Study of Brain Natriuretic Peptide as a Marker of Myocardial Dysfunction during Sepsis in PICU

Thesis

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By

Shereen Mohamed Mostafa
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Under supervision of

Prof. Dr/ Mona Hussein El Samahy
Professor of Pediatrics
Faculty of medicine - Ain Shams University

Prof. Dr/ Hanan Mohamed Ibrahim
Professor of Pediatrics
Faculty of medicine - Ain Shams University

Dr/ Waleed Mohamed El Guindy, MD
Lecturer of Pediatrics
Faculty of medicine - Ain Shams University

Faculty of Medicine
Ain Shams University

INTRODUCTION

Brain natriuretic peptide (BNP) is a 32-amino acid peptide with vasodilatory and natriuretic properties.It was initially identified in porcine brain. BNP is primarily produced by ventricular cardiomyocytes. Secretion of BNP depends on left ventricular (LV) filling pressures and myocardial wall stretch. Elevated BNP plasma levels have been found in patients with myocardial infarction, unstable angina, nonischemic dilated cardiomyopathy, as well as in patients with diastolic dysfunction. Moreover, high BNP plasma levels are correlated with mortality rates in patients with heart failure, myocardial infarction, and acute coronary syndromes without ST-segment elevation **(*Charpentier et al., 2004*).**

Sepsis and septic shock continue to pose clinical and diagnostic challenges. Severe sepsis has been reported to cause more than 200 000 deaths per year, most of which are attributed to cardiovascular collapse. Patients with septic shock were shown to have reversible left ventricular systolic dysfunction with an associated elevation in cardiac index. It was also determined that myocardial depression persists in patients with septic shock until death or recovery. The early assessment and diagnosis of cardiovascular dysfunction and its severity in patients with septic shock requires special equipment and expertise. Thus, a readily measurable circulating biomarker would facilitate the assessment and perhaps prevent cardiovascular dysfunction in these patients **(*Kandil et al., 2008).***

Alteration of myocardial performance in sepsis can be related to structural abnormalities of the heart and so biochemical markers could be used to diagnose sepsis-induced myocardial dysfunction ***(ver Elst et al., 2000).*** A recent study suggests that BNP plasma levels can be used to monitor therapeutic strategies for chronic congestive heart failure ***(Troughton et al., 2000).***

Adding bedside determination of BNP levels to commonly used clinical variables to guide inotrope therapy in hypotensive septic patients deserves to be further investigated ***(Charpentier et al., 2004*).**

AIM OF THE WORK

To investigate the value of brain natriuretic peptide plasma level as a marker of myocardial dysfunction during sepsis and septic shock in pediatric ICU in Ain Shams University hospital.

Sepsis in Critically ill Children

Introduction:

In recent decades the reported incidence of sepsis has increased dramatically, largely due to the advancing age of the population, an increased number of invasive procedures performed, and immunosuppressive therapy. Sepsis is among the most common reasons for admission to intensive care units throughout the world. In the United States alone, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal. Sepsis is now the 10th leading cause of death in the United States. Despite the use of antimicrobial agents and advanced life-support care, the case fatality rate for patients with sepsis has remained between 30% and 50% over the past three decades. Survivors of sepsis and septic shock are observed to have a higher 6- and 12-month mortality rate and a significantly lower health-related quality of life ***(Raghavan and Marik, 2006).***

Definitions:

Severe sepsis and septic shock are the most serious presentations of systemic infection; despite of ongoing scientific and wide-ranging therapeutic efforts both syndromes are still associated with an unacceptably high mortality rate ***(Schmittinger et al., 2010).*** Systemic inflammatory response syndrome (SIRS) was proposed by the American College of

Chest Physicians and Society of Critical Care Medicine to describe the nonspecific inflammatory process occurring in adults after trauma, infection, burns, pancreatitis, and other diseases. Sepsis was defined as SIRS associated with infection ***(Goldstein et al., 2005).*** Infection is a pathologic process caused by the invasion of normally sterile tissue, fluid, or body cavity by pathogenic or potentially pathogenic microorganisms ***(Nguyen et al., 2007)***.

