EFFECT OF CARDIAC OUTPUT ON CIRCULATORY BLOOD VOLUME

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Abstract In anesthetized dogs venous return was drained into a blood reservoir from which blood was pumped to the right atrium at a variable perfusion rate, which was equal to cardiac output in the steady state. When cardiac output was decreased or increased by 25 or 50% of the control, the blood volume in the dog's body was changed in the same direction in the intact reflexic state as well as in the areflexic state prepared by hexamethonium and norepinephrine infusion. The volume change in the reflexic state was twice that in the areflexic state when compared 5 min after stepwise changes in cardiac output. When only the flow through the right heart and lungs was changed by -50%, with systemic flow unchanged, the decrease in blood volume was about one-fifth of that observed on a 50% decrease of cardiac output and not affected by ablation of the reflexes. It is concluded that, on a change in cardiac output, the passive change in blood volume is as large as the active or reflexic change, that the majority of the change in blood volume takes place in the systemic circulation rather than in the pulmonary circulation, and that the receptors for the reflexic change are located in the systemic circulation.

When cardiac output is changed in a preparation in which venous return is drained into a reservoir from which blood is pumped to the right atrium at a desired flow rate, the blood volume in the animal would not change if the circulatory system were composed of rigid tubes. However, since in reality the tubes of the circulatory system have an elastic property, should outflow venous pressure be kept constant, the blood volume changes passively in the same direction as the cardiac output, due to the change in vascular transmural pressure induced by the flow change. This might be called 'passive change' in blood volume induced by changes in cardiac output. In addition to this passive change, active or reflexic change in blood volume will take place with a change in cardiac output, provided that the circulatory system is endowed with reflex adaptability in vascular

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capacity. In the above preparation, the change in blood volume in the animal's body can be measured by monitoring the level of blood in the reservoir.

The change in blood volume, which would induce a change in central venous pressure in the natural closed circulatory system, is assumed to be brought about by changes in blood volume in the venous system. Active venoconstriction mediated by sympathetic vasoconstrictor fibers may be the main cause of the blood mobilization from the veins. In addition to this active change, in the hindquarter of the cat (ÖBERG, 1967) and in the splanchnic circulation of the dog (BROOKSBY and DONALD, 1972; DONALD and AARHUS, 1974), the blood volume in the veins was found to change passively following a change in flow through them. However, these observations are confined to peripheral vascular beds. The relative importance of the active and passive changes in blood volume has not been examined for the total vasculature.

The purpose of the present experiment is to quantify the relationship between circulatory blood volume and cardiac output. We estimated the active and passive components of the changes in blood volume by comparing the flow-volume relationship in the intact reflexic state with that in the areflexic state prepared by hexamethonium and norepinephrine infusion. To examine the role played by pulmonary circulation in the regulation of the blood volume, we observed the change in blood volume when flow through the right heart and lungs was reduced with the systemic flow unchanged. The results were compared with those obtained by reducing flow through the total vasculature.

METHODS

Experimental preparation. Dogs were anesthetized intravenously with thiopentobarbital (20 mg/kg) and alpha chloralose (60 mg/kg). A right thoracotomy was performed at the fourth intercostal space under positive pressure respiration with room air and supplemental oxygen at a rate of 2 to 3 liters/min. About three-fourths of the fourth and fifth ribs were removed.

Figure 1 illustrates the connection between the animal and the perfusion circuit to measure the change in blood volume in the animal. First, the azygos vein was cannulated and connected to the outflow end of the perfusion system which consisted of a roller pump (Tonokura DCH-1), a heat exchanger and an air filter. These instruments were filled with heparinized blood from another dog. The superior vena cava was cannulated and connected to one inflow end of a Y-shaped venous drainage cannula. As soon as the venous return from the upper body was diverted to the reservoir, pump perfusion was started. Then the inferior vena cava was cannulated and total venous return was drained. To avoid venous congestion, venous return was by-passed through cannulas connected to the right femoral and the external jugular veins, while the caval veins were cannulated. The pump flow was set at 80 ml/min/kg, since in most dogs the level of

Fig. 1. Schematic presentation of experimental setup. Venous return was drained into a reservoir and from there pumped to the right atrium through the azygos vein. PA, pulmonary artery; RV, right ventricle; RA, right atrium; SVC, superior vena cava; IVC, inferior vena cava; Azy. v., azygos vein.

blood in the reservoir was most stable at this flow rate. Central venous pressure was measured by a catheter inserted into the thoracic vena cava and was adjusted by raising or lowering the height of the outflow end of the venous drainage cannula to the control level before starting pump perfusion.

