GRAPHIC ANALYSIS OF SEROTONIN EFFECTS IN DOG
HEART-LUNG PREPARATION

YASUO HOJO, M.D.*, KAZUMI TAKI, M.D.*, NAOHISA ISHIKAWA, M.D.
AND TATSURO SHIGEI, M.D.

Graphical analysis of the effects of serotonin on cardiac function and pulmonary circulation was performed, using the dog heart-lung preparation. The equilibrium points, at which the cardiac output (CO)-curve and venous return (VR)-curve cross in the right atrial pressure (RAP) or left atrial pressure (LAP)-CO relations, were directly recorded on two X-Y recorders. CO- and VR-curves were directly depicted by changing the blood level in the reservoir, and by inducing ventricular fibrillation and simultaneously occluding pulmonary arterial trunk, respectively. Single injections of serotonin, 300 μg, into the right or left atrium, induced a negative inotropic response. Low rate (<30 μg/min) of infusion of serotonin had no effect on the CO-cure or on the slope-gradient of VR-curve in the LAP-CO relation. At a rate of 60 or 120 μg/min, however, the CO-cure was moved downwards to the right, indicating a negative inotropic effect. Pulmonary mean filling pressure increased and the slope-gradient of pulmonary VR-curve decreased, indicating an increased resistance to venous return from the pulmonary circulation. Pulmonary arterial pressure was markedly elevated. In order to obtain the capacitance ratio between the extracorporeal circuit and the pulmonary circulation, a shift of blood volume to the pulmonary circulation was induced by elevating the aortic pressure, which also decreased the slope-gradient. The calculated capacitance ratio became greater during the infusion of serotonin, indicating that the capacitance in the pulmonary circulation was lowered. It is likely that serotonin has contractile effects on the pulmonary arterial and venous vascular beds, elevating the pulmonary filling pressure and resistance to venous return.

SEROTONIN, in general, is considered to cause a contraction of vascular smooth muscles as well as positive inotropic and chronotropic actions on the heart! However, it also causes a dilation of some blood vessels, depending on the species of animal, and the dose used? Moreover, its effect on the heart cannot easily be defined, since high doses may induce a release of norepinephrine from the adrenergic nerve terminals as well as some reflexes. Using the isolated, blood-perfused preparation of atrium and ventricle of the dog, Chiba3 reported that serotonin showed a direct negative inotropic and negative chronotropic actions, and an indirect positive inotropic and chronotropic effects via its tyramine-like action.

We have investigated the effect of drugs such

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Department of Pharmacology, Nagoya University School of Medicine, Nagoya; *Department of Pediatrics, Nagoya National Hospital, Nagoya; **Department of Anesthesiology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan
Mailing address: Naohisa Ishikawa, M.D., Department of Pharmacology, Nagoya University School of Medicine, Showa-ku, Nagoya 466, Japan

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as cinobufagin and norepinephrine on the failed heart, by means of a direct graphical analysis denoted by Guyton. The study was based on the hypothesis that the hemodynamics in heart-lung preparation could be identified as a function of equilibrium between venous return (VR), atrial pressure and cardiac output (CO). The equilibrium point can be directly recorded on diagrams for a relation between the right or left atrial pressures (RAP or LAP) and CO, by using two X-Y recorders. Thus, the CO- and VR-curves are able to be depicted separately and analyzed during the experiments. The obtained VR-curves in particular made it possible to know the resistance to the venous return and mean filling pressure in the pulmonary circulation. Furthermore, utilizing these parameters, we were able to see the changes in capacitance in the circulation. The purpose of this study is to assess the effect of serotonin systematically in dog heart-lung preparations and perform graphical analysis.

MATERIALS AND METHODS

Experimental preparation

Thirteen mongrel dogs, weighing 6–12 kg, were anesthetized with pentobarbital sodium (35 mg/kg) i.p. The chest was opened and lungs were ventilated with an artificial respirator (Natsume, KN-50). Each time, blood was collected from a large dog and defibrinated. The heart-lung preparation was made according to Krayen-Mendez’s modification of original Starling method. The blood volume in the preparation was 1000–1300 ml and the temperature was kept at 35°C. The blood level in the reservoir was maintained at 100 mm above the dorsal surface of the superior vena cava (zero reference point). However, it was allowed to be variable during the continuous infusion of serotonin and while changing the aortic pressure. For the artificial respiration, a mixture of equal volumes of air and gas containing 95%O₂ + 5%CO₂ was used.

