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Serotonin Receptor Blockade Improves Cardiac Output and Hypoxia in Porcine ARDS[1,2]

TIMOTHY D. SIELAFF, B.S., JOHN M. KELLUM, M.D., HARVEY J. SUGERMAN, M.D.,[3] JOHN F. KUEMMERLE, M.D., AND JAMES L. TATUM, M.D.

Departments of Surgery and Radiology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0519

The effects of the serotonin receptor blocker, ketanserin, were studied in a porcine *Pseudomonas* adult respiratory distress syndrome model. Swine, weighing 14–30 kg, were anesthetized and ventilated with 0.5 FiO_2 and 5 cm H_2O positive end expiratory pressure. Three groups were studied: saline control (C, $n = 9$), continuous intravenous *Pseudomonas aeruginosa*, 5.0×10^8 CFU/kg/min (Ps, $n = 8$), and *Pseudomonas* and intravenous ketanserin, 0.2 mg/kg, given at 20 and 120 min after the onset of the *Pseudomonas* infusion (KET, $n = 5$). Pulmonary arterial (PAP) and systemic arterial (SAP) pressures, cardiac index (CI), thermal Cardio-Green extravascular lung water (EVLW), pulmonary albumin flux (slope index, SI), arterial blood gases, and whole blood serotonin levels were measured and pulmonary shunt and pulmonary (PVRI) and systemic (SVRI) vascular resistance indices were calculated. At 3 hr the Ps group demonstrated significant ($P < 0.05$) increases in PAP (34 ± 1 vs C 13 ± 2 mm Hg), EVLW (14.4 ± 2.2 vs C 4.3 ± 1.2 ml/kg), SI ($2.05 \pm 0.23 \times 10^{-3}$ vs C $0.38 \pm 0.09 \times 10^{-3}$ U/min), pulmonary shunt ($67 \pm 15\%$ vs C $9 \pm 3\%$), PVRI (1599 ± 89 vs C 184 ± 14 dyn · sec · cm^{-5}/m^2), and SVRI (4542 ± 774 vs C 2087 ± 129 dyn · sec · cm^{-5}/m^2) and decreases in CI (0.9 ± 0.1 L/min/m^2 vs C 2.8 ± 0.2 L/min/m^2), P_aO_2 (93 ± 17 Torr vs C 203 ± 15 Torr) and arterial blood serotonin concentration ($23.5 \pm 13\%$ decrease from basal). Treatment with ketanserin was associated with maintenance of P_aO_2 (KET 207 ± 5 mm Hg vs C 203 ± 15 mm Hg), pulmonary shunt (KET $8 \pm 3\%$ vs C $9 \pm 3\%$), and CI (KET 2.3 ± 0.1 L/min/m^2 vs C 2.8 ± 0.2 L/min/m^2) at control levels and attenuated the *Pseudomonas*-induced increase in PVRI (873 ± 37 vs Ps 1599 ± 89 dyn · sec · cm^{-5}/m^2) and SVRI (2089 ± 287 vs Ps 4542 ± 774 dyn · sec · cm^{-5}/m^2), but did not alter the development of pulmonary edema. These data indicate that serotonin plays a role in the development of the *V/Q* mismatch and arterial hypoxemia observed in this model by a mechanism independent of changes in microvascular injury and permeability and was probably a result of reduced peripheral bronchiolar constriction.

INTRODUCTION

Septic adult respiratory distress syndrome (ARDS) is a complex disorder associated with a pulmonary microvascular injury which results in a decreased ventilation–perfusion ratio, progressive pulmonary edema, and pulmonary arterial hypertension. Studies in animal models, designed to elucidate the pathophysiology of the disorder, have implicated a number of putative chemical mediators [1]. Several studies have shown that thromboxane A_2 may mediate the early severe pulmonary hypertension and hypoxemia associated with a septic insult [2]; however, other investigations have failed to show that it mediates the capillary permeability injury [3–5]. A more prolonged, less severe pulmonary hypertension is seen in the later phases of injury when pulmonary microvascular permeability increases are manifest [3–5]. The aggregation of platelets and the release of the vasoactive amine, serotonin (5-HT), have been implicated in this aspect of the syndrome [6–8]. Serotonin is a smooth muscle constrictor that has been shown to

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[3] To whom requests for reprints should be addressed: P.O. Box 519, Medical College of Virginia, Richmond, VA 23298-0519.

