

Title: INDOMETHACIN IMPROVEMENT OF SEPTIC ACUTE RESPIRATORY FAILURE IN PORCINE MODEL

Authors: DJ Dehring, M.D., BD Lowery, M.D., CA Cloutier, M.D., TE Reilley, D.O., and JS McDonald, M.D.

Affiliation: Departments of Anesthesiology and Surgery, The Ohio State University, 410 West 10th Avenue, Columbus, Ohio 43210

**Introduction.** Treatment of respiratory failure associated with sepsis is nonspecific after the antibiotics are selected. Blockade of the prostaglandin system with indomethacin improves hemodynamic parameters and survival in many experimental models of septic shock.<sup>1</sup> Respiratory dysfunction is not exhibited by dogs or rats after endotoxin. Decreased lung lymph flow in the sheep lung lymph model indicates that this treatment is also beneficial in animals that develop respiratory abnormalities.<sup>2</sup> A continuous infusion of live *Pseudomonas aeruginosa* reliably produces hypoxemia, increased intrapulmonary shunting, pulmonary hypertension, and edema in pigs.<sup>3</sup> Indomethacin was given, after starting the bacterial infusion, to find out if improvement would occur in a model with similar respiratory pathophysiology as found in severe Adult Respiratory Distress Syndrome (ARDS).

**Methods.** Male mixed-breed pigs were lightly anesthetized with pentobarbital for endotracheal intubation, insertion of a jugular vein catheter for bacterial infusion, a femoral artery catheter, and a #7 Swan-Ganz thermodilution catheter in the pulmonary artery via the femoral vein. Bacterial infusate was prepared in saline, using a spectrophotometer to obtain a concentration  $2 \times 10^8$  bacteria/cc. Pulmonary and systemic hemodynamic values were monitored in 3 groups of spontaneously breathing animals: Group I, 4 animals given intravenous indomethacin (2 mg/kg) at 20 and 210 minutes; Group II, 6 animals given a continuous infusion of pseudomonas ( $2 \times 10^8/20\text{kg}/\text{min}$ ); and Group III, 6 animals given both bacteria and indomethacin.

in  $\text{PCO}_2$  and improvement in shunt fractions ( $p \leq 0.05$ ) without change in pulmonary pressures. Group II, receiving bacterial infusion only, developed pulmonary hypertension and a drop in  $\text{PaO}_2$  to less than 50 torr with shunts of 40-50% after the first half hour. In Group III, the indomethacin treatment group,  $\text{PaO}_2$  remained above 65 torr with shunts averaging 25%. The doubling of mean pulmonary artery pressure and tripling of pulmonary vascular resistance that followed bacterial infusion all returned to baseline after indomethacin infusion at 20 minutes. Cardiac indices in Groups II and III were comparable, but Group II developed systemic hypotension. Small but nonsignificant improvements were seen with indomethacin given at 210 minutes. Left lung weight increased 122% (NS) in Group III and 156% ( $p < 0.01$  in Group II over that in Group I without bacteria). Survival doubled from  $234 \pm 32$  to  $458 \pm 16$  minutes ( $p < 0.001$ ) by adding indomethacin.

**Discussion.** Indomethacin decreased respiratory dysfunction and prolonged survival. Pulmonary hypertension was modified, presumably by blocked production of pulmonary vasoconstrictor prostaglandins. Indomethacin is known to restore the hypoxic pulmonary vasoconstriction abolished by endotoxin.<sup>4</sup> The extremely high calculated shunts include ventilation perfusion abnormalities along with intrapulmonary shunts, since determinations were made on room air.

Undesirable effects of indomethacin were documented at autopsy. Group III animals had dark ischemic-appearing kidneys and a 100% incidence of gastritis. This may be due to the blocking of beneficial vasodilator prostaglandins, or simply, to longer survival with sepsis. These complications and the possibility of myocardial depression by indomethacin need to be studied further before this clearly beneficial treatment proposed for humans with ARDS.

#### References

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VAR. GROUP	TIME					
	0	15	45	90	240 min.	
PA mmHg	I	17 ± 2	16 ± 2	12 ± 3	13 ± 1	17 ± 2
	II	15 ± 1	46 ± 2	47 ± 4	36 ± 3	42 ± 4
	III	18 ± 2	43 ± 4	16 ± 1*	25 ± 2*	24 ± 1*
PaO <sub>2</sub> mmHg	I	79 ± 3	79 ± 4	86 ± 3*	85 ± 3	87 ± 2
	II	77 ± 4	71 ± 4	42 ± 3	40 ± 4	45 ± 5
	III	81 ± 4	75 ± 6	74 ± 3*	75 ± 7*	71 ± 6*
Qs/Qt %	I	26 ± 2	26 ± 5	19 ± 1*	19 ± 2	17 ± 2*
	II	20 ± 1	27 ± 4	46 ± 4	57 ± 6	40 ± 6
	III	23 ± 4	26 ± 2	22 ± 2*	22 ± 3*	18 ± 3*
CI L/min 20 kg.	I	3.6 ± 0.3	3.7 ± 0.2	2.7 ± 0.2*	2.7 ± 0.2	2.8 ± 0.2
	II	3.0 ± 0.2	3.6 ± 0.4	2.3 ± 0.3	2.4 ± 0.2	1.7 ± 0.2
	III	2.8 ± 0.2	2.6 ± 0.2	2.9 ± 0.2*	2.5 ± 0.2	1.7 ± 0.2

\* = p 0.05 between Group II and III  
x = p 0.05 within Group I from baseline

Indomethacin is given at 20 and 210 minutes. Values are  $\bar{x} \pm \text{SEM}$ .

**Results.** Group I, receiving indomethacin only, showed decreased cardiac indices with transient decrease