We employed a square wave electromagnetic flowmeter (Nihon Kohden, MF-25) to measure cardiac output (CO). An extra-corpooreal probe was inserted between the arterial Starling resistor and the blood reservoir. The aortic and pulmonary arterial pressures, RAP, LAP and the blood level in the reservoir were recorded using pressure transducers (Nihon Kohden, MPU-0.5 and LPU-0.1). The mean aortic pressure was controlled at 70 mmHg by the Starling resistor, unless the aortic pressure was altered. For purpose of measuring the pulmonary arterial pressure, a cannula was inserted in a reverse direction into a.
branch of pulmonary arteries in the right upper lobe. Heart rate was recorded by a tachometer (Nihon Kohden, RT-5) which was triggered by the R-wave of ECG. The movement of equilibrium point was directly and continuously recorded by means of two X-Y recorders (Yokogawa, Type 3077). RAP and LAP being fed to the X-axes and CO to the Y-axes. As previously described, the beginning of experiments, the equilibrium point in the RAP-CO relation diagram was set on a straight line connecting the point of 500 ml/min on the ordinate and that of 100 mmH₂O on the abscissa.

Experiments started by assessment of the status of cardiac function, recording of CO-curve. This was made by changing the blood level in the reservoir upwards and downwards in the range of ±50 mm.

**VR-curves and pulmonary mean filling pressure (Pmp)**

For purpose of measuring Pmp, the dorsolateral wall of the pulmonary arterial trunk was carefully separated from the aorta, and an umbilical tape of 3 mm width was passed. By tightening the tape, we could stop the blood flow from the right ventricle to the pulmonary arterial trunk repeatedly and reversibly.

A ventricular fibrillation was induced by an electrical stimulation (A.C. 4V), and simultaneously the pulmonary arterial trunk was clamped by tightening the umbilical tape. LAP increased and the pulmonary arterial pressure decreased to the same static level in about 5 seconds. Then the value was taken as Pmp. At that moment, RAP corresponded to the level of the blood reservoir (i.e., systemic mean filling pressure, Pms). After the measurement, the pulmonary arterial clamp was released, and the heart was defibrillated with a counter shock of A.C. 100V.

**Administration of serotonin**

1) One-shot injections of serotonin were made first in three heart-lung preparations. Stock solution of serotonin (5-hydroxytryptamine creatinine sulfate, Sigma) was diluted with saline before use. The doses were expressed as free base. Various doses of serotonin, 3, 10, 30, 100 and 300 μg were administered by one-shot injection via a thin tubing either into the right atrium or into the left atrium of the same dog. The order of injections of each dose was randomized. In two cases, an extradose of 1000 μg was added.

2) Continuous infusions of serotonin were

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TABLE I  EFFECTS OF CONTINUOUS INFUSION OF SEROTONIN ON THE HEMODYNAMIC PARAMETERS OF PULMONARY CIRCULATION

