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Cardiovascular Changes in Group B Streptococcal Sepsis in the Piglet: Response to Indomethacin and Relationship to Prostacyclin and Thromboxane A_2

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Summary

Seventeen piglets were infected with a continuous intravenous infusion of live group B β-hemolytic streptococci (GBS). Hemodynamic changes were recorded, and blood samples were drawn for measurement of thromboxane B_2 (TxB_2) (stable metabolite of thromboxane A_2) and 6-keto-$PGF_{1\alpha}$ (stable metabolite of prostacyclin). Control animals ($n = 9$) received only bacteria, while treatment animals ($n = 8$) received indomethacin, 3 mg/kg IV, 15 min after the start of the bacterial infusion. Control animals responded to the bacteria within 15 min with marked elevation in mean pulmonary artery pressure (Ppa) from 15 ± 8 to 39 ± 6 mm Hg and decline in Pa_{O_2} from 80 ± 11 to 51 ± 6 mm Hg and cardiac output (CO) from 0.24 ± 0.07 to 0.13 ± 0.07 liters/min/kg. Mean arterial blood pressure (AoP) significantly decreased from baseline value of 95 ± 13 to 51 ± 32 mm Hg by 180 min. In animals treated with indomethacin, these changes were reversed or significantly attenuated. The hemodynamic changes were associated temporally with elevations in plasma concentrations of TxB_2 or 6-keto-$PGF_{1\alpha}$. In the first 60 min, TxB_2 levels in both groups correlated with Ppa ($r = 0.72$, $p < 0.001$) and Pa_{O_2} ($r = -0.60$, $p < 0.001$). A strong negative correlation between TxB_2 and CO was observed over the first 180 min ($r = -0.73$, $p \leq 0.001$). There was a statistically significant correlation between AoP and 6-keto-$PGF_{1\alpha}$ concentration between 60 and 180 min ($r = -0.54$, $p < 0.002$). Indomethacin improved the hemodynamic function in this model of GBS sepsis. This improvement was related in part to inhibition of synthesis of thromboxane A_2 and prostacyclin.

Abbreviations

GBS, group B streptococci
AoP, aortic blood pressure
CO, cardiac output
Ppa, pulmonary artery pressure
Ppaw, pulmonary wedge pressure
Pra, right atrial pressure
TxB_2, thromboxane B_2

Since 1962 when Northover and Sabramanian (18) first used sodium salicylate to treat endotoxin shock in dogs, numerous investigators have documented the beneficial effects of nonsteroidal anti-inflammatory agents on hemodynamics and survival in experimental endotoxin shock (6–9, 14, 15, 20–22, 32). These studies have led to further work implicating prostaglandins and thromboxanes in the pathophysiology of endotoxin shock (1–3, 10–12). Particular attention has focused on the roles of thromboxane A_2, a vasoconstrictor and platelet-aggregating agent, and prostacyclin, a vasodilator and anti-aggregating agent.

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The hemodynamic consequences of experimental β-hemolytic GBS disease strongly resemble those of endotoxin-induced illness (16, 23). However, in contrast to the extensive work done in endotoxin models, the effects of cyclooxygenase inhibitors in GBS sepsis models have only recently begun to be studied (24, 26).

The present study was undertaken to assess the effects of treatment with indomethacin on hemodynamics and survival in a highly lethal model of GBS sepsis. The associations between plasma levels of the stable metabolites of thromboxane A_2 and prostacyclin and the observed cardiovascular events were also explored.

MATERIALS AND METHODS

Bacterial preparation. Group B β-hemolytic streptococci (type Ic) were isolated from the blood of an infant who developed early onset disease and died at the University of Miami/Jackson Memorial Hospital Neonatal Intensive Care Unit. Bacteria for each animal experiment were incubated 18 h (16, 23) in Todd-Hewitt broth at 37°C. The broth culture was centrifuged at 1700 rpm for 30 min and the bacterial pellet was resuspended in sterile Ringer's lactate solution with 5% dextrose to an approximate concentration of 10^9–10^{10} organisms/cc.

