

# Evolutionary trophic phases of the systemic acute inflammatory response, oxygen use mechanisms and metamorphosis

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The physiopathological mechanisms involved in the systemic posttraumatic inflammatory response are studied. The successive phases of this inflammatory response are trophic mechanisms of increasing complexity. Moreover, evolutionary complications would give rise to the return to more primitive trophic mechanisms.

*Fases evolutivas tróficas de la respuesta inflamatoria aguda sistémica, mecanismos de utilización del oxígeno y metamorfosis.* Se estudian los mecanismos fisiopatológicos implicados en la respuesta inflamatoria postraumática. Se considera que las sucesivas fases de esta respuesta inflamatoria constituyen mecanismos tróficos de complejidad creciente. Asimismo, las complicaciones evolutivas ocasionarían la regresión a mecanismos tróficos más primitivos.

The body's response to injury is complex, integrated and designed to restore homeostasis and heal the wound as rapidly as possible (Hill and Hill, 1998). This curative objective could be due to the beneficial characteristics of the inflammatory response.

Thus, we have proposed the hypothesis that both the acute local and systemic inflammatory response to injury by mechanical energy is based on the successive functional predominance of the nervous, immune and endocrine systems (Aller et al., 1996). This hypothesis implies that the final and prevalent functions of these systems may represent the consecutive phases of response to stress (Aller et al., 1996; Lorente et al., 1996a; Lorente et al., 1996b; Lorente et al., 1996c; Aller et al., 2001) and that these functions could also have a trophic meaning (Aller et al., 2004).

## The post-traumatic systemic inflammatory response

If we consider that nervous, immune and endocrine functions are expressed by the endothelium and, thus, by the vascular wall, in the post-traumatic systemic inflammatory response, there would be a nervous or immediate phase with vasoconstriction (cardiorespiratory arrest or hypovolemic shock). This phase produces ischemia and cellular edema and is followed by vasodilation (immediate resuscitation) with reperfusion injury, which, in turn, causes exudation secondary to an increase of endothelial permeability and is the cause of interstitial edema (third space). In this hemodynamic instability period, which lasts about three days, the patient ends up with a positive balance of about 4.7 liters on average and clinical edema is obvious in most patients (Hill and Hill, 1998).

Both cellular (by ischemia) as well as interstitial (by reperfusion) edema could represent an ancestral mechanism to feed the cells by diffusion. Thus, small fluctuations of cell hydration can act as separate and potent signals for cellular metabolism and gene expression. Most importantly, cell volume changes can be secondary to cumulative substrate uptake and hormones. Furthermore, it has been especially demonstrated that substances which cause swelling can trigger an anabolic signal (Häussinger, 1996).

Based on this supposition, the intense activation of the hypothalamic-pituitary-adrenal axis and the adrenomedullary system with glucocorticoid secretion and the release of epinephrine into the circulation that occurs in this early evolutionary period (O'Connor et al., 2000) makes the selective accumulation of these substances in the interstitial space of the tissues and organs that suffer ischemia-reperfusion possible because their endothelial permeability is increased.

Therefore, in the cold clammy phase, called the «ebb phase» by Cuthbertson, it could be considered that hypometabolism, anaerobic glycolysis with lactate production, low core temperature and decreased energy expenditure (Hill and Hill, 1998) are associated with primitive cellular trophic mechanisms which may be favored by substances of the neuro-endocrine stress response. This would, therefore, explain the progressive distancing of the epithelial cells from the capillaries, which would favor the persistence of hypoxia and the defective oxygen use represented by excess production of reactive oxygen species or oxidative stress during reperfusion (Table 1).

Both types of edema, cellular and interstitial, imply a primitive mechanism of nutrition by diffusion that would have a low energy requirement. Furthermore, in this phase, the excess production of reactive oxygen species would cause oxidative stress which would, in turn, result in bond cleavage and lipid and protein molecular breakdown whose final products would be a possible substrate in cases of extreme need. Furthermore, oxidative stress is one of the principal factors inducing the expression of nuclear factor (NF)- $\kappa$ B (Thiemermann, 2003)

In the following immune or intermediate phase of the inflammatory response, the epithelial organs, which have suffered ischemia-reperfusion, are infiltrated by inflammatory cells and bacteria. This infiltration occurs in an oxygen-poor environment. In these epithelial organs, which show oxidative stress, symbiosis of the inflammatory cells and bacteria for extracellular digestion, by enzyme release (fermentation), and intracellular digestion, by phagocytosis, could be associated with a hypothetical trophic capacity. This would thus explain why gut-derived bacteremia, even with potent nosocomial pathogens, is an event with a low proinflammatory potential, and is, by itself, an insufficient stimulus for systemic inflammatory response and organ failure (Alverdy et al., 2003).

