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Neonatal Group B Streptococcal Sepsis: Effects of Late Treatment with Dazmegrel

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ABSTRACT. Neonatal group B streptococcal (GBS) sepsis produces pulmonary arterial hypertension and hypoxemia that are preventable by pretreatment with the selective thromboxane A_2 synthase inhibitor, dazmegrel. In the present experiment we administered dazmegrel (8 mg/kg) 2 h after the initiation of a 2½ h infusion of 5×10^8 GBS/kg/h in ten 2- to 3-wk-old piglets. The multiple inert gas elimination technique was used to measure intrapulmonary shunt and alveolar ventilation to pulmonary perfusion mismatching. Thromboxane B_2, the stable metabolite of thromboxane A_2, and 6-keto-prostaglandin $F_{1\alpha}$, the stable metabolite of prostacyclin, were assayed in arterial blood. Pulmonary arterial pressure increased immediately after initiation of the GBS infusion, rising from 12 ± 2 to 34 ± 4 torr ($p < 0.02$); pulmonary vascular resistance increased by 400% ($p < 0.01$). Arterial hypoxemia developed ($p < 0.02$) in association with an increase in the low ventilation-perfusion ratio index but without a significant increase in intrapulmonary shunt. Thromboxane B_2 levels increased 10-fold. Infusion of the carrier substance for dazmegrel after 2 h of GBS infusion produced no change in any variables. In contrast, infusion of the drug resulted in the return to pre-GBS infusion baseline values for both pulmonary arterial pressure and pulmonary vascular resistance. However, no improvement in arterial pO_2 or in the low ventilation-perfusion ratio index occurred. Both pulmonary vascular resistance and pulmonary arterial pressure remained normal for 0.5 h after dazmegrel administration despite continued GBS infusion. Thromboxane B_2 levels were decreased 30 min after dazmegrel ($p < 0.02$), but remained greater than pre-GBS levels. Dazmegrel reversed pulmonary hypertension and elevated pulmonary vascular resistance, but did so without concomitant improvement in pulmonary gas exchange, when administered after 2 h of GBS infusion. (*Pediatr Res* 23: 352–356, 1988)

Abbreviations

P_{pa}, pulmonary arterial pressure
PVR, pulmonary vascular resistance
GBS, group B streptococcus
$\dot{V}_A/\dot{Q}$, ventilation-perfusion ratio
SVR, systemic vascular resistance
T_xA_2, thromboxane A_2
T_xB_2, thromboxane B_2
PGI_2, prostacyclin
$SD\dot{Q}_p$, SD of pulmonary blood flow distribution
$\dot{Q}_p$, pulmonary blood flow
AA, arachidonic acid
P_{cwp}, pulmonary capillary wedge pressure
RIA, radioimmunoassay
cfu, colony-forming units
MIGET, multiple inert gas elimination technique

Intravenous infusion of GBS into a neonatal piglet results in acute derangements of both pulmonary gas exchange and pulmonary hemodynamics. An acute elevation in P_{pa} and PVR develops with onset of GBS infusion (1–3). In addition, arterial hypoxemia develops because of mismatching of ventilation to perfusion characterized by increased $\dot{Q}_p$ to low $\dot{V}_A/\dot{Q}$ areas (3) and from depression of total $\dot{Q}_p$. Vasoactive metabolites of AA help mediate these events (4, 5). The pulmonary hemodynamic response to GBS in neonatal animals has been blocked or blunted by pretreatment or immediate post-GBS infusion treatment by the nonspecific cyclooxygenase inhibitor indomethacin (2), by the specific T_xA_2 synthase inhibitor dazmegrel (1), and by a competitive antagonist of sulfidopeptide leukotriene products of the 5-lipoxygenase pathway of AA metabolism, FPL 55712 (5).