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constrict peripheral airways [9] and cause pulmonary arterial hypertension and arterial hypoxemia [10]. Serotonin receptors on bronchial and vascular smooth muscle have been classified as type 2 5-HT receptors. Blockade of the type 2 5-HT receptor with ketanserin has been shown to have some benefit in patients with ARDS [6] by reducing pulmonary shunt and improving oxygenation and lung function. A similar effect was seen in the late phase of injury in the ovine endotoxemia model [11] when ketanserin was given prior to endotoxin.

In a previous study using a porcine *Pseudomonas*-induced ARDS model [12], it was shown that intervention with a multiagent pharmacologic treatment (including serotonin, prostaglandin, and histamine blockers) was able to ameliorate much of the associated cardiopulmonary deterioration. The present study was designed to study the role played by the serotonin receptor blocker, ketanserin, alone in this porcine *Pseudomonas* ARDS model.

MATERIALS AND METHODS

Experimental Design

Young swine, weighing 14–30 kg, were anesthetized with intramuscular ketamine hydrochloride (25 mg/kg) and atropine (0.4 mg) and were placed supine. The animals were then given intravenous sodium pentobarbital (10 mg/kg). Following intubation with a cuffed endotracheal tube, they were paralyzed with continuous intravenous pancuronium bromide (0.2 mg/min) to permit mechanical ventilation with 0.5 FiO_2, 5 cm H_2O positive end expiratory pressure (PEEP), and 20 cc/kg tidal volume at a rate which produced a P_aCO_2 of approximately 40 Torr at the beginning of the experiment.

Catheters were inserted into the left common carotid artery for monitoring systemic arterial blood pressure (SAP) and arterial blood gases and into the right and left external jugular veins for infusion of *Pseudomonas,* ^{99m}Tc-labeled human serum albumin (Tc-HSA), and the therapeutic agent to be studied. A thermodilution Swan-Ganz catheter was passed through the right jugular vein into the pulmonary capillary wedge position with the balloon inflated, so that a normal pulmonary artery pressure curve was obtained with balloon deflation. The Swan-Ganz catheter was used to monitor central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary wedge pressure (PWP), and thermodilution cardiac output (Mansfield Scientific, Model 3500E). Cardiac output (CO) was converted to cardiac index (CI) by the formula: $CI = CO \div (0.112\ BW^{2/3})$, where BW is body weight in kilograms. Pulmonary vascular resistance index (PVRI) was calculated according to the formula $[(\text{mean PAP} - \text{WP}) \div \text{CI}] \times 80$ and systemic vascular resistance index (SVRI) from the formula $[(\text{mean SAP} - \text{CVP}) \div \text{CI}] \times 80$. Blood gases were measured with a blood gas analyzer (Instrumentation Laboratories, Model 113). Blood samples from the femoral artery cannula and from the Swan-Ganz catheter were drawn into heparinized tubes for serotonin radioimmunoassay (RIA). Samples drawn from the Swan-Ganz catheter with the balloon deflated were termed pulmonary arterial blood or mixed venous blood. Samples drawn with the catheter in the wedge position with the balloon inflated were termed pulmonary capillary blood.

A 5 French femoral artery lung water catheter (American Edwards Laboratories, Model 96-020-5F) was passed into the lower abdominal aorta for measurement of thermal-Cardiogreen extravascular lung water (EVLW) [13]. In this technique, 10 ml of iced, green dye solution (2 mg indocyanine green dye in 10 ml of 5% dextrose) was injected as a bolus through the proximal port of the Swan-Ganz catheter as blood was simultaneously withdrawn through the thermistor-tipped femoral artery catheter and a densitometer cuvette (Waters Instruments Inc., Model 402A) linked to a lung water computer (American Edwards Laboratories, Model 9310). The computer measured the mean transit times of the intravascular dye

(MTD) and freely diffusible thermal component (MTT) as well as the cardiac output (CO). EVLW was calculated according to the formula: EVLW = CO (MTD − MTT)/kg body weight. Pulmonary shunt was calculated from the Berggren equation [14].

