolic response to sepsis or injury is multi-faceted, characterized by the release of cellular, humoral and neuro-endocrine mediators.
- A key target of the stress response is to increase essential substrate availability for cells.
- Failure of the patient to meet the increased metabolic demands in sepsis significantly influences outcome, and mitochondrial function and structural integrity also appear to have a significant bearing.
- Despite advances in intensive care systemic inflammatory response syndrome continues to be associated with significant morbidity and mortality.

Andersen SK, Gjedsted J, Christiansen C, Tonnesen E (2004) The roles of insulin and hyperglycemia in sepsis pathogenesis. *J Leukoc Biol* **75**(3): 413–21

Brealey D, Singer M (2000) Multi-organ dysfunction in the critically ill: epidemiology, pathophysiology and management. *J R Coll Physicians Lond* **34**(5): 424–7

Costa AD, Pierre SV, Cohen MV, Downey JM, Garlid KD (2008) cGMP signalling in pre- and post-conditioning: the role of mitochondria. *Cardiovasc Res* **77**(2): 344–52

Frost RA, Lang CH (1998) Growth factors in critical illness: regulation and therapeutic aspects. *Curr Opin Clin Nutr Metab Care* **1**(2): 195–204

Gauna C, van den Berghe GH, van der Lely AJ (2005) Pituitary function during severe and life-threatening illnesses. *Pituitary* **8**(3-4): 213–17

Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* **330**(24): 1717–22

Jeong SY, Seol DW (2008) The role of mitochondria in apoptosis. *BMB Rep* **41**(1): 11–22

Lang CH, Frost RA, Vary TC (2007) Regulation of muscle protein synthesis during sepsis and inflammation. *Am J Physiol Endocrinol Metab* **293**(2): E453–9

Langouche L, Vanhorebeek I, Van den Berghe G (2005) The role of insulin therapy in critically ill patients. *Treat Endocrinol* **4**(6): 353–60

Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* **29**(4): 530–8

Moriyama S, Okamoto K, Tabira Y, Kikuta K, Kukita I, Hamaguchi M, Kitamura N (1999) Evaluation of oxygen consumption and resting energy expenditure in critically ill patients with systemic inflammatory response syndrome. *Crit Care Med* **27**(10): 2133–6

Pinsky MR, Vincent JL, Deviere J, Alegre M, Kahn RJ, Dupont E (1993) Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality. *Chest* **103**(2): 565–75

Pinsky MR (2007) Sepsis and multiple organ failure. *Contrib Nephrol* **156:** 47–63

Psarra AM, Sekeris CE (2008) Steroid and thyroid hormone receptors in mitochondria. *IUBMB Life* **60**(4): 210–23

Remick DG (2007) Pathophysiology of sepsis. *Am J Pathol* **170**(5): 1435–44

Shoemaker WC, Wo CC, Yu S, Farjam F, Thangathurai D (2000) Invasive and noninvasive haemodynamic monitoring of acutely ill sepsis and septic shock patients in the emergency department. *Eur J Emerg Med* **7**(3): 169–75

Singer M, De Santis V, Vitale D, Jeffcoate W (2004) Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* **364**(9433): 545–8

Singer M (2007) Mitochondrial function in sepsis: acute phase versus multiple organ failure. *Crit Care Med* **35**(9 Suppl): S441–8

Sobotka L, Soeters P (2008) Basics in Clinical Nutrition: Metabolic response to injury and sepsis. *Eur e-Journal of Clinical Nutrition and Metabolism* 1–4 (doi:10.1016/j.eclnm.2008.07.005)

Van den Berghe G (2000) Novel insights into the neuroendocrinology of critical illness. *Eur J Endocrinol* **143**(1): 1–13

Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G (2005) Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* **365**(9453): 53–9

Vincent JL (2007) Metabolic support in sepsis and multiple organ failure: more questions than answers. *Crit Care Med* **35**(9 Suppl): S436–40