# Vascular Responses to Hypercapnia in Anesthetized Dogs

Kenji SHIGEMI

To evaluate the vascular responses to systemic acute mild hypercapnia ($Pa_{CO_2}$ = 65 mmHg), we determined the vascular compliance with the relation between the change in circulating blood volume and the change in central venous pressure during and after fluid infusion in dogs anesthetized with halothane in normocapnia and hypercapnia. Circulating blood volume was measured continuously by $^{51}$Cr-labeled erythrocyte dilution method together with hemodynamic variables. Small reduction in vascular compliance (8.1 ± 1.0 ml·mmHg$^{-1}$·kg$^{-1}$ in normocapnia, 5.8 ± 0.5 ml·mmHg$^{-1}$·kg$^{-1}$ in hypercapnia), large reduction in delayed compliance, which were quantitated by computer simulation using Maxwell's viscoelastic model, and significant increase in blood volume in central circulation were observed in hypercapnia. The essential change in hypercapnia was concluded as the vasoconstriction in capacitance vessels. Simultaneously, the reduction of total peripheral resistance (1.09 ± 0.08 mmHg·min·kg·ml$^{-1}$ in normocapnia, 0.98 ± 0.07 mmHg·min·kg·ml$^{-1}$ in hypercapnia) with no change in transvascular filtration coefficient (0.14 ± 0.02 ml·mmHg$^{-1}$·min$^{-1}$·kg$^{-1}$) suggests the increase in shunt flow in peripheral circulation. (Key words: capacitance vessels, delayed compliance, hypercapnia, transvascular filtration coefficient, vascular compliance)

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Stimulation of central and peripheral chemoreceptors by systemic hypercapnia in anesthetized, paralyzed, controlled-ventilated humans results in increases in cardiac output and pulse pressure and a decrease in total peripheral resistance while no change is observed in mean arterial pressure[1–3]. Perfusion of brain or coronary arteries with hypercapnic blood dilates the vessels and increases their blood flow, while, systemic hypercapnia decreases canine renal blood flow[4]. Recently Rothe et al.[5] reported that severe systemic hypercapnia ($Pa_{CO_2}$ = 115 mmHg) causes a significant active reduction in vascular compliance. In view of these diverse reactions, it is of interest to reevaluate the responses of vascular system to hypercapnia at the level which we encounter during clinical anesthesia. For this purpose, changes in total systemic vascular compliance, delayed compliance and transvascular filtration coefficient were determined in dogs at different levels of inspired carbon dioxide tensions. The method used in this study is based on the continuous measurements of central venous pressure and total circulating blood volume developed in this laboratory[6–8], and has been used successfully for the analyses of blood volume regulation during blood shedding[9], hyperthemia[10] and hypothermia[11].

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## Materials and Methods

*Surgical procedure and measurement*

Experiments were performed on 7 mongrel

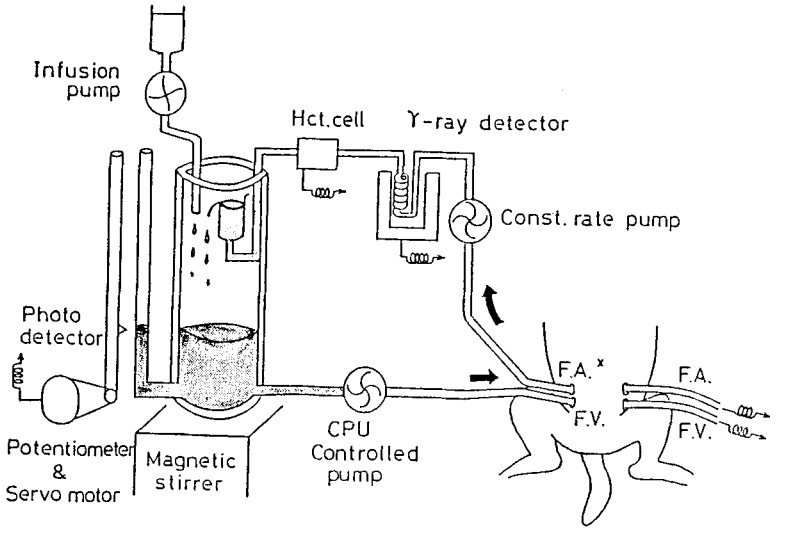



**Fig. 1.** The schema of the system which consists of detectors to measure hematocrit and radioactivity, and blood reservoir with the blood level detector and two pumps.