Animal model. Piglets, ages 2 to 4 weeks, were anesthetized with pentobarbital (30 mg/kg) intraperitoneally and allowed to breathe spontaneously. The femoral arteries and veins were cannulated bilaterally for blood pressure measurement, blood sampling, and fluid infusions. The left external jugular vein was cannulated and the catheter was advanced into the right atrium for measurement of pressure and injection of thermal indicator for cardiac output measurement. A 5 F Swan-Ganz flow-directed thermodilution catheter was introduced into the right external jugular vein and advanced under fluoroscopy into the left pulmonary artery. This catheter was used for measurement of Ppa, Ppaw, and CO (1950-American Edwards Laboratories, Santa Ana, CA). A second thermodilution catheter (4F, American Edwards Laboratories) was advanced from the femoral artery into the high descending aorta. Simultaneous tracings of the thermodilution curves of each catheter were made with a two-channel recorder (Model 15-6327-57, Gould, Inc., Cleveland, OH) in seven animals.

Vascular pressures were measured with pressure transducers (Model P23; Gould-Statham Instruments, Hato Rey, PR) and recorded on a multichannel recorder (Model 5 polygraph, S2-925T25, Grass Instruments, Quincy, MA).

Arterial blood gases were measured at preset intervals (pH/Blood Gas Analyzer 113, Instrumentation Laboratory, Inc., Lexington, MA) and rectal temperature was measured continuously. Skin temperature was maintained constant at 38.0°C by means of a servo-controlled radiant warmer. Two animals had continuous measurements of Pa_{O_2} via an indwelling arterial catheter (Searle Neonatal Oxygen Probe, 4 Fr., Searle Medical Products, Dallas, TX).

Following the cannulations, a stabilization period of 1 h was observed prior to obtaining baseline measurements. Three baseline measurements of vital signs, cardiac output, arterial blood gases, hematocrit, Ppa, Ppaw, Pra, and AoP were obtained at 20-min intervals in the hour preceding the bacterial infusion and averaged. Cardiac output was measured in duplicate, averaged, and corrected for weight. Following the start of the bacterial infusion, these parameters were recorded at 15 and 30 min, and then every 30 min until the animal expired or 6 h had elapsed. Results are displayed graphically for the first 4 h because of the high mortality in the study groups after that time.

Induction of sepsis. Bacterial infusion was begun immediately after baseline values were obtained. Bacteria were infused through a femoral vein at a rate calculated to deliver approximately 1.2×10^8 organisms/kg/min. This infusion was continued until the animal died or 6 h had elapsed. Blood cultures were obtained before, midway through, and at the end of the bacterial infusion in 10 animals.

Animals were randomly assigned to two groups. The control group ($n = 9$) ($\bar{x} \pm$ SD; weight, 3353 ± 1358 g; age, 21 ± 4 days) received only bacteria. The treatment group ($n = 8$) (weight, 3385 ± 1322 g; age, 19.5 ± 4 days) received indomethacin (3 mg/kg, Merck Sharp and Dohme Research Laboratories, West Point, PN) 15 min after the start of the bacterial infusion. Indomethacin was infused through the contralateral femoral vein.

Assay for thromboxane B_2 and 6-Keto-$PGF_{1\alpha}$. Blood samples (1 ml) for radioimmunoassay for TxB_2, the stable metabolite of thromboxane A_2, and 6-keto-$PGF_{1\alpha}$, the stable metabolite of prostacyclin, were collected in tubes containing aspirin and EDTA (0.41 and 1.95 mg/ml for 1 ml blood, respectively) from seven control and eight treatment animals. The assay was not available when the first two experiments were performed. Plasma from these samples was extracted with ethanol, centrifuged, and dried under liquid nitrogen before being reconstituted in 0.5–1.0 ml of phosphate-buffered saline containing gelatin. Antisera for the TxB_2 and 6-keto-$PGF_{1\alpha}$ assay were obtained from Dr. F. Fitzpatrick (5) and Dr. J. Salmon (25), respectively, and the radioimmunoassay was performed as described. Tritiated ligand for each assay was purchased from New England Nuclear Corporation (Boston, MA). After commencement of the bacterial infusion, arterial samples for 6-keto-$PGF_{1\alpha}$ and TxB_2 were drawn at 15, 30, and 60 min, and then hourly.