Presently unknown is the extent to which AA metabolites, or other vasoactive substances (6, 7), sustain or aggravate the hemodynamic and gas exchange derangements during prolonged GBS infusion, and whether a thromboxane synthase inhibitor would alter the natural history of this process. Infusion of endotoxin from *Escherichia coli* (8) or live GBS (9) into adult sheep produces a two-phase response consisting initially of acute elevation in P_{pa} and PVR, followed in 2–3 h by increased pulmonary lymph flow, but with a partial decline toward baseline values in P_{pa} and PVR.

We have previously shown that levels of T_xB_2, the relatively inactive metabolite of the potent vascoconstrictor T_xA_2, remain elevated up to 1 h after the end of an infusion of GBS (1). We hypothesized that elevated TxA_2, produced in response to continuing GBS infusion, is associated with sustained pulmonary arterial hypertension and $\dot{V}_A/\dot{Q}$ mismatching. We further hypothesized that inhibition of ongoing synthesis of T_xA_2 should result in improvement in both hemodynamic and gas exchange variables during established GBS bacteremia due to decreased P_{pa} and improved $\dot{V}_A/\dot{Q}$ matching.

METHODS

Animal preparation. Fifteen healthy piglets, age 14–21 days, were anesthetized with pentobarbital (25 mg/kg intravenously then 5 mg/kg/h). The animals underwent tracheostomy placement. Pulmonary arterial and systemic arterial catheters were then inserted. An additional double-lumen intravenous catheter was introduced for infusion of inert gases (mixed in D_5W in

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normal saline and infused at a rate of 5 ml/kg/h). After instrumentation the animals were paralyzed (pancuronium 0.1 mg/kg) and received assisted ventilation (Harvard Apparatus, Millis, MA) with room air as the inspired gas and frequency established to maintain an arterial pCO_2 of 35–40 torr. The animals were inflated with a tidal volume of twice normal three times in succession, 10–15 min before each experimental manipulation to minimize spontaneous atelectasis.

Heparinized saline (5 ml/h) was administered continuously via the pulmonary arterial catheter except during pressure recordings. All vascular pressure measurements were recorded at end expiration. Animal temperature was maintained with a heating blanket and an overhead warmer as needed to maintain arterial temperature at 38.5 ± 0.5° C. Animals had their urinary bladders drained as needed during the experimental protocol.

Minute ventilation was calculated as previously described (10). Total $\dot{Q}_p$ was calculated by the thermodilution technique (11). An index of PVR was calculated according to the formula PVR $= P_{pa} - P_{cwp} \div \dot{Q}_p$. An index of systemic vascular resistance was calculated by dividing mean systemic arterial pressure by $\dot{Q}_p$, assuming $\dot{Q}_s = \dot{Q}_p$.

Arterial and mixed venous blood gas tensions and pH were measured within two minutes of sampling (Corning 165 Blood Gas Analyzer).

Assessment of ventilation perfusion matching. The multiple inert gas elimination technique (12) was used as previously described (1, 3) to assess intrapulmonary shunt and distribution of $\dot{V}_A/\dot{Q}$ ratios. A unitless index of overall ventilation perfusion heterogeneity, separate from shunt (perfusion to areas of zero ventilation) and dead space (ventilation to areas of zero perfusion) was assessed using the derived variable $SD\dot{Q}_p$ (13, 14). Special care was taken to maintain constant hematocrit and animal temperature during the experimental protocol in order to prevent fluctuations in the blood-gas partition coefficient for each inert gas (15).

Bacterial preparation. Group B β-hemolytic streptococci, type III, were prepared as previously described (1, 3). Bacteria were incubated for 18 h before each experiment in Todd Hewitt broth. The broth culture was then centrifuged and final concentration of the bacteria in saline suspension was calculated on each experimental day, using a previously determined plot relating bacterial cfu to optical density.

