USES OF GLUCOSE, INSULIN AND POTASSIUM INFUSION AS ANTI-INFLAMMATORY AGENT IN INTENSIVE CARE UNIT

Essay

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Critical care

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List of Abbreviations

- **ACC** American College of Cardiology.
- **ADP** Adenosine Diphosphate.
- **AHA** American Heart Association.
- **ALS** Amyotrophic Lateral Sclerosis.
- **AMI** Acute Myocardial Infarction.
- **AMP** Adenosine Monophosphate.
- **AP-1** Activator Protein-1.
- **APCs** Antigen-Presenting Cells.
- **ARDS** Adult Respiratory Distress Syndrome.
- **ATP** Adenosine Triphosphate.
- **BAL** Broncho Alveolar Lavage.
- **CABG** Coronary Artery Bypass Graft.
- **CARS** Compensatory Anti-inflammatory Response Syndrome.
- **cGMP** cyclic Guanosine Monophosphate.
- **COX** Cyclooxygenase.
- **CRP** C Reactive Protein.
- **DAMPs** Damage Associated Molecular Patterns.
- **DC** Dendritic Cells.
- **DIGAMI** Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction.
- **ECLA** Estudios Cardiologicos Latinoamerica.
- **Egr-1** Early Growth Response-1.
- **e-NOS** endothelial Nitric Oxide Synthase.

- **FFA** Free Fatty Acids.
- **GBS** Guillian Barre Syndrome.
- **GCS** Glasgow Coma Scale.
- **GIK** Glucose, Insulin and Potassium.
- **GIST** Glucose Insulin in Stroke Trial.
- **GM-CSF** Granulocyte Macrophage-Colony Stimulating Factor.
- **H_2O_2** Hydrogen Peroxide.
- **HBP** Heparin Binding Protein.
- **HMGB1** High Mobility Group Box 1.
- **HOCl** Hypochlorous Acid.
- **HSP** Heat Shock Protein.
- **ICAM1** Inter-Cellular Adhesion Molecule 1.
- **ICU** Intensive Care Unit.
- **IDDM** Insulin Dependent Diabetes Mellitus.
- **IGF-1** Insulin Like Growth Factor-1.
- **IL** Interleukin.
- **iNOS** Inducible Nitric Oxide Synthase.
- **I–R** Ischaemia–Reperfusion.
- **ISS** Injury Severity Score.
- **LPS** Lipopolysaccharide.
- **MAC** Membrane Attack Complex.
- **MCP-1** Monocyte Chemoattractant Protein-1.
- **MIF** Migration Inhibitory Factor.
- **MNC** Mononuclear Cells.
- **MOF** Multiple Organ Failure.

- **MS** Multiple Sclerosis.
- **NAD** Nicotinamide Adenine Dinucleotide.
- **NF** Nuclear Factor.
- **NK** Natural killer.
- **NO** Nitric Oxide.
- **O_2^-** Superoxide Anions.
- **OH^-** Hydroxyl Radicals.
- **PAF** Platelet Activating Factor.
- **PAI-1** Plasminogen Activator Inhibitor-1.
- **PAMPs** Pathogen-Associated Molecular Patterns.
- **PMNs** Polymorph Nuclear Neutrophils.
- **REE** Resting Energy Expenditure.
- **ROS** Reactive Oxygen Species.
- **SIRS** Systemic Inflammatory Response Syndrome
- **SLE** Systemic Lupus Erythematosus.
- **TF** Tissue Factor.
- **TGIK** Thyroid, Glucose, Insulin and Potassium.
- **TIMI** Thrombolysis In Myocardial Infarction.
- **TLRs** Toll Like Receptors.
- **TNF- α** Tumer Necrosis Factor-Alpha.
- **VCAM1** Vascular Cellular Adhesion Molecule 1.
- **VEGF** Vascular Endothelial Growth Factor.

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Introduction

Intensive care unit patients often have complex disorders. For instance bouts of inflammation, trauma and ischaemia/reperfusion may occur sequentially or synchronously in patients following surgery, sepsis, stroke, myocardial infarction and shock. These lead to inflammatory and metabolic responses including cytokine release, protein breakdown and insulin resistance.

Inspite of elevated insulin levels, insulin resistance at the receptor and the post receptor levels may contribute to hyperglycaemia even in non-diabetic persons, particularly when stress hormones that promote glycogenolysis are released including catecholamines and cortisol **(Groeneveld ABJ et al, 2002)**.

Glucose, insulin and potassium regimen in general and insulin in particular have anti-inflammatory properties by inhibiting production of tumour necrosis factor-α, superoxide radicals and intercellular adhesion molecule-1 in macrophages, leucocytes and endothelium. It may inhibit harmful macrophage-inhibitory factor and it may potentiate release of endothelial nitric oxide synthase and endothelin **(Das UN, 2001)**.

