Effect of Cyclooxygenase and Lipoxygenase Products on Pulmonary Function in Group B Streptococcal Sepsis[1]

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ABSTRACT. The effects of the cyclooxygenase inhibitor, indomethacin, and the leukotriene receptor antagonist, FPL 57231, on changes in dynamic lung compliance and pulmonary resistance associated with a 1-h infusion of live group B streptococci were evaluated in mechanically ventilated piglets. To define mediators of early changes in lung function, animals were given an infusion of either FPL 57231 or indomethacin beginning 15 min after the infusion of group B streptococci was begun. These groups were compared to an untreated group who received only group B streptococci. Within 15 min of starting the bacterial infusion, all groups showed significant increases in pulmonary artery pressure, pulmonary artery wedge pressure, total pulmonary resistance, transpulmonary pressure, and thromboxane B_2, and decreases in tidal volume, dynamic lung compliance, and PaO_2. After treatment with indomethacin there were significant decreases in pulmonary artery pressure (mean ± SEM; 48 ± 1 to 22 ± 3 mm Hg, $p < 0.001$), pulmonary artery wedge pressure (7.5 ± 1.3 to 2.2 ± 0.4 mm Hg, $p < 0.001$) and thromboxane B_2 (6.51 ± 1.56 to 1.01 ± 0.27 ng/ml, $p < 0.01$) and an increase in dynamic lung compliance (1.10 ± 0.10 to 1.28 ± 0.14 ml/cm H_2O/kg, $p < 0.01$) over the study period. Total pulmonary resistance decreased significantly (18.7 ± 1.8 to 15.7 ± 1.5 cm H_2O/liter/s, $p < 0.02$) only at 60 min. In animals treated with FPL 57231 only pulmonary artery pressure (46 ± 3 to 30 ± 2 mm Hg, $p < 0.05$) and pulmonary artery wedge pressure (7.5 ± 0.8 to 4.0 ± 0.9 mm Hg, $p < 0.01$) decreased. These data suggest that cyclooxygenase products of arachidonic acid metabolism play a role in the early changes in pulmonary mechanics in group B streptococci sepsis. (*Pediatr Res* 22: 478–482, 1987)

Abbreviations

Cdyn, dynamic lung compliance
GBS, group B streptococci
Ppa, pulmonary artery pressure
Ppaw, pulmonary artery wedge pressure
Psa, systemic arterial pressure
R_L, total pulmonary resistance

Tx, thromboxane
IV, intravenous

Experimentally induced group B streptococcal infection using live organisms or exotoxin, and infusions of *Escherichia coli* endotoxin result in dramatic alterations in cardiovascular function characterized by elevations in pulmonary artery pressure and pulmonary vascular resistance and decreases in cardiac output and oxygenation (1–9). These early hemodynamic manifestations of gram-positive and gram-negative infections appear to be mediated by products of the cyclooxygenase pathway, especially TxA_2 and prostacyclin (2, 4–6, 8–11). However, recent investigation (12) has shown that a leukotriene receptor antagonist, FPL 57231, ameliorates the early hemodynamic changes associated with an infusion of live GBS in piglets, suggesting a role for leukotriene C_4 and D_4. The possible effects of lipoxygenase products of arachidonic acid metabolism on GBS-induced changes in lung function in a young animal model have not been defined.

Alterations in pulmonary mechanics, which include decreased lung compliance and increased pulmonary resistance, have been reported with *E. coli* endotoxin infused in adult animals and have been attributed to products of arachidonic acid metabolism (8, 13–16). In fact, pretreatment with cyclooxygenase inhibitors prevents these early changes in lung mechanics after endotoxin infusion (8, 13, 15, 16). In these studies TxA_2 has been implicated in the etiology of these abnormalities. Spannhake et al. (15), however, have questioned the relative contribution of TxA_2 to these changes since they were unable to demonstrate a difference in lung compliance between control and endotoxin-treated animals after a Tx synthetase inhibitor was infused. These investigators postulated that either products of the lipoxygenase pathway or a decrease in the autoinactivation of cyclooxygenase may have played a role in the etiology of the pulmonary function abnormalities in endotoxin-treated animals.

The purpose of the present study was to define the role of cyclooxygenase and lipoxygenase products on the changes in pulmonary mechanics occurring secondary to an infusion of live GBS by administering indomethacin, a cyclooxygenase inhibitor, and FPL 57231, a leukotriene receptor antagonist to septic piglets.