Assessment of arachidonate metabolites. At each sampling time in the 10 experimental animals, a 2-ml sample of arterial blood was obtained as previously described (1). The sample was drawn directly into cold inhibitor solution containing indomethacin and sodium EDTA. Samples were centrifuged at 15000 rpm × 10 min and the decanted fluid was frozen and stored at −70° C until RIA for T_xB_2 and 6-keto-$PGF_{1\alpha}$, the stable hydrolysis products of T_xA_2 and PGI_2, respectively, was performed (WRH). Immediately before RIA, samples were deproteinated using ultrafiltration. Matrix effects due to protein present in unknown piglet plasma samples were determined in standard curves run in eicosanoid-free piglet plasma prepared by charcoal stripping. Samples were analyzed in duplicate according to standard protocol (16, 17). The values for 6-keto-$PGF_{1\alpha}$ and T_xB_2 are expressed as the average of the two values obtained with each analysis. T_xB_2 and 6-keto-$PGF_{1\alpha}$ were assayed by the measurement of competitive inhibition of ^3H T_xB_2 to anti-T_xB_2 and ^3H 6-keto-$PGF_{1\alpha}$ to 6-keto-$PGF_{1\alpha}$ binding, respectively. The T_xB_2 or 6-keto-$PGF_{1\alpha}$ was conjugated to porcine thyroglobulin by the mixed anhydride method before immunization of the rabbits. The anti-T_xB_2 and anti-6-keto-$PGF_{1\alpha}$ antisera were produced in rabbits by the method of Jaffe and Behrman (18). The anti-TxB_2 antiserum at a dilution of 1:100,000 had a sensitivity of 1 pg/0.1 ml sample and the following cross-reactivities at B/Bo 50%: PGD_2, 0.53%; $PGF_{2\alpha}$, 0.20%; $PGF_{1\alpha}$, 0.02%; and PGE_2, 6-keto-$PGF_{1\alpha}$, and 6-keto-PGE_1 each less than 0.02%. The anti-6-keto-$PGF_{1\alpha}$ antiserum at a dilution of 1:2,000 had a sensitivity of 10 pg/0.1 ml and the following cross-reactivities at B/Bo 50%: 6-keto-PGE_1, 2.5%; $PGF_{1\alpha}$, 1.43%; $PGF_{2\alpha}$, 0.77%; PGD_2, 0.42%; and T_xB_2, PGE, and PGE_2 each less than 0.11%. Labeled tracers (^3H T_xB_2 and ^3H 6-keto-$PGF_{1\alpha}$) were obtained (New England Nuclear Research Products, Boston, MA). Unlabeled, synthetic standards were the generous gift of Douglas McCarter (Upjohn Co, Kalamazoo, MI).

Preparation of dazmegrel. Dazmegrel (UK 38, 485) (8 mg/kg) was dissolved just before infusion in 1.0 ml of 0.1 N NaOH to which was added 0.9% saline to make a 5 ml solution. Sham injections consisted of the same volume of NaOH-saline solution without the drug.

Experimental protocol. After instrumentation and collection of baseline samples, each animal received an infusion of 5 to 8 × 10^8 cfu/kg/h of live GBS. In five animals, the GBS infusion was continued for 3 h without further intervention in order to establish an infusion rate of GBS which would provide prolonged, sustained elevation of P_{pa} and PVR without inducing systemic hypotension or metabolic acidosis.

In the 10 study animals, GBS was infused for 2.5 h, with blood samples and hemodynamic measurements recorded at 30 min and 2 h after initiation of the infusion. After the 2-h sampling, a sham injection of NaOH-saline mixture was administered to detect any effect on pulmonary hemodynamics of the carrier substance for dazmegrel. Ten min later, 8 mg/kg of dazmegrel in the same carrier was administered. Twenty min after the end of dazmegrel administration, while the GBS infusion continued, a fourth set of samples was obtained, Hemodynamic measurements were continued for 30 min after the end of the bacterial infusion which had been continued for 30 min after the infusion of dazmegrel. Animals were then killed and the lungs promptly removed, inspected for areas of atelectasis, and wet and dry lung weights were obtained by methods previously described (19).

Statistics. The paired *t* test was used to compare the 2 h GBS and the postdazmegrel samples to baseline data. A *p* value of <0.05 was used for establishing significance. The nonparametric Mann Whitney U test was used for analysis of inert gas data (20).