Use of glucose, insulin and potassium (GIK) in patients with myocardial infarction and shock was originally studied decades ago but has recently undergone a revival. In both diabetic and non-diabetic patients with myocardial infarction a high dose GIK infusion may salvage myocardium and improve heart function without an increase in myocardial oxygen demand and decrease mortality by an absolute 10% provided that hyperglycaemia is prevented **(Gordana Krljanac et al, 2005)**.

GIK infusion in diabetic and non-diabetic persons after cardiac surgery may improve heart function and enhance recovery. It was also mainly considered an antiarrhythmic solution reducing the incidence of cardiac rhythm disorders in ischemic hearts and a metabolic cocktail fueling the heart with an energy-saving substrate and increasing myocardial oxygen efficiency **(Howell NJ et al, 2011)**.

A bolus infusion of hyperosmolar GIK improved cardiac output and heart function in septic shock **(Iwan CC van der Horst et al, 2003)**.

Treatment with GIK may also improve outcome in stroke patients **(Scott JF et al, 2001)**.

In clinical ischemic syndromes plasma free fatty acids (FFA) levels are increased secondary to the lipolytic action of endogeous or therapeutically administered catecholamines. High levels of plasma FFA increase its uptake by the myocyte. Increased levels of myocyte FFA depress myocardial contractility, inhibit glycolytic flux and increase cyclic AMP levels which accumulate as intacellular toxic fatty acid derivatives. This cause membrane damage and arrhythmias and increase myocardial oxygen consumption without increase in myocardial work **(Sack MN et al, 2003)**.

Administration of exogenous GIK shifts substrate utilization in the ischemic tissue from FFA to glucose. The number of ATP produced per mole of oxygen consumed is 11 % higher for glucose than for FFA oxidation. GIK therapy has also anti FFA actions. In the presence of a high glucose and insulin substrate the inhibition of glycolysis by FFA is minimal and high circulating levels of glucose and insulin both depress plasma levels of FFA. This minimizes intracellular FFA toxicity **(Chaudhuri A et al, 2007)**.

Aim of work

The aim of this work is to explain and evaluate the anti-inflammatory effect of glucose, insulin and potassium infusion in intensive care unit .

Pathophysiology of inflammation and ischemia reperfusion

A. Pathophysiology of inflammation

The biological immune response to trauma is a host-defence response. The process of inflammatory reaction to trauma involves mediators (cytokines, chemokines, complement, oxygen radical, eicosanoid and nitric oxide (NO) and effector cells (neutrophil, monocytes/macrophages and endothelial cells). All these factors are interrelated and interconnected by up-regulatory and down-regulatory mechanisms which lead to systemic inflammatory response syndrome (SIRS). However, uncontrolled systemic inflammation and imbalance of the production of these inflammatory factors as the result of massive systemic immunological activation after severe trauma results in organ dysfunction. The level of immunological alteration which leads to SIRS following multiple organ failure (MOF) is regulated by the degree of injury, the type of injured tissue, age, sex, polymorphism and physical condition (exo- and endogenic factors). The purpose of this study is to highlight our current knowledge on the pathophysiology of MOF after trauma **(Takeshi Tsukamoto et al, 2010)**.

❖ *Mediators after trauma*

1. Cytokines

The cytokine response is an important factor in the development of SIRS. During SIRS, pro-inflammatory cytokines (IL-1, TNF-α, IL-6, IL-8, IL-12, IL-18, granulocyte macrophage-colony stimulating factor “G-CSF” and GM-CSF) are released excessively. With the release of pro-inflammatory cytokines during the initial phase of trauma anti-inflammatory cytokines, including IL-1Ra, IL-4, IL-10, IL-11

and IL-13 are released. The role of the anti-inflammatory cytokines is to down-regulate the production of pro-inflammatory cytokines (Figure 1) **(Takeshi T et al, 2010)**.

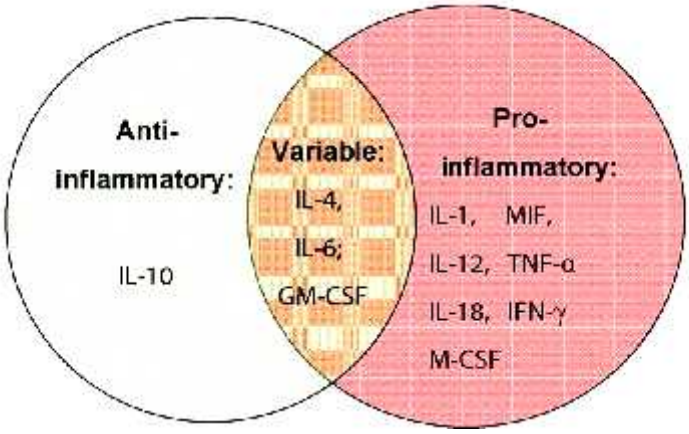

Figure 1: Types of cytokines **(Takeshi T et al, 2010)**.

