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Hemodynamic Consequences of Tolazoline in Neonatal Group B Streptococcal Bacteremia: an Animal Model

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Summary

Using a piglet model of neonatal sepsis, we have determined that Group B streptococcal (GBS) bacteremia is associated with a state of vascular hyper-resistance in both the pulmonary and systemic circulations. This elevated vascular resistance is accompanied by a significant fall in cardiac output despite the assurance of constant intravascular fluid volume. Pulmonary artery pressure rises extensively while systemic blood pressure remains essentially unchanged during this GBS infusion protocol.

We report here our attempts to relieve the vascular hyper-resistance of GBS infusion by administration of an α-sympathetic antagonist, tolazoline (Tz). We found that Tz, in a dose-related fashion, decreased both systemic and pulmonary vascular resistance over the entire range from 2 to 25 mg/kg. Further, at all doses tested, the resistance-reducing effect of Tz was equal in the systemic and pulmonary vascular beds. No selective pulmonary or systemic vasodilatory effect was demonstrated by Tz in this model of neonatal pulmonary hypertension.

The reduction of systemic vascular resistance was accompanied by a significant elevation in total body cardiac output at all Tz doses. Compared to pre-Tz values, cardiac output rose by 24, 55, and 55% after Tz at 2, 8.3, and 25 mg/kg respectively. In addition, administration of Tz to septic normovolemic piglets reliably produced a transient decrease of systemic blood pressure. For Tz doses of 2 and 8.3 mg/kg, steady state systemic blood pressure returned to pre-Tz levels within 10 min. However, after Tz at 25 mg/kg, steady state systemic blood pressure remained significantly below pre-Tz levels.

Abbreviations

AOP, aortic pressure
PAP, pulmonary artery pressure
LAP, left atrial pressure
CVP, central venous pressure
PVR, pulmonary vascular resistance
SVR, systemic vascular resistance
GBS, Group B streptococci
Tz, tolazoline

The morbidity of neonatal sepsis derives in large part from the fact that the time course of antibiotic sterilization of infected tissue (days) is long compared to the time course of hemodynamic collapse in septic shock (hours) (1, 18, 24, 27, 29, 34, 38). It is therefore likely that therapy directed specifically at reversing the hemodynamic sequelae of newborn sepsis might play an important adjunctive role in prevention of the pathologic outcomes currently associated with this disease.

We report here in an animal model that neonatal Group B streptococcal bacteremia is associated with a number of potentially morbid hemodynamic sequelae, among which are vascular hyper-resistance in both the pulmonary and systemic circulations, markedly elevated pulmonary artery pressure, and progressively diminished total body cardiac output. We describe in addition the effects of one mode of hemodynamic intervention, intravenous infusion of the α-sympathetic antagonist tolazoline, on the cardiovascular sequelae of neonatal Group B β-streptococcal sepsis.

MATERIALS AND METHODS

Surgical preparation. Newborn piglets (1–4 weeks old) were endotracheally intubated, paralyzed with curare or pancuronium, and anesthetized with nembutal and 50% O_2/50% N_2O. Mechanical ventilation (Harvard Medical Supplies, Dover, MA) was adjusted to maintain $Paco_2$ at 30–35 torr during the entire experiment. Water-filled warming blankets and overhead thermal heating lamps were used to maintain body core temperature at 37–38°C. A suprapubic cystostomy catheter was placed to establish urinary drainage in the paralyzed animal. Polyethylene catheters providing venous access were surgically introduced into the femoral vein, and external and internal jugular veins. Intravascular catheters attached to pressure transducers were placed in the aorta (via femoral artery), pulmonary artery and left atrium (via left lateral sternotomy), and right atrium (via internal jugular vein). An external electromagnetic flow probe (Carolina Medical Products, King, NC) was placed around the pulmonary artery, visualized via left lateral sternotomy. Flow probes were balanced electrically and mechanically for each experiment.