MATERIALS AND METHODS

Animal model. Twenty-two piglets were anesthetized with pentobarbital (30 mg/kg, intraperitoneally). A femoral artery and vein were cannulated and used for Psa measurement, blood

sampling, and the infusion of fluids and bacteria. A 5F Swan-Ganz thermodilution catheter was introduced into the right external jugular vein and advanced under fluoroscopy into the left pulmonary artery. This catheter was used to measure Ppa and Ppaw. Vascular pressures were measured with pressure transducers (model P23-1D; Gould Instruments, Cleveland, OH) and recorded on a multichannel recorder (Model 5 polygraph, S2-925T25, Grass Instrument, Quincy, MA).

A tracheostomy was performed and a special 3.5 mm endotracheal tube inserted (Hi-Lo Tracheal Tube, NCC Division, Mallinckrodt Inc., Argyle, NY). This tube has a main lumen for ventilation and a separate pressure monitoring lumen (internal diameter, 1 mm) that opens into the main lumen 0.5 cm above the distal end of the tube.

The animals were ventilated with a time-cycled, pressure limited, infant ventilator (Sechrist, Model IV-100 B Infant Ventilator, Sechrist Industries, Anaheim, CA). Ventilator settings included the following: peak inflation pressure of 12 cm H_2O, positive end-expiratory pressure of 2 cm H_2O, respiratory rate of 40 breaths/min, and inspiratory time of 0.50 s. Animals were ventilated with room air, and respirator settings were not altered during the study period. Arterial blood gases were measured prior to and every 15 min until 60 min after the bacterial infusion was started (pH/Blood Gas Analyzer 113, Instrumentation Laboratories, Lexington, MA).

The rectal temperature was continuously monitored with a thermistor probe (Yellow Springs Instrument Co., Yellow Springs, OH), and maintained at 38° C by means of a servo controlled radiant warmer.

The animals received an infusion of 6 ml/kg/h of 5% dextrose solution through a peripheral vein and a heparinized saline solution (10 U/ml) through the pulmonary artery catheter.

The animals were paralyzed with pancuronium bromide by using an initial dose of 0.2 mg/kg IV, which was followed by a continuous infusion of 0.4 mg/kg/h. After allowing a 60-min stabilization period, baseline cardiovascular measurements (Psa, Ppa, and Ppaw), pulmonary mechanics (Cdyn and R_L) and arterial blood gases were obtained prior to bacterial infusion. These values will be hereafter referred to as baseline.

Systemic pressure and Ppa were measured continuously throughout the baseline and study periods and Ppaw measured prior to and during the bacterial infusion and at 15, 30, and 60 min after infusion of GBS was begun.

Pulmonary mechanics. Lung mechanics were measured prior to and 15, 30, and 60 min after onset of bacterial infusion. Respiratory flow was measured with a heated Fleisch no. 0 pneumotachometer (Oem Medical, Richmond, VA) placed between the endotracheal tube and ventilator circuit. The differential pressure output from the pneumotachometer was measured with a transducer (model MP 45, Validyne Engineering Co., Northridge, CA) and amplified by a pressure amplifier (Gould Instruments, Cleveland, OH). The pneumotachometer was calibrated using constant flows and a Tissot spirometer. Output was linear from 0 to 15 liter/min. The flow signal was electronically integrated to obtain tidal volume using a Gould integrator amplifier. Calibration of tidal volume was done before and after each study using a calibrated glass syringe. An 8F water filled feeding tube was placed in the lower esophagus to measure esophageal pressure by means of a pressure transducer (model P23-ID; Gould Instruments) and a Gould pressure amplifier calibrated with a water manometer. This tube was flushed before each recording of esophageal pressure. The tip of the tube was positioned in the lower portion of the esophagus by recording pressures while pulling the tube from the stomach into the esophagus. This position reduces cardiac artifact. The accuracy of the esophageal pressure signal was tested by comparing airway and esophageal pressure during airway occlusion before paralysis. Distal airway pressure was measured by connecting the monitor lumen of the endotracheal tube to a pressure transducer (model P23-ID; Gould Instruments) and amplifying the signal with a

