Endotoxin in Newborn Septic Shock: Significance, Metabolic, and Cardiovascular Changes*†

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ABSTRACT

The role of endotoxin in newborn septic shock is reviewed. Metabolic and cardiovascular changes, as known to us, are described with special emphasis that the newborn is not a "small adult." Developmental or maturational changes are hypothesized to be the major cause of these differences between age groups. Finally, it is our belief that newborn septic shock is an important topic for further investigation.

Introduction

The goal of this review is to heighten the awareness of endotoxin (ET) in newborn septic shock; the review is divided into three parts. First, the importance of gram negative infection in newborn septic shock will be addressed. Second, the role of ET will be integrated in the developing newborn with septic shock. Third, the metabolic and cardiovascular dyshomeostasis, as known in newborn septic shock, will be noted.

The incidence of human newborn infection is one to five per 1,000 live births. Newborn infection has a high morbidity and mortality. Specifically, gram negative infection is the most common nosocomial infection. In spite of high technology instrumentation, newborn gram negative infection carries a mortality of approximately 50 percent. Neurologic morbidity is also very high with gram negative septic shock, especially if meningitis is present. Endotoxin is part of the outer membrane of gram negative bacteria. Since ET is an integral part of gram negative bacteria, it cannot be separated in the pathophysiologic process of newborn gram negative septic shock.

Endotoxin can cause a myriad of effects on the body, and many of these effects are well characterized in adult animal models. However, ET in the newborn human and animal models demands further investigation. It is with the intimate role of ET in gram negative septic shock that the review of newborn...
human and animal metabolic and cardiovascular dysfunction in endotoxicosis is approached.

Endotoxin in Newborn Septic Shock

Endotoxin has been shown to cause newborn septic shock.27 Scheifele documented endotoxin-like activity (ELA) of 2500 ng per ml in a complex septic newborn. Endotoxin-like activity decreased after enteral treatment with polymyxin B. This case documented ELA in septic human infant. Furthermore, ELA decreased with enteral polymyxin B rejuvinating autointoxication as a reasonable theory in this sick infant case study.

Scheifele has also documented ELA activity in cord blood.26 Scheifele studied ELA in the stool and found ELA increased markedly with a physiologic process, such as feeding. Scheifele, in the aforementioned report, demonstrated that 80 percent of the 20 children with necrotizing enterocolitis had ELA in the plasma. However, the amount of ELA for human pathology is unknown. These human newborn reports, in conjunction with volumes of animal ET literature, have led the current authors to pursue ET as a component of gram negative newborn septic shock.

Metabolic Consequences of Endotoxicosis in the Developing Organism

Hypoglycemia was first described in human septic shock by Yeung in 1970.35 Yeung evaluated admission blood glucose concentration in 56 septic infants in the neonatal period. Seventeen of these children had hypoglycemia. Yeung was successful in alerting physicians to recognize the association of newborn septic shock and hypoglycemia. Since these organisms were predominantly gram negative, Yeung hypothesized ET may be involved.

Three years later, Yeung utilized intravenous glucose tolerance testing (IVGTT) and showed an increased glucose disappearance in the infected infants when compared to age matched controls. Four septic patients had normal glucose and insulin values at five and 15 minute post IVGTT. Yeung concluded marked hyperinsulinemia was not the major factor in hypoglycemia of septic shock. The role of ET was again mentioned as a possible cause, as well as inadequate glucose release. Intravenous glucagon stimulation was employed by Yeung to evaluate mobilizable glycogen, i.e., glucose release. No difference in glucose rise was reported, and Yeung discarded inadequate mobilization of glucose as an etiology for hypoglycemia. The role of ET in hypoglycemia was not further investigated. Hyperglycemia and hypoglycemia have been reported in young rats37 and rabbits18,19 given ET. The full explanation for the euinsulinemic hypoglycemia remains to be delineated in the human newborn (figure 1). However, hypoglycemia in newborn rat endotoxicosis is not due to elevated circulating insulin,38 although it may indeed be related to decreased glycogen stores and enhanced insulin-like activity.