dogs weighing 10.5 – 15.2 kg. At least a week before experiments, they were splenectomized under thiopental anesthesia (induction: 25 $mg \cdot kg^{-1}$, maintenance: 10 $mg \cdot kg^{-1} \cdot h^{-1}$). On the study day, anesthesia was induced with i.v. injection of thiopental sodium (25 $mg \cdot kg^{-1}$). Each dog was weighed and placed in the supine position, and its trachea was intubated and its lungs were ventilated with 1.5% halothane in 40% $O_2$ and 58.5% $N_2$ with a volume-limited respirator. The ventilation rate was set at 18 $times \cdot min^{-1}$ with tidal volume of 20 $ml \cdot kg^{-1}$. Heparin sodium was administered at an initial dose of 5 $mg \cdot kg^{-1}$ and at a maintenance dose of 2.5 $mg \cdot kg^{-1} \cdot h^{-1}$ thereafter. Pancuronium was administered at an initial dose of 2 mg and maintained thereafter with a dose of 0.5 $mg \cdot h^{-1}$ to prevent spontaneous respiration which influences the systemic hemodynamics.

Blood volume and hematocrit of circulating blood were monitored continuously using the special extracorporeal shunt which was established by catheters inserted into the right femoral artery and vein[6–8]. Blood was led by a pump at a speed of 40 $ml \cdot min^{-1}$ to a conductivity cell for hematocrit determination and a well type γ-counter for continuous determination of blood volume using the dilution method of $^{51}Cr$-labeled erythrocytes. Systemic arterial and central venous pressures were monitored continuously by two strain gauge transducers via catheters, the tips of which were placed in the descending aorta and in the inferior vena cava at the level of the diaphragma through the left femoral artery and vein (fig. 1).

Cardiac output and blood volume in central circulation (cardiopulmonary circulation) were determined by the dye-dilution method[12]. Indocyanine green (Diagno-Green Daiichiseiyaku, Tokyo) was injected rapidly into the inferior vena cava. Simultaneously the blood was withdrawn from the aortic catheter through a cuvette densitometer (Erma Optical Works, Tokyo) to determine a dye concentration curve, from which the cardiac output and the mean transit time were calculated. The blood withdrawn was reinfused into the animal through the femoral vein catheter after the determination. The blood volume in central circulation was calculated by multiplying the cardiac output by mean transit time of the indicator and was presented at the percentage of total blood volume. Systemic vascular resistance was calculated from the mean systemic arterial pressure, central venous pressure and cardiac output. Heart rate was monitored by the systemic arterial pressure pulse. The stroke volume was calculated from the cardiac output and the heart rate. Blood samples (150 μl) were collected every 10 min and the plasma protein concen-

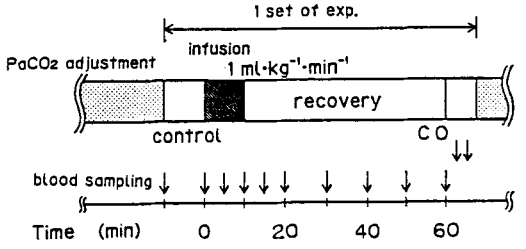


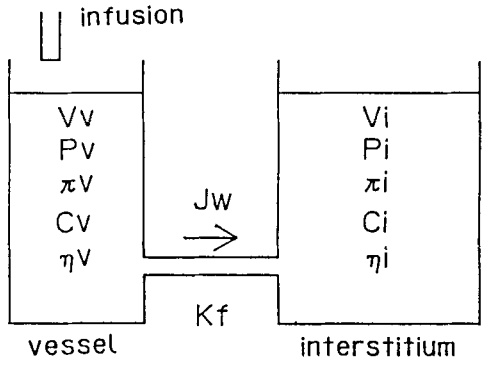

**Fig. 2.** Experimental protocol used during normocapnia and hypercapnia. CO, determination of cardiac output and central blood volume.