The incorrect use of oxygen, both on a local as well as a systemic level, persists in this immune phase. On a local level, the oxidative burst is part of the physiological function of phagocytes connected to massive production and release of reactive oxygen intermediates (respiratory burst). Furthermore, systemically, the importance of oxygen and of capillary blood circulation are reduced while lymphatic circulation is favored. First, in the Systemic Inflammatory Response Syndrome (SIRS) and then after, with the development of sepsis, the defect in oxygen extraction and in oxygen use by the tissues successively increases. This would result in a state with a high density of stop-flow capillaries (Bauer, 2002).

This state would be secondary to capillary endothelial cell swelling, with a decrease in luminal cross-sectional area, to blood viscosity increase, to leukocyte-endothelial cell adhesion in post-capillary venules, which increases the capillary outflow resistance and, finally, to opening of peripheral arteriovenous shunts which would centralize blood flow and cause tachycardia and signs of peripheral vasodilation (Bauer, 2002). All of these alterations together would contribute to patients presenting an acute respiratory

insufficiency with tachypnea. However, the oxygen deficit is associated with hypermetabolism, raised core temperature, and, even with fever and increased energy expenditure (1).

The Cuthbertson's «flow phase» is characterized by this state in which the patient seems to use the metabolism more to produce heat (combustion) than for adenosine triphosphate (ATP) synthesis. This heat production, in turn, could be used to drive other cellular processes. Because the metabolic reactions are wasted in the form of heat generated (uncoupled reaction) and only a small part of the energy is used to do work, it seems logical that the patient would have anorexia, somnolence and lethargy (Table 1).

The capacity to use oxygen in the oxidative metabolism is recovered when the patients recover their capillary function and, therefore, the nutrition mediated by them (endocrine or late phase). This type of metabolism is characterized by a large production of ATP (coupled reaction), which is used to drive multiple specialized cellular processes with limited heat generation and would determine onset of the healing. In a long convalescence phase, the dedifferentiated epithelia specialize again, the energy stores that supplied the substrates necessary for this demanding type of metabolism are replenished and complete performance is reached, thus making active life possible (Table 1).

The hypothetical capacity of the organism to involute or dedifferentiate could represent a return to early stages of development. Therefore, this could be an effective defense mechanism against injury because it would make it possible to retrace a well-known route; i.e. the prenatal specialization phase, during the endocrine phase of the inflammatory response. This specialization would require return of the prominence of oxidative metabolism, and thus angiogenesis in the affected epithelial organs, to create the capillary bed that would make the regeneration of the specialized epithelial cells possible (Aller et al., 2004a) (Table 1)

*Table 1*  
Evolution of the post-traumatic systemic acute inflammatory response

Phases	Trophic Mechanisms		Symptoms
Nervous	Ischemia (Vasoconstriction)	Cellular edema	Diffusion Cardiorespiratory arrest Hypovolemic Shock
	Reperfusion (Vasodilation)	Interstitial edema	Anaerobic glycolysis Resuscitation Vasodilatory shock
			Oxidative Stress Multiorganic Failure (MOF)
Immune	Infiltration	Extracellular digestion (enzymes)	Fermentation Respiratory burst
	- Inflammatory Cells (diapedesis)	Intracellular digestion (phagocytosis)	Hypermetabolism Systemic Inflammatory Response Syndrome
	- Bacteria (Bacterial translocation)	Lymphatic circulation	Heat hyperproduction Sepsis
			ATP hypoproduction
Endocrine	Catabolism	Dedifferentiated epithelia	Autophagia Body weigh decrease
	Anabolism	Regeneration Differentiated epithelia	Nutrition mediated by blood capillaries Convalescence
		Repletion of energetic stores - Carbohydrates - lipids - proteins	Oxidative Metabolism Oxidative phosphorylation ATP hyperproduction Epithelial differentiation Body weight increase