Computerized gamma scintigraphy was used as a second indicator of pulmonary capillary permeability through the measurement of pulmonary transcapillary albumin flux [15–18]. Animals were placed beneath a Searle Pho-Gamma V scintillation camera fitted with a low energy parallel hole collimator linked with a Digital Equipment Corporation (DEC) mobile acquisition system. Tc-HSA was injected via the right external jugular catheter at 60 min (10 mCi) and 105 min (7 mCi) after baseline. Using the computerized gamma camera, data were collected at 1-sec intervals for 60 sec, so that the heart and lungs could be scintigraphically defined, and thereafter at 1-min intervals. The counts were stored on floppy disc, transferred to magnetic tape, and regions of interest, i.e., right lung and heart, were selected using a DEC Gamma 11 medical computer system. Lung:heart radioactivity ratios were constructed with a VAX 8600 computer. The slope index (SI) was calculated by least-squares linear regression analysis over a 30-min period after a 15-min postinjection delay to allow for isotope equilibration. SI was reported for the period 75–105 and 150–180 min following baseline.

Three groups of animals were studied: a *Pseudomonas* group (Ps, $n = 8$) received a continuous intravenous infusion of live *Pseudomonas aeruginosa,* PAO strain, 5×10^8 CFU/ml at 0.3 cc/20 kg/min; a saline control group (C, $n = 9$) received an equivalent volume infusion of 0.9% saline; the third group (KET, $n = 5$) received Ps and ketanserin (0.2 mg/kg) given as a bolus at 20 and 120 min post-*Pseudomonas.*

Serotonin Radioimmunoassay

Arterial, mixed venous, and pulmonary capillary blood serotonin levels were measured by radioimmunoassay as previously described by Kellum and Jaffe [19]. Briefly, immediately following collection in heparinized tubes, samples were processed to precipitate plasma proteins. To 1.0 ml of blood was added 5.0 ml of distilled water (to lyse cellular elements and platelets) and 1.0 ml of 10% $ZnSO_4$. After thorough mixing, 0.5 ml of 1.0 *N* NaOH was added and the suspensions were centrifuged at 1200*g* for 30 min. The resulting protein-free supernatants were frozen until assayed. As described, the radioimmunoassay system was sensitive to 100 pg of 5-HT. The intra- and interassay coefficients of variance were 9.9 ± 1.1 and 9.4 ± 1.7%, respectively. Neither the precursors tryptophan or 5-hydroxytryptophan, nor any related metabolite, nor 5-hydroxyindole acetic acid, the major metabolite, displayed significant cross-reaction. All reagents were obtained from Sigma Chemical Co. (St. Louis, MO) and the radiolabel from New England Nuclear (Boston, MA).

Statistics

All data, except SI and serotonin levels, were collected at baseline and at 15-min intervals thereafter and are expressed as means ± SEM. Differences between and within groups were tested using the repeated-measures analysis of variance and Tukey's studentized range test. The level of statistical significance was $P \leq 0.05$.

RESULTS

The data are presented in graphic and tabular forms in Figs. 1–7 and Tables 1–3. No significant changes from baseline were seen in any parameters measured in the saline control animals except for a transient increase in arterial blood serotonin levels at 60 min. However, infusion of *Pseudomonas* produced marked physiological deterioration. Group Ps showed a significant decrease in SAP (Fig. 1) compared to Group C at 60 min (Ps 102 ± 7 mm Hg vs C 128 ± 7 mm Hg) and thereafter. SVRI (Table 2) was significantly elevated above control throughout the study period. In addition, CI (Fig. 3) and

