GRAPHICAL ANALYSIS OF DRUG EFFECTS IN THE DOG HEART-LUNG PREPARATION—WITH PARTICULAR REFERENCE TO THE PULMONARY CIRCULATION AND EFFECTS OF NOREpinephrine AND 5-HYDROXYTRYPTAMINE

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Abstract—Our new method for the graphical analysis of drug effects in the dog heart-lung preparation was extended to pulmonary circulation. The equilibrium points, at which the cardiac output (CO) curve and venous return (VR) curve cross each other in the right atrial pressure (RAP)-CO and left atrial pressure (LAP)-CO relations, were directly recorded on two X-Y recorders. The VR curves were obtained by inducing cardiac fibrillation and simultaneously occluding the pulmonary arterial trunk. The competence test, which was utilized previously for recording the CO curve in the RAP-CO relation (Ishikawa et al., 1978), was confirmed to be a good procedure for the CO curve in the LAP-CO relation. During the competence test, the mean pulmonary pressure (Pmp) which is the intercept of the pulmonary VR curve on the LAP axis in the LAP-CO relation was changed as much as the change in the systemic reservoir blood level, with little change in the slope of the pulmonary VR curve. When the reservoir blood level was 100 mmHg above the superior vena cava and the aortic pressure was 70 mmHg (control), the Pmp value was 136±7 mmH2O (n=24). The slope of the pulmonary VR curve was not so different from that of the systemic VR curve in RAP-CO relation. Raising aortic pressure to 100 mmHg caused a shift of the equilibrium point to the right and slightly downwards, increased the Pmp value by 42.9±9.9 mmH2O (dPmp) and decreased the reservoir blood volume by 26.2±6.4 ml (dV). The ratio dV/dPmp was 0.66±0.11 ml/mmH2O. The continuous infusion of norepinephrine 4 µg/min caused a shift of the equilibrium point almost vertically and downwards, increased the reservoir blood volume by 35.3±7.2 ml. The ratio dV/dPmp was 0.56±0.16 ml/mmH2O. The continuous infusion of 5-hydroxytryptamine at the rate of 60 µg/min caused a shift of the equilibrium point almost vertically and downwards, increased the reservoir blood volume by 45.8±10.1 ml. The ratio dV/dPmp was 0.88±0.10 ml/mmH2O.

Guyton (1) described a given cardiac output (CO) and right atrial pressure (RAP) as an equilibrium point at which the RAP-CO relation curve and the RAP-venous return (VR) relation curve cross when both curves were plotted against the common RAP axis. In a previous paper (2), we described a graphical analysis of the equilibrium between the systemic RAP-VR relation and the RAP-CO relation determined in the canine heart-lung preparation (HLP). The equilibrium point and its movement were registered directly on an X-Y recorder. This enabled us to establish a uniform control condition and
Fig. 1. Comparison between the hemodynamics of the intact circulation and that of the heart-lung preparation (HLP). The left panel shows the venous return (VR)-right atrial pressure (RAP)-cardiac output (CO) relationship and the equation for the venous return (Guyton). The right panel shows a simulated circuit for the systemic circulation in HLP and the equation derived from Ohm’s law. Note that $P_{ms}$, the mean systemic pressure, corresponds to $H$, the height of blood level in the reservoir. $R_v$: venous resistance, $R_a$: arterial resistance, $C_v$: venous capacitance, $C_a$: arterial capacitance, $r$: the resistance to VR.

Hemodynamic events in the vascular beds of the systemic and pulmonary circulations are functionally interrelated. Either of them determines the preload of a ventricle and at the same time the afterload for the other ventricle. A change in blood volume in one vascular bed induces an inverse change in blood volume in the other vascular bed. The resistance to venous return and the mean filling pressure which regulates the venous return in either vascular bed are affected not only by the tone of the blood vessels and the extravascular pressures, but also by the blood volume in that section of the circulation. The effects of vasoactive agents and blood volume change have been analyzed in such a context on the systemic vascular bed (5–10). However, little analysis of this kind has been made on actions in the pulmonary vascular bed (11). For this reason, we analyzed the equilibrium between the pulmonary LAP-VR and LAP-CO curves with special reference to the actions of norepinephrine (NE) and 5-hydroxytryptamine (5-HT).