Five hemodynamic parameters were measured directly and continuously: phasic and mean AOP, phasic and mean PAP, phasic and mean LAP, phasic and mean CVP, and phasic and mean pulmonary artery blood flow. In the documented absence of right-to-left or left-to-right vascular shunts (see below), pulmonary artery blood flow was taken as equivalent to total body cardiac output. From these directly observed hemodynamic values, two vascular resistances were calculated as the ratio of mean driving pressure to mean blood flow: PVR = (PAP − LAP)/cardiac output SVR = (AOP − CVP)/cardiac output. Mean left atrial pressure was maintained constant during the entire experimental protocol by appropriate adjustments in the rate of intravenous fluid administration (D5/lactated Ringer's).

Preparation of bacteria. Group B β-streptococci serotype 1b,

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previously isolated from an infected human newborn, were grown in 250 cc Todd-Hewitt broth to late log phase (~10^9 organisms/cc). The bacteria were then centrifuged, the supernatant was decanted, and the organisms were resuspended to their original concentration in D5/lactated Ringer's. Quantitative cultures of the bacterial inoculum were performed by serial dilution to allow retrospective calculation of the rate of bacterial infusion.

Experimental protocol. Control hemodynamic observations were taken and determined stable for at least 1 h following the completion of surgery. Continuous infusion of live, washed, resuspended GBS organisms was then begun. The rate of GBS infusion was increased in a stepwise fashion, beginning at approximately 0.5×10^7 organisms/kg/min, and increasing to a maximum of 10^8 organisms/kg/min, until the cardiac output had fallen by 30% compared to control. At this point, with the GBS infusion continuing, Tz was administered at one of three pre-selected dosages (2, 8.3, or 25 mg/kg). As is standard practice in the human clinical setting, Tz was given as a slow intravenous bolus (taking approximately 20 sec for the smallest doses and up to 2 min for the largest doses) followed by continuous Tz infusion at 2, 8.3, or 25 mg/kg/h, respectively. Hemodynamic observations were continued throughout the duration of Tz administration.

Statistical analysis. Data were analyzed utilizing a two-tailed *t* test. Data were compiled from a series of experimental trials ($n \geq 5$) at each of three distinct Tz dosages, and were compared to a series of 15 animals each of whom received continuous GBS infusion followed by intermittent D5/lactate Ringer's aliquots in volumes equal to those of the largest Tz bolus ($\leq$ 5 cc for the largest dose in the largest animal).

Table 1. *Hemodynamic effects of Group B streptococcus infusion in the neonatal piglet**

	PRE-GBS	POST-GBS
Cardiac output (cc/min)	385.0 ± 88.0	261.1 ± 79.6†
AOP (mm Hg)	102.8 ± 7.2	110.6 ± 9.2‡
PAP (mm Hg)	9.0 ± 2.0	29.8 ± 4.6†
LAP (mm Hg)	5.8 ± 0.8	5.6 ± 1.4‡
Heart rate (bpm)	123 ± 23.6	119 ± 24.9‡
SVR (mm Hg/cc/min)	0.279 ± 0.072	0.420 ± 0.12†
PVR (mm Hg/cc/min)	0.0184 ± 0.0042	0.105 ± 0.0031†

* Values are mean ± SD for cardiac output, AOP, PAP, LAP, heart rate, SVR, and PVR. Data are summarized for $n = 6$ piglets, mean age 2.5 weeks, mean weight 2.85 kg.

† p = NS.

‡ $p < 0.02$.

RESULTS

The baseline hemodynamic status of the experimental animals immediately prior to the onset of GBS infusion is displayed in Table 1. It is apparent that, despite the surgery and anesthesia described in this experimental protocol, the cardiovascular status of the piglets was not different from previously published reports in other laboratory models (3, 13).

Table 1 also displays the effects of GBS infusion on the seven hemodynamic parameters of interest prior to the administration of Tz. At the time cardiac output had decreased to 73% of control in response to GBS infusion, pulmonary artery blood pressure had risen to 337% of its control value, while systemic blood pressure was not significantly changed. GBS infusion also effected increases in systemic vascular resistance and pulmonary vascular resistance which were both significant with respect to control and distinguishable from each other ($t = 8.64$; $p < 0.002$ PVR *versus* SVR).