<table>
<thead>
<tr>
<th>No.</th>
<th>Dose</th>
<th>ΔCO</th>
<th>ΔRAP</th>
<th>ΔPAP</th>
<th>ΔLAP</th>
<th>ΔBV</th>
<th>Pmp (1)</th>
<th>Pmp (2)</th>
<th>ΔPmp</th>
<th>S.G. (1)</th>
<th>S.G. (2)</th>
<th>ΔS.G.</th>
</tr>
</thead>
<tbody>
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<td>49</td>
<td>10</td>
<td>-230</td>
<td>+19</td>
<td>+40</td>
<td>-24</td>
<td>0</td>
<td>150</td>
<td>100</td>
<td>-50</td>
<td>6.4</td>
<td>8.8</td>
<td>+2.37</td>
</tr>
<tr>
<td>50</td>
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<td>-100</td>
<td>+17</td>
<td>+45</td>
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<td>+28</td>
<td>116</td>
<td>95</td>
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<td>7.2</td>
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<td>+0.03</td>
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<tr>
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<td>30</td>
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<td>+23</td>
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<td>+25</td>
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<td>84</td>
<td>-34</td>
<td>7.5</td>
<td>7.5</td>
<td>+0.05</td>
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<tr>
<td>52</td>
<td>30 -90</td>
<td>+13</td>
<td>+68</td>
<td>0</td>
<td>-10</td>
<td>140</td>
<td>145</td>
<td>+5</td>
<td>5.1</td>
<td>5.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td>-144</td>
<td>+18</td>
<td>+66</td>
<td>-12</td>
<td>+11</td>
<td>131</td>
<td>106</td>
<td>-25</td>
<td>6.6</td>
<td>7.2</td>
<td>+0.61</td>
</tr>
<tr>
<td>± S.E.</td>
<td></td>
<td>±32</td>
<td>±2</td>
<td>±16</td>
<td>±5</td>
<td>±9</td>
<td>±8</td>
<td>±13</td>
<td>±12</td>
<td>±0.5</td>
<td>±0.8</td>
<td>±0.59</td>
</tr>
</tbody>
</table>

Upper and lower sets of data are separated on the basis of doses of serotonin, i.e. at lower (10, 30 µg/min) and higher infusion rate (60, 120 µg/min). ΔCO: change in cardiac output (mL/min); ΔRAP: change in right atrial pressure (mmHg); ΔLAP: change in left atrial pressure (mmHg); ΔBV: changes in reservoir blood volume (mL); Pmp(1) and Pmp(2): pulmonary mean filling pressures before and during the infusion of serotonin (mmHg); S.G.(1) and S.G.(2): slope-gradients of pulmonary venous return curve before and during the infusion of serotonin (mL/min×mmHg). *, **: v.s. lower dose, significant (p < 0.05, < 0.01).

performed in eight heart-lung preparations. The movement of equilibrium point and changes in Pmp and VR-curve for the pulmonary circulation (VRp-curve) were analyzed. Infusion was made using a pump (Natsume, KN-202) at a rate of 10, 30, 60 and 120 µg/min into a tube directly connecting to the right atrium. The CO- and VR-curves were depicted before and during the infusion, on the atrial pressure-CO relation diagrams. No more than two different infusion rates were used for each dog.

Assessment of capacitance change in pulmonary circulation

The calculation of the capacitance ratio between the systemic and pulmonary circulations (Cs/Cp) was performed through a procedure of aortic pressure change in eight preparations. Changing the aortic pressure caused a shift of blood volume between the extracorporeal circuit and pulmonary circulation, and we assumed that the volume change in the heart and pulmonary circulation was the same as in the extracorporeal circuit. The ΔPmp/ΔPms value was calculated as Cs/Cp, by measuring the decrease in reservoir blood level (ΔPms) and the increase in Pmp (ΔPmp).

The Pms and Pmp values were measured at first while the mean aortic pressure was kept at 70 mmHg, and the level of blood in reservoir at 100 mm above the zero reference point. Then, the mean aortic pressure was elevated to 100 mmHg, 120 mmHg or 130 mmHg and fixed. The blood level in the reservoir was left variable, and was continuously recorded as a hydrostatic pressure via a tube attached at the bottom of the reservoir. After the aortic pressure was raised, the blood level decreased and steadily leveled off. Thus, elevation of the aortic pressure resulted in a shift of blood volume from the extracorporeal circuit to the pulmonary circulation.

The slope-gradient of VRp-curve was also obtained as ΔCO/ΔLAP (mL/min/mmHg) before and after the aortic pressure change. Thereafter, during the continuous infusion of serotonin at a speed of 60 µg/min or 120 µg/min, ΔPmp/ΔPms and the slope gradient of VRp-curve were again obtained in the same way in five

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**Statistical analysis**
Data are expressed as mean ± S.E. The statistical significance of difference between means was evaluated by Student’s t-test. Changes in LAP caused by the serotonin infusion were analyzed by χ²-test as well. The level of significance was taken as p < 0.05.

**RESULTS**

**Mean pulmonary pressure in control**
The control Pmp values were determined, when the mean aortic pressure was 70 mmHg and the level of blood reservoir was 100 mm. Then, Pmp and slope-gradient of VRp-curve were 127 ± 8 mmH₂O and 6.85 ± 0.77 ml/min/mmH₂O (n = 8), respectively.