Materials and Methods

Male mongrel dogs of 8–12 kg were anesthetized with pentobarbital sodium, 35 mg/kg i.p. The HLP was prepared according to Krayer-Mendez’s modification of original Starling’s methods, details of which were the same as those described previously (2, 12). The scheme is shown in Fig. 2. The cardiac output (aortic flow) was recorded by means of a square wave electromagnetic flowmeter (E.M.F., Nihon Kohden MF-25). An extracorporeal type EMF probe was placed between a pneumatic Starling resistor (S. R.) connected to the arterial cannula and a spiral glass tube in the warming bath (BATH). Mean right and left atrial pressures (RAP and LAP) were recorded through atrial cannula and a pressure transducer (P.T., Nihon Kohden MPU-0.1). The flow and pressure signals were fed into the Y- and X-axes of two X-Y recorders (Yokokawa Electric Co., Model 3077), through low frequency pass filters with time constants of 1 and 2 sec for flow and pressure, respectively. Aortic and pulmonary arterial pressures were recorded by pressure transducers (P.T., Nihon Kohden MPU-0.5), the former via a side branch of the arterial cannula and the latter through a catheter inserted into the pulmonary
Fig. 2. Scheme of heart-lung preparation. Defibrinated blood in the venous reservoir (V.R.) runs to the right atrium (R.A.) via the cannula inserted into the superior vena cava (S.V.C.). There is a resistance against the venous return (R.V.R.) between the venous cannula and V.R. Right and left atrial pressures are monitored with the pressure transducers (P.T.) via catheters inserted in the right and left atria (R.A. and L.A.) and fed to two XY-recorders (XY-1, XY-2). The arterial cannula inserted to the brachiocephalic artery has two branches connected to the pressure transducer (P.T.) and to an air cushion (A.C.). The blood flow is measured with the electromagnetic flowmeter (E.M.F.) between the Starling’s resistor (S.R.) and the heating bath (BATH). P.A.: pulmonary artery, I.V.C.: inferior vena cava, Az.V.: azygos vein. The arrows indicate the direction of blood flow.

artery of the right upper lobe. Heart rate was recorded by a tachometer (Nihon Kohden PT-5) which was triggered by the R-wave of the ECG. The height of blood in the reservoir was monitored with a pressure transducer (Nihon Kohden LPU-0.1) through the catheter inserted into the reservoir.

For each experiment, blood was collected from a large donor dog anesthetized with thiamylal sodium, and this was defibrinated. The blood volume present outside the heart and lungs was 600–900 ml, and the temperature was kept at 35°C. During the experiment, 100 mg of dextrose was added into the blood once every 15 min to maintain the level of blood sugar between 1 and 1.5 mg/ml. The lungs were ventilated artificially with a mixture of equal volumes of air and 95% O₂+5% CO₂. The ventilation was performed 16 times/min, with a tidal volume of 20 ml/kg and an endexpiratory pressure of 20 mmH₂O. The tracheal pressure was monitored by a water manometer. The peak inspiratory pressure was about 70 mmH₂O. The partial pressures of O₂ and CO₂ in the arterial blood were measured by a blood gas analyzer (IL meter, Model 113, SL) and found to be 200–350 mmHg and 20–30 mmHg, respectively. The pH was 7.35–7.50.

At the beginning of the experiments, the hydrostatic level of the dorsal surface of the superior vena cava was referred to as the zero point for recording the RAP, LAP, pulmonary arterial pressure and the level of blood in the reservoir. The aortic pressure was controlled at 70 mmHg by the Starling resistor, and hydrostatic level of blood in the reservoir was maintained at 100 mmH₂O by adjusting the height of the reservoir. The resistance in the venous return path (R.V.R.) from the blood reservoir to the cannula in the superior vena cava (the systemic venous resistance) was adjusted so as to make the equilibrium point for the RAP-CO relation on the recording paper to be on or near the straight line which intersected the abscissa at 100 mmH₂O and the ordinate at 500 ml/min.

