Comparison of Septic Shock Due to Gram-Negative and Gram-Positive Organisms[1] (34882)

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The high fatality rate of patients in septic shock and the intrigue generated by the complex reactions to endotoxin, have prompted extensive investigation of the role of endotoxin in the pathogenesis of shock. In spite of these studies, a definite pathogenesis of shock due to sepsis is not established. Nowotny (1) in a review of the current status of our knowledge regarding the endotoxin macromolecule, emphasized that although there is no generally acceptable evidence regarding a specific tissue or "target cell," the most significant factor may relate to the response of the host rather than the specific toxic component of the macromolecule. Recently, renewed efforts to simulate clinical septic shock have included the use of live organisms rather than endotoxin preparations, and the primate rather than canine animal model. Although live *E. coli* organisms produced somewhat different effects than endotoxin in the canine animal model (2), the major difference between the effect of endotoxin and *E. coli* in the rhesus monkey was the rapidity of onset of measurable physiological changes and not the quality of the changes (3). Concern regarding the validity of the endotoxin shock model is amplified by the problem of septic shock due to gram-positive organisms which do not contain endotoxin. Kwaan and Weil (4) suggested that patients with gram positive septicemia and hypotension differed physiologicaly from patients with gram-negative septicemia and hypotension. He suggested that those with the gram-positive septicemia had a hyperdynamic circulation, characterized by an elevated cardiac output and low peripheral vascular resistance, whereas those with gram-negative septicemia had reduced cardiac output and frequently an increased peripheral resistance. Blain *et al.* (5) studied patients with bacteremia and found more severe hemodynamic alterations in those with gram-negative bacteremia than those with gram-positive bacteremia.

This study was conducted to evaluate the cardiorespiratory effects of gram-negative organisms as compared to gram-positive organisms in a well-controlled animal model, the rhesus monkey.

Materials and Methods. Twelve rhesus monkeys of both sexes ranging from 2.6 to 9.8 kg who had no evidence of other disease, were utilized in this study. Six animals received live *E. coli* organisms and six received live staphylococcus organisms intravenously.

Ventilatory, blood–gas exchange and hemodynamic data were collected by techniques previously described in detail (3). The animals were anesthetized by injection of pentobarbital sodium, 20–30 mg/kg intravenously. They were then intubated with a cuffed endotracheal tube to permit the collection of expired gases. A cutdown was performed on the femoral artery and vein and catheters advanced to the right atrium and femoral artery. Pressures were recorded by Statham P23Db pressure transducers and cardiac output was determined by the indicator-dilution technique. After the initial hemodynamic and ventilatory studies were performed, the organisms were infused continuously over a 30-min period utilizing a Holter infusion pump. Hemodynamic and ventilatory measurements were repeated at 30-min intervals for the entire 4 hr of the study. One animal in the *E. coli* group died prior to the

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180-min evaluation and 2 animals in the staphylococcal group died, at 120 and 210 min, respectively.

The organisms were prepared as previously described for the *E. coli* organisms (2). The coagulase positive, *Staphylococcus aureus* organisms were initially obtained from a patient who had staphylococcal pneumonia and septicemia which was fatal. These suspensions of saline-washed organisms, in the logarithmic growth phase, were prepared immediately prior to infusion into the animals, and 4 ml/kg were then infused. Final quantitation of the organisms was performed by colony counts. The *E. coli* counts ranged from 6.4×10^9 to 2.7×10^{10} organisms/kg of body weight and the staphylococci ranged from 7.2×10^9 to 1.9×10^{10} organisms/kg.

Statistical analysis was conducted by the Student's *t* test.