Figure 1 depicts the effect of tolazoline at 2 mg/kg on the cardiac output of a single septic newborn piglet. Prior to the administration of tolazoline, GBS infusion produced a monotonic decline in cardiac output. This progressive decrease in cardiac output was precipitously reversed by tolazoline. Within seconds of the intravenous tolazoline bolus, and despite the continuing infusion of GBS organisms, cardiac output began to rise, and reached a peak within 10 min after the Tz bolus was completed. Thereafter, cardiac output tended to fall slowly, again reflecting the competing effects of continuing GBS infusion and continuous Tz infusion.

The ratio of the peak plateau value of cardiac output after tolazoline therapy to the cardiac output immediately prior to Tz administration provides a quantitative measure of the hemodynamic effect of Tz intervention in neonatal GBS sepsis. These data are compiled in Table 2 for a series of piglet trials at each of three distinct Tz dosages. At all doses tested, Tz produced a

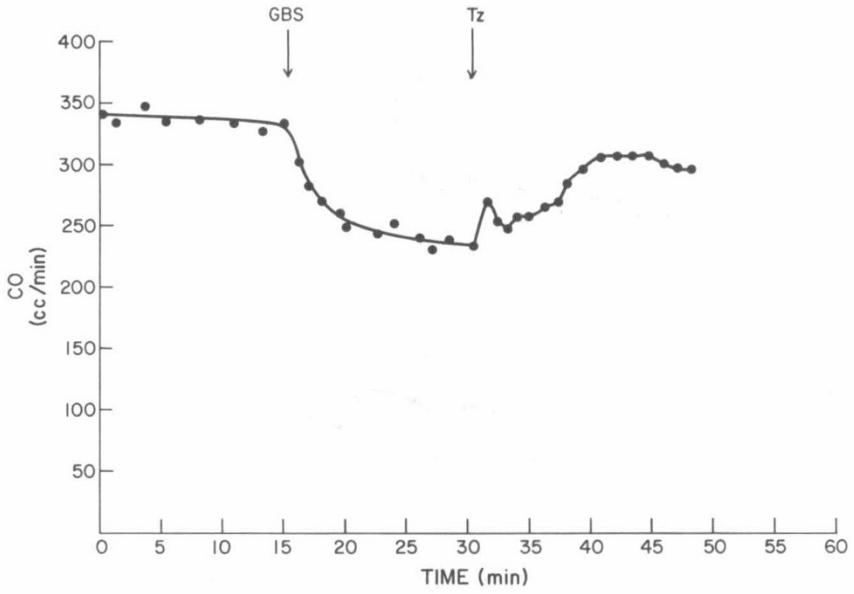

Fig. 1. Time course of changes in cardiac output (*CO*) during GBS infusion and subsequent tolazoline administration. Data displayed for one piglet, 2.9 kg, 2.5 wk old. Control observations displayed between time = 0 and time = 15 min. (Complete control period duration = 75 min, not shown.) At time = 15 min, continuous infusion of live GBS organisms was begun 10^7 organisms/kg/min. At time = 31 min, tolazoline was administered as a bolus of 2 mg/kg (duration = 90 sec) followed by continuous infusion of Tz at 2 mg/kg/h.

significant elevation in cardiac output during GBS bacteremia. Tz at 8.3 mg/kg elevated cardiac output approximately twice as much as did the 2 mg/kg dose ($t = 2.72$, $p < 0.02$ with cardiac output at 2 *versus* 8.3 mg), while no additional effect on cardiac output was observed when the Tz dose was raised to 25 mg/kg, compared to the 8.3 mg/kg dose ($t = 0.0$, p = NS with cardiac output at 8.3 *versus* 25 mg/kg).