Heparin was given at a dose of 3 mg/kg prior to cannulation and thereafter added at hourly intervals (1 mg/kg). Immediately before the thoracotomy, the dogs were immobilized with gallamine triethiodide (3 mg/kg). Arterial pressure was measured through a catheter placed in the abdominal aorta *via* the right femoral artery. Zero pressure reference was set at the junction between the inferior vena cava and the right atrium under direct inspection. Blood volume in the reservoir was continuously recorded by monitoring the hydrostatic pressure with a pressure transducer. The system was calibrated by observing the pressure change corresponding to a known amount of change in reservoir volume. The flow rate of the roller pump was calibrated using a graduated cylinder and a stop watch.

Experiment in which flow through the total vasculature was changed. In ten dogs weighing between 9.5 and 13.0 kg effects of changes in pump flow of $\pm 25\%$ of the control on the arterial pressure and the blood volume were observed. In

another group of ten dogs weighing between 8.0 and 13.0 kg effects of flow changes of $\pm 50\%$ were observed.

The pump flow was suddenly reduced by 25 or 50% of the control and then returned to the control level after a 5 min period of observation. Five minutes thereafter, the flow rate of the pump was increased by 25 or 50% of the control and the responses were recorded for another 5 min.

After observations in the intact reflexic state, a ganglion blockade, hexamethonium bromide (7 mg/kg), was administered. As soon as the arterial pressure began to decline, continuous infusion of norepinephrine was started to maintain the arterial pressure at the level before ganglion blockade. The volume of blood in the reservoir, which was once decreased by ganglion blockade, usually returned to the pre-blockade level on the infusion of norepinephrine. This state, prepared by hexamethonium and norepinephrine, was designated 'areflexic', since the animal was assumed to be devoid of circulatory reflexes with the normal vascular tone. The infusion rate of norepinephrine ranged between 0.0012 and 0.006 mg/min/kg. The pump flow was changed according to the same schedule as described above about 20 min after the infusion of hexamethonium bromide.

Right to left heart by-pass experiment. To examine whether the receptors responsible for the reflex change in vascular capacity are located in the cardiopulmonary region, the change in blood volume was observed when the flow through the right heart and lungs was reduced by a partial by-pass from the right heart to the left while the systemic flow was kept unchanged.

Figure 2 illustrates the connection between the perfusion system for the by-pass and the animal's circulatory system. The perfusion line was divided into two, each provided with one pump. One line was connected to the right atrium and the other to the left atrium through a pulmonary vein. A membrane oxygenator (Lande-Edwards Model 5110-3) was interposed to the latter line as shown in the figure. In the control state, the line was interrupted at point b with a hemostat so that the total venous return was led to the right atrium. To reduce the flow through the right heart and lungs, the line was closed at point a and the hemostat at b was released so that the venous return was partially by-passed to the left heart *via* the lower pump in the figure.

We selected 50% as the by-pass rate and 5 min as the period of observation. Responses of arterial pressure and blood volume were recorded before vagotomy, after bilateral vagotomy and in the areflexic state produced by ganglion blockade and continuous infusion of norepinephrine.

RESULTS

Effect of changes in flow through the total vasculature

An example of the experimental record is shown in Fig. 3. The change in mean arterial pressure was much smaller in the reflexic state than in the areflexic

Fig. 2. Schematic illustration of the connection between circulatory system and the perfusion circuit to reduce the flow through the right heart and lungs while maintaining systemic flow constant. Circulatory system is represented by lumped arterial and venous systems with resistance connecting them. P_a , arterial pressure; P_v , venous pressure; R_a , arterial resistance; LH, left heart; RH, right heart; Q , pump perfusion rate. See text for details.

state. On the contrary, the change in reservoir volume was larger in the reflexic state than in the areflexic state.

