Regulation of Vascular Compliance and Stress Relaxation by the Sympathetic Nervous System

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Abstract We measured the changes in central venous pressure (CVP) and circulating blood volume (CBV) in dogs consequent to fluid infusion under halothane anesthesia, and compared the CVP and CBV responses to those obtained after blocking the autonomic nervous system by total spinal anesthesia (TSA) and stimulating the α receptor with methoxamine (MTX). Under TSA, the change in CVP consequent to fluid infusion was less than that under halothane anesthesia, while with MTX, the change in CVP was larger than that under halothane anesthesia. The recovery time of CVP response toward the baseline level after the end of fluid infusion was fastest under halothane anesthesia, while the recovery time of CVP was two times longer under TSA and MTX. Based on the relationship between changes in CVP and BV, we quantified effective vascular compliance and stress relaxation using mathematical analysis. The effective vascular compliance increased to 13.3 ± 3.2 ml·mmHg⁻¹·kg⁻¹ under TSA as compared to 5.6 ± 0.3 ml·mmHg⁻¹·kg⁻¹ under halothane anesthesia, and it decreased to 2.6 ± 0.2 ml·mmHg⁻¹·kg⁻¹ with MTX. Stress relaxation was determined as the time constant in the unit response of CVP. The time constant for stress relaxation was 39 ± 7 min under halothane, 74 ± 12 min with TSA, and 92 ± 25 min with MTX. These results suggest that the autonomic nervous system modifies cardiac preload by changing effective vascular compliance and stress relaxation.

Key words: total spinal anesthesia, methoxamine, central venous pressure, circulating blood volume.
Viscoelastic properties of vascular space play an important role in regulating cardiac preload and cardiac output, and they are known to consist of two parameters: vascular compliance and stress relaxation. Vascular compliance has been measured with the mean circulatory filling pressure (MCFP) method (Guyton et al., 1975; Rothe, 1983; Green, 1987) and the reservoir method (Shoukas and Sagawa, 1971). Using the reservoir method, Greene and Shoukas (1986) have shown that change in vascular capacity is the primary mechanism responsible for changes in cardiac output during activation of the carotid sinus baroreflex, but the efferent limb of the reflex has not been clarified. In addition, both the MCFP method and the reservoir method determine an instantaneous vascular compliance, but the time course of change in vascular compliance cannot be determined. Gauer et al. (1956) and Echt et al. (1974) succeeded in showing a relationship between CVP and circulating blood volume (CBV) in humans and rats. They defined this as "effective vascular compliance." We previously developed a method to determine CBV continuously (Tanaka et al., 1981; Nose, 1982; Morimoto et al., 1983; Miki et al., 1983; Shigemi, 1988; Sugimoto et al., 1989). In this study we applied this method to determine the effective vascular compliance and to analyze the effect of autonomic nervous activity on the effective vascular compliance and stress relaxation of the vascular space. This method has the advantage that both parameters of viscoelastic properties of vascular space can be determined simultaneously.

**METHODS**

Experiments were performed on 21 mongrel dogs weighing 8.5–12.5 kg. At least 1 week before experiments, dogs were splenectomized under thiopental anesthesia. On the study day, anesthesia was induced with an intravascular injection of thiopental sodium (25 mg·kg⁻¹). Each dog was weighed and placed in the supine position and ventilated with mixed gases of 30% O₂ and 68.5% N₂ with 1.5% halothane, by a volume-limited respirator. The ventilation rate was set at 15–20 times·min⁻¹ with a tidal volume of about 250 ml which maintained blood gases in the ranges of PaO₂=180–200 mmHg and PaCO₂=35–45 mmHg. Heparin sodium was administered at an initial dose of 5 mg·kg⁻¹ and at a maintenance dose of 2.5 mg·kg⁻¹·h⁻¹ for avoiding the blood coagulation. Pancuronium bromide was administered at an initial dose of 0.2 mg·kg⁻¹ and maintained with a dose of 0.05 mg·kg⁻¹·h⁻¹ to prevent muscle movement during the experiment.

**MEASUREMENTS**

CBV was determined continuously using an extracorporeal shunt (Fig. 1). Blood was led by a pump at a constant rate (40 ml·min⁻¹) into the arterio-venous extracorporeal shunt which includes a cuvette densitometer (Erma Optical Works Ltd., Tokyo), a γ-ray detector (Osaka Dempa, Osaka, Japan) and a blood reser-
Regulation of Vascular Compliance

Fig. 1. Experimental scheme for continuous measurement of circulating blood volume. F.A., femoral artery; F.V., femoral vein.