Figure 2 displays the effect of a dose of Tz at 2 mg/kg on aortic blood pressure and pulmonary artery blood pressure for the same septic piglet displayed in Figure 1. Prior to Tz administration, PAP rose rapidly and extensively in response to GBS infusion, while AOP remained essentially unchanged during the same infusion interval ($t = 12.17$, $p < 0.002$ for PAP *versus* AOP). The Tz bolus in the septic piglet was initially followed by a decrease in aortic blood pressure. This fall (reflecting the immediate reduction in systemic vascular resistance effected by Tz) was transient, and the extent of decrease in AOP could be modulated by the speed with which the Tz bolus was administered intravenously (not shown). Later, as the bolus of Tz finished and the continuous Tz infusion began, AOP was rapidly restored toward its initial value, reaching a steady state within 10 min after the Tz bolus had begun. Comparison of Figures 1 and 2 reveals that the time course of the restoration of AOP to its steady state level after Tz bolus paralleled the time course of the increase of cardiac output after Tz. This temporal concurrence of the rise in AOP and rise in cardiac output was found to hold for each individual Tz administration, at all Tz doses tested.

Table 2. *Hemodynamic consequences of tolazoline in neonatal GBS sepsis**

	Tolazoline dose		
	2 mg/kg ($n = 6$)	8.3 mg/kg ($n = 6$)	25 mg/kg ($n = 5$)
Cardiac output	1.24 ± 0.07†	1.55 ± 0.27†	1.55 ± 0.09†
AOP	1.03 ± 0.04‡	0.99 ± 0.06‡	0.93 ± 0.07§
PAP	0.95 ± 0.06‡	0.93 ± 0.09‡	0.77 ± 0.18†
PVR	0.78 ± 0.06†	0.56 ± 0.11†	0.40 ± 0.05†
SVR	0.81 ± 0.10†	0.55 ± 0.08†	0.46 ± 0.05†

* Data are expressed as ratio (mean ± SD) of steady state post-Tz value to pre-Tz value for cardiac output, AOP, PAP, PVR, and SVR.
† $p < 0.02$.
‡ p = NS.
§ $p < 0.05$.

The effect of Tz on AOP could be quantified by determining the ratio of the steady state value of AOP after Tz administration to the value of AOP prior to Tz administration. These data are compiled in Table 2 for a series of Tz administrations at three distinct dosages. For Tz doses of 2 and 8.3 mg/kg, AOP was completely restored to its pre-Tz value by the time a steady state was achieved. For a Tz dose of 25 mg/kg, the increase in cardiac output was not quite sufficient to restore AOP completely, and AOP achieved a new steady state at 93% of its pre-Tz value.

PAP was markedly elevated by GBS infusion, decreased transiently after Tz bolus, and then rapidly recovered toward its pre-Tz value (Fig. 2). This transient fall in PAP associated with intravenous Tz bolus was reliably less extensive than the transient fall in AOP associated with Tz ($t = 2.36$; $p < 0.05$). At Tz doses of 2 and 8.3 mg/kg, steady state PAP levels were not significantly different from pre-Tz values, while after 25 mg/kg of Tz, steady state PAP was restored only to 77% of its pre-Tz level (Table 2).

Figure 3 reveals the effect of a Tz dose of 2 mg/kg on systemic and pulmonary vascular resistance for the same single septic piglet displayed in Figure 1 and 2. These data are again compiled in Table 2 for a series of septic piglets at three Tz doses. Prior to Tz administration, both PVR and SVR were significantly elevated by GBS infusion compared to control, with the increase in PVR (571%) significantly greater than the increase in SVR (150%) ($t = 8.64$, $p < 0.002$ for PVR *versus* SVR). After Tz, and despite the continuing GBS infusion, both SVR and PVR were significantly diminished at all three Tz dosage schedules. Furthermore, for all Tz doses, SVR and PVR were reduced equivalently: Tz displayed no tendency to reduce either pulmonary or systemic vascular resistance preferentially ($t = 0.63$, p = NS; $t = 0.18$, p = NS; $t = 1.89$, p = NS; SVR *versus* PVR for Tz doses of 2, 8.3, and 25 mg/kg, respectively).

The decrease in both SVR and PVR was approximately twice as large for the 8.3 mg/kg Tz dose compared to 2 mg/kg ($t = 4.97$, $p < 0.002$; $t = 4.30$, $p < 0.002$; for 2 *versus* 8.3 mg/kg SVR & PVR, respectively). Increasing the Tz dose to 25 mg/kg effected a small but significant further decrease in both SVR and PVR ($t = 2.17$, $p < 0.05$; $t = 2.98$, $p < 0.01$; for 8.3 *versus* 25 mg/kg SVR and PVR, respectively). These data are summarized in Figure 4, a dose-response curve of the effects of Tz administration on SVR and PVR in neonatal GBS sepsis.