pressure amplifier. The response time for the distal airway pressure measurement was tested in vitro by simultaneously measuring pressure changes in a glass container directly using a Validyne pressure transducer (model MP-45, diaphragm no. 28, Validyne Engineering Co.) which has a flat frequency response up to 60 Hz, and measuring the same pressure changes via the pressure monitoring line of the endotracheal tube (Hi-Lo) which was inserted inside the glass container. The difference in pressure measurements was less than 1.5% at rates up to 18 Hz. Pressure changes were produced using a high frequency oscillator (BMO-20N, Hummingbird, Tokyo, Japan). Air flow, tidal volume, and airway and esophageal pressures were recorded on a multichannel recorder (model 2400; Gould Instruments). Cdyn was calculated by dividing the tidal volume by the change in transpulmonary pressure (airway pressure minus esophageal pressure) measured at the moment of zero flow between end-inspiration and end-expiration. R_L was calculated at mid-tidal volume by determining the transpulmonary pressure difference between the points of midinspiration and midexpiration, and dividing this by the sum of the inspiratory and expiratory flows measured at the same points in time (17).

Bacterial preparation. Group B β-hemolytic streptococci (type Ic) were isolated from the blood of an infant who developed early onset sepsis at the University of Miami/Jackson Memorial Medical Center Neonatal Intensive Care Unit. Bacteria for each experiment were incubated 18 h 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 1.5×10^9 colony forming units per ml. The number of colony forming units was determined by serial plate dilutions.

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 5×10^7 organisms/kg/min. This infusion was continued throughout the entire study period. Fifteen min after the bacterial infusion was begun all measurements were repeated and the animals were randomly assigned to one of three groups. For groups receiving drug therapy, administration of indomethacin and FPL 57231 were begun immediately after the measurements were completed.

The untreated group ($n = 7$) (mean ± SD; weight, 2677 ± 501 g; age, 10 ± 2 days) received only bacteria throughout the study period. The indomethacin group ($n = 8$) (weight, 2419 ± 213 g; age, 9 ± 3 days) received GBS and a cyclooxygenase inhibitor, indomethacin (3 mg/kg IV). The FPL group ($n = 7$) (weight, 2848 ± 623 g; age, 11 ± 2 days) received the GBS and leukotriene receptor antagonist, FPL 57231 (1 mg/kg/min IV for 30 min followed by 0.5 mg/kg/min for 30 min) (Fisons Ph, Loughborough, England).

Assay for TxB₂. Blood samples were obtained from untreated and treated animals for radioimmunoassay of TxB_2, the stable metabolite of TxA_2, and collected in tubes containing aspirin and EDTA (0.41 and 1.95 mg/ml for 1 ml blood, respectively). Plasma from these samples was extracted with ethanol, centrifuged to remove precipitated protein and dried under nitrogen before being reconstituted in 0.5–1.0 ml of phosphate-buffered saline containing 0.1% gelatin. The method used for their determination has been described previously (2). Values were drawn prior to infusion of GBS and 15, 30, and 60 min after the infusion was begun.

Data analyses. Data are expressed as mean ± SEM. To ensure that there were no differences in initial values among the groups, a one-way analysis of variance was performed at baseline and 15 min after GBS infusion. The changes from baseline to 15 min after infusion of GBS was started were compared using a matched paired t test. The paired t test was also used to compare values from 15 to 60 min. Repeated measure analysis of variance was used to compare the pattern of response to treatment over time from a point 15 min after GBS infusion was started to the

subsequent points for the three groups for all variables. To further elucidate the changes from 15 min post-GBS infusion to 60 min, values were expressed as a percent of baseline and evaluated with one-way analysis of variance followed by Duncan's multiple range test using a p of 0.05. The correlations between Cdyn and $\bar{P}pa$, $\bar{P}paw$, and TxB_2 were obtained by using linear correlation analyses and power curves.

RESULTS

Lung mechanics, arterial blood gases, and $\bar{P}pa$ and $\bar{P}paw$ values at baseline and 15 min after the onset of bacteria infusion did not differ among the three groups. Combining all groups, the data showed that after 15 min of GBS infusion, PaO_2 decreased from 81 ± 2 to 46 ± 2 mm Hg ($p < 0.001$) while $PaCO_2$ increased from 29 ± 1 to 36 ± 2 mm Hg ($p < 0.001$). Mean pulmonary artery pressure increased from 13 ± 1 to 46 ± 1 mm Hg ($p < 0.001$) and $\bar{P}paw$ from 2.4 ± 0.3 to 7.6 ± 0.6 mm Hg ($p < 0.001$). Tidal volume decreased from 11.39 ± 0.58 to 8.53 ± 0.46 ml/kg ($p < 0.001$) while the transpulmonary pressure increased from 8.08 ± 0.32 to 8.90 ± 0.33 cm H_2O ($p < 0.001$) due to a decrease in Cdyn from 1.45 ± 0.09 to 1.00 ± 0.07 ml/cm H_2O/kg ($p < 0.001$). The inspiratory flow decreased from 6.17 ± 0.20 to 5.72 ± 0.20 liter/min ($p < 0.001$) while the transpulmonary pressure at mid-tidal volume increased from 2.78 ± 0.14 to 3.24 ± 0.20 cm H_2O ($p < 0.02$), as a result of an increase in R_L from 13.5 ± 0.5 to 18.3 ± 1.0 cm H_2O/liter/s ($p < 0.001$). The time constant of the respiratory system ($R_L \times$ Cdyn) was 0.0497 ± 0.0025 prior to and 0.0461 ± 0.002 s 15 min after the infusion of GBS was begun. These values were not significantly different.

