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Myocardial Dysfunction in Group B Streptococcal Shock

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ABSTRACT. A rabbit model of group B Streptococcal (GBS) shock was used to determine if myocardial dysfunction contributes to GBS shock and, if so, to ascertain if prostaglandins modulate this dysfunction. The infusion of heat-killed GBS (group I) produced a dramatic decrease in the first derivative of left ventricular pressure with respect to time (LVdP/dt) from baseline values ($p < 0.05$). LVdP/dt remained stable in rabbits pretreated with indomethacin (group II) and in saline-infused control rabbits (group III), and was significantly different at 30 min from LVdP/dt in group I ($p < 0.05$). Values for group I mean arterial pressure, cardiac output, pulmonary vascular resistance, and heart rate and for pH and pO_2 after GBS infusion were all significantly different from baseline values and from postinfusion values for groups II and III ($p < 0.05$). Systemic vascular resistance and left ventricular end diastolic pressure did not change significantly in any group at any time interval. These results indicate a primary role for myocardial dysfunction in the pathogenesis of GBS shock, and suggest strongly that prostaglandins modulate GBS-induced myocardial dysfunction. (*Pediatr Res* 19:511–513, 1985)

Abbreviations

GBS, group B Streptococcus
PG, prostaglandins
PAP, pulmonary artery pressure
CO, cardiac output
HR, heart rate
LVdP/dt, the first derivative of left ventricular pressure with respect to time
PVR, pulmonary vascular resistance
IND, indomethacin
TB2, thromboxane B2
MAP, mean arterial pressure

Septic shock due to GBS is a significant cause of mortality in the human fetus and neonate (1, 2). Efforts to identify at-risk pregnancies and to prevent vertical transmission to the fetus are often unsuccessful (1). Conventional treatment of the septic neonate with antibiotics and pressor agents frequently fails to reverse the shock process (1). Improved survival in neonates affected by GBS shock depends on a clearer understanding of the pathogenesis of septic shock, and on the development of new therapeutic modalities aimed at interrupting the shock process.

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A variety of animal models for GBS sepsis has been developed for the study of therapeutic strategies and to assess the hemodynamic and hematologic alterations produced by GBS shock. Short *et al.*[3] demonstrated an increased survival in the suckling rat model of GBS when animals were treated with prostaglandin synthetase inhibitors. In separate studies in piglets, Runkle et al. (4) and Lunyong and Smith (5) found that infusions of live GBS produced elevated TB2 levels and an increase in PAP. The changes in TB2 and PAP were inhibited by treatment with IND, further suggesting a role for PG in GBS shock. Rojas *et al.* (6) have isolated a toxic agent from GBS which in sheep produces elevated PAP, increased pulmonary vascular permeability, granulocytopenia, and increased levels of thromboxane and a prostacyclin metabolite (6-Keto-PGFlα) in lung lymph. Pretreatment with IND prevented the increased PAP and prevented the rise in TB2 and 6-Keto-PGFlα levels in lung lymph. These data from different animal models support previous studies of endotoxin shock suggesting a major pathogenetic role for PG endoperoxides (7).

Although PG are strongly implicated in GBS shock, the possibility that PG may modulate shock through the production of myocardial dysfunction has not been investigated. The purposes of this study were to determine if myocardial dysfunction contributes to GBS shock, and, if so, to ascertain if PG modulate this dysfunction.

MATERIALS AND METHODS

Animal preparation. Adult New Zealand White rabbits received pentobarbital anesthesia and were placed on a small animal ventilator after tracheostomy. A midline sternotomy was performed, and catheters were inserted into the main pulmonary artery and left ventricle for measurement of PAP, LVdP/dt, and left ventricular end diastolic pressure. Femoral arterial and venous catheters were placed for measurement of MAP, HR, arterial blood gases, and administration of GBS and pharmacologic agents. A 5.0 mm Statham flow probed attached to a Zepada flow meter was placed on the ascending aorta for measurement of CO. Pulmonary vascular resistance (PVR) was calculated as mean PAP/CO and systemic vascular resistance was calculated as MAP/CO. All hemodynamic variables were recorded on a model R411 Beckman chart recorder. After surgery, animals were stabilized for 30 min. Arterial blood gases were measured every 15 min and ventilation adjusted to maintain an alkalotic, hyperventilated state (pH $\geq$ 7.6) so that anticipated GBS-induced alterations in pH would have minimal impact on MAP, CO, and LVdP/dt.

GBS preparation. A strain of GBS isolated from the blood of an infant dying with shock was used in all experiments. Before each series of experiments the organism was injected into mice, and isolated colonies from a heart blood subculture were grown overnight on blood agar. Bacteria were suspended in sterile, nonpyrogenic saline to a quantified density of 10^{11} colony-

forming units per milliliter and then killed by heating to 100° C for 15 min.