Figure 4 summarizes the time courses of mean arterial pressure and blood volume in response to changes in pump flow of $\pm 25\%$ and $\pm 50\%$ of the control. The change in mean arterial pressure is expressed as percent change from control value (102 ± 13.8 mmHg, mean $\pm$ SD). Minus sign of the change in blood volume indicates that blood was expelled from the animal to the reservoir.

The arterial pressure was changed in the same direction as the pump flow in the reflexic as well as in the areflexic state. However, the changes in mean arterial pressure were much larger when the reflexes were abolished: the changes in the areflexic state were approximately twice as those in the reflexic state.

When the pump flow was decreased, blood was expelled toward the reservoir both in the reflexic and areflexic states. The amount of the blood mobilization in the first 30 sec was slightly but significantly smaller in the areflexic state than in the reflexic state. The blood mobilization in the reflexic state increased markedly

Fig. 3. An example of simultaneous recording of mean arterial pressure, mean central venous pressure and reservoir volume when pump flow was changed stepwise by $\pm 50\%$ of the control value (80 ml/min/kg). In the left side responses in the intact reflexic state are shown and in the right side when the animal was made areflexic by ganglion blockade and continuous infusion of norepinephrine. Central venous pressure was kept at the pre-perfusion level throughout the perfusion experiment by adjusting the height of the outflow end of the venous drainage cannula.

Fig. 4. The time courses of arterial pressure and blood volume in response to changes in the pump flow in the reflexic state (solid circle) and in the areflexic state (open circle). Each mean $\pm$ SD, $n=10$. Q: percent change from control flow of 80 ml/min/kg.

thereafter in contrast to the only slight increase in the areflexic state. The expelled blood volume in the areflexic state was about one-half of that in the reflexic state 5 min after the flow change. When the pump flow was increased by 25 or 50% of the control, the blood volume was changed similarly but in the opposite direction.

The relationship of the pump flow to the arterial pressure and the blood volume is shown in Fig. 5. Each point represents the mean response from ten

Fig. 5. Pressure-flow and blood volume-flow relationships of the total vasculature in the reflexic (solid circle) and areflexic (open circle) states. Pump flow was changed stepwise to 50, 75, 125, and 150% of the control value. The data were collected 5 min after stepwise changes in the flow. Each data point represents mean $\pm$ SD ($n=10$). The rectilinear lines were obtained by the linear regression analysis.

dogs 5 min after the flow change both in the reflexic and areflexic states.

The relationship between the pump flow and the arterial pressure was approximated by a linear line in the areflexic state. The broken line in the figure obtained by the linear regression analysis from the pooled data has a slope of 0.96, a pressure intercept of 4.0% and a correlation coefficient of 0.987. On the other hand, when the linear regression analysis was applied to the relationship in the reflexic state, the correlation was not good as in the areflexic state ($r=0.884$).

The relationships between the pump flow and the blood volume both in the reflexic and areflexic states were approximated by linear lines as seen in the figure. Their correlation coefficients were 0.970 and 0.966 for the reflexic state and the areflexic state, respectively. The slope of the regression line in the reflexic state was about twice (9.6 to 4.9) as that in the areflexic state.

Effect of reduction in flow through the right heart and lungs

Figure 6 shows recording of the responses of mean arterial pressure and blood volume to the reduction of flow in the right heart and pulmonary circulation. Blood was expelled toward the reservoir following the flow change while the arterial pressure did not change significantly. The change in the blood volume was small and not affected by bilateral vagotomy. Furthermore, the response remained almost unchanged even after the animal was made areflexic.

Fig. 6. An example of experimental record of arterial pressure and reservoir volume in response to reduction in flow through the right heart and lungs under three different conditions. From left to right, before vagotomy, after vagotomy and in the areflexic state.