Results. Hemodynamic studies. The mean cardiac output during the control period was 158 ml/kg (SE = 13) for the animals receiving *E. coli* and 233 ml/kg (SE 50) for the group receiving staphylococci. Figure 1A illustrates the change in cardiac output following the onset of infusion of the organisms. At the end of the 30-min infusion, the mean cardiac output was increased in the group that received staphylococci, but was less than control at all subsequent periods. The mean cardiac output decreased progressively in the animals which received *E. coli*. The change in cardiac output was not significantly different between the two groups at any of the times measured. The mean control systemic pressure was 113 mm Hg (SE = 11) in the *E. coli* group and 120 mm Hg (SE = 6) in the staphylococcal group. Figure 1B illustrates the change in systemic arterial pressure. The hypotension was greater at 30 and 60 min in the staphylococcal group ($p < .05$) than the *E. coli* group and the pressure remained lower at 240 min. Initial total peripheral resistances in the *E. coli* and staphylococcal group were 9950 (SE = 1620) and 10,450 (SE = 520) dynes-sec-cm^{-5}, respectively. As is apparent, the marked decrease in systemic arterial pressure in the face of a smaller decrease in cardiac output, resulted in a marked decrease in systemic resistance in both groups, but this decrease was only significantly greater in the staphylococcal group at 30, 60, and 240 min (Fig. 1C). The mean systemic resistance increased above control values at 150 min in the *E. coli* group, but did not return to control values in the staphylococcal group. This difference was only significant at 240 min. The heart rate increased minimally but significantly in both groups during the study as illustrated in Fig. 1D.

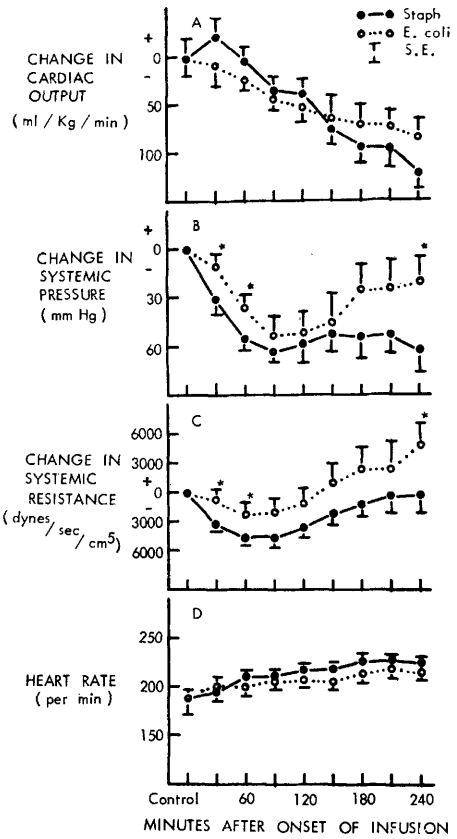

FIG. 1. Hemodynamic data in animals receiving *E. coli* or staphylococci: (A) change in cardiac output; (B) change in systemic pressure; (C) change in systemic resistance; (D) heart rate. *indicates $p < .05$ when *E. coli* compared to staphylococci.

Ventilatory data and blood–gas exchange. The mean control oxygen consumption was 9.0 ml/kg/min (SE = 0.7) in the group which received *E. coli* and 10.2 ml/kg/min (SE = 1.8) in the group which received staphylococci. There were no significant changes in ox-

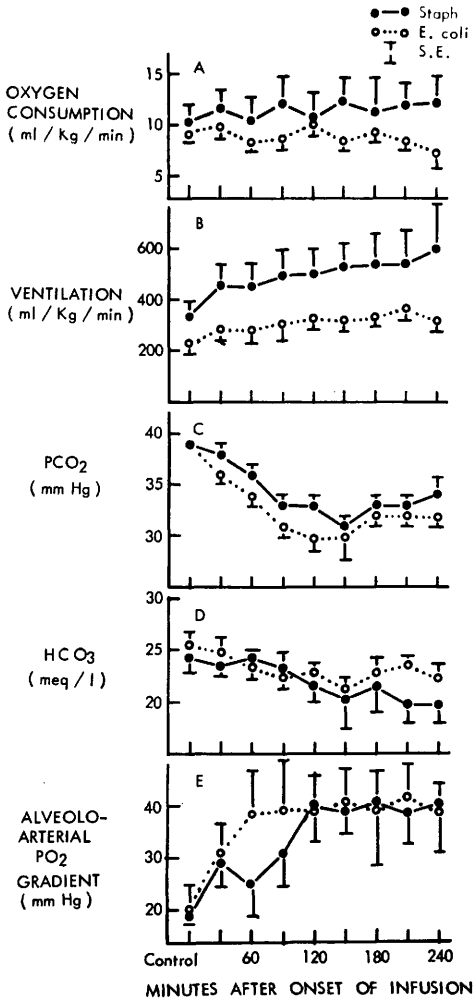

FIG. 2. Ventilatory data and blood-gas exchange in animals receiving *E. coli* or staphylococci: (A) oxygen consumption; (B) minute ventilation; (C) arterial partial pressure of carbon dioxide; (D) calculated bicarbonate concentration; (D) alveolo–arterial oxygen tension gradient.