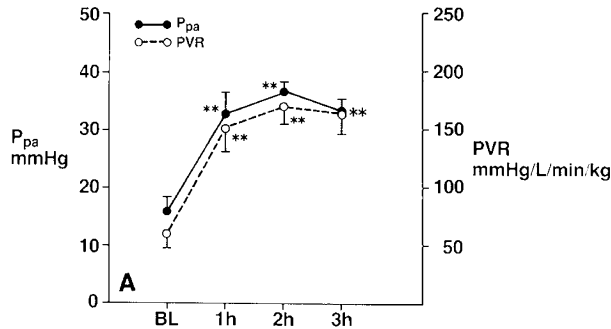
RESULTS

The results of the continuous infusion of GBS in the five pilot animals are shown in Figure 1 *A* and *B*. P_{pa} and PVR both increased with the onset of GBS infusion (Fig. 1*A*) and remained elevated throughout the course of the infusion. Arterial pO_2 (Fig. 1*B*) declined shortly after initiation of the infusion and hypoxemia persisted throughout the 3-h period. There was no change in pH or pCO_2 during the course of the infusion. Neither mean systemic arterial pressure nor systemic vascular resistance changed in these five animals during the 3-h period.

Hemodynamic data for the 10 animals receiving dazmegrel at 2 h postinitiation of the GBS infusion are illustrated (Figs. 2–4). A prompt decline in P_{pa} (Fig. 2) and PVR (Fig. 4) occurred with dazmegrel infusion. There was a small increase in $\dot{Q}_p$ after dazmegrel (Fig. 3). Arterial pO_2 results are illustrated (Fig. 5, *top*); there was no increase in PaO_2 after dazmegrel administration. The percentage of intrapulmonary shunt and $SD\dot{Q}_p$ at each experimental time is also shown (Fig. 5, *bottom*); a sustained increase in $SD\dot{Q}_p$ occurred with no significant effect on shunt with GBS infusion; this did not diminish with dazmegrel. No change in SVR, pH, or pCO_2 occurred in these 10 animals during any of the experimental conditions. Also, there was no change in peak airway pressure recorded at any of the experimental times.

The results of arterial T_xB_2 and 6-keto-$PGF_{1\alpha}$ measurements are shown in Figure 6. As expected, TxB_2 increased significantly with the onset of the GBS infusion. There was a decrease in T_xB_2 levels 30 min after the administration of dazmegrel but T_xB_2 did not decline back to pre-GBS values. In contrast, 6-keto-$PGF_{1\alpha}$ continued to be elevated even after the infusion of dazmegrel.

The mean (± SD) dry weight to wet weight ratio for the five



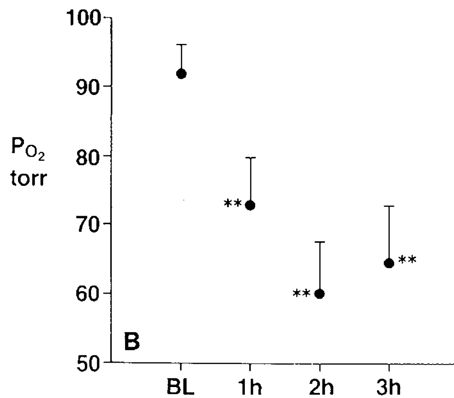


Fig. 1. *A*, P_{pa} and PVR are plotted against time of GBS infusion for five animals who received a continuous infusion. *B*, arterial pO_2 is plotted against time of GBS infusion for five animals who received a continuous infusion of bacteria. Data shown as mean X ± 1 SD. *BL*, baseline. $^{**}p < 0.02$ compared to baseline.