The SIRS criteria were developed for use in adults and therefore contain a number of clinical signs and laboratory values specific to adults. A number of modifications of these criteria for a pediatric population can be found in the literature ***(Goldstein et al., 2005).***

1-Infection: A suspected or proven infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura ***(Goldstein et al., 2005).***

2-Bacteremia: The presence of viable bacteria in the blood ***(Bone et al., 2005).***

3-Systemic inflammatory response syndrome: The systemic inflammatory response is a response to a variety of severe clinical insults. Consistent with the criteria set forth by the

International Pediatric Consensus Conference this response is manifested by two or more of the following conditions:

a. Temperature >38˚c or <36˚c.
b. Heart rate >90th percentile for age
c. Respiratory rate >90th percentile for age or apnea for > 15 seconds or mechanical ventilation
d. WBC > 12,000 cells/mm^3, <4,000 cells/ mm^3, or >10% immature (band) forms

(Domico et al., 2008)

The definition of SIRS is applicable to the pediatric population yet tachycardia and tachypnea are common presenting symptoms of many pediatric disease processes. Therefore, the major difference in the definition of SIRS between adults and children is that the diagnosis of pediatric SIRS requires that temperature or leukocyte abnormalities be present (i.e., SIRS should not be diagnosed if a pediatric patient exhibits only elevated heart and respiratory rates). In addition, numeric values for each criterion need to be modified to account for the different physiology of children. Finally bradycardia may be a sign of SIRS in the newborn age group but not in older children (in whom it is a near terminal event). Table (1) gives the age specific cutoffs for each criterion ***(Goldstein et al., 2005).***

Table (1): Age-specific vital signs and laboratory variables (lower values for heart rate, leukocyte count, and systolic blood pressure are for the 5th and upper values for heart rate, respiration rate, or leukocyte count for the 95th percentile)

Age Group	Heart Rate, Beats/Min		Respiratory Rate, Breaths/Min	Leukocyte Count, Leukocytes × 10^3/mm	Systolic Blood Pressure
	Tachycardia	Bradycardia			
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 month	>180	<100	>40	>19.5 or <5	<75
1 month to 1 year	>180	<90	>34	>17.5 or <5	<100
2-5 years	>140	NA	>22	>15.5 or <6	<94
6-12 years	>130	NA	>18	>13.5 or <4.5	<105
13 to <18	>110	NA	>14	>11 or <4.5	<117

NA (not applicable) ***(Goldstein et al., 2005)***

4-Sepsis: Sepsis was defined as SIRS associated with infection ***(Goldstein et al., 2005).***

5-Severe sepsis: Sepsis is associated with organ dysfunction, hypotension or hypoperfusion. Hypoperfusion abnormalities may include, lactic acidosis, oliguria, or an acute alteration in mental status ***(Levy et al., 2003).***

6-Early septic shock: Clinical diagnosis of sepsis syndrome plus hypotension (systolic blood pressure below 90 mmHg or 40 mmHg decrease below baseline systolic blood pressure) that lasts for less than 1 hour and is responsive to conventional therapy (intravenous fluid administration or pharmacological intervention) ***(Balk, 2004)***.

7-Refractory septic shock: Clinical diagnosis of sepsis syndrome plus hypotension (systolic blood pressure below 90 mmHg or 40 mmHg decrease below baseline systolic blood pressure) that lasts for more than 1 hour despite adequate volume resuscitation and that requires higher doses of dopamine ***(Balk, 2004)***.