Phases of glucose dyshomeostasis have been intensely investigated in adult animal ET shock by Filkins.7 Filkins described an early phase endotoxicosis response that resulted in hyperglycemia caused by increase gluconeogenesis, glycogenolysis, and increasing glucose use. The late phase endotoxicosis response leads to hypoglycemia as a result of glycogen depletion, decreased gluconeogenesis and increased tissue glucose use. Adult rat hypoglycemia in endotoxicosis is greatly influenced by increased insulin.4

Lactate

Newborn rat lactic acidosis has been shown to be a part of endotoxicosis,37 but
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Endotoxin

**Direct Effect?**

- Hyperglycemia
- Gluconeogenesis ↑
- Glycogenolysis ↓
- Glucose Utilization ↑

**Indirect Effect?**

- Mediators

**Figure 1. Effect of endotoxin on glucoregulation in the developing organism.**

it is not found in the rabbit.\textsuperscript{18,19} The present authors\textsuperscript{38} have confirmed Young's work in the rat.\textsuperscript{37} The lactic acid elevation has been described to be a result of anaerobic metabolism, but the specific mechanism(s) is/are yet unknown in both the newborn and adult animal and humans in septic shock.

### Glucagon

Manson and Hess\textsuperscript{16} have hypothesised the importance of glucagon in cardiac and metabolic dysfunction in septic shock. Pancreatic and gastrointestinal derived glucagon are both elevated in adult rabbit endotoxic shock. Ishida\textsuperscript{15} postulated the role of glucagon as a glycogenolytic participating in the early phase of septic shock hyperglycemia. Hypertriglyceridermia was also noted in these endotoxic rabbits. The role of glucagon in lipid metabolism is well described, although it needs further clarification regarding mechanism of action. Glucagon elevation has been reported in newborn rat septic shock,\textsuperscript{38} but the full significance of glucagon likewise remains to be elucidated in newborn septic shock.

### Glycogen

Glycogen is a major energy source in the newborn rat.\textsuperscript{10} Glycogen stores are important to maintain plasma glucose concentration in health and disease.\textsuperscript{30} Yeung,\textsuperscript{35} as previously mentioned, disregarded glycogen depletion as a cause of human hypoglycemia because these hypoglycemic septic human newborns increased their glucose concentrations comparable to controls after glucagon administration. In animal models, the hypoglycemic late phase of sepsis is accompanied by glycogen depletion.\textsuperscript{38} Since the human newborn is very prone to hypoglycemia, the present authors believe glycogenolysis and glycogen stores may play an important role in the etiology of hypoglycemia in newborn septic shock.

### Adrenal

Many examples of clinical and animal studies have addressed the controversies of adrenal function in septic shock.\textsuperscript{5,29,31} Most recent adult human studies, Hinsman et al\textsuperscript{14} and Bone et al\textsuperscript{3}, found no efficacy in steroid treatment in adult
septic shock. No clinical trials have been reported with steroids for newborn septic shock. Yet steroids in multiple adult animal models are effective treatment in septic shock. It is our belief that this is related to modeling, and further adrenal pathophysiology in septic shock must be explored. The pathophysiology of the newborn adrenal in septic shock is yet unknown. Animal adrenal function most definitely varies with age and again differs from the adult. Newborn septic shock adrenal function is being pursued.*

**Hemodynamic Changes in Human Newborn Endotoxic Shock (figure 2)**

The hemodynamic changes in adult endotoxic shock have been well defined. Hyperdynamic state, termed “warm shock,” is increased cardiac output and heart rate with decreased blood pressure and systemic vascular resistance. Hypodynamic state, “cold shock,” is decreased cardiac output and blood pressure with increased heart rate and systemic vascular resistance.\(^2\) The hyperdynamic state is followed by the hypodynamic state. Poor peripheral perfusion and multiple system organ failure are observed in the hypodynamic state. The progression of these states marches on to death.