Arterial oxygen tension remained low throughout the study period in the untreated group (Table 1). In contrast, PaO_2 increased toward baseline values over the study period and was significantly different at 30 and 60 min in the indomethacin group compared to untreated animals (Table 1). In the FPL group, the PaO_2 increased slowly, and a statistically significant difference occurred from the untreated group at 60 min of bacterial infusion. The arterial carbon dioxide tension was not different between groups.

After an initial increase in $\bar{P}pa$ with GBS infusion, the $\bar{P}pa$

remained fairly stable with a gradual decline over time in the untreated group (Fig. 1). Animals treated with indomethacin displayed a dramatic decrease in $\bar{P}pa$ to values which were significantly lower than those of the untreated group. FPL-treated animals also had a significant decrease in $\bar{P}pa$ when compared to the untreated group, however, this decline was more gradual than in the indomethacin group. Pulmonary wedge pressure increased throughout the study period in untreated animals (Fig. 1). The decrease in $\bar{P}paw$ in both treated groups was significantly different from the untreated group.

Lung compliance fell with infusion of GBS by 15 min and remained low throughout the study period in untreated animals (Fig. 2). In the FPL group Cdyn was not significantly different from untreated animals, however, indomethacin-treated animals showed a significant improvement in Cdyn. There was a negative correlation between Cdyn and $\bar{P}pa$ ($y = 1.62 \ x^{-0.016}$, $r = -0.55$, $p < 0.001$) as well as between Cdyn and $\bar{P}paw$ ($y = 1.44 \ x^{-0.23}$, $r = -0.61$, $p < 0.001$) when all groups were combined.

Pulmonary resistance increased significantly by 15 min after bacteria infusion in all groups and was represented by a mean percent change from baseline of approximately 40% (Fig. 2). Pulmonary resistance was not statistically different between groups during the study period in either absolute values or as a percent change from baseline. Although both treatment groups showed a tendency for pulmonary resistance to decrease by 60 min, only in the indomethacin group did the pulmonary resistance at 60 min become significantly lower than the 15-min value.

Mean TxB_2 levels at 15 min were significantly increased ($p < 0.01$) compared to baseline values in all the groups and remained elevated in the untreated and FPL groups (Table 1). In the indomethacin group, TxB_2 decreased significantly and remained low throughout the study period. There was a negative correlation between Cdyn and TxB_2 levels ($y = 1.30 \ x^{-0.16}$, $r = -0.60$, $p < 0.01$), in this group.

Table 1. *Effect of GBS infusion on gas exchange and plasma TxB_2 for all experiments (mean $\pm$ SEM) in untreated (n = 7), indomethacin (n = 8), and FPL (n = 7) groups*

	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	TxB_2 (ng/ml)
Baseline			
Untreated	78 ± 4	28 ± 2	0.633 ± 0.238
Indomethacin	82 ± 4	28 ± 1	0.440 ± 0.047
FPL	82 ± 4	33 ± 4	0.707 ± 0.145
Post-GBS infusion			
15 min			
Untreated	46 ± 5	35 ± 4	8.359 ± 2.715
Indomethacin	48 ± 3	36 ± 2	6.515 ± 1.563
FPL	46 ± 2	37 ± 2	5.937 ± 1.232
30 min			
Untreated	46 ± 4	36 ± 5	15.264 ± 6.089
Indomethacin	$70 \pm 3*$	33 ± 2	$2.087 \pm 0.467†$
FPL	55 ± 4	36 ± 3	9.907 ± 1.781
60 min			
Untreated	47 ± 3	38 ± 5	16.307 ± 5.823
Indomethacin	$69 \pm 4*$	33 ± 2	$1.010 \pm 0.271†$
FPL	$59 \pm 4†$	37 ± 3	15.301 ± 2.401