tration was determined with refractometry (ATAGO, Tokyo). Colloid osmotic pressure was calculated based on the equation by Landis-Pappenheimer[13]. Blood gases were analyzed by a blood gas analyzer (IL-meter Model 213). $Pa_{O_2}$ was maintained over 180 mmHg and $Pa_{CO_2}$ was manually adjusted to keep at 35 mmHg or 65 mmHg by changing the concentration of carbon dioxide in inspiratory gas of the respirator.

Urinary output was not measured. The effect of urinary output on blood volume is negligible, because urinary output was 1.5 $ml \cdot kg^{-1} \cdot h^{-1}$ [10] and urine was made from circulating blood (8%), interstitial fluid (25%) and intracellular fluid (67%) – water in whole body (60% in body weight) is distributed to plasma (5%), interstitium (15%) and intracellular space (40%)[14]. During one set of the experiment, urine which reduces blood volume is only 0.12 $ml \cdot kg^{-1} \cdot h^{-1}$.

*Experimental protocol*

The experiment consists of four parts: periods of normocapnia, carbon dioxide loading, hypercapnia, and carbon dioxide withdrawal. During normocapnia and hypercapnia, lactated Ringer's solution was infused. After 10 min of control phase, lactated Ringer's solution amounting 1% of the measured body weight was infused intravenously at a constant rate over 10 min. Thereafter, 50 min were allowed for recovery from volume loading. After the period of normocapnia carbon dioxide was loaded by increasing the concentration of carbon dioxide in inspiratory gas, with the




$$Jw = Kf((Pv-\pi V)-(Pi-\pi i))$$

$$\frac{dVv}{dt} = -Jw + inf$$

$$\frac{dVi}{dt} = Jw$$

$$\frac{dPv}{dt} = \frac{1}{Cv} \cdot \frac{dVv}{dt} - \frac{1}{Cv \cdot \eta V}(Pv - PvO)$$

$$\frac{dPi}{dt} = \frac{1}{Ci} \cdot \frac{dVi}{dt} - \frac{1}{Ci \cdot \eta i}(Pi - PiO)$$

$$\frac{d\pi V}{dt} = -\frac{\pi V}{Vv(1-Hct/100)} \cdot \frac{dVv}{dt}$$

$$\frac{d\pi i}{dt} = -\frac{\pi i}{Vi} \cdot \frac{dVi}{dt}$$

**Fig. 3.** The mathematical model discussed in this paper is shown schematically. The left and right side compartments represent the intravascular and interstitial spaces respectively, and the channel connecting these compartments represents the capillary wall through which fluid shift occurs. P, V, and $\pi$ stand for the hydrostatic pressure, fluid volume, and colloid osmotic pressure of each space. The variables of intravascular and interstitial spaces are distinguished by suffixes v and i. inf and Jw represent rates of infusion and water flow across the capillary wall.

Differential equations are used for the computer simulation to fit three measured variables: the changes of circulating blood volume, central venous pressure and colloid osmotic pressure. First equation is based on the hypothesis of Starling's theory. The second and the third equation are the changes of the fluid volume in intravascular and interstitial space. The forth and the fifth show the change of hydrostatic pressure in each space using Maxwell's model of viscoelastisity[21]. The sixth and the seventh are the changes in colloid osmotic pressure in each space.