ygen consumption in either group throughout the study (Fig. 2A). The mean control minute ventilation was 240 ml/kg/min (SE = 38 in the *E. coli* and 330 ml/kg/min (SE = 60) in the staphylococcal group. The ventilation increased in both groups during shock (Fig. 2B). The arterial P_{CO_2} decreased during the study (Fig. 2C), and the calculated bicarbonate decreased (Fig. 2D). Since the mean pH decreased from 7.43 to 7.42 in the *E. coli*, and 7.40 to 7.38 in the staphylococcal group the changes suggest the development of metabolic acidosis. There was no significant difference between the groups in any of these parameters. The abrupt increase in mean P_{CO_2} and mean bicarbonate at 150 min in the *E. coli* group is a result of death in one animal with a very low P_{CO_2} and bicarbonate whose values considerably decreased the mean. The alveolo–arterial oxygen tension gradient was 21 mm Hg (SE = 0.5) in the *E. coli* group and 20 mm Hg (SE = 1) in the staphylococcal group during the control period. This gradient increased markedly with the development of hypotension and was comparable in the two groups.

Discussion. Several recent studies have emphasized a hemodynamic difference in patients with bacteremia due to gram-positive organisms as compared to gram-negative organisms. In the study of Blain *et al.* (5), the bacteremia was not associated with shock, and was associated with an increase in cardiac output and decreased peripheral resistance when due to gram-negative organisms. Patients with gram-positive organisms had little hemodynamic variation from the nonbacteremic patients. On the other hand, Kwaan and Weil (4) studying patients with bacteremia and shock, found decreased cardiac output and frequently increased peripheral resistance in those with gram-negative organisms, as compared with an elevated cardiac output and low peripheral resistance in those with gram-positive organisms. These physiological discrepancies may be related to the stage of bacteremia, preexisting or associated disease, severity of the septicemia, or other factors. Additional suggestions regarding the significance of the type of organism, were made by Gallin *et al.* (6) who found increased levels of total serum lipids in patients with infections due to gram-negative organisms as compared to those with gram-positive infections.

In the present study, infusion of similar numbers of washed, live gram-negative or gram-positive organisms resulted in similar respiratory, hemodynamic, and metabolic effects in the lightly anesthetized rhesus monkey. Although the cardiac output was higher, and the peripheral resistance significantly lower in the animals receiving staphylococci

30 min after the onset of infusion of the organisms, these differences were not apparent 90 min after the onset of infusion. The hyperventilation, metabolic acidosis, and elevated alveolo–arterial oxygen tension gradients were comprable in both groups and similar to those previously described in animals receiving live *E. coli* or endotoxin (3). The hemodynamic findings are generally similar to those reported by Elsberry *et al.* (7) in the unanesthetized rhesus monkey after *E. coli* endotoxin or staphylococcal enterotoxin B. Their animals generally had little decrease in peripheral resistance, but a marked decrease in cardiac output.

The hemodynamic differences between the two groups during the first 60 min may be related to basic differences in response to the live organisms, however the group numbers are small. The striking similarity of physiological responses to the different organisms suggests a final common host response which is not dependent on endotoxin *per se*. The possibility that enterotoxin was the effective agent in the staphylococcal infusions cannot be entirely excluded, however the method of preparation of the organisms was thought to preclude this as a major consideration. It is likely that the dramatic host response in shock due to septicemia, or after enterotoxin or endotoxin administration is determined by a final common pathway rather than a specific toxin–target relationship.

Summary. Cardiorespiratory effects of gram-negative and gram-positive septicemia were compared in the lightly anesthetized rhesus monkey. Thirty to 60 min after the onset of infusion of organisms, the cardiac output was higher and the peripheral resistance was lower in the group that received staphylococci, as compared to the group that received *E. coli.* Subsequently, the cardiac output decreased, systemic pressure decreased, minute ventilation increased, alveolo–arterial oxygen tension gradients increased and arterial P_{CO_2} and bicarbonate decreased as previously described in septic shock and to a comparable degree in both groups. These findings suggest a common host response to gram-positive and gram-negative organisms.

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