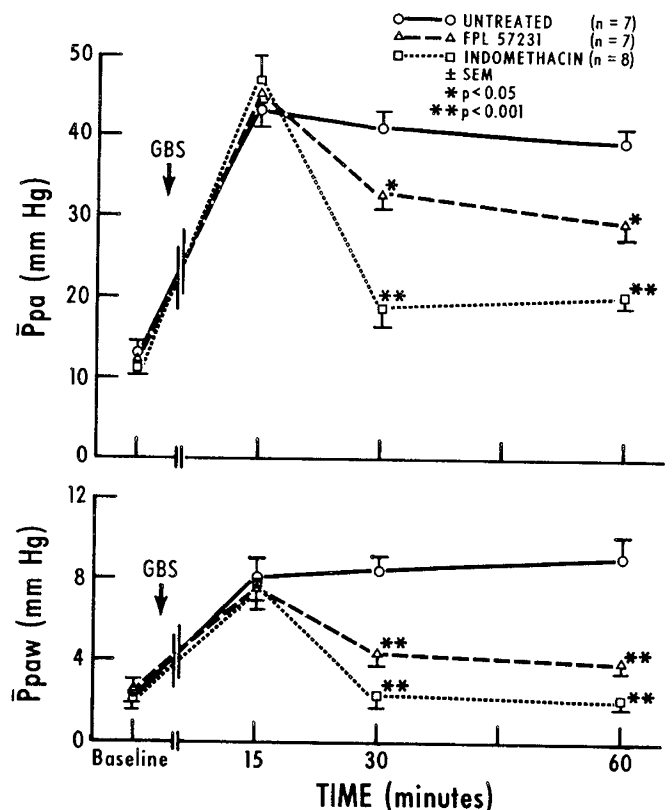$* p < 0.01$ † $p < 0.05$, significance refers to comparison of untreated to treated.

Fig. 1. Response of $\bar{P}pa$ and $\bar{P}paw$ to GBS infusion. *, ** Significant difference refers to comparison of untreated to treated group.
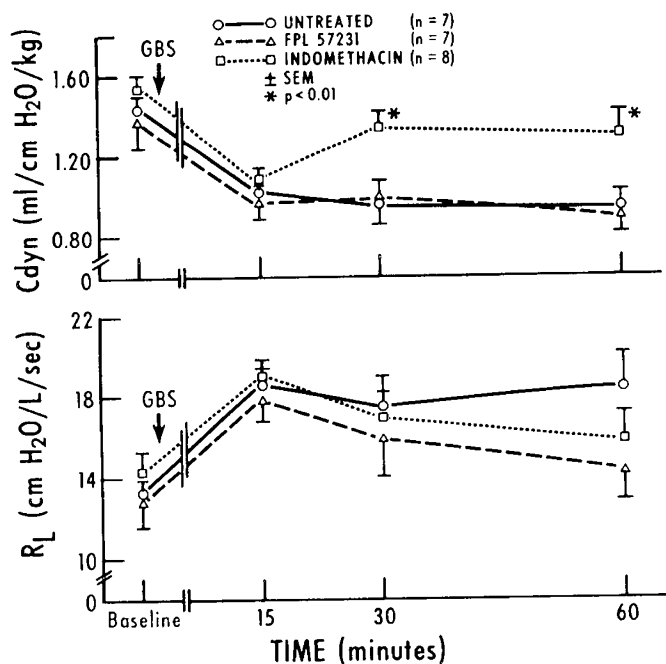
Fig. 2. Responses of Cdyn and R_L to GBS infusion. * Significant difference refers to comparison of untreated to treated group.

DISCUSSION

The results of the present study suggest that the early changes in pulmonary compliance and resistance occurring after an infusion of live-GBS are largely mediated by cyclooxygenase products of arachidonic acid. This is consistent with previously published data showing that cyclooxygenase metabolites were responsible for the changes in pulmonary mechanics observed in E. coli endotoxin-treated animals (8, 13, 15, 16).

