Serotonin, Pulmonary Hypertension, and Airway Constriction in the Anesthetized Dog[1] (35898)

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(Introduced by N. S. Assali)

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Infusion of serotonin into the pulmonary circulation of the anesthetized dog is followed by an immediate increase in pulmonary artery pressure that has been attributed by most investigators to active pulmonary vasoconstriction (1, 2). However, serotonin is also known to cause active constriction of smooth muscle of the bronchi, respiratory bronchioles, and alveolar ducts, resulting in an increase in pulmonary resistance, a decrease in pulmonary compliance, increased transpulmonary pressure and decreased lung volume (3), changes which can also cause pulmonary hypertension (4–6). Since there is no data in the literature comparing dose–response relationships for the pulmonary arterial pressor effect of serotonin with the airway constrictor effect, this study was done to determine if a pulmonary arterial pressor response to serotonin infusion into the pulmonary circulation of the anesthetized dog could be demonstrated in the absence of any effect on pulmonary resistance and compliance and, if so, the threshold for the pressor effect. The results of the study show that pulmonary arterial hypertension is caused by small doses of serotonin (30–100 μg) that have no measurable effect on the mechanical properties of the lung, suggesting that changes in the mechanical properties of the lungs are not responsible for the development of pulmonary hypertension.

Methods. Three mongrel dogs (18, 22, 26.5 kg) were anesthetized with pentobarbital sodium (30 mg/kg), intubated, and placed supine. They were allowed to breathe spontaneously except for periodic hyperinflation to +40 cm H_2O as described below. Cournand catheters (No. 8) were placed (under fluoroscopic control) into the right ventricle, main pulmonary artery, and left atrium. Pulmonary artery pressure (P_{pa}), left atrial pressure (P_{la}), and the pulmonary artery–left atrial pressure gradient (P_{pa}–P_{la}) were measured with a differential strain gauge (Statham P23H) placed at the midchest level. Mean pressures ($\bar{P}_{pa}$, $\bar{P}_{la}$, and $\bar{P}_{pa}$–$\bar{P}_{la}$) were obtained by electrical integration and recorded by an oscilloscopic photographic recorder (Electronics for Medicine, Inc., Model DR8). A Malecot catheter (No. 10) was inserted into the right pleural space leaving a 10-ml pneumothorax, and transpulmonary pressure was measured with a differential strain gauge (Statham PM5 ± 0.3 PSID), one side connected to the pleural catheter and the other to the endotracheal tube. Air flow was measured with a Fleisch pneumotachograph (No. 1), and a differential strain gauge (Statham PM97 ± 0.05 PSID). Tidal volume was measured by electronic integration of the flow signal. Pulmonary resistance (R_L) and pulmonary compliance (C_L) were measured using the loop method with electrical subtraction (7).

When stable base line measurements of $\bar{P}_{pa}$, $\bar{P}_{la}$, $\bar{P}_{pa}$–$\bar{P}_{la}$, R_L, and C_L had been obtained, various doses of serotonin creatinine sulfate (10–500 μg, diluted in physiological saline to 100 μg/ml) were infused rapidly into the right ventricle via the right ventricular catheter, which was then flushed with physiologic saline. Approximately 15 min elapsed between each serotonin infusion. Serial measurements of intravascular pressures

[1] This study was supported by U.S. Public Health Service Grant HE 11066, and a grant from the American Thoracic Society.

($\overline{P}_{pa}$, $\overline{P}_{la}$, $\overline{P}_{pa}$–$\overline{P}_{la}$) and R_L, C_L were made immediately before, during, and following the infusion of each dose of serotonin. Following each rapid infusion, measurements were continued until the maximal pulmonary arterial pressor response had occurred, which was within 1 min after infusion. When no hemodynamic response was noted, the measurements were made for at least 5 min following the infusion. When the measurements were completed the lungs were hyperinflated to +40 cm H_2O several times.

At the conclusion of the experiment, each dog was sacrificed with a rapid infusion of 20 ml of saturated potassium chloride into the right ventricle via the right ventricular catheter. The lungs were removed and examined for the presence of macroscopic pulmonary edema and atelectasis. All pulmonary arteries down to a diameter of 1–2 mm were carefully dissected to determine whether thrombi were present.

Results. Mean $\overline{P}_{pa}$, $\overline{P}_{la}$, and $\overline{P}_{pa}$–$\overline{P}_{la}$ for the three dogs prior to the infusion of any serotonin were 8.2 ± 1.3, 2.5 ± 0.3, and 5.7 ± 1.3 mm Hg, respectively. The mean values for R_L and C_L for the three dogs were 3.6 ± 0.2 cm H_2O/L/sec and 5.4 ml/cm H_2O/kg before serotonin infusion and had not changed significantly at the conclusion of the experiment after all serotonin effect had worn off.