Statistics. Statistical analysis was performed using the paired *t* test, two-sample rank test, and repeated measures analysis of variance.

RESULTS

Hemodynamic measurements at baseline and 15 min after the onset of GBS infusion were comparable in control and indomethacin-treated animals. Pulmonary artery pressure increased early in both groups (Fig. 1) and was markedly elevated compared to baseline at 15 min ($p < 0.001$). Arterial oxygen tension (Fig. 1) was significantly lower than baseline at 15 min ($p < 0.002$). In the two animals with indwelling arterial P_{O_2} catheters, the decline in Pa_{O_2} was noted to occur after the rise in Ppa.

After 15 min, Ppa in control animals declined slowly and by 120 min had reached a plateau still significantly higher than baseline ($p < 0.002$) (Fig. 1). Animals treated with indomethacin at 15 min after the start of the bacterial infusion displayed an immediate reduction in Ppa to baseline values, followed by a gradual increase after 60 min. The pattern of Ppa in the two groups was significantly different between 30 and 120 min ($p < 0.001$). After 120 min, however, the pattern of Ppa in the treatment animals was comparable to that of the controls.

Arterial oxygen tension in control animals remained low throughout much of the study, then increased gradually after 120 min. In contrast, Pa_{O_2} increased to baseline values immediately following the administration of indomethacin and was significantly different in the two groups until 120 min ($p < 0.05$).

After the initial marked reduction at 15 min ($p < 0.001$), cardiac output remained stable in control animals throughout the experiment (Fig. 2). By 60 min after the onset of the bacterial infusion, cardiac output in the treatment group had risen to values similar to baseline. Cardiac output remained stable until approximately 240 min and declined thereafter. A significant difference in cardiac output ($p < 0.05$) between controls and treatment animals was observed during the period from 30 to 120 min following the onset of bacterial infusion.

Aortic blood pressure in the control group was maintained at baseline levels until 60 min, after which a steady deterioration was observed (Fig. 2). Indomethacin-treated animals, on the other hand, maintained a normal blood pressure for at least 4 h. The pattern of blood pressure in the two groups was significantly different between 30 and 180 min ($p < 0.05$).