Voir. Cardiac output and blood volume in the central circulation (cardiopulmonary circulation) were determined by the dye-dilution method (Meier and Zierler, 1954). Indocyanine green (Diagno-Green, Daiichiseiyaku, Tokyo) was injected rapidly into the inferior vena cava. Simultaneously, the blood was withdrawn from the aortic catheter through the cuvette densitometer to determine a dye concentration curve, from which the cardiac output and the mean transit time of the indicator through the central circulation were calculated. The blood withdrawn was reinfused into the dog through the femoral vein catheter after these parameters were determined. The blood volume in the central circulation was calculated by multiplying the cardiac output by the mean transit time. The blood level in the reservoir was kept constant by a photo-level detector and a computer controlled pump (Tanaka et al., 1981). Systemic arterial pressure and CVP were monitored continuously with a strain gauge transducer (Statham-Gauld, P23XL) via catheters. A tip of the arterial catheter was placed into the descending aorta through a left femoral artery and another catheter was inserted in the inferior vena cava at the level of the diaphragm via a femoral vein. The systolic, diastolic and mean arterial pressures and CVP were sampled every 0.1 s and recorded with a desktop computer (M243, SORD, Tokyo) every 30 s as mean values. Systemic vascular resistance was calculated from the value of mean systemic arterial pressure minus CVP divided by cardiac output.

CBV was determined every 30 s using the dilution method of erythrocytes labeled with $^{51}$Cr. The system included the cell in the well of the $\gamma$-ray detector.

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The volume of the cell was 2.5 ml, and it was perfused with a constant blood flow of 40 ml·min⁻¹. The initial blood volume was determined with the traditional dilution method and the change in blood volume was continuously determined using these counts.

The effective vascular compliance of the systemic vascular bed and stress relaxation were determined from the relationship between the changes in CVP and CBV consequent to the intravenous infusion of lactated Ringer's solution modifying our previous analysis (Isogai et al., 1983; Shigemi, 1988) as follows.

**DATA ANALYSIS**

A gradual decrease in CVP after fluid infusion could be attributed to two factors. The first is a gradual decrease in CBV due to a transvascular fluid shift from the intravascular space to the interstitial space, and the second is an increase in vascular compliance and stress relaxation. The increase in vascular compliance and stress relaxation causes a decrease in intravascular pressure even when the volume in the vessel is kept constant. Because we determined CBV continuously, the effect of the filtrated volume on the reduction in CVP was excluded.

Effective vascular compliance and stress relaxation were analyzed using the step function (Eq. (1)) of Maxwell's viscoelastic model. Equation (2) is described by the variables of circulation in dogs. CBV (V) is the input and CVP (P) is the output in this analysis. The changes in CVP and CBV respectively correspond to the force of the tension (F) and the changes in the length of the system (L) in Maxwell's model (Isogai et al., 1983). Coefficient k in Eq. (1) is defined as the reciprocal of vascular compliance (C) in Eq. (2). Stress relaxation is shown as the time constant (τ) in the exponential decay term.

\[
F = k \cdot L \cdot e^{-\frac{t}{\tau}},
\]

(1)

F, the force of the tension; L, the change in the length of the system; k, the coefficient of the coil; τ, the time constant; τ, time.

\[
P = \frac{1}{C} \cdot V \cdot e^{-\frac{t}{\tau}},
\]

(2)

\[
\phi(t) = \begin{cases} 
\frac{1}{C} \cdot \delta(t) \\
\frac{1}{C \cdot \tau} \cdot V \cdot e^{-\frac{t}{\tau}} 
\end{cases} \quad (t = 0),
\]

(3)

\[
\phi(t) = \begin{cases} 
\frac{1}{C} \cdot \delta(t) \\
\frac{1}{C \cdot \tau} \cdot V \cdot e^{-\frac{t}{\tau}} 
\end{cases} \quad (t > 0).
\]

When input (V) is given as a step function, output (P) can be shown as a unit response (Eq. (2)), and when input (V) is an impulse, output (φ) is shown as an impulse response (Eq. (3)). To determine vascular compliance (C) and the time constant (τ) of stress relaxation, CVP (P) was calculated from Eq. (3), which was utilized for convolution analysis using the measured CBV as input (V). The
calculation of the convolution is as follows:

\[ P(t) = \int_0^t V(t-s) \phi(s) ds = \int_0^t \left\{ V(t-s) \cdot \frac{1}{C} \delta(s) \right\} ds + \int_t^t \left\{ V(t-s) \cdot \left( -\frac{1}{C \cdot \tau} \cdot V(t-s) \cdot e^{-\left(\frac{t-s}{\tau}\right)} \right) \right\} \]

The calculated CVP (P) was fitted to the measured values by means of the least squares method, and the most reliable values of C and \( \tau \) were determined. We used a desktop computer (PC9801, NEC, Tokyo) to calculate \( P(t) \) from the equation as follows:

\[ P(i) = \frac{1}{C} V(i) - \frac{1}{C \cdot \tau} \sum_{j=1}^{i} V(i-j)e^{-\left(\frac{j-1}{\tau}\right)}, \]

\[ i = 1, 2, \cdots, 120, \quad j = 1, 2, \cdots, i. \]

The results are presented as means with standard errors. All values were compared using of Student's t-test and the null hypothesis was rejected when \( p < 0.05. \)