Figures 1 and 2 summarize the effects of serotonin infusion on pulmonary vascular pressures and pulmonary mechanics. Changes in pulmonary vascular pressures ($\overline{P}_{pa}$, $\overline{P}_{la}$, and $\overline{P}_{pa}$–$\overline{P}_{la}$) and pulmonary mechanics at the time of the maximal pulmonary arterial pressor response were measured. Because of the limited number of infusions at any dose level the responses were grouped for the dose ranges 10, 20 μg; 30, 40 μg; 50, 60 μg; 70, 80 μg; 90, 100 μg; and 200–500 μg.

There was a minimal but progressive increase in the preserotonin mean $\overline{P}_{pa}$ and $\overline{P}_{pa}$–$\overline{P}_{la}$ throughout the course of the experiment with no change in the preserotonin mean $\overline{P}_{la}$ (Fig. 1).

Hemodynamic and mechanical effects of serotonin began within 5–10 sec after com-

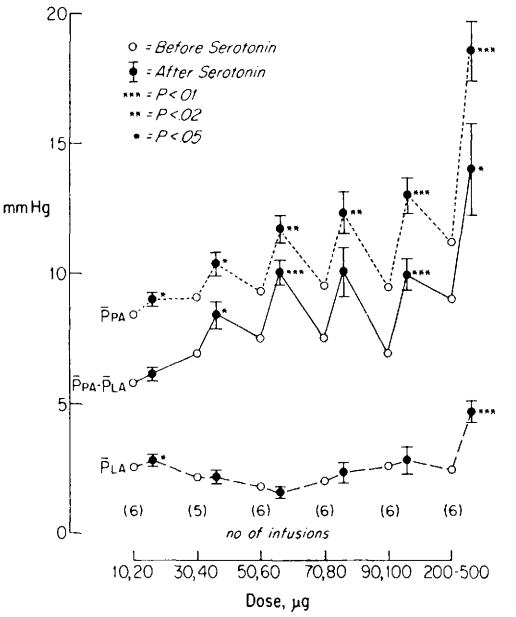

FIG. 1. (O) Mean values for pulmonary artery pressure ($\overline{P}_{pa}$), left atrial pressure ($\overline{P}_{la}$), and the pulmonary artery–left atrial pressure gradient ($\overline{P}_{pa}$–$\overline{P}_{la}$) for the three dogs prior to the infusion of each dose of serotonin; (●) mean values at the time of the peak pressor response following each dose of serotonin; (bars) standard error of the mean for the change in $\overline{P}_{pa}$, $\overline{P}_{la}$, and $\overline{P}_{pa}$–$\overline{P}_{la}$ following each dose of serotonin. The p values indicate the level of significance of the change in $\overline{P}_{pa}$, $\overline{P}_{la}$, and $\overline{P}_{pa}$–$\overline{P}_{la}$.

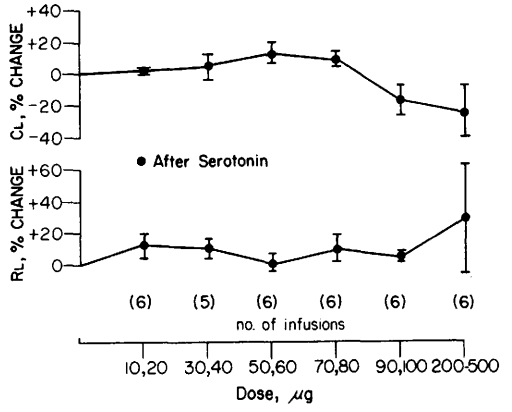

FIG. 2. (●) Mean values for the relative changes in pulmonary resistance (R_L) and compliance (C_L) following each dose of serotonin at the time of the peak pressor response; (bars) standard error of the mean for the percentage change in R_L or C_L from the preinfusion value.

pletion of the infusion and were maximal within 60 sec. Hyperinflation of the lungs usually reversed changes in R_L and C_L caused by serotonin. The vascular response was not reversed by hyperinflation, but slowly dissipated over 5 to 10 min. There was a significant increase in $\overline{P}_{pa}$–$\overline{P}_{la}$ with infusions of 30 μg or more of serotonin except at the 70, 80 μg dose (Fig. 1). At 30, 40 μg the increase was 1.5 mm Hg (21%) and the increase was greater as the dose of serotonin was increased. Following 200–500 μg of serotonin, $\overline{P}_{pa}$–$\overline{P}_{la}$ rose 5.3 mm Hg (60%). The significant increases in $\overline{P}_{pa}$–$\overline{P}_{la}$ were due to an increase in $\overline{P}_{pa}$. There were no significant decreases in $\overline{P}_{la}$ following serotonin infusion at any dose level.

In contrast to the significant increases in $\overline{P}_{pa}$–$\overline{P}_{la}$ at a dose of serotonin of 30 μg or more, significant changes in R_L and C_L could not be demonstrated at any dose level (Fig. 2). There was a slight fall in mean C_L (24%) and a slight increase in mean R_L (34%) at the 200–500 μg dose level (Fig. 2).