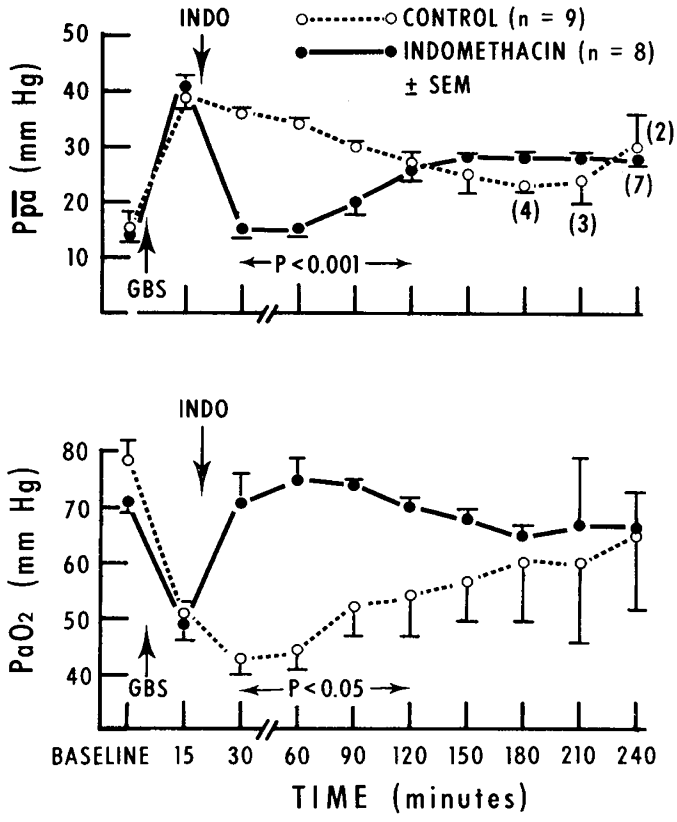

Fig. 1. Responses of mean pulmonary artery pressure and Pao_2 to infusion of GBS. Effect of indomethacin (*INDO*) on these measurements in the treatment group compared to the control group are shown. *Numbers* represent animals surviving during that time period. Significant differences between groups are indicated.

Mean TxB_2 levels (Fig. 3) were significantly increased ($p < 0.01$) compared to baseline values at 15 min in both groups, and remained high in the control animals. Values of TxB_2 in treatment animals returned to baseline after indomethacin administration and remained at that level throughout the remainder of the experiment. Treatment animals had significantly lower TxB_2 levels than control animals from 30 to 180 min ($p < 0.01$).

In the first 60 min, TxB_2 levels in both groups correlated with $\overline{Ppa}$ ($r = 0.72$, $p < 0.001$) and Pao_2 ($r = -0.60$, $p < 0.001$). A strong negative correlation between TxB_2 and CO was observed over the first 180 min ($r = -0.73$, $p < 0.001$) (Fig. 4).

Plasma concentrations of 6-keto-$PGF_{1\alpha}$ (Fig. 3) were low at first in both groups and remained low in control animals until 120 min, at which time levels tended to increase ($p < 0.08$) compared to baseline. This trend became significant ($p < 0.05$) by 180 min. In treatment animals, 6-keto-$PGF_{1\alpha}$ remained at low levels throughout the experiment. The pattern of 6-keto-$PGF_{1\alpha}$ concentrations differed significantly between the two groups from 30 to 180 min ($p \leq 0.05$). There was a statistically significant correlation between $\overline{AoP}$ and 6-keto-$PGF_{1\alpha}$ concentration between 60 and 180 min ($r = -0.54$, $p < 0.002$).

Blood cultures obtained before the start of the bacterial infusion were sterile, while all the cultures obtained during and at the end of the infusions grew group B streptococci.

Animals alive after 6 h of bacterial infusion were considered survivors. All of the control animals died, while three of eight indomethacin-treated animals survived. Mean survival time in the treatment group was 311 ± 49 min, as compared to 202 ± 62 min in controls ($p < 0.01$).

DISCUSSION

The effects of cyclooxygenase inhibitors in experimental models of GBS sepsis have recently been examined. Rojas and colleagues (23, 24) described the pulmonary vascular effects of infusion of GBS and its extracellular toxin in yearling sheep. The effects observed (*i.e.*, an initial period of marked pulmonary hypertension followed by evidence of increased pulmonary vascular permeability) were similar to those described by Ogletree *et al.* in an endotoxin model (19). In both studies, the initial phase of pulmonary hypertension was prevented by indomethacin pretreatment and subsequent continuous infusion; however, the second phase of increased pulmonary vascular permeability was not affected. Both TxB_2 and 6-keto-$PGF_{1\alpha}$ measured in lung lymph in Rojas' study increased during the initial phase of pulmonary hypertension and decreased, although not to baseline levels, in the second phase (24). When indomethacin was given prior to administration of GBS toxin, no increase in these substances was found. It should be noted that the dose of GBS exotoxin used resulted in pulmonary vascular changes without any reduction of cardiac output or systemic blood pressure. Thus, the possible effect of indomethacin on either shock or survival could not be evaluated. Using a different model, Short *et al.* (26) were able to demonstrate a significant increase in survival in suckling rats when indomethacin was administered either concomitantly with or 4 h after injection of GBS.