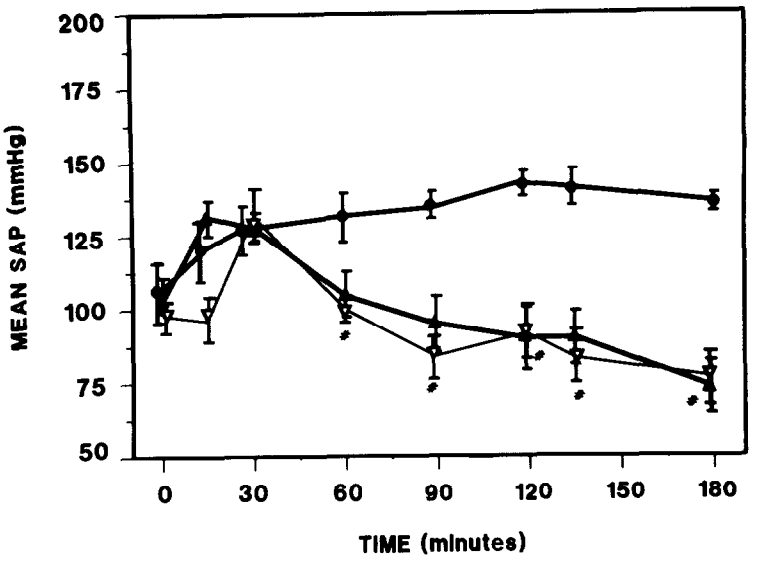

FIG. 1. Failure of ketanserin (0.2 mg/kg) to alter the fall in systemic arterial pressure (SAP) following a continuous infusion of *Pseudomonas* in the pig. (▽) Ketanserin, (●) control, (▲) *Pseudomonas*. $^{\#}P < 0.05$, ketanserin vs control. $^{*}P < 0.05$, ketanserin vs *Pseudomonas*.

P_aO_2 (Fig. 4) in group Ps showed progressive declines becoming significantly different from C at, and after, 30 min (CI, Ps 1.3 ± 0.1 liters/min/m^2 vs C 2.6 ± 0.2 liters/min/m^2) and 90 min (P_aO_2, Ps 138 ± 26 Torr vs C 201 ± 22 Torr), respectively. Mean PAP (Fig. 2) showed a marked increase immediately following administration of *Pseudomonas* (15 min, Ps 48 ± 2 mm Hg vs C 14 ± 4 mm Hg). Pulmonary arterial hypertension persisted at levels significantly above C. PVRI (Table 3) was maintained significantly above control

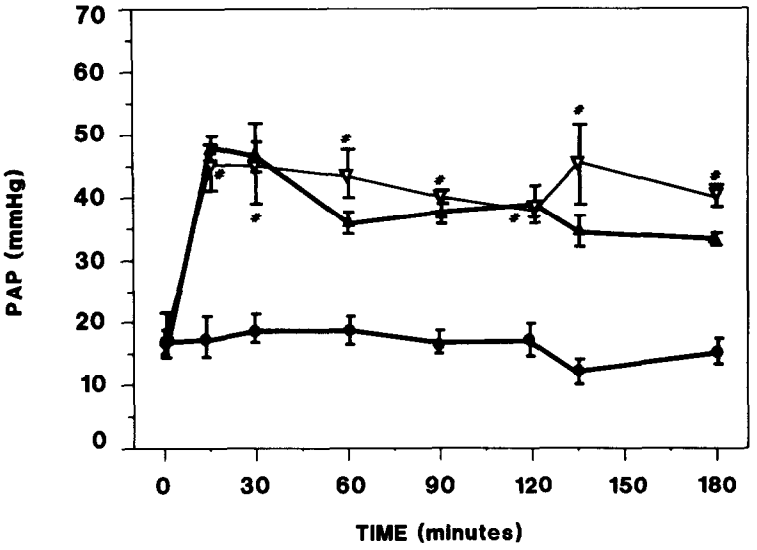

FIG. 2. Failure of ketanserin (0.2 mg/kg) to alter the marked rise in pulmonary artery pressure (PAP) following a continuous infusion of *Pseudomonas* in the pig. (▽) Ketanserin, (●) control, (▲) *Pseudomonas*. $^{\#}P < 0.05$, ketanserin vs control. $^{*}P < 0.05$, ketanserin vs *Pseudomonas*.