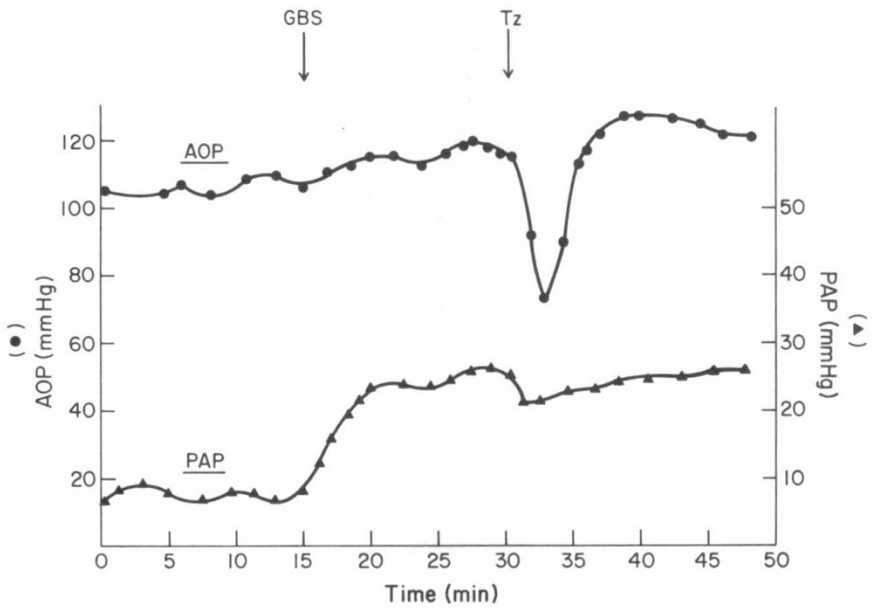

Fig. 2. Time course of changes in AOP and PAP during GBS infusion and subsequent tolazoline administration. Data are displayed for same single piglet shown in Figure 1 (2.9 kg, 2.5 wk). GBS infusion was begun at time = 15 min, and Tz was administered as 2 mg/kg bolus at time = 31 min, followed by continuous Tz infusion at 2 mg/kg/h.

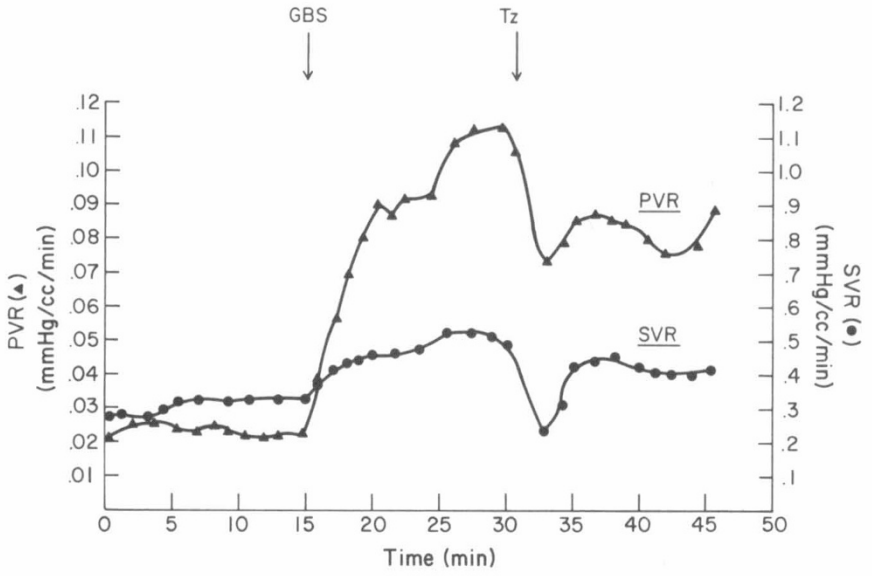

Fig. 3. Time course of changes in SVR and PVR during GBS infusion and subsequent tolazoline administration. Data are displayed for the same single piglet shown in Figs. 1 and 2 (2.9 kg, 2.5 wk). GBS infusion was begun at time = 15 min, and Tz was administered as 2 mg/kg bolus at time = 31 min, followed by continuous Tz infusion at 2 mg/kg/h.