The present study supports and extends the previously cited works by evaluating the hemodynamic correlates of GBS sepsis and their relationship to TxB_2 and 6-keto-$PGF_{1\alpha}$ over a prolonged

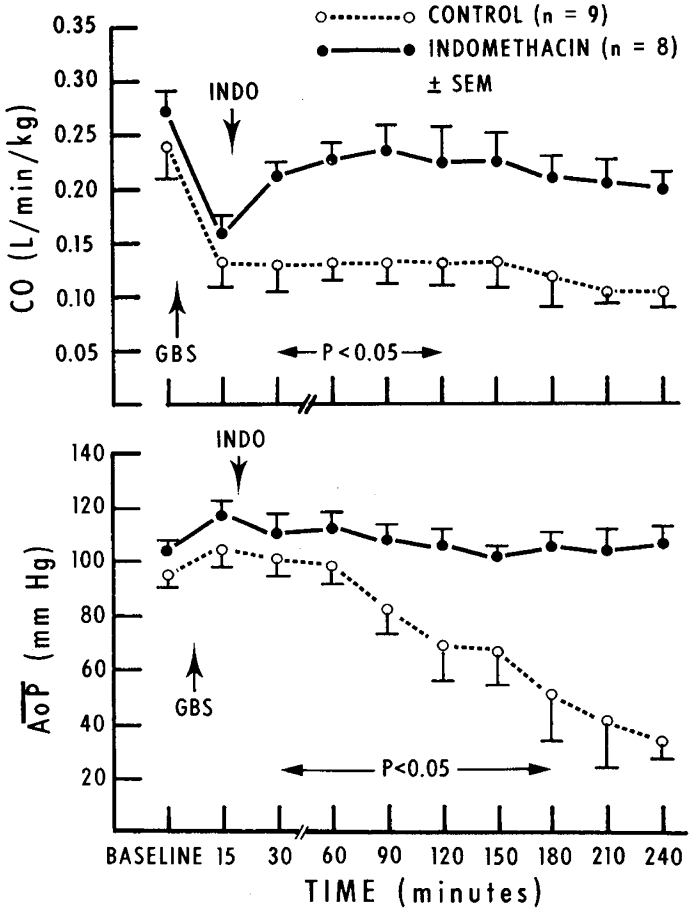

Fig. 2. Responses of cardiac output and mean systemic arterial pressure to infusion of GBS. Effect of indomethacin (*INDO*) on these measurements in the treatment and control group is shown. Significant differences between groups are indicated.

period of time. Our model differs from the above GBS models and from endotoxin models in that it employs a continuous infusion of organisms rather than a bolus of either toxin or bacteria and, in fact, this may result in an infusion of both toxin and live bacteria. In addition, indomethacin is given 15 min after GBS sepsis is induced. The presence of an ongoing bacterial stimulus may account for the persistent elevation in plasma TxB_2 concentrations seen in control animals, in contrast to the peak and later decline in concentrations of TxB_2 reported in other models (10, 12).