The CO curves for the right and left sides of the heart were obtained by raising and lowering the blood level in the reservoir step by step, each 25 mm, in the range of -50 to +50 mm from the control level (1). This procedure will be referred to as the competence test (3, 4). To obtain the VR curves, we fibrillated the heart with an alternating electric current of 4 volts and simultaneously occluded the pulmonary arterial trunk with
an umbilical tape in order to isolate the pulmonary vascular bed from the extracorporeal simulated systemic circuit. By this procedure, CO became zero in about 5 sec after fibrillation, the pulmonary arterial pressure (PAP) decreased, and LAP increased to the same static level. This static pressure is termed as the mean pulmonary pressure, P_{mp}, by Guyton (1). After the measurement, the pulmonary artery was released, and the heart was defibrillated with a counter shock of 100 V a.c. The equilibrium point returned to the original position within several min. Before and during the infusion of drugs or after raising the aortic pressure from 70 to 100 mmHg, CO and VR curves were recorded on both X-Y recorders.

We calculated the ratio ΔV/ΔP_{mp}, where ΔV is the change of blood volume in the heart and pulmonary circulation, which can be calculated from the changes in blood volume in the reservoir and the air cushion, and ΔP_{mp} is the change in P_{mp} value. When these changes were induced by raising aortic pressure, this ratio indicates the capacitance of pulmonary circulation plus left heart. In cases of drug infusion, however, the ratio is not necessarily the capacitance, but a simple index, since drugs may act on the vascular smooth muscles. We also calculated the total pulmonary vascular resistance, R_{a+v}, which is the ratio of the differences between PAP and LAP to CO.

The drugs used were norepinephrine (1-arterenol bitartrate, Sigma: NE) and 5-hydroxytryptamine (5-hydroxytryptamine creatinine sulfate, Sigma: 5-HT). The doses of NE and 5-HT were expressed in terms of the free bases. Continuous infusion of NE or 5-HT was performed with an infusion pump (Natsume Seisakusho, KN-202). These drugs were infused into the venous cannula which comes from the blood reservoir (V.R.). The statistical significance of differences between means was evaluated by the Student's t-test. The level of significance was taken as 0.05.

**Results**

**Cardiac output and venous return curves and the effect of changing aortic pressure**

Typical examples of the VR curves actually obtained in the LAP-CO relation diagram are shown in the right panel of Fig. 3. Almost linear VR curves were recorded. Therefore, we drew a line for each VR curve, connecting the equilibrium point with the P_{mp}-point on the abscissa. In two experiments, we obtained VR curves during the competence test when

![Fig. 3. Effects of raising systemic arterial pressure on the cardiac output (CO) and venous return (VR) curves. The systemic arterial pressure was raised from 70 to 100 mmHg. The CO curves were obtained by changing the reservoir blood level, i.e., the competence test (CT). The VR curves were obtained by inducing ventricular fibrillation (VF) with simultaneous occlusion of the pulmonary arterial trunk. During the latter procedure, the equilibrium point moved to the pressure axis as shown by the solid tracing.](image-url)
the reservoir blood levels were 50, 100 and 150 mm above the zero reference point. The three VR curves were almost parallel, and the $P_{pm}$ value was increased or decreased by the same amount as the change in the reservoir blood level. As shown in Fig. 3, two VR curves in the LAP-CO relation diagram were obtained with the reservoir blood level of 100 mmH$_2$O, one curve with aortic pressure at 70 mmHg and the other curve at 100 mmHg. Raising aortic pressure from 70 to 100 mmHg increased LAP by 50 mmH$_2$O and decreased blood level in the systemic venous reservoir by 6 mm, or the blood volume by 42 ml, which indicated an identical increase in the blood volume in the heart and the pulmonary vascular bed. When aortic pressure was increased, the VR curve in the LAP-CO relation diagram was obtained after the reservoir blood level was reset to 100 mmH$_2$O. The $P_{pm}$ value was 142 mmH$_2$O when aortic pressure was 70 mmHg and 190 mmH$_2$O when it was 100 mmHg. In 5 determinations, each of which was obtained from one dog, the average of the increase in $P_{pm}$ was 42.2±9.9 mmH$_2$O. The blood volume in the heart and pulmonary circulation calculated from the change in reservoir and air cushion blood levels was increased by 26.2±6.4 ml. The average ratio $\Delta V/\Delta P_{pm}$ was 0.66±0.09 ml/mmH$_2$O. The mean±S.E. of the $P_{pm}$'s obtained from 24 experiments with aortic pressure set at 70 mmHg was 136±7 mmH$_2$O.