In Table 1, the mean values $\pm$ SD for the expelled blood volume under three different conditions are presented. The values for a -50% change of flow through the total vasculature are also listed in the table for comparison. The latter has

Table 1. Decrease in the blood volume when the flow through the total vasculature or the right heart and lungs was reduced by 50% of control under three different conditions.

	When flow through the total vasculature was reduced	When flow through the right heart and lungs was reduced
Intact	19.7 ± 4.54	2.02 ± 0.96
Vagotomized	—	1.85 ± 1.36
Areflexic	10.3 ± 2.40 $n=10$	2.19 ± 0.51 $n=4$

Each mean $\pm$ SD in terms of ml/kg of body weight

been graphically presented in Fig. 4 already. The systemic flow was always held at 80 ml/min/kg and the mean arterial pressure which was 87 ± 10.3 (SD) mmHg in the control state did not change significantly throughout the experiment.

The decrease in the blood volume when the flow through the right heart and lungs was reduced was not influenced by bilateral vagotomy. The blood mobilization which was also unaffected by ablation of the circulatory reflexes was approximately one-fifth of that induced by the 50% reduction in flow through the total vasculature in the areflexic state.

DISCUSSION

When flow through a vascular system is increased or decreased, changes in the transmural vascular pressure take place in the same direction as the flow if the outflow pressure is kept unchanged as in the preparation used in this study. Then the blood volume contained therein is passively changed according to the pressure-volume relationship of the vascular system. Thus, the blood volume is positively related to the pump flow as shown in Fig. 5 even in the areflexic state.

Arterial pressure is changed considerably in the areflexic state following a flow change. Therefore, the change in blood volume in the arterial system may form a significant part of the total passive change in blood volume. Several investigators have measured lumped arterial compliance and reported variable results (GUYTON *et al.*, 1956; IRIUCHIJIMA *et al.*, 1971; SHOUKAS and SAGAWA, 1973). Applying the values reported by SHOUKAS and SAGAWA (1973) to our result, 50 mmHg decrease in arterial pressure accompanying the 50% decrease in the pump flow corresponds to a passive decrease of blood volume in the arterial system of approximately 3.4 ml/kg. This indicates that more than a half of the passive blood mobilization to the reservoir is from the capacitance vessels, since the total passive blood mobilization was about 10 ml/kg.

In the present study the animal was made areflexic by ganglion blockade and continuous infusion of norepinephrine. The blood volume returned to the pre-blockade level together with the arterial pressure on the infusion of norepinephrine. To compare the tones of the total vasculature in the reflexic and areflexic states,

we measured venous pressure response to removal of a known amount of blood under steady systemic perfusion. We interposed a roller pump between the caval veins and the right atrium to control cardiac output at a steady level just as SHOUKAS and SAGAWA (1971) did. An example of the recording of the arterial, peripheral venous and central venous pressures is presented in Fig. 7. This experiment was performed on four dogs. The total systemic vascular compliance

Fig. 7. A simultaneous recording of mean arterial, peripheral venous and central venous pressures when 5 ml/kg of blood was withdrawn from the animal. Cardiac output was kept constant (80 ml/min/kg) by interposing a roller pump between the caval veins and the right atrium.

calculated as the ratio of the change in the blood volume to that in the venous pressure was not significantly different between the reflexic (1.4 ± 0.61 ml/mmHg/kg, mean $\pm$ SD) and areflexic (1.3 ± 0.36 ml/mmHg/kg, mean $\pm$ SD) states. Therefore, we considered that the normal vascular tone devoid of the reflex adaptability was realized in our areflexic preparation and that the difference in the blood volume response between the intact reflexic state and the areflexic state was induced by circulatory reflexes and superimposed on the passive change.