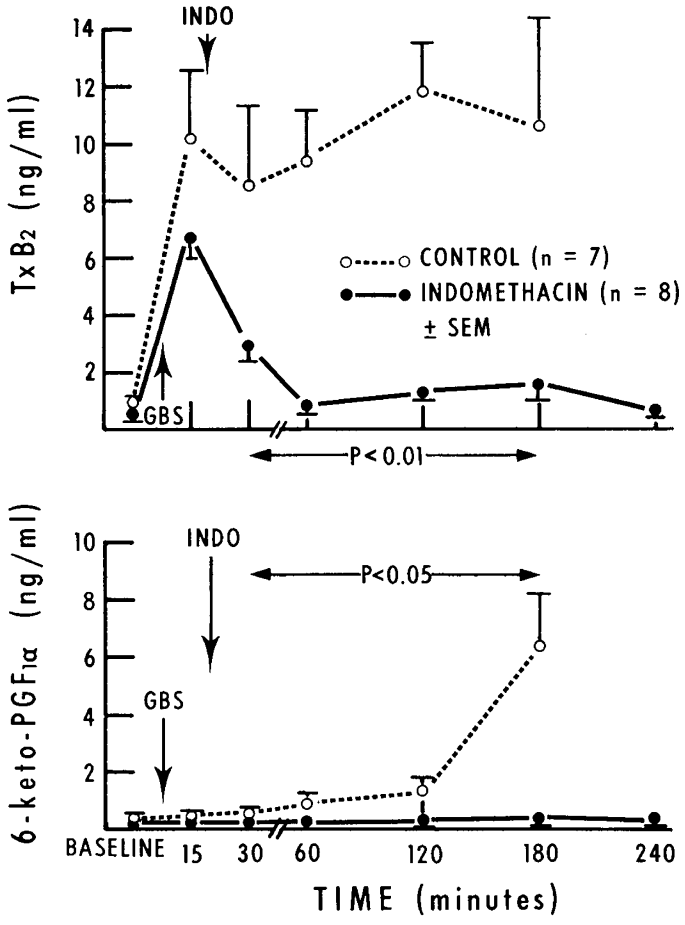

Fig. 3. Levels of TxB_2 and 6-keto-$PGF_{1\alpha}$ in treatment and control groups are shown. Significant differences between groups are indicated. *INDO*, indomethacin.

The temporal association of early pulmonary hypertension with an elevation in TxB_2 concentrations has been previously observed in Rojas' model, as well as in various endotoxin models (10, 12, 24). Thromboxane A_2, a potent vasoconstrictor, appears to mediate the early increase in pulmonary artery pressure. Interestingly, pulmonary artery pressure in control animals in the present study begins to decline slowly and levels off at approximately 120 min, despite persistently high TxB_2 concentrations. This pattern of Ppa has been observed by Ogletree and colleagues in their endotoxin model (19). Furthermore, in the indomethacin-treated animals in the current study, Ppa increases in the face of persistently low TxB_2 concentration. This suggests that the late, less pronounced, pulmonary hypertension is not related to a cyclooxygenase metabolite.

The etiology of the decline in CO in this and other septic shock models is not clear. Right heart failure secondary to severe pulmonary hypertension has been postulated (13), but Ogletree *et al.* (19) have produced marked increases in Ppa in sheep, by administering endotoxin in a dose too low to cause any systemic changes. Rojas *et al.* (23) have elicited the same response with group B streptococcal exotoxin. If pulmonary vasoconstriction alone were responsible for the reduction in CO, then an immediate return of CO to baseline levels would be expected as soon as Ppa returns to normal. In fact, although Ppa is normal by 10–15 min after indomethacin administration, CO does not return to baseline values until 30 min after indomethacin, suggesting the involvement of another mechanism. A humoral myocardial depressant has been postulated to occur with high levels of positive end expiratory pressure (4) and with experimental pulmonary embolism (30). Depression of myocardial function in these studies has been prevented by pretreatment with either indomethacin or a selective inhibitor of thromboxane A_2 synthesis (4, 30). The possibility that thromboxane A_2 itself, or a related substance, has direct effects on cardiac function is suggested in the present study by the inverse correlation between plasma TxB_2 and CO.

The role of prostacyclin in the endotoxin model is also unclear. Fletcher and Ramwell (9) found 6-keto-$PGF_{1\alpha}$ levels to peak simultaneously with a decline in AoP in a baboon endotoxin