CO and VR curves during the continuous infusion of drugs

a) Norepinephrine: The effects of continuous infusion of NE at the rate of 4 $\mu$g/min were examined in four preparations. The $P_{pm}$ values and the VR curves during the continuous infusion were compared with those of the control. Qualitatively similar results were observed among the four preparations. One typical result is shown in Fig. 4. The control $P_{pm}$ value was 95 mmH$_2$O. After the equilibrium point returned to the original position, infusion of NE was started. The equilibrium point was shifted upwards to the left, depicting a counterclockwise loop, and reached a new stable point in about 1.5 min. Such a shift of the equilibrium point to the left in the LAP-CO relation suggested a positive inotropic action of norepinephrine. The level of blood in the reservoir increased by 2.5 mm, which indicated a decrease in

![Fig. 4. Effects of continuous infusion of norepinephrine (NE) on the VR-curves in RAP-CO and LAP-CO relations. NE was infused into the tube between the reservoir and the right atrium at the rate of 4 $\mu$g/min. The VR curves were depicted before the infusion (broken lines) and after the equilibrium point reached a new stable position (dotted lines). The CO-curve (competence test) was obtained before infusion.](image-url)
the cardiovascular blood volume of 17.5 ml. The blood level in the systemic venous reservoir was corrected to 100 mmH\(_2\)O, then ventricular fibrillation and occlusion of pulmonary arterial trunk were performed, and new VR curves (dotted lines) were obtained. The resultant P\(_{\text{mP}}\) value was 59 mmH\(_2\)O. The slope of the VR\(_p\) curve increased compared with that in the control. The heart rate increased from 140 to 192/min. The P\(_{\text{mP}}\) value was decreased by 67.1±19.1 mmH\(_2\)O. The reservoir blood volume was increased by 35.3±7.2 ml and the ratio \(\Delta V/\Delta P_{\text{mP}}\) was 0.56±0.16, which was not significantly different from the values obtained by raising aortic pressure. The total resistance of the pulmonary vascular bed changed from 0.37±0.13 to 0.26±0.11 mmH\(_2\)O•min/ml.

b) 5-Hydroxytryptamine: The effects of continuous infusion of 5-HT at 60 \(\mu\)g/min were examined in seven preparations. The results were similar, and one representative case is shown in Fig. 5. The control CO curves (broken lines) and VR curves (dotted lines) were first obtained. During the infusion, heart rate was not changed and the equilibrium point in the RAP-CO relation shifted downwards, not along the control VR curve. The PAP value increased from 134 to 279 mmH\(_2\)O. The level of blood in the reservoir decreased from 100 to 94.5 mm (~38.5 ml). It took approx. 3.5 min to reach a steady state. Then, CO curves (2) and VR curves (dotted lines) were obtained. The P\(_{\text{mP}}\) value increased from 107 to 143 mmH\(_2\)O. The slope of the VR\(_p\) curve became smaller, indicating that the resistance to venous return had increased. When averaged from seven experiments, the P\(_{\text{mP}}\) value was increased by 34.8±3.2 mmHg, and the reservoir blood volume was decreased by 45.8±10.1 ml. The ratio \(\Delta V/\Delta P_{\text{mP}}\) was 0.88±0.10, which was significantly higher than that in raising aortic pressure. The total pulmonary vascular resistance increased significantly from 0.40±0.08 to 1.01±0.21, indicating a marked vasoconstriction.

Relations of mean pulmonary pressure to pulmonary arterial pressure and to left atrial pressure

Figure 6 summarizes the relations between P\(_{\text{mP}}\) and PAP or LAP obtained in the present study. The numbers of experiments are given in parentheses. Five-HT elevated PAP and P\(_{\text{mP}}\) significantly but not LAP.

