Effect of Group B Streptococcal Sepsis on Diaphragmatic Function in Young Piglets

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ABSTRACT. Recent studies indicate that diaphragmatic pressure generation (Pdi) is impaired by bacterial infection. However, group B *streptococcus* (GBS) had no effect on Pdi when infused into 4-wk-old piglets. As responsiveness to GBS is age-dependent, we therefore studied the acute effect of GBS infusion on Pdi, using a younger, 2-wk-old piglet model. Using trans-Pdi with phrenic nerve stimulation, we studied the effect of continuous GBS infusion in seven anesthetized, spontaneously breathing 2-wk-old piglets. Pdi was measured under baseline conditions (50% O₂/50% N₂) and at 1, 2, and 4 h of GBS infusion. GBS was infused at a rate which caused a doubling of the pulmonary artery pressure but which avoided hypotension or acidosis—both of which can decrease Pdi. In addition, the piglets were kept hyperoxic [PaO₂ > 13.3 kPa (100 torr)], and no piglet with hypercapnia [PaCO₂ > 8.7 kPa (65 torr)] was included, as hypoxia and hypercapnia can also cause respiratory muscle dysfunction. For the GBS group, diaphragmatic contractility declined significantly by 1 h at 30-, 50-, and 100-Hz stimulation frequency and, by 2 h, was significantly decreased at all frequencies. We conclude that 2-wk-old piglets, in contrast to 4-wk-old piglets, demonstrate a decline in Pdi during GBS infusion. These data demonstrate an age-related response to GBS in the piglet. This finding implies that a decline in Pdi during acute GBS infusion is not due to a secondary effect from shock (*i.e.* acidosis, hypercapnia, or hypoxemia) or due to the catabolic effects of a chronic infection, but is due to a direct effect of sepsis on diaphragmatic muscle function. (*Pediatr Res* 33: 10–14, 1993)

Abbreviations

BP, blood pressure
cfu, colony-forming units
CO, cardiac output
FRC, functional residual capacity
GBS, group B streptococcus
HR, heart rate
P_{PA}, pulmonary artery pressure
Pdi, transdiaphragmatic pressure generation
Qdi, diaphragmatic blood flow
RR, respiratory rate
V_E, minute ventilation
V_T, tidal volume
Paw, airway pressure
Pga, intragastric pressure
ANOVA, analysis of variance

TNF α , tumor necrosis factor α
PaO₂, arterial O₂ tension
PaCO₂, arterial CO₂ tension

Systemic bacterial infections can cause respiratory muscle impairment (1–3). Studies of this problem have focused on the effect of either an overwhelming infection (*i.e.* septic shock) or a chronic infection (*i.e.* >2 d) on diaphragmatic contractility (1–3). Chronic infections can alter muscle structure, but the reason for altered diaphragmatic function after only hours of sepsis is unknown (4–6). It is unknown if bacteria exert a direct effect on muscle function or if the changes are due to alterations in substrate delivery, oxygenation, blood flow, or acid/base status or via the release of inflammatory mediators.

We recently demonstrated that GBS had no deleterious effect on force generation of the 4-wk-old piglet diaphragm (7). Our initial study examined the acute effects of a 4-h infusion of GBS given at a rate that avoided shock. Our assumption was that an alteration in Pdi during bacteremia without alterations in substrate delivery, oxygenation, Qdi, or acid/base status would imply that the altered contractility was due to a local effect of bacteria or inflammatory mediators on the muscle. However, under these experimental conditions, the 4-wk-old piglet demonstrated no change in Pdi (7).

GBS is highly lethal in the newborn human but is not associated with clinical disease in children greater than 3 mo of age (8). Rats also exhibit an age-related response to GBS (9). Developmental changes in piglet response to GBS are unknown, but the age-related susceptibility to GBS in humans and rats led us to examine the effects of GBS on diaphragmatic force generation in a younger piglet. We therefore repeated our study of the acute effect of GBS infusion on Pdi in younger, 2-wk-old piglets, using an identical experimental protocol. The GBS infusion dose was again set to avoid acidosis, hypoxemia, hypercapnia, or hypotension—conditions shown to reduce Pdi in several animal models (10–14). We hypothesized that GBS infusion, without shock, would cause a decrease in Pdi in the 2-wk-old piglet.