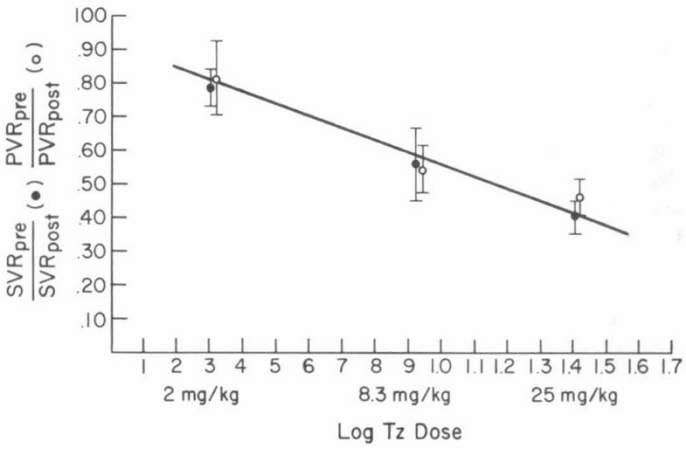

Fig. 4. Effect of Tz on SVR (post-Tz/pre-Tz) and PVR (post-Tz/pre-Tz) plotted *vs.* log [Tz] during GBS infusion. Each *point* represents mean ± SD for a series of septic piglets at each Tz dose ($n = 6$ at 2 mg/kg; $n = 6$ at 8.3 mg/kg; $n = 5$ at 25 mg/kg).

DISCUSSION

In these experiments, the hemodynamic response of the neonatal piglet to GBS infusion was characterized by progressively elevated systemic and pulmonary vascular resistance, with pulmonary hyper-resistance significantly more marked (571% of control) than was systemic hyper-resistance (150% of control). This elevated vascular resistance was accompanied by a reduction in systemic blood flow to 73% of its control value, despite assurance of constant left ventricular filling pressure. Pulmonary artery pressure increased to 3.3 times control value while systemic blood pressure was successfully preserved by the septic animal despite the diminished cardiac output.

A number of the hemodynamic consequences of GBS bacteremia in the neonatal piglet were reversed by tolazoline as administered in this experimental protocol. In contrast to previous observations in other experimental models which have supported the conclusion that neonatal myocardial function has little reserve capacity during periods of hemodynamic stress (10, 11, 30, 32), we found that tolazoline improved cardiac output in the septic piglet by 24–55% for doses between 2 and 25 mg/kg. For Tz doses equal to or less than 8.3 mg/kg, the increase in cardiac output was associated with the maintenance of steady state blood pressure at pre-Tz levels. However, no additional increase in cardiac output was apparent when the Tz dose was raised to 25 mg/kg compared to 8.3 mg/kg, and the additional vasodilation produced by this highest dose of Tz resulted in post-Tz systemic blood pressure significantly lower than control.

The observation in these septic piglets that PAP rose significantly more than did AOP corresponds to the association in septic human newborns of GBS bacteremia and elevation of pulmonary artery pressure without concurrent increases in systemic pressure (8, 21). In human infants, these hemodynamic changes can lead to right-to-left shunting of blood through the patent ductus arteriosus or foramen ovale. In this experimental protocol, neither the ductus arteriosus nor the foramen ovale was patent, and no shunting was demonstrated.

In these septic neonatal piglets with pulmonary hypertension, Tz reduced both systemic and pulmonary vascular resistance, and the reduction in vascular resistance was equivalent in the pulmonary and systemic vascular beds at all Tz doses tested. This nonselective effect of Tz on the systemic *versus* pulmonary circulations has been demonstrated in other experimental settings (25, 36). Our findings provide additional justification for the continuing search for selective pulmonary vasodilators to use in the clinical context of human neonatal pulmonary hypertension syndromes.