**Table 1** Cardiovascular response at during normocapnia and hypercapnia

| | NORMOCAPNIA | HYPERCAPNIA |
|---|---|---|
| $Pa_{CO_2}$ (mmHg) | 35 ±5 | 65 ± 5* |
| mean arterial pressure (mmHg) | 90.6 ±3.5 | 93.5 ± 3.5 |
| central venous pressure (mmHg) | 3.7 ±0.6 | 4.3 ± 0.4 |
| heart rate ($min^{-1}$) | 146.8 ±7.9 | 153.1 ±10.9 |
| pulse pressure (mmHg) | 32.9 ±2.0 | 43.4 ± 4.0* |
| cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$) | 85.9 ±6.2 | 98.0 ± 6.5* |
| stroke volume ($ml \cdot beat^{-1} \cdot kg^{-1}$) | 0.56±0.04 | 0.62± 0.03 |
| TPR ($mmHg \cdot min \cdot kg \cdot ml^{-1}$) | 1.09±0.08 | 0.98± 0.07* |
| Cv ($ml \cdot mmHg^{-1} \cdot kg^{-1}$) | 8.1 ±1.0 | 5.8 ± 0.5 |
| $\eta$v ($min \cdot mmHg \cdot kg \cdot ml^{-1}$) | 7.3 ±1.9 | 17.9 ± 8.3* |
| Ci ($ml \cdot mmHg^{-1} \cdot kg^{-1}$) | 3.8 ±0.9 | 4.4 ± 0.6 |
| $\eta$i ($min \cdot mmHg \cdot kg \cdot ml^{-1}$) | 4.2 ±1.6 | 19.4 ± 4.9* |
| Kf ($ml \cdot mmHg^{-1} \cdot min^{-1} \cdot kg^{-1}$) | 0.14±0.02 | 0.14± 0.02 |
| CBV (% of total BV) | 27.9 ±4.4 | 32.6 ± 7.3* |

Values are means ±S.E. of 7 experiments. $Pa_{CO_2}$, carbon dioxide tension in arterial blood; TPR, total peripheral resistance; Cv, vascular compliance; $\eta$v, coefficient of vascular delayed compliance; Ci, compliance in interstitial fluid space; $\eta$i, coefficient of delayed compliance in interstitial fluid space; Kf, transvascular filtration coefficient; CBV, central blood volume. *, Paired t test ($P < 0.05$).

fixed respiratory rate and ventilation volume. After 30 min of steady state, data of the control phase under hypercapnia were taken, and then lactated Ringer's solution was infused. After the period of hypercapnia, dog was ventilated with $CO_2$-free gas to washout carbon dioxide (fig. 2).

*Analysis*

The effective compliance of the systemic vascular bed was determined from the relation between changes in central venous pressure and blood volume induced by the loading of lactated Ringer's solution. The value Cv was used to express instantaneous compliance while the value of $1/(Cv \cdot \eta v)$ was used to express the magnitude of delayed compliance, where smaller value of $\eta$v indicates higher delayed compliance[15]. The results of quantitative analysis of the compliances are summarized in table 1.

Transvascular filtration coefficient and the effective compliance of interstitial fluid space were determined from the simulation analysis[11]. The changes in total blood volume, central venous pressure, and colloid osmotic pressure were fitted to a mathematical model based on a two compartments model, i.e. vascular and interstitial fluid compartments, and describing transcapillary fluid shift using the Starling's hypothesis by means of computer simulation (fig. 3). Differential equations are used for the computer simulation to fit three measured variables: the changes of circulating blood volume, central venous pressure and colloid osmotic pressure. First equation is based on the hypothesis of Starling's theory. The second and the third equation are the changes of the fluid volume in intravascular and interstitial space. The fourth and the fifth show the changes of hydrostatic pressure in each space using Maxwell's model of viscoelastisity[15]. The sixth and the seventh are the changes in colloid osmotic pressure in each space.

The results are presented as means and standard errors. The effects of acute hypercapnia on each variable were compared on the basis of paired analysis using t-test and null hypothesis was rejected at 5% level unless otherwise noted.