In human newborns, the hemodynamic changes of endotoxic shock are not well defined. To the best of our knowledge, there is no report which clearly describes the hyperdynamic state in human newborn endotoxic shock. Although there are reports which suggest the hyperdynamic state in human newborn endotoxic shock, no closely monitored case has been reported.\(^2\) Although heart rate, peripheral perfusion, and body temperature changes are supportive of the diagnosis of endotoxic shock, blood pressure decrease is the most important criteria. Therefore, the hyperdynamic state without significant hypotension may not be diagnosed as endotoxic shock. The lack of documented hyperdynamic state of newborn endotoxic shock is probably due to the criteria of hypotension in the diagnosis of endotoxic shock. When cardiac output can be noninvasively monitored in ill human newborns, the hemodynamic changes will be more clearly delineated. Cardiac output may become a more important index for the diagnosis of newborn endotoxic shock.

**Hemodynamic Studies in Experimental Newborn Endotoxic Shock**

Hemodynamics in the various animals have been studied in endotoxic shock. Many adult animal models such as hyperdynamic, hypodynamic and chronic endotoxemic have been used to simulate experimental human endotoxic shock. However, few animal models have been developed to define the cardiovascular pathophysiology of newborn endotoxic shock.

Reddin, et al\(^2\) studied hemodynamic changes in newborn and adult canine endotoxic shock. In adult dogs, hypotension occurred immediately after ET injection. Blood pressure recovered slightly, then decreased thereafter. The
heart rate increased. In newborn dogs, blood pressure was initially maintained, then gradually decreased. The increased heart rate was not observed. Connors et al. observed the same hemodynamic changes in newborn dog endotoxic shock. Bech-Jansen et al. observed the lack of increased heart rate and initial stability of blood pressure in newborn lamb endotoxic shock. We observed the similar blood pressure and heart rate changes in 10 day old rats with endotoxic shock. Griffin et al. also studied the hemodynamics including serial cardiac output measurements in newborn dog endotoxic shock. The changes of blood pressure and heart rate were similar to other investigators. The cardiac output decreased immediately after ET injection and recovered slightly, then gradually decreased. These newborn animal models demonstrate the hypodynamic state without the presence of hyperdynamic state.

Pollock et al. explained the lack of tachycardia in newborn endotoxic shock to be due to decreased myocardial muscle mass. As a result of the myocardial muscle mass decrease, there is decreased cardiac distensibility; therefore, the heart rate compensates for the poor cardiac distensibility. As the increased heart rate for the compensation is approximately maximum even in the normal state, the heart rate cannot increase in shock. However, the initial stability of blood pressure is not clearly understood.

It has been shown in adult animals that many factors and mediators such as cardiac depressant factors, catecholamines, and prostaglandins contribute to the hemodynamic changes in endotoxic shock. However, the role of these factors and mediators is not well understood in developing newborn with endotoxic shock. The newborn is anatomically and functionally immature when compared to adults. For example, myocardial catecholamine contents and receptors are less in the newborns than adult animals. In our work, the enzymatic activity of dopamine-beta-hydroxylase is immature in newborn dogs (2 to 10 days old). These immaturities may modulate the hemodynamic changes in endotoxic shock. After better understanding of this complex developmental physiology, the characteristic hemodynamic changes in newborn endotoxic shock will also be more clearly understood. These different hemodynamic changes in newborn endotoxic shock show that “newborns are not small adults.”

Cardiac output is an essential hemodynamic parameter. In adult endotoxic shock, there is a good relationship between cardiac output and prognosis. The prognosis of endotoxic shock was better in high cardiac output state than low cardiac output state. However, because of technical difficulty and relatively invasive technology, cardiac output has not been routinely observed in newborns. The lack of hyperdynamic state in newborn endotoxic shock may be due to no measurement of cardiac output. As medical technology advances, cardiac output measurements must be done in newborn endotoxic shock.

Summary

This review has incriminated ET in the developing human and in animal models of septic shock. By evaluating the pediatric endotoxin shock literature, it can be demonstrated that the glucoregulatory changes in the developing human and animal are different from the adult. Cardiovascular function and dysfunction in endotoxic shock in the human infant and in animal models also appear to be different from that described in the adult. The pediatric shock patient is not simply a small adult in shock. Most importantly, this review should reinforce
the need for further study on the metabolic and cardiovascular aspects of shock in the pediatric patient.

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References