MATERIALS AND METHODS

Animal preparation. Fifteen mixed-breed piglets (14-d old, range 11–18 d) were studied in accordance with NIH and institutional guidelines regarding animal research. Animals in the two experimental groups were not different in age or weight (wt $\pm$ SD): GBS group, mean age = 14 d (range 11–18 d), mean body weight = 5.2 $\pm$ 1.1 kg; control group, mean age = 14 d (range 11–17 d), mean body weight = 4.1 $\pm$ 0.8 kg. Animals were anesthetized with chloralose (45 mg/kg) and urethane (200 mg/kg) *i.v.*, anticoagulated with heparin (1000 IU *i.v.*), and studied in the supine position. Small additional doses of anes-

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thetic (chloralose 5–7 mg/kg, urethane 30–50 mg/kg) were given if the animal developed jaw clonus. The piglets were required to have an arterial pH >7.25, a PaO_2 >13.3 kPa (100 torr) in 50% oxygen, and a PaCO_2 <8.7 kPa (65 torr), at baseline and throughout the study, for inclusion. The piglets breathed through a surgically placed tracheostomy tube attached to a Hans Rudolph miniature two-way nonbreathing valve (model 2384, Hans Rudolph, Inc., Kansas City, MO). $\dot{V}_E$ was measured by electronic integration (Hewlett Packard 8815A, Hewlett Packard, North Hollywood, CA) of the respiratory flow trace from a Fleisch pneumotachometer. A 4.1 French pediatric pigtail catheter (Cook Inc., Bloomington, IN) was positioned in the left ventricle via the left carotid artery using fluoroscopy. Femoral arterial catheters were placed to permit sampling of blood for measurement of gas tensions and pH (Corning 170 pH/Blood Gas Analyzer, Corning Medical, Medfield, MA), BP, and withdrawal of microsphere reference samples. A left internal jugular venous catheter was used for infusion of bacteria, and the right internal jugular vein was used to position a No. 5 French Swan-Ganz thermodilution catheter with 10-cm proximal port (American Edwards Laboratories, Irvine, CA) in a branch of the left pulmonary artery to determine CO, P_{PA} and for sampling of mixed venous blood and monitoring of central body temperature. Measures of CO (model 9520A Cardiac Output Computer, American Edwards Laboratories, Irvine CA) were obtained in triplicate using 2-mL aliquots of iced 5% dextrose in water. The piglet's temperature was maintained between 37.5° and 39.5°C by a radiant heat warmer.

Measurement of diaphragmatic contractility. Diaphragmatic contractility was assessed by measuring the trans-Pdi during airway occlusion and bilateral transvenous phrenic nerve stimulation (Grass S48 Stimulator, Grass Medical Instruments, Quincy, MA) at supramaximal voltage at frequencies of 20, 30, 50, and 100 Hz (11). Pdi is obtained by subtracting the Paw from the Pga ($\text{Pdi} = \text{Pga} - \text{Paw}$), using a Validyne differential pressure transducer (model MP45-2, Validyne Engineering Corp., Northridge, CA) (15). Pga was measured by positioning a thin-walled latex balloon-tipped catheter (1.65-mm internal diameter) containing 0.5- to 0.8-mL of air in the stomach. Paw was measured via an 18-gauge needle inserted in the tracheostomy tube proximal to the nonbreathing valve.

To ensure a consistency in diaphragmatic muscle shortening, a rigid plaster cast covering the abdomen and lower third of the chest was applied during phrenic nerve stimulation. Between episodes of data gathering, the animals were allowed to breathe without restriction. To prevent the development of atelectasis, every 20–30 min the piglets were given three to five 2-s “sighs” to 2.9 kPa (30 cm H_2O) pressure. Changes in diaphragm muscle length were indirectly assessed from end-expiratory lung volume, or FRC, as measured by the nitrogen washout technique (16).