**Effects of one-shot injection of serotonin**
In total, 30 one-shot injections of serotonin were given, using three preparations. The heart rate was either constant or variable within a small percentage range. Both RAP and PAP increased in all cases, while CO decreased. LAP remained constant or decreased by less than 10 mmH₂O, except one where a slight increase of 5 mmH₂O was recorded by a 300 µg injection into the left atrium.

Figure 1 shows the relationship between CO and RAP or LAP, which was directly recorded by X-Y recorders when one-shot injection of serotonin was administered. At first, we recorded the CO-curve by competence test, showing a large slope-gradient, which indicated that the cardiac function of preparations was in good condition. When 0.5 µg of norepinephrine was injected into the left atrium, the equilibrium point moved upwards to the left, counterclockwise, showing an increase in CO as well as decreases in atrial pressures, reflecting an improvement of cardiac function. The competence test and the injection of norepinephrine were two routine procedures used to determine the status of preparations.

After norepinephrine, serotonin was injected. In the RAP-CO relation diagram, the equilibrium point moved downwards to the right, almost along the control VR-curve, and then returned to the initial point, counterclockwise. In the LAP-CO relation diagram, the equilibrium point moved downwards to the left by injection into the right atrium, and then returned to the initial
point, counterclockwise. By injection into the left atrium, it moved straight downward or down to the right, nearly along the control VR-curve, and then returned to the initial point. Serotonin injection always caused movement of the equilibrium point in a clear contrast to norepinephrine injection, and no positive inotropic effect of serotonin was observed.

Figure 2 shows the responses of RAP and PAP to each dose of serotonin, for injections both into the right and left atria. These two pressures both increased, dose-dependently. The injection into the left atrium caused smaller changes in PAP and RAP than that into the right atrium. Almost the same responses were observed repeatedly by several one-shot injections of the same dose, and no tachyphylaxis was noted.

**Effects of continuous infusion of serotonin**

In total, 10 continuous infusions of serotonin were performed with eight preparations. As shown in Table I, CO decreased significantly from 381 ± 14 ml/min to 276 ± 26 ml/min (n = 10), and RAP increased significantly from 30 ± 5 mmHg to 46 ± 6 mmHg. The changes in LAP were significantly different between the two groups of different infusion rates: i.e., LAP decreased from 77 ± 8 mmHg to 65 ± 6 mmHg at an infusion rate of 10 and 30 μg/min, whereas LAP increased from 67 ± 8 mmHg to 73 ± 7 mmHg at the higher rate of 60 and 120 μg/min. Analysis by the χ²-test also showed that the decrease in LAP at lower infusion rates and the increase in LAP at higher rates were significantly different (χ² = 6.67, p < 0.05). The pulmonary arterial pressure was markedly elevated dose-dependently. The increase in Pmp and the decrease in slope-gradient of VRp-curve were remarkable in all six cases in which it was possible to measure Pmp and VRp-curve before and after continuous infusion. Figures 3 and 4 show such examples. The slope gradient of VRp-curve changed only slightly at lower infusion rates (Table I and Fig. 3). Infusion of lower rates did not affect the CO-curve, whereas serotonin at higher rates moved the CO-curve downwards to the right, indicating a negative inotropic action of serotonin (Fig. 4).

**Effects of changing aortic pressure**

A procedure to change the aortic pressure was performed in eight preparations, out of which five received the continuous infusion of serotonin as well. The results are shown in Table II, and one example recorded by two X-Y recorders is shown in Fig. 5. When the aortic pressure was

![Graph showing the effects of serotonin infusion on cardiac output (CO) and venous return (VR) curves.](image)

**Fig. 4. Effects of continuous infusion of serotonin (120 μg/min) on the cardiac output (CO) and venous return (VR) curves.** VF1 and VF2 indicate VR-curves obtained before and during the continuous infusion of serotonin at an infusion rate of 120 μg/min, respectively. Continuous infusion of serotonin caused a shift of CO and VR curves, from CT1 and VF1 to CT2 and VF2. As shown, the Pmp value, which is the intersect of the VR curve on the abscissa (LAP axis), was increased by serotonin, and the slope-gradient of VRp curve was decreased.
TABLE II  EFFECTS OF SEROTONIN ON THE CHANGES IN HEMODYNAMIC PARAMETERS OF PULMONARY CIRCULATION CAUSED BY THE AORTIC PRESSURE CHANGE