![Fig. 5](image)

**Fig. 5.** Effects of continuous infusion of 5-hydroxytryptamine (5-HT) on the CO and VR curves. 5-HT was infused into the tube between the blood reservoir and the right atrium, at the rate of 60 \(\mu\)g/min. The CO and VR curves were depicted before the infusion and after the equilibrium point reached a new stable position.
Fig. 6. Relations between the mean pulmonary pressure ($P_{mp}$), the mean pulmonary arterial pressure (PAP) and the mean left atrial pressure (LAP) and effects of norepinephrine (NE) and 5-hydroxytryptamine (5-HT). The control responses were collected from all the experiments and are shown in the left panel. NE and 5-HT were infused continuously. The numbers in parentheses indicate the numbers of experiments. Vertical bars: ±S.E. of the mean. *$P<0.05$, compared with controls in each group.

Discussion

The CO curve as defined by Guyton (1) should be determined without an alteration of myocardial contractility. This is difficult to achieve in intact animals because of the reflexes which affect the contractility. In the HLP, the CO curve can be obtained either by changing the resistance to the flow from the blood reservoir or by changing the blood level in the reservoir (competence test). As discussed previously (2), the former method changes the slope of the VR curve, whereas the latter makes the curve shift to the left or right in a parallel manner. From a technical viewpoint, the competence test is preferable because the blood level can be raised or lowered easily and accurately by moving the blood reservoir up or down. The $P_{mp}$ value rose or fell to about the same degree as changes in the blood level in the systemic venous reservoir, suggesting that a single competence test would allow us to determine the CO curves in the LAP-CO relation diagram simultaneously with that in the RAP-CO relation diagram. During the competence test, the slope of the VR curve in the LAP-CO relation diagram was hardly changed in the range of venous reservoir blood level of 50 to 150 mm, especially in the control condition, and the parallel shift of VR curve was also predictable in the LAP-CO relation diagram.

Guyton’s VR curve (1) can be obtained by changing the myocardial contractility step-wise while keeping the vascular tone unaltered. In the previous study (2), we attempted to obtain the VR curve in this manner by inhalation of chloroform or by injection of ACh, not only by injection of pentobarbital, in the RAP-CO relation diagram. However, these agents may possibly affect the vascular smooth muscle, as well as the bronchial smooth muscle, which may alter the extravascular pressure. Therefore, in the present experiment, we obtained the VR curves simply by fibrillating the ventricle and simultaneously occluding the pulmonary arterial trunk. The latter procedure dissociated the pulmonary circuit, including the left atrium and left ventricle, from the artificial systemic circuit. To determine $P_{ma}$ in a whole animal (13, 14), arterial blood must be rapidly transferred into the venous bed by a bypass pump as soon as the ventricle is fibrillated. In the present experiment, however, PAP and LAP approached an equilibrium pressure (i.e., $P_{ma}$) so fast that the additional bypass of blood was not needed. We assumed that the line connecting the $P_{ma}$ point with the equilibrium point in the diagram approximates the pulmonary venous return curve. By this method, we could determine
the VR curves at least five times in one preparation, and the $P_{mp}$ value showed little variation (less than 5%). In one dog, the measurement was repeated as many as twenty times. Because we could not obtain any data point in a steady state except $P_{mp}$ and the equilibrium point, the linear assumption remains to be verified.

The CO recorded in the RAP-CO relation was not the flow in pulmonary arterial trunk (i.e., right ventricular cardiac output), but was the aortic flow just as that in the LAP-CO relation. Therefore, the true equilibrium points in the RAP-CO relation diagram could be assessed only at a steady state. During a steady state, the pulmonary arterial flow is equal to the aortic flow, and CO is equal to VR. All of the data obtained in this study were assessed under such a condition.

Cournand and his associates (15) consider that the resistance to the pulmonary venous return is approx. one seventh of the resistance to the systemic venous return. However, such a large difference was not observed in the present study; the slope of the VRp curve was similar to that of the VRS curve. In the HLP, the chest was opened and the lungs were ventilated with a positive pressure. Consequently, the resistance to pulmonary venous return might have been higher than in a closed-chest dog. The mean±S.E. ($n=24$) of $P_{mp}$ values was $136\pm 7\text{ mmH}_2\text{O}\ (10.0\pm 0.5\text{ mmHg})$, when the height of the systemic reservoir blood level was 100 mm and the aortic pressure was 70 mmHg. The $P_{mp}$ value was larger than the blood level in the reservoir. Guyton (1) states that $P_{mp}$ was approx. 5 mmHg in a closed-chest dog which has an average intrathoracic pressure of $-4\text{ mmHg}$. Therefore, if he measured $P_{mp}$ in reference to the negative intrathoracic pressure, the value could be very close to 10 mmHg.