## Results

The results obtained during normocapnia

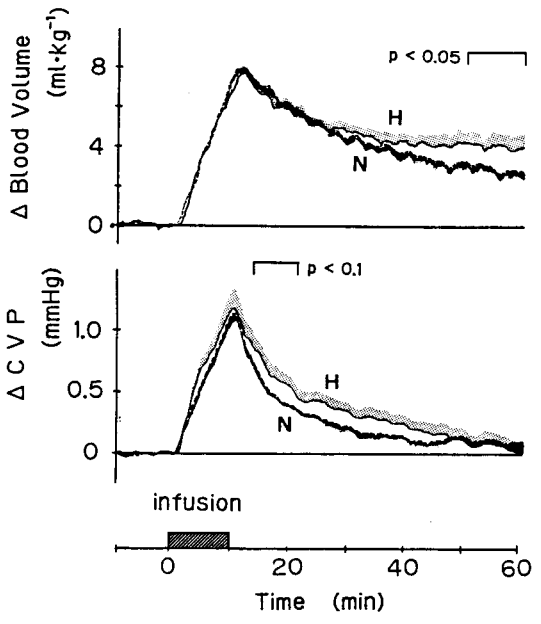



**Fig. 4.** The changes of circulating blood volume (upper) and central venous pressure (lower) before, during, and after infusion of lactated Ringer's solution under normocapnia (N, broken lines) and hypercapnia (H, solid lines). Heavy lines represent mean values of 7 experiments, and hatched area above or below mean values represent ± S.E.

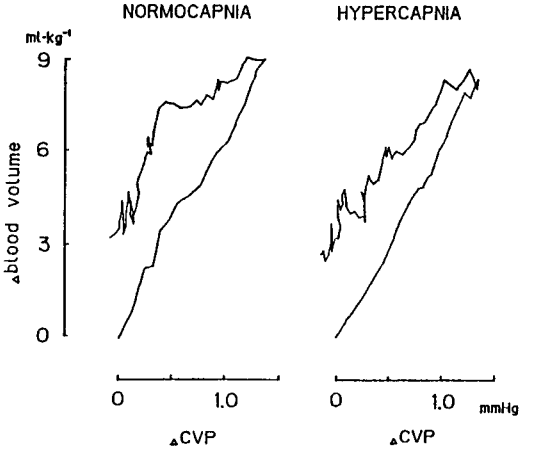



**Fig. 5.** One pair of typical courses of the relationship between the change in central venous pressure (△CVP) and the change in circulating blood volume (△BV) during and after the infusion of lactated Ringer's solution under normocapnia (left) and hypercapnia (right). Vascular delayed compliance appeared as the non linear relationship between △CVP and △BV. Smaller vascular delayed compliance during hypercapnia is observed as slender hysteresis.

and hypercapnia are summarized in table 1. $Pa_{CO_2}$ was 35 ± 5 mmHg in normocapnia and 65 ± 5 mmHg under hypercapnia. No significant differences were observed in mean arterial pressure, central venous pressure and heart rate. In hypercapnia, significant increases in pulse pressure, cardiac output and blood volume in central circulation were observed, while total peripheral resistance decreased significantly. Stroke volume increased under hypercapnia but the increase was not significant.

The changes in blood volume and central venous pressure during the infusion and recovery phases are shown in figure 4 as the differences from the mean values of control phase (means ± SE of 7 observations). During the infusion of lactated Ringre's solution and 20 min immediately following the infusion, the changes in blood volume were almost identical between normocapnia and hypercapnia, while the retention of infused fluid under hypercapnia was significantly larger during the last 10 min of recovery phase. The central venous pressure during hypercapnia had a tendency to show higher level (significantly higher, when the null hypothesis was rejected at 10% level, for 5 min from the 4th min after the end of infusion). Total protein mass in plasma was constant and leak of protein from intravascular space to interstitial space was negligible. Thus, the decrease of colloid osmotic pressure followed the increase in vascular fluid volume due to the infusion of lactated Ringer's solution.