Experimental sequence. Animals were assigned randomly to one of three experimental groups. Animals in group I ($n = 10$) were given heat-killed GBS by constant infusion (0.3 to 0.5 ml/kg/min of 10^{11} GBS/ml) to a total dose of 10^{12} organisms per kilogram. Values for the measured and derived hemodynamic variables and for arterial blood gases were obtained at baseline and 30 min after the beginning of the infusion. Three animals in group I were given IND (4 mg/kg) after 30-min variables were determined. Animals in group II ($n = 6$) were pretreated with IND (4 mg/kg) 30 min before an infusion of heat-killed GBS was given in the same manner as in group I. Hemodynamic and blood gas values were determined at baseline, after IND, and at 30 and 60 min after the beginning of the GBS infusion. Control animals (group III) ($n = 6$) received a volume of sterile saline equal to the volume of heat-killed GBS used in groups I and II and had each variable assessed at the same times.

Statistical analysis was performed on each variable between groups at baseline and 30 min using one-way analysis of variance, and within groups at baseline and 30 min using the complete block design analysis of variance with Duncan's test. Survival to 120 min was compared for untreated animals in group I ($n = 7$), all IND-treated animals in group I ($n = 3$) and II ($n = 6$), and control animals ($n = 6$) using χ^2 analysis. A p value of <0.05 was considered significant for all comparisons.

RESULTS

Table 1 shows the values for LVdP/dt and the other hemodynamic variables at baseline and 30 min in control animals (group III) and in the animals infused with GBS in the presence (group II) or absence (group I) of IND. The greater than 50% fall in LVdP/dt seen in group I ($p < 0.05$) was prevented by pretreatment with IND in group II. The LVdP/dt in group II animals were comparable to that in the control group.

The hemodynamic variables obtained from the three study groups are shown in Table 1. Group I values for MAP, CO, PVR, and HR at 30 min were significantly different from the values at 30 min in groups II and III. There were no significant differences within or between groups II and III at any time interval.

Table 2 lists values for pH and pO_2 at baseline and 30 min for each group and at 60 min for groups II and III. The pH and pO_2 fell significantly in group I by 30 min. A small but statistically significant drop in pH from baseline was noted in group II at 60 min but the value was not significantly different from that in group III.

Survival was monitored for a minimum of 120 min in all groups. The six control animals survived to 120 min. Seven animals in group I received only GBS. Four animals survived to 60 min and two to 120 min. Three animals in group I received IND after the 30-min assessment of variables. All three of those animals and all of the animals pretreated with IND (six of six) in group II survived to 120 min. Survival at 120 min was compared using χ^2 analysis of GBS-infused rabbits with and without IND treatment. IND-treated animals had significantly greater survival ($\chi^2 = 6.32$, $p < 0.05$).

DISCUSSION

Our study demonstrates myocardial dysfunction in an adult rabbit model of septic shock induced by GBS. Deterioration of LVdP/dt in response to heat-killed GBS infusion was rapid and was associated with significant declines in MAP, CO, HR, pH, and pO_2, and a rise in PVR. The hemodynamic changes produced by GBS (group I) were prevented by the prostaglandin synthetase inhibitor IND (group II). This suggests that alteration of myocardial function in GBS shock is PG dependent.

The magnitude of LVdP/dt is affected by HR, SVR, preload, and the intrinsic contractile state of the heart (8, 9). The 20% fall in HR induced by GBS in group I could be partly responsible for the observed decline in LVdP/dt. However, the relatively

Table 2. *Values for pH and pO_2 measured at baseline and at 30-min intervals after the initiation of GBS infusion (groups I and II) or saline infusion (group III) (mean ± SE)*

	pH	pO_2 (torr)
Group I		
Baseline	7.62 ± 0.03	88 ± 5
30 min	7.41 ± 0.05*	53 ± 6*
Group II		
Baseline	7.65 ± 0.07	79 ± 9
IND	7.67 ± 0.06	90 ± 7
30 min	7.61 ± 0.05†	85 ± 5†
60 min	7.56 ± 0.05*	92 ± 6
Group III		
Baseline	7.60 ± 0.03	73 ± 12
30 min	7.55 ± 0.03	70 ± 10
60 min	7.59 ± 0.05	84 ± 9

* Value significantly different from baseline ($p < 0.05$).

† Values significantly different than 30-min value in group I ($p < 0.05$).