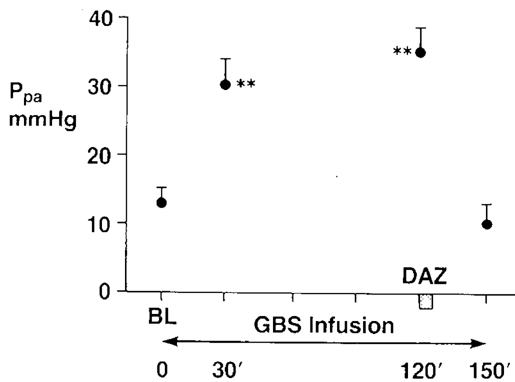


Fig. 2. Pulmonary arterial pressure is plotted against time for the 10 animals who received dazmegrel (*daz*). Duration of infusion is shown on the *abscissa*. *BL*, baseline. $^{**}p < 0.02$ compared to baseline data.

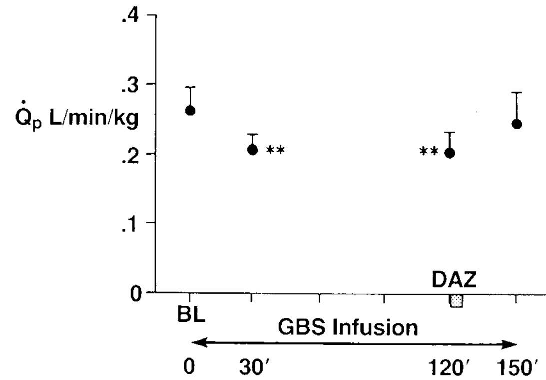


Fig. 3. $\dot{Q}_p$ is plotted against time for the 10 experimental animals. Abbreviations are the same as in Figure 2. $^{**}p < 0.02$.

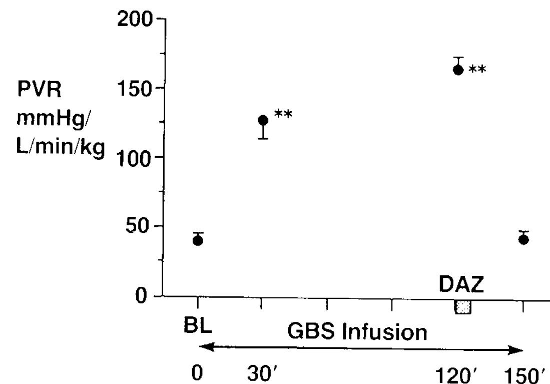


Fig. 4. PVR is plotted against time. Abbreviations are the same as in Figure 2. $^{**}p < 0.02$.

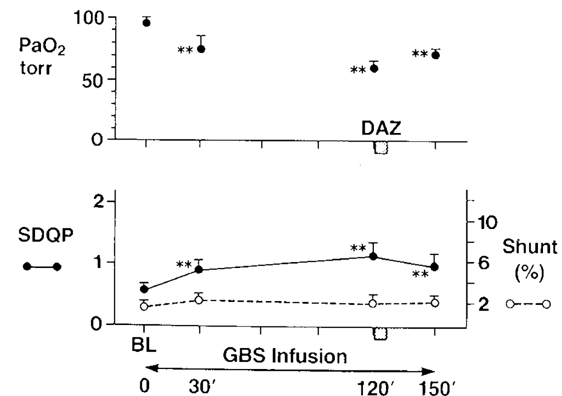


Fig. 5. Arterial PO_2 is plotted against time (*top*). The $SD\dot{Q}_p$ and % intrapulmonary shunt are plotted respectively on the left and right *ordinate* against time (*bottom*). Abbreviations are the same as in Figure 2. $^{**}p < 0.02$ compared to baseline.

animals that received a 3-h GBS infusion was 0.19 ± 0.11. The dry to wet weight ratio was 0.188 ± 0.04 for the 10 experimental animals. These data are similar to those found in piglets similarly instrumented but not subjected to GBS infusion (21).

Infusion of the carrier substance for dazmegrel without the active drug caused no detectable change in any of the pulmonary or systemic hemodynamic data or in gas exchange measurements.