### The evolutive complications of the systemic inflammatory response

This sequence in the expression of progressively more elaborate and complex nutritional systems could be considered to be the essence of the evolution of seriously traumatized patients. In this way, the incidence of harmful influences during their evolution could involve regression to the most primitive trophic stages in which nutrition by diffusion (nervous phase), which is simpler but also less expensive, facilitates the temporal survival until a more favorable environment makes it possible to initiate more complex nutritional methods (immune and endocrine phases).

This regression, on involving oxidative stress (ischemia-reperfusion), also causes ulterior increases in the nuclear levels of NF- $\kappa$ B. It is stated that NF- $\kappa$ B occupies a central role in signaling pathways important in sepsis and that greater levels of nuclear accumulation of NF- $\kappa$ B are associated with higher rates of mortality and worse clinical outcome. Therefore, the elevated NF- $\kappa$ B nuclear levels are correlated with a greater incidence of sepsis-induced organ failure development (Abraham, 2003).

In addition, an intriguing finding from the autopsy study in patients with sepsis was that there was a discordance between histologic findings and the degree of organ dysfunction in patients dying of sepsis (Hotchkiss and Karl, 2003). Cell death in the heart, kidney, liver and lung was relatively minor and did not reflect the clinical evidence of more profound organ dysfunction (Hotchkiss and Karl, 2003).

NF- $\kappa$ B increase in multiorgan failure (MOF) and the discordance between histologic and functional alterations in patients with sepsis who develop MOF are both findings that could be explained by the above mentioned hypothesis of regression to primitive mechanisms of nutrition by diffusion that would have a low energetic need. This explains why Hotchkiss and Karl (Hotchkiss and Karl, 2003) consider that much of the organ dysfunction in patients with sepsis can be explained by «cell hibernation» or «cell stunning» which could represent a state of low cellular energetic need by a primitive trophic mechanism designed to survive in extreme conditions. Therefore, «cell stunning» could be considered to be a situation of dedifferentiation in which specialized functions would not be expressed, although primitive trophic functions would be maintained. The reactivation of these primitive trophic mechanisms (ischemia-reperfusion, edema and oxidative stress) progressively increases nuclear levels of NF- $\kappa$ B since it is the mediator of these early phases of the inflammatory response.

Therefore if the neuro, immune and endocrine phases which make up the inflammatory response represent the succession of increasingly complex trophic functional systems (Aller et al., 2004b; Aller et al., 2004a), when there is injury during these evolutive phases, the tissue/body could possibly return to earlier or more primitive phases (ischemia-reperfusion) that represent the expression of simpler nutritional mechanisms (diffusion, oxidative stress) for the cells. This regression, by involving oxidative stress, also causes an ulterior increase in the nuclear levels of NF- $\kappa$ B. Thus, with minimum metabolic requirements, a longer survival of the injured tissue/body would be guaranteed.

### Systemic acute inflammatory response and phylogenia

Since the nervous, immune and endocrine phases of the inflammatory phases go from ischemia to development of oxidative metabolism, it is also tempting to speculate on whether the body reproduces the successive stages by which life passes from its origin without oxygen until it develops an effective, although costly, system for the use of oxygen every time we suffer post-traumatic acute inflammation.

If so, the succession of progressively more complex trophic mechanisms could represent the successive evolutive phases which made up the evolution of life on earth. Thus, after an anaerobic situation (ischemia), there would be a period of defective use of oxygen with production of reactive oxygen species, great heat production and little production of usable energy (ischemia-revascularization and activation of inflammatory cells), and finally, compartmentalization of oxygen would be produced for its specialized use by very differentiated cells in the blood capillaries with the development of a high metabolic level, that principally produces usable energy while limiting the production of heat energy.

Probably, the phylogenetic evolution of our body is written in the successive phases which make up the acute inflammatory response. Therefore, it could be considered that when evolution of the serious traumatized patient is favorable, he could first undergo a dedifferentiation followed by a process of differentiation or specialization which would represent a complete metamorphosis as occurs with lepidoptera.

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