Table 1. *Hemodynamic variables assessed at baseline and at 30-min intervals after the initiation of GBS infusion (groups I and II) or saline infusion (group III) (mean ± SE)*

	LVdP/dt (mm Hg/s)	MAP (mm Hg)	CO (L/min)	PVR (mm Hg/L/min)	Systemic vascular resistance (mm Hg/L/min)	Left ventricular end diastolic pressure (mm Hg)	HR (beats/min)
Group I ($n = 10$)							
Baseline	4838 ± 250	77 ± 3	0.190 ± 0.014	8.3 ± 0.9	42.5 ± 3.7	0.6 ± 0.3	253 ± 9
30 min	2358 ± 555*	47 ± 7*	0.101 ± 0.022*	23.4 ± 8.0*	48.1 ± 10.0	1.9 ± 0.6	216 ± 9*
Group II ($n = 6$)							
Baseline	4858 ± 333	78 ± 5	0.195 ± 0.020	7.2 ± 0.8	42.3 ± 5.6	2.2 ± 0.9	251 ± 3
IND	4678 ± 458	75 ± 6	0.183 ± 0.022	7.9 ± 1.0	44.9 ± 6.9	1.8 ± 0.9	255 ± 7
30 min	4981 ± 399†	82 ± 4†	0.211 ± 0.031†	9.5 ± 2.0†	43.9 ± 7.8	3.2 ± 1.1	246 ± 8†
60 min	4770 ± 371	85 ± 8	0.201 ± 0.034	11.1 ± 3.0	41.2 ± 7.2	3.8 ± 0.9	231 ± 6
Group III ($n = 6$)							
Baseline	5208 ± 581	79 ± 8	0.219 ± 0.017	8.5 ± 0.8	36.3 ± 0.2	1.3 ± 0.9	244 ± 8
30 min	5417 ± 480†	81 ± 7†	0.212 ± 0.014†	8.5 ± 1.2†	38.5 ± 2.3	2.2 ± 1.0	246 ± 9†
60 min	4970 ± 335	76 ± 5	0.189 ± 0.020	8.5 ± 1.3	41.0 ± 2.0	2.3 ± 0.9	242 ± 7

* Significantly different from baseline ($p < 0.05$).

† Significantly different than 30-min value in group I ($p < 0.05$).

small change in HR would not totally explain the rapid 50% fall in LVdP/dt as shown in Table 1. Since systemic vascular resistance and left ventricular end diastolic pressure (index of preload) did not change significantly in any group, the observed fall in LVdP/dt induced by GBS could not be related to changes in these variables.

Alterations in pH may have a significant impact on myocardial contractility (8, 10). We attempted to minimize these affects by hyperventilatory alkalosis prior to GBS infusion. Although a significant fall in pH occurred by 30 min in group I, the absolute value was still within the acceptable physiological range (7.41). Thus, it is unlikely that the change in pH associated with GBS infusion produced the dramatic fall of LVdP/dt. Furthermore, a significant fall in pH occurs 1 h after GBS infusion in group II animals; this was not associated with any significant change in LVdP/dt.

Profound hypoxemia may also cause myocardial dysfunction (10). While the 30-min value for pO_2 in group I fell significantly from baseline, the absolute value was greater than 50 mm Hg and was not statistically different from the 30-min value in control animals. Thus, while reduction of HR, pH, and pO_2 may have played a small role in producing the myocardial dysfunction seen in this model, they do not adequately explain the magnitude of the fall in LVdP/dt induced by GBS.

The protective effect of IND observed in group II suggests that PG may in some way modulate the myocardial dysfunction produced by GBS. Theoretical possibilities for PG involvement in septic myocardial dysfunction include: 1) a PG-mediated increase in coronary vascular resistance resulting in diminished or altered distribution of coronary perfusion (11, 12); 2) a PG-mediated change in PVR producing excessive right ventricular afterload with right ventricular dilatation, septal dysfunction, and mechanical interference with left ventricular function (13); 3) a direct effect of PG on myocardial contractile function due to modulation of calcium channels or ion exchange mechanisms (14, 15).

Survival of animals in this study was prolonged when IND was given either before or after GBS-induced shock. While the primary purposes of our study were to evaluate the effects of GBS and PG synthetase inhibition on myocardial function, the prolonged survival demonstrated in response to IND is interesting and confirms earlier small animal studies of GBS and PG synthetase inhibition (3–5).

In summary, we have shown that myocardial dysfunction occurs in a rabbit model of GBS shock. PG synthetase inhibition by IND prevented GBS-induced myocardial dysfunction and significantly prolonged the survival of animals receiving GBS. These data suggest primary cardiac involvement in the evolution of GBS shock. Further studies are needed to delineate the mechanism(s) which produce myocardial dysfunction in GBS sepsis.

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