To our knowledge, few studies comparable to these documenting cardiovascular sequelae of bacteremia in the neonate have previously been published. Our model differed from other protocols of sepsis (4, 15, 16, 19, 20, 31, 33) in three major aspects. First, live bacteria were introduced by continuous, relatively low dose intravenous infusion ($\sim 10^7$ organisms/kg/min), as opposed to a larger, more rapid bolus of organisms ($\sim 10^9$/kg) or toxin. As the rate of fall of cardiac output was proportional to the rate of infusion of GBS organisms (*cf.* Fig. 1), this modification produced a degree of experimental control over the extent of the hemodynamic decompensation accompanying the early phases of septic shock studied here.

Second, in this protocol, mean left atrial blood pressure was maintained constant throughout the duration of GBS infusion. This control was achieved by increasing the rate of intravenous fluid administration as necessary (up to 30–40 cc/kg/h) to counter the tendency toward hypovolemia which accompanied bacterial sepsis. This deliberate experimental manipulation ensured that left ventricular preload, a major determinant of cardiac performance, was comparable at all times during our observation

period. Without maintenance of constant LAP, central hypovolemia (secondary to increased capillary permeability and/or increased venous pooling) is recognized to occur in septicemia (4, 16, 31). As LAP falls, both cardiac output and systemic blood pressure diminish, while SVR and PVR increase. These hemodynamic changes can all be restored toward normal by the simple maneuver of fluid bolus replenishing LAP to its original value (26). The effectiveness of this restorative maneuver is widely recognized, and fluid replacement is a standard therapy in the clinical context of suspected septic shock (23, 28).

However, it is also widely recognized that not all septic infants are completely restored by intravenous fluid administration: some children remain ill after a fluid push. It is at this level that we have attempted to explore the cardiovascular consequences of septicemia. Consequently, in the experiments reported here, we have arbitrarily chosen not to observe the compensatory hemodynamic responses to hypovolemia in sepsis, responses which have been adequately described elsewhere in both adult animal models and the adult clinical context (17, 23, 38). In our protocol, we have deliberately removed hypovolemia as an experimental variable by regulating LAP homeostatically. Consequently, we are documenting here the effects of GBS bacteremia in the normovolemic state; a situation which we suggest corresponds to the progression of sepsis in the human infant after the repletion of fluid volume.

The third modification of our protocol compared to previously described models of septic shock is that a decrease in cardiac output (not blood pressure) has been selected as the hemodynamic parameter which best quantifies the extent of shock produced. As revealed in Figures 1 and 2 and Table 1, systemic blood pressure is relatively insensitive to large variations in cardiovascular performance during the early phases of sepsis, hemodynamic effects which are readily perceived as alterations in cardiac output.

In these experiments, systemic cardiac output was determined by direct and continuous observation of pulmonary artery blood flow. This technique assumed that the pulmonary and systemic circulations were aligned in series, with neither right-to-left nor left-to-right shunting present. The absence of such systemic/pulmonary shunts was documented for each piglet during each individual experimental protocol. Left-to-right shunts were precluded by the demonstration of simultaneous equivalent central venous and pulmonary artery oxygen saturations. Right-to-left shunts were precluded by the demonstration of the absence of venous admixture to systemic (aortic) oxygen saturation, both prior to and during GBS infusion. The aortic Pao_2 before GBS infusion in these six animals was 182 ± 34 torr (range, 160–240), not significantly different from the mean Pao_2 value of 174 ± 43 torr (range, 110–225) determined when cardiac output had fallen by 30% during GBS sepsis ($t = 0.36$; $p = \text{NS}$).

The question of the appropriateness of this piglet model for the human newborn situation should be addressed explicitly. Four points of comparison seem particularly pertinent. First, the unstressed newborn piglet has been demonstrated to possess quantitative and qualitative cardiovascular function quite similar to that of the human newborn (2, 3, 13). Second, when stressed with GBS, the piglets were shown here to display hemodynamic responses (systemic hypoperfusion, elevated systemic vascular resistance, greatly elevated pulmonary artery pressure) much like those reported in infected human infants (7, 9, 14, 29). Third, from a qualitative bacteriologic standpoint, the constant infusion of GBS organisms seems a not unreasonable model for the constant leakage of GBS organisms from lungs to blood which is presumed to occur in fulminant GBS aspiration syndromes. Finally, from a quantitative bacteriologic standpoint, serial blood cultures taken from the piglets during GBS infusion revealed a density of bacteria in the bloodstream (10^4–10^5 organisms/cc) comparable to that observed in human neonates presenting with early onset sepsis (6).