Blood flow determination. Qdi was measured with radiolabeled microspheres, 15 microns in diameter, labeled with either ^{46}Sc , ^{95}Nb , ^{103}Ru , ^{113}Sn , or ^{141}Ce (Dupont Co., Wilmington, DE), injected into the left ventricle over a 30-s period, with a reference flow sample withdrawn from the femoral artery (17). Adequate mixing of the microspheres within the blood was checked by comparing the right and left kidney samples. If the cpm of the two kidneys differed by more than 15%, the data were not used (no animals were excluded). A reference sample, withdrawn starting 5 s before microsphere injection and for 30 s after completion of injection, was suspended in agar. Following completion of the experiment, the animal was killed and the costal and crural diaphragm were stripped of fat and tendon, weighed, put in counting vials, and, along with the reference samples, counted with a Packard Mini-axi Autogamma 5000 (Packard Instrument Co., Downers Grove, IL). Crossover between isotopes was corrected by using a spectral stripping technique (17) on a personal computer.

GBS strain and preparation. The GBS strain is a type III clinical isolate (COH-1) (18). The culture conditions, mode of

resuspension in sterile nonbacteriostatic saline, tests of culture purity, measurement of bacterial concentrations, and quantitative blood cultures ($n = 4$) were performed as described previously (19).

Experimental protocol. In previous work, we determined that a dose of 2 to 8×10^8 cfu/kg/h would approximately double the P_{PA} and cause a 20–30% drop in CO but not cause hypotension (7). Both experimental (GBS) and control piglets underwent baseline data collection after a 20- to 30-min stabilization period. In the GBS group, individual animals' infusion rates were determined by starting GBS infusion at 2×10^8 cfu/kg/h and then increasing the infusion rate by 2×10^8 cfu/kg/h every 10 min until the P_{PA} was doubled, and then remaining at that infusion rate throughout the experiment. All GBS piglets doubled their P_{PA} at an infusion rate between 2 and 8×10^8 cfu/kg/h within 30 min of starting the infusion (mean = 5×10^8 cfu/kg/h). Data were then collected at 1, 2, and 4 h after the start of GBS infusion. In the control group, data were collected at 1, 2, and 4 h after the baseline run. Two of the control animals received sham saline infusion, and these animals showed no different response over time than the controls given no saline infusion. In previous studies from this laboratory, saline infusion is not associated with any change in Pdi over time (11, 12).

At each time point, data were collected in the following sequence: blood samples were drawn; BP, HR, RR, V_T , $\dot{V}_E$, and P_{PA} were recorded; CO was determined; radiolabeled microspheres were injected; FRC was measured in triplicate; and the Pdi was determined. At the end of data collection, the animal was killed with an overdose of anesthesia and KCl, and organ tissues were collected for blood flow determinations.

Statistical analysis. The data were collected over a 2-y period, with the GBS group data collected in the earlier part of this time period and the control data collected in the latter part. Over that 2-y period, average Pdi values obtained increased, such that the mean baseline Pdi at all frequencies was higher in the control group than in the GBS group. In addition, this larger-than-expected variability in Pdi between animals led to a larger-than-expected SD, i.e. for 100-Hz stimulation frequency, $\text{SD} = 29$ versus previously published $\text{SD} = 9$ (7). The reason for this upward trend in Pdi is not clear. No change in technique or methodology can account for it. The vendors claimed no changes in the care of the animals, i.e. feeding, iron supplementation, etc. (no antibiotics or steroids are given to the animals from our two vendors). A three-way (group, time, and frequency of stimulation) ANOVA was performed on Pdi to measure change over time. This analysis found a p value by time equal to 0.011, without any two- or three-way interactions. Because of the large variability in SD and differing baseline Pdi values, an ANOVA was then performed on Pdi, expressed as a percentage of baseline, for intergroup comparisons. This analysis found a p value by group of <0.002, without any two- or three-way interactions. Significance by ANOVA was determined at the $p < 0.02$ level, followed by intragroup comparisons by paired t test, with significance determined at the 0.05 level (SPSS/PC + v3.0; SPSS, Inc., Chicago, IL). For all nonendpoint variables, p values <0.02 for paired t tests are presented for the readers' interest.