DISCUSSION

This study demonstrated that administration of dazmegrel 2 h after the onset of pulmonary arterial hypertension and arterial hypoxemia induced by GBS infusion in a neonatal animal resulted in prompt decline in P_{pa} and PVR to baseline levels where they remained for at least 0.5 h after the administration of dazmegrel during ongoing bacterial infusion. The hemodynamic results are analagous to the results obtained with treatment with dazmegrel before bacterial infusion (1). In contrast, there was no concomitant improvement in pulmonary gas exchange as assessed by both respiratory gas tensions and by tracer inert gas analysis to evaluate matching of alveolar ventilation to pulmonary perfusion.

Our results suggest that delayed treatment with dazmegrel resulted in a decrease in P_{pa} without any improvement in pulmonary gas exchange, in contrast to the finding of a <5 torr mean decrease in PaO_2 during GBS infusion in animals pretreated with daz (1) and a decrease of 17 torr (1) to 40 torr (2, 3) when GBS was infused into control animals during ambient air

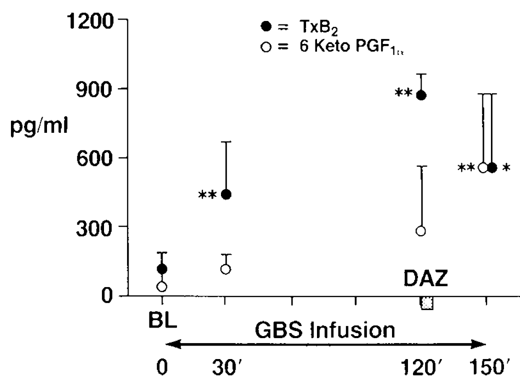


Fig. 6. TxB_2 and 6-keto $PGF_{1\alpha}$ are plotted against time. Abbreviations are the same as in Figure 2. $*p < 0.05$; $**p < 0.02$.

breathing. There are two possible reasons why arterial pO_2 failed to improve when T_xA_2 synthesis was inhibited and PVR was diminished with dazmegrel treatment. Animals may have developed substantial interstitial or alveolar edema after 2 h of bacterial infusion and pulmonary hypertension, which would result in mismatched $\dot{V}_A/\dot{Q}$. Julien *et al.* (22) tested whether changes in lung wet weight to dry weight ratios accurately reflected edema development, by creating two different forms of pulmonary edema, induced by increased hydrostatic pressure and by oleic acid infusion. All animals had significant increases in wet weight to dry weight ratios compared to nonmanipulated animals. In contrast in our study, the dry to wet weight ratio data obtained from animals infused with GBS, as well as experimental animals posttreated with dazmegrel, are similar to data obtained from control piglets in other laboratories (21). However, relatively small changes in edema may contribute to the decrease in arterial oxygen tension (23).

An additional cause of hypoxemia in this setting may be that the selective T_xA_2 synthase inhibitor resulted in an unbalanced vasodilator effect of PGI_2, measured as 6-keto-$PGF_{1\alpha}$. PGI_2 has been demonstrated to sustain pulmonary blood flow to hypoxic lung regions, overcoming local hypoxic pulmonary vasoconstriction (24). If a small amount of alveolar edema had already formed, creating poorly ventilated lung regions, continuing pulmonary blood flow to these otherwise vasoconstricted regions would produce an increase in $SD\dot{Q}_p$ after 2 h of GBS infusion. The lack of change in SVR, mean systemic arterial pressure, or systemic pH suggests that these are local effects occurring only in the lung. The prompt fall in P_{pa} without improvement in arterial pO_2 also suggests that the elevated PVR was not primarily due to hypoxic pulmonary vasoconstriction in this model.