8-Multiple organ dysfunction syndrome: Presence of altered organ functions in an acutely ill patient such that homeostasis cannot be maintained without intervention ***(Levy et al., 2003).***

Criteria for organ dysfunction are summarized in Table 2

Table (2): Organ dysfunction criteria

Cardiovascular dysfunction Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr ● Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age OR ● Need for vasoactive drug to maintain BP in normal range (dopamine >5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)s OR ● Two of the following Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate >2 times upper limit of normal Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 secs Core to peripheral temperature gap >3°C
Respiratory ● PaO2/FIO2 <300 in absence of cyanotic heart disease or preexisting lung disease OR ● PaCO2 >65 torr or 20 mm Hg over baseline PaCO2 OR ● Proven need for >50% FIO2 to maintain saturation > 92% OR ● Need for non elective invasive or noninvasive mechanical ventilation

Neurologic

● Glasgow Coma Score ≤11

Glasgow Coma Score		
Eye Opening (E)	**Verbal Response (V)**	**Motor Response (M)**
4=Spontaneous 3=To voice 2=To pain 1=None	5=Normal conversation 4=Disoriented conversation 3=Words, but not coherent 2=No words.....only sounds 1=None	6=Normal 5=Localizes to pain 4=Withdraws to pain 3=Decorticate posture(abnormal flexion) 2=Decerebrate posture(abnormal extension) 1=None
		Total = E+V+M

OR

● Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

Hematologic

● Platelet count <80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)

OR

● International normalized ratio (INR) >2

Renal

● Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatic

● Total bilirubin ≥4 mg/dL (not applicable for newborn)

OR

● ALT 2 times upper limit of normal for age

BP, blood pressure; **ALT,** alanine transaminase; **PaO2,** partial pressure of oxygen in arterial blood; **PaCO2,** partial pressure of carbon dioxide in arterial blood ; **FIO2,** fraction of inspired oxygen in a gas mixture

(Goldstein et al., 2005)

Etiology:

Bacteria, viruses, fungi and parasites can cause SIRS. Organisms that cause sepsis vary with age. In newborns, the most common pathogens are those isolated from the maternal gastrointestinal and genital tracts. Group B streptococcus is currently the most common etiologic agent of neonatal sepsis in the United States, although Escherichia coli, Enterococcus organisms, Listeria organisms, Haemophilus influenzae, Staphlococcus aureus, Pseudomonas aeruginosa, Candida albicans, and Salmonella may also be implicated ***(Moloney-Harmon, 2005).***

In infancy Hemophilus influenza type b, Streptococcus pneumonia, Neisseria meningitides and Salmonella species are the most frequent causes of bacterial sepsis. Streptococcus pneumonia and Neisseria meningitides predominate in the United States and the developed world because conjugate Hemophilus influenza type b vaccination has essentially eliminated disease caused by Hemophilus influenza type b. In regions where malaria occurs, plasmodium falciparum is a frequent cause of SIRS in infancy ***(Carrigan et al., 2006).***

In childhood the same pathogens cause SIRS in childhood, although the presence of encapsulated organisms generally becomes less frequent as the child's immune response to polysaccharide antigens improves with age ***(Carrigan et al., 2006).***

Special considerations:

Some underlying conditions predispose to infection with particular pathogens.

- Acquired immunodeficiency syndrome (AIDS) predispose to SIRS from various usual and unusual pathogens, particularly pneumococcus.
- Children with hemoglobin S disease have a 400-fold increased risk of sepsis due to pneumococcus and salmonella, among other pathogens.
- Splenic dysfunction or immunoglobulin deficiency, predispose to sepsis due to encapsulated organisms.
- Congenital heart disease is a risk factor for endocarditis and SIRS.
- Infants and children with significant burns are at risk for SIRS, caused by skin flora and nosocomial gram-negative pathogens in particular.
- Genitourinary anomalies often increase the risk of urosepsis

(Lebel & Tapiero, 2002)

- Cytomegalovirus should also be considered in the immunocompromised patient who presents with a clinical sepsis syndrome ***(Moloney-Harmon, 2005).***

Incidence and risk factors:

The incidence of sepsis has been increasing over the last years. The reasons for this increasing incidence are many:

- Increased use of invasive devices such as intravascular catheters.
- Widespread use of cytotoxic and immune suppressive drug therapies.
- Increase in infection due to antibiotic resistant organisms

(Raghavan and Marik, 2006).