RESULTS

Force generation. For the GBS group, diaphragmatic contractility declined significantly by 1 h at 30-, 50-, and 100-Hz stimulation frequency and by 2 h was significantly decreased at all frequencies (Fig. 1A). At 4 h, the force generation at 20- and 30-Hz stimulation frequencies remained significantly less than baseline. There was no consistent pattern of change in force generation in the control group (Fig. 1B). Pdi, as a percentage of baseline, was significantly different during GBS infusion between the GBS and control groups ($p = 0.002$) by ANOVA.

Ventilatory measures and gas exchange. Table 1 presents data on the V_T , RR, $\dot{V}_E$, and FRC. Neither the GBS group nor the

Fig. 1. Mean Pdi values (kPa) for GBS (A) and control (B) piglets are plotted vs time, in side-by-side graphs. Values are expressed as mean $\pm$ SEM. A, GBS causes a loss of Pdi in the 2-wk-old piglet ($n = 7$). B, control 2-wk-old piglets demonstrate no consistent pattern of change in Pdi ($n = 8$). * denotes $p < 0.05$ for intragroup comparison (paired t test) referenced to the baseline (BL).

Table 1. Ventilatory measures*

	<i>n</i>	Baseline	1 h	2 h	4 h
Tidal volume (mL/kg)					
GBS	7	7.8 $\pm$ 1.6	7.1 $\pm$ 1.6	6.6 $\pm$ 1.0 (0.011)	7.4 $\pm$ 2.4
Control	8	5.8 $\pm$ 1.2	6.5 $\pm$ 1.2 (0.014)	7.1 $\pm$ 1.9	7.3 $\pm$ 2.6
RR (breaths/min)					
GBS	7	18.9 $\pm$ 5.4	20.4 $\pm$ 5.7	21.9 $\pm$ 6.4	21.7 $\pm$ 6.8
Control	8	21.0 $\pm$ 5.0	20.6 $\pm$ 6.5	23.8 $\pm$ 6.6	26.0 $\pm$ 5.0
$\dot{V}_E$ (mL/kg/min)					
GBS	7	143 $\pm$ 31	140 $\pm$ 36	139 $\pm$ 35	150 $\pm$ 33
Control	8	118 $\pm$ 18	129 $\pm$ 28	162 $\pm$ 46	185 $\pm$ 60
FRC (mL/kg)					
GBS	6	17.9 $\pm$ 3.3	15.8 $\pm$ 3.0	15.8 $\pm$ 3.7	16.1 $\pm$ 4.6
Control	7	16.6 $\pm$ 3.4	15.2 $\pm$ 3.5	15.8 $\pm$ 2.6	15.5 $\pm$ 4.1

* All values are mean $\pm$ SD; *n*, total no. of animals studied/experimental group; *p* values are for paired t tests <0.02 compared with baseline.

control group demonstrated any consistent trend in ventilatory measures. In the GBS-infused group, the V_T decreased at 2 h, whereas the respiratory rate and the $\dot{V}_E$ did not significantly change. The FRC did not change during GBS infusion. In the control group, the RR, $\dot{V}_E$, and FRC did not change, but the V_T was noted to be significantly elevated at 1 h. Table 2 presents data on gas exchange. In the GBS-infused group, the pH and PaCO_2 did not change during GBS infusion. The PaO_2 significantly declined by 4 h of GBS infusion, but the PaO_2 remained above 13.3 kPa (100 torr) in all animals. In the control group, no significant changes were noted in pH, PaCO_2 , or PaO_2 .

Table 2. Blood gas measures*

	<i>n</i>	Baseline	1 h	2 h	4 h
pH					
GBS	7	7.36 $\pm$.06	7.31 $\pm$.06	7.34 $\pm$.05	7.29 $\pm$.04
Control	8	7.33 $\pm$.08	7.34 $\pm$.07	7.35 $\pm$.07	7.36 $\pm$.07
PaCO_2 (kPa)					
GBS	7	6.8 $\pm$ 0.9	7.5 $\pm$ 1.0	7.2 $\pm$ 1.1	7.5 $\pm$ 1.4
Control	8	7.5 $\pm$ 0.9	6.8 $\pm$ 0.7	7.0 $\pm$ 1.4	6.7 $\pm$ 0.9
PaO_2 (kPa)					
GBS	7	26.9 $\pm$ 3.6	21.9 $\pm$ 7.6	24.6 $\pm$ 5.1	22.6 $\pm$ 5.0 (0.003)
Control	8	25.6 $\pm$ 3.9	25.6 $\pm$ 3.7	25.6 $\pm$ 3.4	25.9 $\pm$ 3.9

* All values are mean $\pm$ SD; *n*, total no. of animals studied/experimental group. *p* values are for paired t tests <0.02 compared with baseline (1 mm Hg = 0.1333 kPa).