Normally, the equilibrium between pro- and anti-inflammatory cytokines maintains biological homeostasis. However, when this natural balance of cytokines is unbalanced with the release of predominantly pro-inflammatory cytokines, this leads to SIRS (Figure 2), while predominance of anti-inflammatory cytokines causes immunosuppression, which can increase the likelihood of infection and sepsis (compensatory anti-inflammatory response syndrome: CARS). Both ongoing SIRS and sepsis after CARS can result in MOF **(Sivalingam SP et al, 2007)**.

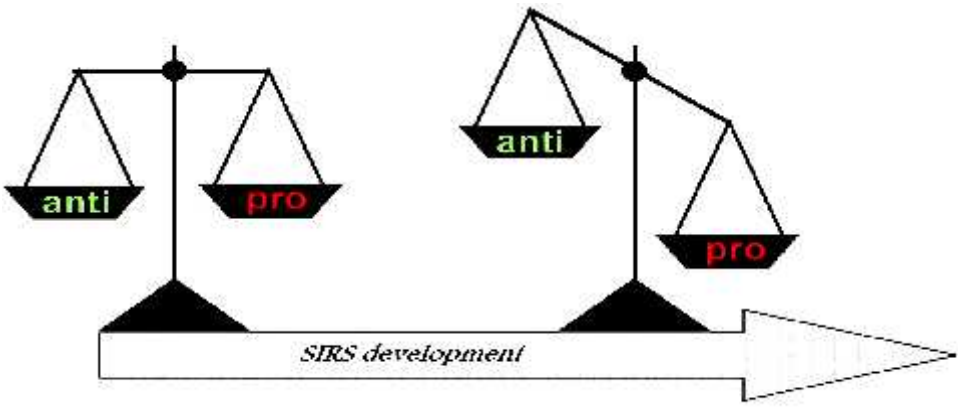

Figure 2: SIRS development **(Sivalingam SP et al, 2007).**

a) Pro-inflammatory cytokines :

Pro-inflammatory cytokines play a key role as intercellular messengers to initiate, amplify and perpetuate an inflammatory response that can act both locally and systemically. The bioactivity of cytokines is complex. They have multiple targets and they act in a pleiotropic manner. After trauma, overproduction of proinflammatory cytokines, such as TNF-α, IL-1b, IL-6 and IL-8, is initiated by monocytes and macrophages as part of an acute phase response **(Jiang JX et al, 2007)**.

TNF-α and IL-1b have a similar function, although their structure and receptors are different. TNF-α and IL-1b are regarded as the main inducers of pro-inflammatory mediators of an acute phase response. TNF-α increases the production of NO and activates cyclooxygenase (COX) enzymes, resulting in the increase and release of thromboxanes, prostaglandins and platelet activating factor (PAF) with subsequent promotion of procoagulated activity of endothelial cells. In addition, TNF-α increases the expression and release of adhesion molecules, such as (Inter-Cellular Adhesion Molecule 1: ICAM1), or E-selectin and induces the permeability of endothelial cells, which mediates neutrophil migration into tissue **(Kim PK et al, 2000)**.

A number of reports have shown that high serum levels of TNF-α are detected during sepsis. Thus, TNF-α is an available marker of severity of sepsis. However, in clinical sepsis, the correlation of the serum levels of TNF-α and mortality are in conflict **(Martin C et al, 1997)**.

Furthermore, a number of investigations have demonstrated the correlation of TNF-α with trauma. However, the results are inconsistent and no data are available as an adequate indicator of whether TNF-α is correlated to the initial pathphysiological response to trauma. According to a report of **Rabinovici** and his colleagues in 1993, the serum TNF-α level tended to be elevated in 100 trauma patients, but was not

significantly different compared to healthy controls and did not correlate with the Injury Severity Score (ISS) and the Glasgow Coma Scale (GCS) **(Rabinovici et al, 1993)**.

In support of these data, **Yao** and his colleagues in 1998 described that the release of TNF-α might occur transiently during the early phase of insult, and is further released into the system in a later stage of shock, leading to the development of MOF and poor outcome **(Yao YM et al, 1998)**.

On the other hand, it was reported earlier that TNF-α was not detectable in a swine model of trauma/haemorrhagic shock with or without the resuscitation mode **(Stylianos S et al, 1991)**.

IL-6 is produced by many different cell types, such as activated monocytes and macrophages, neutrophils, endothelial cells, T and B cells and smooth muscle cells. The biological effects of IL-6 are mainly to regulate the acute phase response, including the generation of C reactive protein (CRP), procalcitonin, serum amyloid A, fibrinogen, α1-antitrypsin and complement factors. In addition, IL-6 regulates the growth and differentiation of lymphocytes and activates natural killer (NK) cells and neutrophils (Figure 3). Many studies have tried to elucidate the role of IL-6 as an inflammatory mediator. According to their results, there is evidence that trauma induces significant levels of serum IL-6 that are proportional to the degree of tissue injury; and serum IL-6 level correlates with the severity of trauma and the risk of subsequent adult respiratory distress syndrome (ARDS) and MOF after trauma. Thus, IL-6 is a clinically relevant and feasible parameter to estimate the severity of injury and prognosis after trauma **(Pape HC et al, 2007)**.