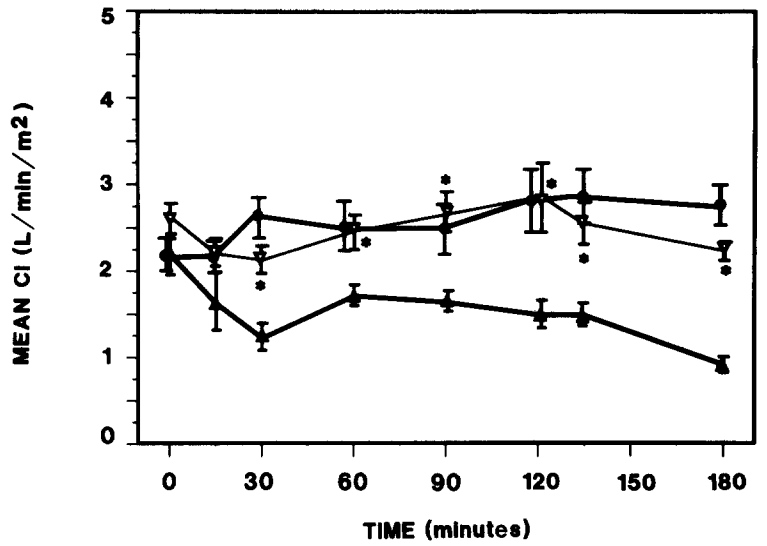

FIG. 3. Preservation of cardiac index (CI) at control levels with ketanserin (0.2 mg/kg) following a continuous infusion of *Pseudomonas* in the pig. (▽) Ketanserin, (●) control, (▲) *Pseudomonas*. $^{*}P < 0.05$, ketanserin vs control. $^{*}P < 0.05$, ketanserin vs *Pseudomonas*.

throughout the experimental period. EVLW (Fig. 5) showed a progressive increase becoming significantly different from C at 60 min (Ps 7.9 ± 0.9 vs C 3.7 ± 1.2 ml/kg). Both values for pulmonary albumin flux (Fig. 6) were significantly elevated when compared to C (SI 75–105, Ps 1.80 ± 0.15 × 10^{-3} U/min vs C 0.43 ± 0.05 × 10^{3} U/min; SI 150–180 Ps 2.05 ± 0.23 × 10^{-3} U/min vs C 0.38 ± 0.09 × 10^{-3} U/min). Pulmonary

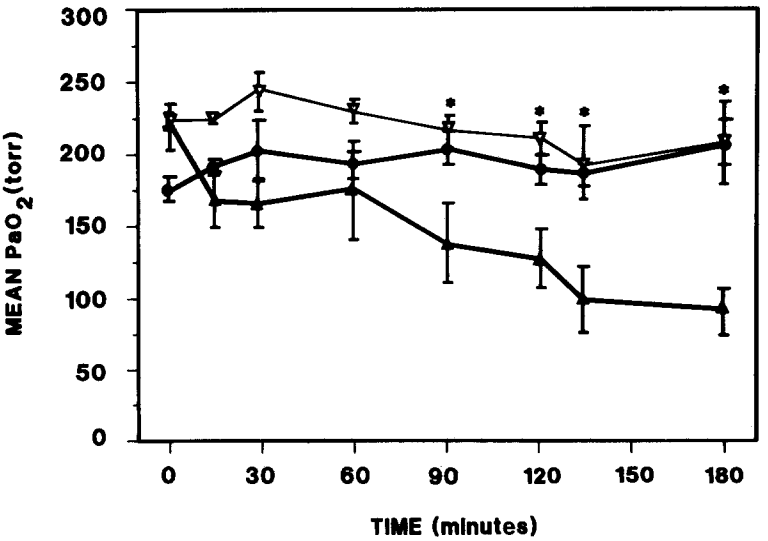

FIG. 4. Maintenance of arterial oxygen tension (P_aO_2) at control levels with ketanserin (0.2 mg/kg) following a continuous infusion of *Pseudomonas* in the pig. (▽) Ketanserin, (●) control, (▲) *Pseudomonas*. $^{*}P < 0.05$, ketanserin vs *Pseudomonas*.