However, two areas of significant difference between this piglet model and the human clinical situation are clear. In contrast to the suprasystemic levels of pulmonary artery pressure associated with persistence of fetal circulation in septic human infants with GBS disease (7, 9), PAP in these septic piglets at all times remained significantly below AOP (*cf.* Fig. 2 and Table 1). Second, the hemodynamic changes documented here with GBS infusion and subsequent Tz administration occurred in nonacidotic septic animals. The mean pH of the animals at the time of Tz administration was not significantly different from the pH prior to GBS infusion. Consequently, these experiments reflect hemodynamic changes during the early phases of GBS sepsis, before protracted acidosis had developed. We can draw no inferences from these data concerning effects of Tz in the severely acidotic later stages of septic shock.

When considering potential extrapolation of these data to the human newborn, we emphasize that extreme caution is warranted. The use of vasodilators in the presence of marginal intravascular fluid volume is potentially dangerous, and protracted systemic hypotension is a well recognized complication of Tz administration in the human newborn at doses within the range reported here (7, 9, 12, 22, 35). Accurate assessment of intravascular fluid status (as is ensured in this experimental model) is not a simple matter in most clinical situations. Every effort should be made to monitor and provide adequate myocardial preload before vasodilator therapy is considered in ill human infants.

As a final note, we recognize that the ability to reverse a number of the hemodynamic consequences of bacterial infusion is not necessarily equivalent to reversing the morbid metabolic decompensation known to follow protracted septicemia. It is by no means certain that hemodynamic decompensation is the cause of metabolic deterioration in sepsis (5, 37), nor is it clear that restoration of hemodynamic function will reverse metabolic decline. The studies reported here represent only a first step toward a more complete understanding of the pathophysiology of cardiovascular alterations in newborn septicemia. These studies document the effects of a single agent, tolazoline, and reveal the potential of this experimental model to assess the therapeutic efficacy of other attempts at hemodynamic intervention in neonatal sepsis.

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Experimental Neonatal Syphilis. I. Evidence of Resistance to Symptomatic Infection in Neonatal Rabbits following Intradermal Inoculation with *Treponema pallidum* (Nichols Strain)

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Summary

Resistance of 5- to 8-day-old neonatal rabbits to dermal lesion development after intradermal inoculation of *Treponema pallidum* was demonstrated. Clinical evidence of infection following inoculation of 1×10^6 *Treponema pallidum* at each of two sites was either minimal or absent. Atypical, nonprogressive, nonulcerative lesions occurred in 59% of the inoculated neonates and at 45% of inoculated sites. Differences in incubation periods, duration, and maximum diameters of lesions among adult controls *versus* neonatal rabbits were significant. The age of waning resistance was determined by inoculating groups of neonates ranging from 1 to 7 weeks of age. Five-week-old (31–36 days) neonates demonstrated waning resistance by the appearance of typically ulcerative, progressive lesions, though their parameters (duration, size) were not yet those of adult control lesions. The resistance demonstrated by neonates may be due in part to group housing (nesting) which could create unfavorable temperatures for *T. pallidum* survival; comparison of lesion development between nesting and individually housed neonates, 31 to 46 days of age, revealed a greater percentage of typical lesions developing among those individually housed (95 *versus* 52%). However, these differences may reflect the variability of typical lesion development found among animals of this age when resistance begins to wane. In both groups, the duration of typical lesions was significantly shorter than for adult controls. A heat-stable serum factor(s) was demonstrated in 19 of 20 basal sera from neonates 4 to 6 days of age; this presented another possible mechanism of resistance. The neutralizing serum factor(s) was not demonstrable in the sera of does either before mating, during gestation, or shortly after kindling. The relationship of temperature, serum

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