Hemodynamics and blood flow. Table 3 presents hemodynamic data. In the GBS-infused group, the CO progressively declined, falling by 36% after 4 h of infusion. By design, the P_{PA} rose immediately and remained elevated throughout infusion. The HR showed an increase at 4 h. In the control group, no changes were seen in CO or P_{PA} . The HR progressively increased throughout the study. Both costal and crural Qdi remained unchanged during the experiment in both the GBS-infused and control groups (Table 4).

DISCUSSION

Infusion of GBS led to a decrease of Pdi in the 2-wk-old piglet. This is the first description of bacteria leading to an acute alteration of Pdi without the development of shock, hypoxemia, or acid/base derangement. This result adds to existing evidence that bacterial infections can lead to an impairment of muscle contractility and demonstrates that the response to GBS is greater in younger animals.

The present study demonstrates that bacteremia will acutely lead to diminished Pdi without an alteration in oxygen delivery. Although the PaO_2 was diminished significantly over time, the mean PaO_2 remained above 13.3 kPa (100 torr). Although the CO fell progressively by 36% over 4 h, the decline in Pdi developed by 1 h. Moreover, the BP was maintained within 0.8 kPa (6 mm Hg) of baseline levels, and Qdi did not change from baseline or control during GBS infusion. Thus, impaired tissue oxygen delivery does not account for the alteration in Pdi.

Table 3. Hemodynamic measures*

	<i>n</i>	Baseline	1 h	2 h	4 h
CO (mL/kg/min)					
GBS	6	261 ± 24	218 ± 76	187 ± 57 (0.017)	168 ± 61 (0.011)
Control	7	257 ± 40	263 ± 49	247 ± 34	248 ± 38
P _{PA} (kPa)					
GBS	7	1.7 ± 0.3	4.0 ± 0.8 (<0.001)	3.5 ± 1.1 (0.006)	3.3 ± 0.5 (<0.001)
Control	8	1.7 ± 0.3	2.0 ± 0.5	1.7 ± 0.3	1.7 ± 0.3
Systemic BP (kPa)					
GBS	7	11.2 ± 1.6	11.9 ± 1.7	12.1 ± 1.5	11.5 ± 2.4
Control	8	11.3 ± 0.7	11.2 ± 1.6	11.2 ± 1.6	10.5 ± 1.2
HR (beats/min)					
GBS	7	174 ± 31	204 ± 42	207 ± 36	248 ± 34 (0.008)
Control	8	152 ± 43	159 ± 51	177 ± 51 (0.005)	203 ± 52 (0.001)

* All values are mean ± SD; *n*, total no. of animals studied/experimental group; *p* values are for paired *t* tests <0.02 compared to baseline (1 mm Hg = 0.1333 kPa).

Table 4. Q_{di}*

	<i>n</i>	Baseline	1 h	2 h	4 h
Q _{di} -costal (mL/100 g/min)					
GBS	6	22.3 ± 5.6	20.7 ± 8.9	22.9 ± 12.1	20.2 ± 8.0
Control	7	20.7 ± 5.3	19.4 ± 6.1	19.8 ± 7.5	20.0 ± 9.0
Q _{di} -crural (mL/100 g/min)					
GBS	6	26.6 ± 8.8	27.3 ± 10.1	31.8 ± 12.5	27.0 ± 8.9
Control	7	33.2 ± 13.3	27.3 ± 8.5	32.2 ± 10.1	34.3 ± 17.7

* All values are mean ± SD; *n*, total no. of animals studied/experimental group.