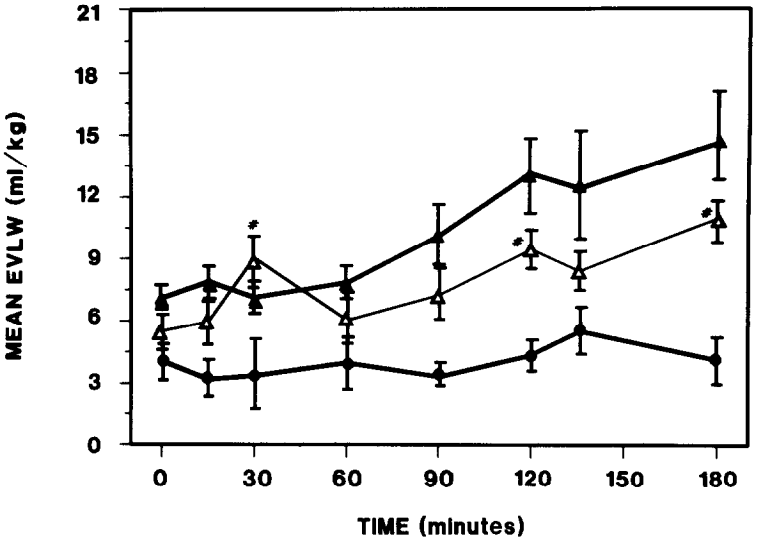

FIG. 5. Failure of ketanserin (0.2 mg/kg) to alter the marked rise in extravascular lung water (EVLW) following a continuous infusion of *Pseudomonas* in the pig. (▽) Ketanserin, (●) control, (▲) *Pseudomonas*. *$P < 0.05$, ketanserin vs control. *$P < 0.05$, ketanserin vs *Pseudomonas*.

shunt (Table 1) was significantly elevated from control at 180 min (Ps 67 ± 15% vs C 9 ± 3%).

In those animals treated with ketanserin at 20 and 120 min after the onset of the *Pseudomonas* infusion, neither CI nor P_aO_2 changed significantly from Group C levels during the 180-min experiment. However, SAP showed a progressive decline becoming significantly different from C at 60 min (KET 85 ± 6 mm Hg vs C 128 ± 7 mm Hg).

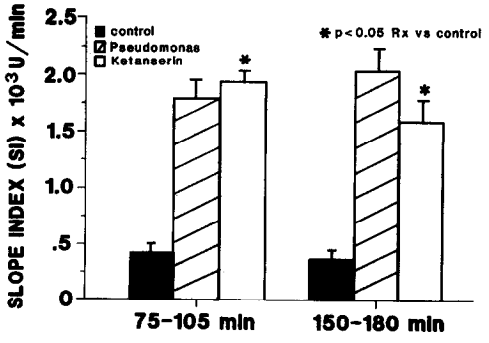

FIG. 6. Failure of ketanserin (0.2 mg/kg) to prevent the marked increase in albumin flux, measured scintigraphically as slope index (SI), following a continuous infusion of *Pseudomonas* in the pig. (■) Control, (▨) *Pseudomonas*, (□) ketanserin. *$P < 0.05$ Rx vs control.

SVRI (Table 2) was elevated above control at 15 min; however, following treatment a progressive decline was seen, returning to control levels by 90 min. Treatment with ketanserin did not alter the course of pulmonary hypertension when compared to the *Pseudomonas* group; ketanserin-treated animals were significantly different from C at 15 min (KET 44 ± 5 mm Hg vs C 14 ± 4 mm Hg) and thereafter. PVRI (Table 3) remained significantly above control throughout the experimental period and significantly below Ps at 90 and 180 min. Group KET also showed a progressive increase in EVLW, which was significantly different from C at 30, 120 and 180 min. In addition, both measurements of SI were significantly elevated from C (SI 75–105, KET 1.96 ± 0.10 × 10^{-3} U/min vs C 0.43 ± 0.05 × 10^{-3} U/min; SI 150–180 KET 1.58 ± 0.25 × 10^{-3} U/min vs C 0.38 ± 0.09 × 10^{-3} U/min). Pulmonary shunt in the ketanserin-treated group (Table 1) was significantly reduced from the *Pseudomonas* group at 180 min (KET 8 ± 3% vs Ps 67 ± 15%).

In control pigs whole blood serotonin levels from samples drawn from the femoral artery cannula at 0 and 180 min were 691 ± 171 and 947 ± 203 ng/ml, respectively ($P = 0.24$). In the *Pseudomonas* group corre-