<table>
<thead>
<tr>
<th>No.</th>
<th>Dose</th>
<th>AP1→AP2</th>
<th>ΔCO</th>
<th>ΔLAP</th>
<th>ΔPms</th>
<th>ΔPmp</th>
<th>ΔPmp/ΔPms</th>
<th>S.G. (1)</th>
<th>S.G. (2)</th>
<th>ΔS.G.</th>
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<td>46</td>
<td>70→130</td>
<td>-160</td>
<td>+25</td>
<td>-6</td>
<td>+55</td>
<td>9.2</td>
<td>13.0</td>
<td>3.5</td>
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<td></td>
</tr>
<tr>
<td>48</td>
<td>70→130</td>
<td>-155</td>
<td>+21</td>
<td>-14</td>
<td>+55</td>
<td>3.9</td>
<td>2.4</td>
<td>1.2</td>
<td>-1.20</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
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<tr>
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<td>7.4</td>
<td>6.4</td>
<td>3.5</td>
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</tr>
</tbody>
</table>

* S.E. = ± 1.91 ± 3 ± 1 ± 4 ± 0.6 ± 1.5 ± 0.7 ± 1.07

The aortic pressure was changed from 70 mmHg to 100, 120 or 130 mmHg. The dose of serotonin was expressed as an infusion rate (μg/min). ΔCO: change in cardiac output (ml/min); ΔLAP: change in LAP (cmHg); ΔPms: change in blood level in the blood reservoir (mmHg); ΔPmp: change in pulmonary mean filling pressure (mmHg); S.G.(1) and S.G.(2): slope-gradients of pulmonary venous return curve before and during the infusion of serotonin (ml/min/mmHg). The ΔPmp/ΔPms value (25.7) in experiment No. 53 was rejected from the calculation of mean. **: v.e. no treatment with serotonin, significant (p < 0.01).

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DISCUSSION

Generally serotonin is thought to have a positive inotropic action and positive chronotropic action on the heart of various animals. Using cat papillary muscle and dog heart, Bucchino concluded that a high dose of serotonin increased myocardial contractility. However, in 1964, James et al observed a negative chronotropic action of serotonin on the sinus node of the canine heart. As mentioned before, Chiba argued that the positive inotropic and chronotropic actions of a high dose of serotonin were indirect effects. Toda also reported similar effects using rabbit atrium.

We analyzed the effect of serotonin on the hemodynamics of dog heart-lung preparations. The results showed a negative inotropic action rather than a positive one. Although an increase in afterload to the right ventricle possibly affects the cardiac function, we could eliminate such an
Fig. 5. Effects of changing the aortic pressure on the venous return (VR) curves before and during the continuous infusion of serotonin (60 µg/min).

Raising the aortic pressure from 70 to 100 mmHg caused movements of the equilibrium point from closed circles to open circles. The VR curves in the RAP-CO relation diagram (left panel) were almost unaffected, whereas those in the LAP-CO relation diagram (right panel) shifted from solid lines to dashed lines. It was noted that the change in Pmp induced by the aortic pressure change was increased by serotonin.

Effect by injecting serotonin via the left atrium, since the agent would reach the cardiac muscle before reaching the pulmonary vasculature. Actually, the equilibrium point moved downwards to the right along the control VRs-curve after one-shot injection into the left atrium, suggesting that serotonin has a direct negative inotropic action.

Pmp and VRp-curves provide useful informations for the analysis of drug effects on the cardiopulmonary hemodynamics. Serotonin caused increases in Pmp, and decreases in the slope of VRp-curve (Fig. 4, Table II).

According to Guyton, the pulmonary mean filling pressure is increased by three factors, i.e., an increase in blood volume, an increase in vascular tension and an increase in external pressure on blood vessels (alveolar pressure, for example). In respect to the effect of serotonin, the Pmp value was influenced by all of these factors. The alveolar pressure seemed to increase, since the tracheal pressure was elevated (data not shown).