Other factors increase the risk of nosocomial infection as shown in Table 3.

Table (3): Risk factors of nosocomial infection

Chronic disease
Congenital or acquired immune defeficiency
Immunosuppressive therapy
History of antibiotic use
Clinical conditions such as bone marrow transplantation
Long term use of central venous access
Bladder catheter
Endotracheal tubes
Prolonged hospitalization

(Stockwell, 2007)

Pathophysiology of Sepsis:

When the body is challenged by foreign microbial agents, homeostatic mechanisms come into play that attempt to rid the body of the foreign agent without damaging the host. This involves the activation of pro and anti-inflammatory pathways, which are tightly controlled and regulated. In most individuals, the body is able to achieve a balance between pro-inflammatory and anti-inflammatory mediators and homeostasis is restored. In some patients, however, this balance is upset with an excessive pro-inflammatory response resulting in systemic inflammatory response syndrome (SIRS), multi-system organ dysfunction, septic shock and, ultimately, death ***(Raghavan and Marik, 2006).***

Microbial triggers of disease:

1. Gram-negative bacteria = endotoxins, exotoxin and proteases
2. Gram-positive bacteria=exotoxins, superantigens(toxic shock syndrome toxin), streptococcal pyogenic exotoxin A, enterotoxins, hemolysins, peptidoglycans and lipotechoic acid.
3. Fungal cell wall material

(Haeney, 2003)

A series of pathogenic events are responsible for the transition from sepsis to severe sepsis/septic shock. The initial reaction to infection is a neurohumoral, generalized pro- and anti-inflammatory response. This begins with a cellular activation of monocytes, macrophages, and neutrophils that

interact with endothelial cells through numerous pathogen recognition receptors. A further host response includes the mobilization of plasma substances as a result of this cellular activation and endothelial disruption. These plasma substances include cytokines such as tumor necrosis factor, interleukins, caspase, proteases, leukotrienes, kinins, reactive oxygen species, nitric oxide, arachidonic acid, platelet activating factor, and eicosanoids. Activation of the complement and coagulation cascades further amplifies this elaborate chain of events ***(Nguyen et al., 2006)***.

This systemic inflammatory cascade is initiated by various bacterial products and triggers, illustrated in figure (1) ***(Haeney, 2003)***.

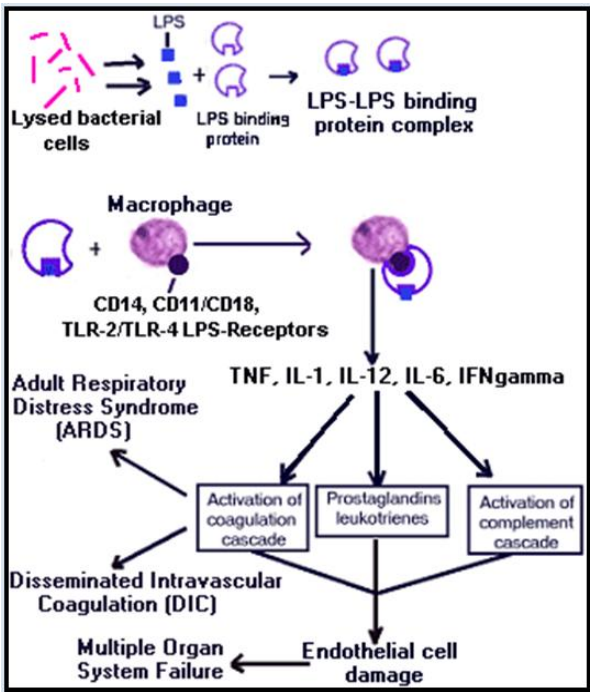

Figure (1): Systemic inflammatory cascade initiated by various bacterial products and triggers ***(Haeney, 2003).***