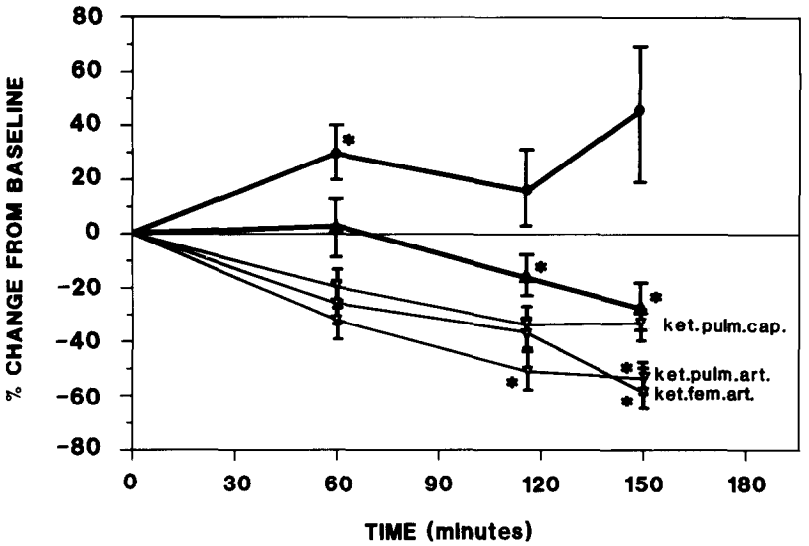

FIG. 7. Significant fall in serotonin (5-HT) levels in arterial blood following a continuous infusion of *Pseudomonas* in the pig. Ketanserin (0.2 mg/kg) did not alter this decrease in mixed venous, pulmonary capillary, or arterial blood. (●) Control, (▲) *Pseudomonas*, (▽) ketanserin. *$P < 0.05$ percentage change from baseline.

sponding circulating 5-HT levels fell 18.3 ± 7% from basal ($P < 0.05$) by 2 hr and remained depressed during the remainder of the experiment (Fig. 7). Pulmonary artery and capillary blood serotonin levels also declined below basal levels. Ketanserin did not prevent the fall in circulating serotonin levels induced by *Pseudomonas* and was associated with a 38.1 ± 12% fall from basal ($P < 0.05$) at 2 hr. In three pigs subjected to the *Pseudomonas* infusion, peripheral arterial platelet counts fell from 510,000 to 250,000/mm^3 or by 51%.

DISCUSSION

These findings demonstrate that type 2 serotonin (5-HT) receptor blockade, introduced after the onset of injury, prevented the arterial hypoxemia and reduced cardiac output associated with this fulminant model of septic ARDS in the pig. Platelet aggregation, which initiates the release reaction for 5-HT, has been associated with well-defined injury to the lung, including ARDS [6, 17, 19]. Serotonin is known to induce smooth muscle constriction in the lungs causing both intense peripheral bronchoconstriction [9] and, depending on the species, vasoconstriction of small pulmonary arterioles or veins [1, 13, 20, 21].

However, since ketanserin did not reverse the rise in pulmonary artery pressure induced by *Pseudomonas*, our findings do not support serotonin release as the dominant cause of the pulmonary hypertension observed in this model, though treatment with ketanserin did significantly ameliorate elevated PVRI. We have previously reported in studies of the same model [22] that the cyclo-oxygenase inhibitor ibuprofen abolished the release of the potent vasoconstrictor, thromboxane A_2, and the early, but not the late (after 1 hr), pulmonary hypertension. Therefore, it appears that thromboxane A_2 is the dominant mediator of the early pulmo-

TABLE 1

PULMONARY SHUNT % ± SEM

	0	180
Control	9.5 ± 4.8	8.6 ± 2.6
Pseudomonas	4.9 ± 2.2	66.8 ± 15.5
Ketanserin	3.3 ± 1.1	7.9 ± 3.3*

Note. Percentage mean ± SEM.
* $P < 0.01$ ketanserin vs *Pseudomonas*.

TABLE 2

SYSTEMIC VASCULAR RESISTANCE INDEX (SVRI)

	0	15	30	90	180
Control	1835 ± 150	1957 ± 91	1966 ± 55	2109 ± 87	2087 ± 129
Pseudomonas	2431 ± 123	3832 ± 428[a]	3753 ± 172[a]	2927 ± 344[a]	4542 ± 774[a]
Ketanserin	2472 ± 220	3344 ± 516[a]	2664 ± 229[a,b]	2139 ± 181	2089 ± 287[b]

Note. Mean ± SEM.
[a] Ketanserin or *Pseudomonas* vs control.
[b] Ketanserin vs *Pseudomonas.*

nary hypertension in this ARDS model. This does not exclude the possibility that serotonin-induced pulmonary vasoconstriction was masked by the more powerful initial action of the prostanoids or that, as suggested by Demling *et al.* [11], it may become more important in the later phases of sepsis-induced ARDS. In a sheep endotoxin model, these investigators noted that ketanserin did block pulmonary hypertension, but only beginning 3 hr after endotoxin.