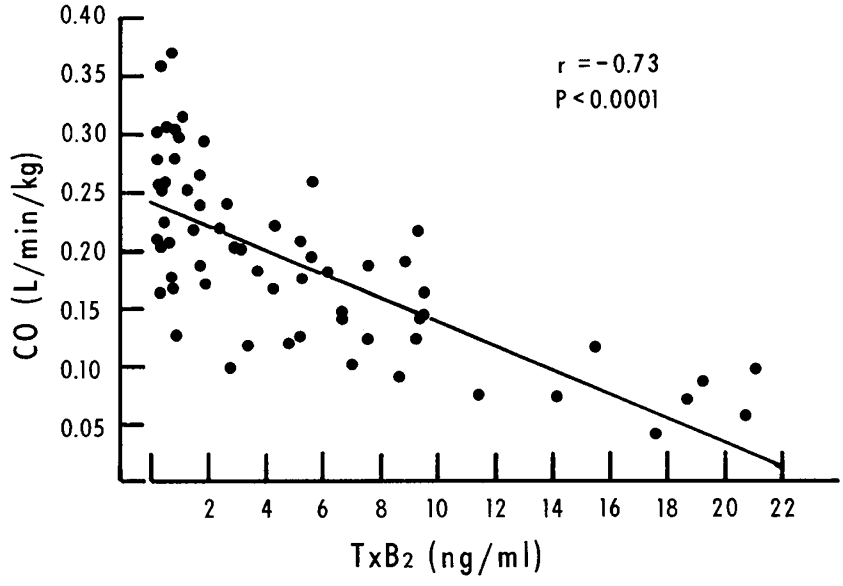

Fig. 4. Relationship between TxB_2 and cardiac output over the first 180 min of the experiment.

model. This was not confirmed by Webb *et al.* (31), who found no detectable levels of 6-keto-$PGF_{1\alpha}$ in pigs given a bolus of endotoxin. In the latter study, prostacyclin infusion actually prevented the late drop in $\overline{AoP}$. The fact that the latter authors sampled blood from the inferior vena cava may have had some bearing on the low concentration of 6-keto-$PGF_{1\alpha}$, as this substance is thought to be inactivated in peripheral tissues (17). Our findings suggest a temporal relationship between increasing levels of 6-keto-$PGF_{1\alpha}$ and the late decline in $\overline{AoP}$ in control animals.

The hypoxemia noted in our model closely follows the onset of pulmonary hypertension. Early hypoxemia has been observed in endotoxin models (19, 27) and is thought to result from perfusion of areas of lung poorly ventilated as a result of bronchoconstriction. Snapper (27) has measured increases in airway resistance accompanying infusion of endotoxin and has shown that these changes were ameliorated by a cyclooxygenase inhibitor. Thromboxane A_2 has been implicated in the etiology of these abnormalities (29). However, Spannhake *et al.* (28) have questioned the relative contribution of thromboxane A_2 in the bronchoconstrictive response to endotoxin by demonstrating no difference in bronchoconstriction between control and endotoxin-treated animals when a thromboxane A_2 synthetase inhibitor was used. They suggest a role for lipoxygenase products or a decrease in the autoinactivation of cyclooxygenase in the etiology of pulmonary function abnormalities in endotoxin-treated animals.

The theoretical possibility of right-to-left shunting across a probe-patent foramen ovale as a cause of hypoxemia related to pulmonary hypertension is of some concern. However, simultaneous thermodilution curves obtained from thermistors in both the pulmonary artery and high descending aorta did not give evidence of a right-to-left shunt in our animals, even when probe patency of the foramen ovale was found. Ductal patency was not observed.

Caution must be exercised in attempting to extrapolate the results of this experiment to the clinical setting. The model used is rapidly lethal unlike most cases of neonatal GBS disease. In addition, the dose of indomethacin is much higher than the dosage clinically employed for patent ductus arteriosus in the neonate. The absence of extrapulmonary right-to-left shunting also distinguishes this animal model from the human neonate.

In conclusion, the findings of the present study suggest that 1) indomethacin significantly improves hemodynamics and survival in a highly lethal model of group B β-hemolytic streptococcal sepsis, 2) the hemodynamic alterations observed in controls coincide temporally with significant elevations in plasma concentrations of TxB_2 and 6-keto-$PGF_{1\alpha}$, and 3) the hemodynamic improvements observed following indomethacin administration are in part related to either reduction in circulating thromboxane A_2 or prevention of an increase in prostacyclin.

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