The decline in P_{pa} occurred while thromboxane levels remained elevated, as assessed by the T_xA_2 metabolite, T_xB_2. T_xB_2 has been used as an index of T_xA_2 production because it is a stable metabolite of T_xA_2. T_xB_2 itself has only minimal vasoconstrictive activity. However, recent studies have questioned the role of T_xB_2 measurements as a marker of thromboxane activity, as this substance is derived nonenzymatically from the breakdown of T_xA_2 (25, 26). Thus, T_xB_2 can be readily generated from T_xA_2, even with careful drawing of blood into an inhibitor mixture (25). Others (26) have used the enzymatically derived metabolite 11 dehydro-T_xB_2 as a more sensitive reflection of T_xA_2 production. However, the highly significant increases in T_xB_2 in response to GBS infusion and the sharp decline in circulating T_xB_2 30 min after dazmegrel administration likely reflect physiologically important changes. Levels of 6-keto-$PGF_{1\alpha}$, the inactive metabolite of the vasodilator prostacyclin, increased throughout the GBS infusion period, especially after dazmegrel infusion. This may have occurred because of "shunting" of the precursor-product reaction in the direction of this metabolite or it may have occurred in direct response to GBS infusion without regard to inhibition of the T_xB_2 synthetic pathway. We previously found an insignificant change in PGI_2 levels during GBS infusion (1), although Runkle *et al.* (2) found an increase in both T_xB_2 and PGI_2 during GBS infusion. The effect of a prolonged infusion of GBS into neonatal animals followed by dazmegrel treatment on PGI_2 levels had not been reported before our study.

The MIGET provides quantitative data about the range of $\dot{V}_A/\dot{Q}$ distributions in the lung (12, 14). The technique allows precise measurement of intrapulmonary shunt and anatomical dead space and semiquantative measurements of intermediate $\dot{V}_A/\dot{Q}$ distributions. As originally described, the technique used a theoretical 50-compartment lung model, one compartment representing shunt, another dead space, and the remaining 48 compartments were assigned a $\dot{V}_A/\dot{Q}$ ratio equally spaced along a logarithmic scale (12). Because the lung models had more compartments than there were pieces of data available, the equations predicting fractional Q_p and V_A to each compartment were underdetermined and had nonunique solutions. However, mathematical analysis of the technique provides evidence that within the bounds of physiologically possible results, *i.e.* constraint of nonnegative blood flow to each compartment, all the possible solutions are nearly identical (27). The MIGET was used herein to provide a quantitative measurement of intrapulmonary shunt and $\dot{V}_A/\dot{Q}$ mismatching separate from shunt. The index of $\dot{V}_A/\dot{Q}$ mismatching, the log $SD\dot{Q}_p$, provides a semiquantitive estimate of the extent of mismatching of $\dot{V}_A$ to $\dot{Q}$ in lung regions that are both perfused and ventilated. The $SD\dot{Q}_p$ summarizes $\dot{V}_A/\dot{Q}$ heterogeneity detected by the 50-compartment model yet avoids the uncertainty inherent in assigning a specific fraction of the total $\dot{Q}_p$ to a particular $\dot{V}_A/\dot{Q}$ region. $SD\dot{Q}_p$ agrees experimentally with other indices of $\dot{V}_A/\dot{Q}$ maldistribution that have been derived from MIGET data (28). Overall reproducibility of MIGET has recently also been shown to be very satisfactory (29).

Neonatal piglets can serve as a reasonable model of neonatal GBS sepsis based on similar postnatal pulmonary vascular morphometric features (30, 31). However, extrapolation of results obtained in this or other animal studies to human newborns should be done cautiously. This study does suggest that multiple vasoactive mediators derived from arachidonic acid may participate in sustaining or aggravating the various pathophysiologic mechanisms present after hours of GBS sepsis and helps define the pathophysiologic role of T_xA_2, even in "late" sepsis. Leukotrienes C4 and D4, products of the 5-lipoxygenase pathway of AA metabolism, have recently been demonstrated to be important in early experimental GBS sepsis (4) and in idiopathic persistent pulmonary hypertension in the newborn (32). Other vasoactive substances, such as tumor necrosis factor (33), may also contribute to sepsis-associated pulmonary pathology. Step by step analysis of the effects of specific blocking agents on the end metabolites of the various AA metabolic pathways should help establish their relative causative importance in the hemodynamic and gas exchange abnormalities occurring with GBS infusion.

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