Ketanserin-treated pigs maintained their P_aO_2 at control levels, while pigs receiving *Pseudomonas* alone demonstrated a progressive, significant decline in this parameter. Ketanserin blocked the dramatic increase in pulmonary arteriovenous shunting observed in the *Pseudomonas* group. Though ketanserin treatment did not alter the *Pseudomonas*-induced pulmonary arterial hypertension, a significant decrease in PVRI was demonstrated. The reduced PVRI as well as inhibition of 5-HT-induced bronchospasm [9] were probably important in this protection. Ketanserin has been previously shown to reduce arteriovenous shunting both in patients with early ARDS [6] and in an animal model of pulmonary embolism [23]. Ketanserin, by virtue of its effects on vascular smooth muscle, is used clinically as a treatment for hypertension. The improved cardiac index with ketanserin may be explained as a consequence of afterload reduction [24, 25], as suggested by the decreased SVRI, or, less likely, by a direct cardiac inotropic effect.

The lack of any effect of ketanserin on pulmonary water or protein leak in these experiments is consistent with the present understanding of the pathophysiologic effects of serotonin. Brigham and Owen [10] reported that an intravenous infusion of serotonin in awake sheep resulted in a modest increase in pulmonary artery pressure, associated with increased transmural pressure and filtration, but no increase in microvascular permeability. It has been recently reported [12] that the microvascular permeability injury in this porcine ARDS model is amenable to treatment with a combination of H_1 and H_2 re-

TABLE 3

PULMONARY VASCULAR RESISTANCE INDEX (PRVI)

	0	15	30	90	180
Control	181 ± 25	139 ± 34	161 ± 23	165 ± 16	184 ± 14
Pseudomonas	212 ± 21	1097 ± 140[a]	1143 ± 115[a]	990 ± 65[a]	1599 ± 89[a]
Ketanserin	218 ± 14	961 ± 195[a]	870 ± 166[a]	765 ± 55[a,b]	873 ± 37[a,b]

Note. Mean ± SEM.
[a] Ketanserin or *Pseudomonas* vs control.
[b] Ketanserin vs *Pseudomonas.*

ceptor blockers, methylprednisolone, ibuprofen, and ketanserin, suggesting multiple interacting inflammatory mediators.

The apparently contradictory fall in systemic, pulmonary arterial, and pulmonary capillary blood serotonin levels beginning 2 hr into the *Pseudomonas* infusion is consistent with a pathophysiologic role for the vasoactive amine in this animal model of ARDS. In these experiments, whole blood serotonin was extracted for RIA. With massive platelet sequestration in the lungs and other capillary beds, one would expect a fall in both platelet counts and in total blood serotonin concentrations, since Kellum and Jaffe [19] demonstrated that virtually all of the circulating 5-HT in the blood is bound to platelets.

In this regard, Demling *et al.* [11] noted a transient but significant fall in platelet counts associated with a 10-fold rise in lung lymph 5-HT output at 3 hr after endotoxin in a sheep ARDS model. Indeed, it has been suggested that the late phase of ARDS in animal models more closely resembles the clinical disease. Sibbald *et al.* [7] noted that patients with sepsis-induced ARDS had a lower platelet concentration than controls, but a significantly higher 5-HT concentration in the platelet-poor plasma. They noted a direct relationship of pulmonary hypertension and the level of 5-HT in the serum of platelet-poor plasma. These findings suggest that pulmonary platelet sequestration and serotonin release play a part in the pathophysiology of sepsis-induced ARDS.

Thus, it is likely that serotonin released from platelets is rapidly removed from the circulation by pulmonary endothelial cells. This process is consistent with a higher local concentration of the free vasoactive amine with resultant bronchoconstriction, vasospasm, and the development of V/Q mismatch and arterial hypoxemia.

Certainly, this injury is only one part of the overall syndrome of ARDS, which is the result of the liberation of multiple putative inflammatory mediators, including prostanoids, oxygen-derived free radicals, histamine, and bradykinin, as well as serotonin. Further investigation is needed to establish whether specific pharmacologic interventions will be of benefit to patients with established acute respiratory distress syndrome.

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