In one of the three dogs, there was a pulmonary arterial pressor response to all doses of serotonin. In a second, the pressor response to greater doses was consistently less μg. In the third dog, there was no pressor response until 50 μg was given and the response to greater doses was consistently less than that observed in the first two dogs. The changes in R_L and C_L due to serotonin were comparable in the three dogs.

Examination of the lungs and pulmonary arteries, grossly, revealed no thrombi, pulmonary edema, or atelectasis in any of the three dogs.

Discussion. This study demonstrates that serotonin has a pulmonary arterial pressor effect on the pulmonary circulation at doses which do not produce a measurable effect on the mechanical properties of the lung. The pressor response is characterized by an increase in pulmonary artery pressure ($\overline{P}_{pa}$) and an increase in the pulmonary artery–left atrial pressure gradient ($\overline{P}_{pa}$–$\overline{P}_{la}$) without any decrease in left atrial pressure ($\overline{P}_{la}$). The threshold for the response was 30, 40 μg of serotonin with an increasing response to larger doses.

Since there were no measurements of pulmonary blood flow the mechanism of the increase in pulmonary artery pressure cannot be determined. The only comments that can be made are relative to the role of a change in the mechanical properties of the lungs with a change in transpulmonary pressure or lung volume in the genesis of the pulmonary arterial pressor response to serotonin. It is unlikely that changes in the mechanical properties of the lungs were responsible for the increase in $\overline{P}_{pa}$–$\overline{P}_{la}$ even though serotonin has been reported to cause constriction of bronchi, bronchioles, and alveolar ducts in the anesthetized dog, which is associated with an increase in total pulmonary resistance, a fall in pulmonary compliance, an increase in transpulmonary pressure, and a decrease in lung volume (3) for the following reasons: First, significant changes in R_L and C_L were not observed. This is not surprising since the dose of serotonin required to significantly alter R_L and C_L in the dog is probably 200 μg or more (3). In only 5 of 35 infusions, did the dose infused exceed 200 μg. However, minimal changes in R_L and C_L could have occurred, which would not have been detectable, since the error of the method for a single measurement of R_L and C_L is approximately $\pm 5\%$. Second, the increase in transpulmonary pressure following 200 μg of serotonin in the dog is only 0.2 cm H_2O (3). Roos *et al.* (8) and Permutt *et al.* (5) found that a 1 cm H_2O increase in transpulmonary pressure caused $\overline{P}_{pa}$–$\overline{P}_{la}$ to increase only 0.4 and 1.0 mm Hg, respectively. Thus, if changes in transpulmonary pressure occurred following 30–100 μg of serotonin they would have been less than 0.2 cm H_2O and could not account for the observed increases in $\overline{P}_{pa}$–$\overline{P}_{la}$, which ranged from 1.5 mm Hg (30, 40 μg) to 3.0 mm Hg (90, 100 μg). It is also unlikely that a change in lung volume due to serotonin could be responsible for the observed increase in $\overline{P}_{pa}$–$\overline{P}_{la}$ for the following reason. The decrease in lung volume following 200 μg of serotonin in the dog is 24 ml (3). Assuming that a 20-kg dog has a functional residual

capacity of 600 ml, this would represent a 4% decrease in lung volume. Simmons *et al.* (4) found that a 30% decrease in lung volume caused only a 2 mm Hg increase in $\overline{P}_{pa}$–$\overline{P}_{la}$.

Assuming that the mechanism of the pulmonary arterial pressor effect following small doses of serotonin (30–100 μg) is active pulmonary vasoconstriction, the implication of this study is that in order to study the pure pulmonary vasoconstrictor effect of serotonin in the dog, doses larger than 100–200 μg should not be used since such doses could cause a change in the mechanical properties of the lung with a passive change in pulmonary artery pressure.

Summary. Serotonin (10–500 μg) was infused into the pulmonary circulation of anesthetized, spontaneously breathing dogs and the effect on pulmonary hemodynamics [pulmonary artery pressure ($\overline{P}_{pa}$), left atrial pressure ($\overline{P}_{la}$), the pulmonary artery–left atrial pressure gradient ($\overline{P}_{pa}$–$\overline{P}_{la}$)] and pulmonary mechanics [pulmonary resistance (R_L) and compliance (C_L)] was determined. Pulmonary arterial hypertension, manifested by an increase in $\overline{P}_{pa}$ and $\overline{P}_{pa}$–$\overline{P}_{la}$ with no change in $\overline{P}_{la}$, was caused by small doses of serotonin (30–100 μg) which had no measurable effect on R_L and C_L. These findings are consistent with the hypothesis that serotonin causes pulmonary arterial hypertension as a result of active pulmonary vasoconstriction rather than as a result of changes in the mechanical properties of the lungs.

The authors express their appreciation to Mrs. Sandra K. Smith for her technical assistance.

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Received April 19, 1971. P.S.E.B.M., 1971, Vol. 138.