Shoukas (8) estimated the total vascular capacitance in the perfused dog lung as 0.3 ml/kg/mmHg, when pulmonary arterial and venous pressures were within their physiological ranges. Since the average body weight of our dogs was about 10 kg, the capacitance in the pulmonary circulation can be assumed to be 3 ml/mmHg (0.22 ml/mmHg$^2$). This is almost one-third of our $\Delta V/\Delta P_{mp}$ value, 0.66 ml/mmHg$^2$, which was obtained by raising the aortic pressure from 70 to 100 mmHg. At present, the reason for this discrepancy is obscure.

The positive inotropic effect of norepinephrine was clearly shown in the LAP-CO relation diagram (Fig. 4). The equilibrium point was moved upwards to the left. Norepinephrine caused the shift of blood volume from the pulmonary vascular bed and the heart into the venous reservoir, which possibly caused the decrease in the $P_{mp}$ value. Because of the relatively small pulmonary vascular capacitance (8), even a little change in the pulmonary blood volume can induce a large change in the $P_{mp}$ value. In in vitro experiments, norepinephrine exhibits a constrictor effect on the pulmonary arterial (16) and venous smooth muscles (16–18). However, we could not get such a result since the $R_{a+}$ value tended rather to decrease than to increase with the administration of norepinephrine. Furthermore, the volume-pressure ratio, $\Delta V/\Delta P_{mp}$, was not so different from that obtained by raising aortic pressure, from 70 to 100 mmHg. The change in the pulmonary vascular smooth muscle tone seemed to make, if any, very little contribution to the blood volume shift. Interestingly, the slope of the pulmonary VR curve was increased, indicating a decrease in resistance against the pulmonary VR flow. The finding may suggest that the venous smooth muscle was relaxed by norepinephrine, though we can't exclude the possibility that the change in the pulmonary blood volume affected the slope of the pulmonary VR curve.
On the other hand, 5-hydroxytryptamine is a commonly known vasoconstricting agent. With the administration of 5-hydroxytryptamine, the increase in \( R_{x+y} \) value, which resulted from a marked increase in PAP (Fig. 6) and a decrease in CO, indicated an increase in the pulmonary vascular resistance. Since the ratio \( \Delta V/\Delta P_{mp} \) was significantly different from that obtained by raising aortic pressure from 70 to 100 mmHg, it is unlikely that the increase in \( P_{mp} \) value was induced just by an increase in the blood volume. The decrease in the slope of the VR curve in the LAP-CO relation diagram was another evidence for the increase in pulmonary circulatory resistance.

The response of the equilibrium point in the LAP-CO relation during the infusion of 5-hydroxytryptamine was quite different from that in the RAP-CO relation. The equilibrium point in the RAP-CO relation was moved downwards and somewhat to the right along the VR curve, whereas the equilibrium point in the LAP-CO relation was moved almost vertically downwards, not along the control VR curve (Fig. 5). This observation suggests that a severe incompetence occurred in the right heart. The marked increase in pulmonary arterial pressure might be responsible, at least mainly, for the apparent right heart failure. Thus, the simultaneous observation of RAP-CO and LAP-CO relation diagrams provided useful information, which was not to be expected from either diagram alone. Although the positive inotropic effect of 5-hydroxytryptamine is generally accepted (19, 20), no such sign was observed in the present experiment.

As regards to our graphical method of analysis, two problems remain to be solved. One is that we could not completely separate the pulmonary circulation from the heart. Therefore, the value \( \Delta V/\Delta P_{mp} \) in the case of raising aortic pressure was actually the sum of two capacitances in the left heart and pulmonary circulation. Secondly, when we analyze the effect of a drug which causes both a decreased myocardial contractility and an increase in the arterial afterload, it is at present impossible to separate the two effects quantitatively.

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