Septic shock is often associated with uncompensated metabolic acidosis and hypercapnia (1, 20). In piglets, PaCO₂ levels >10 kPa (75 torr) are associated with diminished P_{di} (12) and, for this reason, a PaCO₂ >8.7 kPa (65 torr) at any point was chosen as an exclusion criterion for this study. No animals were excluded from either group for this reason. The GBS group did not vary over time in either PaCO₂ or pH and did not differ from the control group in these measures. Maintenance of adequate oxygenation, tissue perfusion, and acid/base status was part of our experimental design, and this differs from previous work examining the effects of sepsis on diaphragmatic muscle function (1–3).

A canine model of endotoxemia demonstrated that an endotoxin bolus led to a decrease in P_{di}, but this came just before the animal's death (1). The finding of a diminished P_{di} was accompanied by hypotension, diminished CO, hypoxemia, and an uncompensated metabolic acidosis (1)—all conditions which have been associated with diminished P_{di} in the dog (10, 14, 20–22). Shock due to hypovolemia and/or tamponade is indistinguishable from endotoxemic shock in its effect on canine diaphragmatic function (21), suggesting that the secondary effects of shock might alone account for the decrease in P_{di} attributed to endotoxin (1).

The effect of sepsis on P_{di} in the rat has also been studied. Rats develop diminished P_{di} 3 d after *Streptococcus pneumoniae* injection (2) and 2 d after injection of *Escherichia coli* endotoxin (3). In these two experiments, the decline in P_{di} was seen despite maintenance of normal BP, suggesting that, in this case, the effects of shock were not to blame for the decline in P_{di}. The effect of endotoxin on P_{di} was prevented by indomethacin, a cyclooxygenase inhibitor (3). The eicosanoid products, prostaglandin F_{2α} and prostaglandin E₂, induced during sepsis (4), have been shown to have a net catabolic effect on muscle (5). Yet the decrease in P_{di} induced by endotoxin came despite no alteration in diaphragmatic mass or histology, whereas the nonrespiratory muscles demonstrated significant wasting (3). These data imply that eicosanoids may exert an effect on diaphragmatic function

distinct from the effects associated with septic shock or muscle wasting. As the diaphragms of the rats in these studies were not obviously wasted, the decline in P_{di} may reflect a late effect of sepsis upon muscle function, such as an alteration in the resting membrane potential or intramuscular electrolyte concentrations (6, 23).

An age-related susceptibility to GBS has been described in rats and humans (8, 9) in which the severity of the infection appears to be a function of the chronologic age of the host. In this experiment, we chose to study 2-wk-old piglets, as the 2-wk-old is still able to tolerate the extensive instrumentation required, whereas the newborn piglet is not. Both the 2- and 4-wk-old piglets (7) were given continuous GBS infusion at a mean rate of 5×10^8 cfu/kg/h. In the 2-wk-old animals, though, levels of bacteremia were almost 40-fold higher than in the 4-wk-old animals (7). A relative immaturity in white cell bactericidal activity or chemotaxis could account for the age-related difference in bacterial clearance (24). An altered regulation of the release of inflammatory mediators might also account for the age-related response seen (25, 26). One inflammatory mediator, TNF α , has been implicated in the alterations of P_{di} during sepsis (27). Production of TNF α by piglets was not studied in this experiment, but in a similar GBS model, TNF α is a late-phase mediator only (28) and thus would not account for the early fall of P_{di} at 1 h in this study.

In summary, our experiment sought to define the acute effects of GBS on diaphragmatic function that were separate from the effects of shock or chronic infection. For this reason, we used a dose of GBS known to cause pulmonary hypertension and the release of vasoactive and proinflammatory mediators, but that would not cause systemic hypotension, acidosis, or hypoxemia. Under these conditions, 2-wk-old piglets, in contrast to 4-wk-old piglets, demonstrated a decline in P_{di}. These data demonstrate an age-related response to GBS in the piglet. This finding implies that a decline in P_{di} during acute GBS infusion is not due to a secondary effect from shock (*i.e.* acidosis, hypercapnia, or hypoxemia), or the catabolic effects of a chronic infection, but

rather to a direct effect of sepsis on diaphragmatic muscle function.

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