Some investigators have also suggested that the changes in lung function during sepsis may also be mediated by lipoxygenase products of arachidonic acid metabolism (15). This is supported by studies in which E. coli endotoxin infusion resulted in increased concentrations of lipoxygenase as well as cyclooxygenase products in plasma and lung lymph (5, 16, 18, 19). In addition, there is also evidence that leukotriene C_4 and D_4 play a role in the early as well as late cardiovascular and pulmonary manifestations of both E. coli endotoxin (20) and GBS sepsis (12, 21). The present data, however, do not support a significant role for leukotriene C_4 and D_4 in the pulmonary manifestations of sepsis secondary to GBS in a young animal model. These results differ from those reported for E. coli endotoxin-treated adult animals in which FPL 57231 completely blocked the endotoxin-induced changes in Cdyn and R_L (20). The reason for this difference is not clear but may involve the use of endotoxin at sublethal doses in adult sheep as opposed to our use of a lethal dose of live-GBS bacteria in piglets. In addition, our animals were treated after the GBS infusion began while previous studies involved pretreated animals.

The changes in lung mechanics noted in this study were associated with increases in $\overline{Ppa}$ and $\overline{Ppaw}$. Investigators have described alterations in lung compliance with increases in pulmonary blood volume secondary to an increase in left atrial pressure alone or with elevated $\overline{Ppa}$ (22–26). The resulting pulmonary vascular engorgement has been shown to produce a 20 to 40% decrease in lung compliance in laboratory animals with normal lungs when left atrial pressure is increased to 10–25 mm Hg (23). Although the mechanism for this is unclear, it is possible that competition between pulmonary blood and gas volume within certain ranges of vascular and transpulmonary pressures may cause changes in functional residual capacity and/or a reduction in the caliber of the terminal airways (23). This may result in a decrease in pulmonary compliance. It is also possible

that an increase in pulmonary vascular rigidity secondary to vascular engorgement may effect lung function.

Our data suggest a relationship between Cdyn and $\overline{Ppa}$ and $\overline{Ppaw}$. However, the magnitude of increase in $\overline{Ppaw}$ in the present study was less than those cited above (22, 23, 26), making it unlikely that changes in vascular pressure measured in our study alone resulted in alterations in lung function. One difference between the present study and those cited previously that may influence the magnitude of the changes in vascular pressure and lung function is the presence of pulmonary pathology in our subjects. Previous work (22–26) evaluating the relationship between vascular pressure changes and lung function were performed using animals with normal lungs.

Another possible explanation for these changes in lung function during sepsis may involve edema formation. During GBS infusion there is an abrupt rise in lymph flow accompanied by a decreased lymph to plasma protein concentration ratio (1). This is thought to result from an increase in microvascular hydrostatic pressure (8). In addition, there is evidence that changes in vascular permeability begin within 30 min of E. coli endotoxin infusion in sheep (27). Although changes in lung compliance occur prior to significant interstitial or alveolar edema (7, 28) these changes in edema formation which appear early may in part contribute to the alterations in lung compliance and explain why in this study Cdyn does not return to baseline despite treatment with indomethacin. Changes in pulmonary mechanics secondary to hypoxia should also be considered, however, it is unlikely that the decreases in Cdyn can be explained by hypoxia alone, for hypoxia causes only modest alterations in lung mechanics (29).

Elevation in TxA_2 has been correlated with a decrease in Cdyn. Both changes may be blocked by a selective inhibitor to TxA_2 synthesis (30). In the present study, there was a correlation between Cdyn and TxB_2 in the indomethacin group, but this does not necessarily imply a causal relationship. We speculate that TxB_2 may mediate changes in Cdyn, but as other products of arachidonic acid metabolism (e.g. prostaglandin $F_{2\alpha}$) were not measured, their role cannot be excluded.

Infusions of E. coli endotoxin and GBS exotoxin into both adult and neonatal animals have resulted in a 3- to 10-fold increase in R_L, a finding that can be prevented by cyclooxygenase inhibitors (7, 13, 15, 16, 18, 31). This dramatic increase in R_L contrasts to the modest increase observed in the present study. Although treatment resulted in a decrease in R_L in this animal model the results were not statistically different from the untreated group. The lack of marked changes in R_L before and after treatment may be partially explained by the use of young piglets who have less airway smooth muscle (32) and may therefore not have the ability to develop significant bronchoconstriction. Lung volume was not measured and as a result the possibility that an increase in volume due to increased resistance may have dampened the effect of the GBS infusion on R_L cannot entirely be excluded. However, the likelihood of gas trapping is small because the time constant of the respiratory system did not change after the bacterial infusion. In addition, the expiratory time was almost 20 times longer than the time constant, making gas trapping unlikely.

In summary, these data suggest that the acute decrease in lung compliance in GBS infection may, in part, be mediated by cyclooxygenase byproducts of arachidonic acid metabolism. We speculate that the fall in Cdyn may be partially related to a combination of pulmonary vascular engorgement and edema.

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