As in Fig. 4, the blood volume response in the reflexic state was twice that in the areflexic state 5 min after the stepwise change in the pump flow. In other words, the ratio of the active blood mobilization (difference in the mobilized blood volume between the reflexic and areflexic states) to the passive one (the mobilized blood volume in the areflexic state) was approximately 1:1. The

active change in blood volume is supposed to be induced by a reflex change in venous capacity. If the reflex change in venous capacity were larger than it actually is, the slope of the flow-volume relation would be steeper than in Fig. 5. The flow-volume relation ideal for the maintenance of cardiac output would be a vertical line through the control flow. However, this is not the case and the relation in the reflexic state is as shown by the solid line in Fig. 5. This figure demonstrates that the change in flow for a given change in blood volume is reduced to approximately one-half by the reflexes.

The preparation used in this experiment was different from the natural circulatory system in that the circulatory loop was opened at the caval veins and the outflow venous pressure was constant. In the closed system as in the open system, a change in cardiac output may induce a change in peripheral blood volume and a resulting change in venous return. The latter would subsequently affect the central venous pressure. One might think that the change in central venous pressure prevents a further change in blood volume. However, it is known that the total blood mobilization from the veins is not influenced by the outflow venous pressure because the active venoconstriction is more pronounced at higher venous pressures and the passive recoil of the veins at lower venous pressures (ÖBERG, 1967). Thus, despite the changes in central venous pressure, changes in cardiac output do not fail to change blood volume in the same direction even in the natural closed system. In the closed system, the change in blood volume would induce a change in venous return to mitigate the original change in cardiac output.

As seen in Table 1, the change in blood volume was slight when the flow through the right heart and lungs alone was reduced. The amount of blood mobilization was not influenced by section of the vagi which are supposed to contain the sensory fibers from the cardiopulmonary region. It was not affected by the abolition of circulatory reflexes either. Considering the large active blood mobilization in response to the change in flow through the total vasculature, it is concluded that the receptors that initiate the reflex change in vascular capacity are located in the systemic circulation instead of the pulmonary circulation. Several investigators have demonstrated that total systemic vascular capacity is influenced by carotid sinus baroreceptor reflex (RASHKIND *et al.*, 1953; ROSS *et al.*, 1961; SHOUKAS and SAGAWA, 1973). According to KUMADA and SAGAWA (1970), variations in blood volume can be subtly detected by the aortic baroreceptors. Presumably, the baroreceptors in the carotid sinus and aortic arch play the main role in this reflex.

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REFERENCES

- BROOKSBY, G. A. and DONALD, D. E. (1972) Release of blood from the splanchnic circulation in dogs. *Circ. Res.*, **31**: 105-118.
- DONALD, D. E. and AARHUS, L. L. (1974) Active and passive release of blood from canine spleen and small intestine. *Am. J. Physiol.*, **227**: 1166-1172.
- GUYTON, A. C., ARMSTRONG, G. G., and CHIPLEY, P. L. (1956) Pressure-volume curves of the arterial and venous systems in live dogs. *Am. J. Physiol.*, **184**: 253-258.
- IRIUCHIJIMA, J., KUMAZAWA, A., and KAWAKAMI, K. (1971) Measurement of aortic compliance *in vivo*. *Jap. Heart J.*, **14**: 546-554.
- KUMADA, M. and SAGAWA, K. (1970) Aortic nerve activity during blood volume changes. *Am. J. Physiol.*, **218**: 961-965.
- ÖBERG, B. (1967) The relationship between active constriction and passive recoil of the veins at various distending pressure. *Acta Physiol. Scand.*, **71**: 233-247.
- RASHKIND, W. J., LEWIS, D. H., HENDERSON, J. B., HEIMAN, D. F., and DIETRICK, R. B. (1953) Venous return as affected by cardiac output and total peripheral resistance. *Am. J. Physiol.*, **175**: 415-423.
- ROSS, J., FRAHM, C. J., and BRAUNWALD, E. (1961) Influence of carotid baroreceptors and vasoactive drugs on systemic vascular volume and venous distensibility. *Circ. Res.*, **9**: 75-82.
- SHOUKAS, A. and SAGAWA, K. (1971) Total systemic vascular compliance measured as incremental volume-pressure ratio. *Circ. Res.*, **28**: 277-289.
- SHOUKAS, A. and SAGAWA, K. (1973) Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ. Res.*, **33**: 22-33.