It is well known that serotonin has a strong pressor effect on the pulmonary circulation in many kinds of animals. Its main effect is thought to be a contraction of pulmonary arterial smooth muscles. It also causes the contraction of pulmonary veins. In such respect, Parker et al. studied the effect of serotonin angiographically in the dog. They reported that large pulmonary arteries dilated, while peripheral ones contracted, and pulmonary veins contracted with decreased capillary filling. Rudolph also observed increases in PAP and differences between pulmonary artery wedge pressure and LAP in dogs, and presumed a contraction of pulmonary veins. Shepherd et al. performed experiments with continuous infusion of serotonin into the right atrium of dog, and a single injection into isolated lungs. They concluded that a small dose of serotonin increased the resistance of precapillary vessels, while a large dose additionally caused contraction of pulmonary veins.

In the present experiments, PAP increased dose-dependently, indicating a strong contractile effect of serotonin on the pulmonary arteries. As shown in Fig. 4 and Table I, higher doses of serotonin induced a decrease in slope-gradient of VRp-curve, namely an increase in the resistance to the pulmonary venous return, confirming our previous observation. This is probably due to
venoconstriction, as discussed below. Lower rates of infusion possibly caused contraction only in the arterial region.

A decrease in the slope-gradient of VRp-curve, however, was also induced by elevating the aortic pressure (Fig. 5). This suggests that an increase in the pulmonary blood volume may have increased the resistance against the venous return without venoconstriction. Since serotonin infusion caused a blood volume shift to the lungs, this factor should also be considered. The main capacitance vessels in the pulmonary circulation is known to be capillaries, and elevation of capillary pressure can cause an increase in the pulmonary blood volume15,16. How was the capillary pressure increased? There are two possibilities: an increase in LAP or venoconstriction. The former could be induced by changing the aortic pressure, whereas serotonin affected the LAP value less than the aortic pressure change (Table II). Therefore, it is most likely that venoconstriction was the main factor in serotonin infusion, whereas LAP elevation was in changing aortic pressure, to cause the observed decreases in the slope-gradient of VRp-curve. How the pulmonary blood volume affected the resistance to venous return is still obscure.

The increase in RAP (Fig. 2) possibly resulted from a relative failure of the right ventricle due to an increase in the afterload. This is reflected in the consistent decreases in CO and the consistent increases in RAP in comparison with the variable changes in LAP (Table I). The changes in RAP and PAP were smaller in cases of injection into the left atrium rather than into the right atrium. This happens presumably because of the eventual dilution of serotonin during the passage from injection point in the left atrium up to the pulmonary vessels.

The effect of serotonin on capacitance vessels in lungs was analyzed by calculating the capacitance ratio $\Delta P_{mp}/\Delta P_{ms}$. According to the definition of capacitance, $Cs/Cp = (\Delta V_s/\Delta P_{ms})/(\Delta V_p/\Delta P_{mp})$, which equals to $\Delta P_{mp}/\Delta P_{ms}$, since $\Delta V_s = \Delta V_p$. The heart, lungs, air cushion and blood reservoir are main blood reserving sites in the heart-lung preparation. By aortic pressure change, the blood volume in the reservoir can shift to the lungs, the heart and air cushion. Provided that the changes in left heart volume caused by serotonin are small enough to be neglected, the effect of serotonin on capacitance ratio could presumably be estimated by the difference between $\Delta P_{mp}/\Delta P_{ms}$ values in the presence and absence of serotonin. It increased Cs/Cp to almost double the control value, indicating a decrease in lung vascular capacitance, since Cs was constant.

In conclusion, serotonin increases the Pmp value and possibly the capillary pressure by inducing the vaso- and venoconstrictions in the pulmonary circulation. The blood volume was increased in the pulmonary circulation by the increased capillary pressure. Venoconstriction and an increase in the blood volume may increase the resistance to venous return. It is also possible that the constriction of vascular smooth muscles as well as possible bronchoconstriction contribute to a decrease in the capacitance of pulmonary circulation. Furthermore, in canine heart-lung preparation, serotonin exhibits a negative inotropic action, without a clear chronotropic effect.

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