In figure 5, changes in blood volume and central venous pressure shown in figure 4 are replotted to present the change in compliance of vascular space during and after the infusion. The abscissa is the change in central venous pressure and ordinate is the change in blood volume. The slope of the CVP-BV line in figure 5 at the beginning of infusion was smaller in hypercapnia than in normocapnia though the difference was not significant at 5% level. In other words,

instantaneous compliance of the vascular space or the compliance at the beginning of infusion was smaller in hypercapnia than in normocapnia (significantly smaller, when the null hypothesis was rejected at 10% level). Meanwhile, the value of $\eta v$ increased significantly, which indicates the decrease in the delayed compliance during hypercapnia.

The value of instantaneous compliance of interstitial fluid space (Ci), delayed compliance of interstitial fluid space ($\eta i$), and transvascular filtration coefficient (Kf) during both normocapnia and hypercapnia are also shown in table 1. Ci during hypercapnia was not significantly different from Ci during normocapnia. $\eta i$ during hypercapnia decreased significantly. Kf during hypercapnia was almost identical with that during normocapnia.

## Discussion

Hypercapnia used in this experiment ($Pa_{CO_2}$ = 65 mmHg) induced significant increases in cardiac output and pulse pressure, significant decrease in total peripheral resistance, while, no significant changes were observed in mean arterial pressure, central venous pressure and heart rate. These findings coincide with the report by Prys – Roberts et al.[1] In addition, we measured circulating blood volume continuously, which enabled us to determine vascular compliance and transvascular filtration coefficient quantitatively, and gave more informations concerning hemodynamics changes due to hypercapnia.

The increase in the blood volume in central circulation suggests the constriction in systemic capacitance vessels in hypercapnia. Blood was redistributed from systemic circulation to the central circulation (heart and lung). Increases of blood circulation in brain and skin during hypercapnia have also been described[16]. Thus, constriction of splanchnic circulation or capacitance vessel is suggested, or else, central venous pressure would fall because of the reduced blood volume in systemic circulation.

Vascular compliance determined with the infusion of lactated Ringer's solution tended to be lower in hypercapnia than in normocapnia, although the difference was significant only when null hypothesis was rejected at 10% level. While, vascular compliance was significantly less in hypercapnia than in normocapnia after the end of fluid infusion, because $\eta v$ in hypercapnia was much larger than in normocapnia. (Large $\eta v$ has little effect on the linear relationship between Pv and Vv by reducing the second term of the fourth equation in figure 3 to zero.) These findings suggest that after the fluid infusin, stress relaxation of vessels was found in normocapnia, while in hypercapnia vascular compliance was kept constant. The delayed compliance showed lower value during hypercapnia than during normocapnia.

The cause of constriction in capacitance vessels is attributed to the action of autonomic nervous system stimulated by both central and peripheral chemoreceptors in hypercapnia[16].

Total peripheral resistance was significantly reduced in hypercapnia. Generally the reduction in total peripheral resistance is due to the relaxation of precapillary sphincters, which should cause the increase of capillary fluid exchange and the increase in transvascular filtration coefficient, because the relaxation of precapillary sphincters should increase the area available for diffusion. In the present experiment, the change in blood volume during infusion of lactated Ringer's solution and recovery phase was almost same during both normocapnia and hypercapnia. The result of simulation analysis also showed the same value of transvascular filtration coefficient. These findings suggest the increase in shunt flow in peripheral circulation under hypercapnia.

In summary, changes in circulating blood volume during hypercapnia ($Pa_{CO_2}$ = 65 mmHg) were determined continuously together with hemodynamic variables on dogs. Vascular compliance, delayed compliance and transvascular filtration coefficient were determined using computer simultation on the changes in blood volume and hemodynamic responses consequent on the infusion of

lactated Ringer's solution. Small reductions in vascular compliance and large reductions in delayed compliance were observed during hypercapnia, and the essential change in hypercapnia was concluded as the vasoconstriction in capacitance vessels due to the action of autonomic nervous system. This result suggests that unstressed blood volume in splanchnic circulation is mobilized to central circulation during hypercapnia. Further experiments are needed to clarify the change in unstressed blood volume.

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