**EXPERIMENTAL PROTOCOL**

The experiment was performed on 21 dogs. All animals were anesthetized with 1.5% halothane and control measurements were performed. After the control measurements, 16 animals, the group with the blockade of the autonomic nervous system, were subjected to total spinal anesthesia with 0.5% bupivacaine, and the other animals, the group with stimulated autonomic nervous system, were subjected to continuous intravascular infusion (8.3 mg·kg⁻¹·min⁻¹) of an \( \alpha \) receptor agonist (methoxamine: Mexan, Nippon Shinyaku Ltd., Kyoto) under halothane anesthesia (1.5%). In each experiment, after a 10 min control phase, lactated Ringer's solution at the volume of 1% of the measured body weight was infused intravenously at a constant rate for 10 min. Thereafter, 50 min were allowed for recovery. During each set of experiments, the systolic, mean, and diastolic arterial pressures, and CVP were continuously measured and recorded in a desktop computer every 30 s as mean values during the experiments. In animals with total spinal anesthesia (TSA group), the cisterna magna was tapped by a 23 gauge needle and 0.5% bupivacaine (Marcaine, Sankyo Ltd., Tokyo) (0.5 ml·kg⁻¹) with blue dye (Indigocarmine, Daiichisefiyaku Ltd., Tokyo; 1 ml) was slowly injected into the subdural space to block the autonomic nervous system, thereafter, halothane inhalation was stopped. After the completion of the experiment, the dogs were laminectomized to confirm that the subarachnoidal membrane of the spinal cords were stained. If they were not stained the results were excluded from the analysis. In the methoxamine treated group (MTX group), methoxamine was infused starting 40 min before volume loading. Three cases of control measurements were excluded from the analysis because of changes in CVP due to the change in anesthetic level.
RESULTS

Control measurements taken before the fluid infusion for each condition are summarized in Table 1. Mean arterial blood pressure and CVP reduced significantly in the TSA group, while they increased significantly in the MTX group as compared to the control group with halothane anesthesia. With total spinal anesthesia, CBV increased significantly, while the administration of methoxamine caused an insignificant decrease compared to the control group. Cardiac output in both the TSA and MTX groups was significantly lower than that in the control group. Total peripheral resistance was about a half in the TSA group, while in the MTX group, the peripheral resistance was significantly higher than that in the control group. In both the TSA and MTX groups blood volume in central circulation showed a decrease compared to the control group, though the reduction in the TSA group was not significant. The percentage of the blood volume in central circulation to CBV was 15.9 (TSA group), 15.5 (MTX group), and 24.1% (control group).

Changes in CVP and CBV during and after fluid infusion are shown in Fig. 2 as means with standard errors for each group. Although 10 ml·kg⁻¹ of lactated Ringer's solution was infused into the intravascular space, at the end of the infusion, 9.3±0.4 (TSA group), 7.9±0.3 (control group), and 7.1±0.6 ml·kg⁻¹ (MTX group) of the fluid were maintained in the intravascular space. The retention was significantly higher in the TSA group than the control group. Fifty minutes after the end of the infusion, the fluid retained in the vascular space was

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>T.S.A.</th>
<th>Methoxamine</th>
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<tbody>
<tr>
<td>Number of animals</td>
<td>18</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>102.4±5.4</td>
<td>55.8±2.7**</td>
<td>138.1±7.7*</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>4.8±0.9</td>
<td>3.3±0.6*</td>
<td>7.7±1.4**</td>
</tr>
<tr>
<td>Blood volume (ml/kg)</td>
<td>81.4±2.3</td>
<td>92.0±3.5**</td>
<td>76.0±1.3</td>
</tr>
<tr>
<td>Cardiac output (ml/(min·kg))</td>
<td>93.1±8.9</td>
<td>59.7±9.7*</td>
<td>51.0±10.3*</td>
</tr>
<tr>
<td>Blood volume in the central circulation (ml/kg)</td>
<td>19.6±2.1</td>
<td>14.6±2.6</td>
<td>11.8±2.0*</td>
</tr>
<tr>
<td>Total peripheral resistance (mmHg·min·kg/ml)</td>
<td>1.38±0.16</td>
<td>0.76±0.10**</td>
<td>2.46±0.38*</td>
</tr>
<tr>
<td>Effective vascular compliance (C) (ml/(mmHg·kg))</td>
<td>5.6±0.3</td>
<td>13.3±3.2*</td>
<td>2.6±0.2**</td>
</tr>
<tr>
<td>Time constant of stress relaxation (t) (min)</td>
<td>39±7</td>
<td>74±12*</td>
<td>92±25**</td>
</tr>
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</table>

Values are mean±S.E.  *p<0.05,  **p<0.01. Halothane, halothane anesthesia group; T.S.A., total spinal anesthesia group; Methoxamine, the group administered methoxamine. Vascular parameters were determined before intravascular infusion of lactated Ringer's solution. Compliance and time constant of stress relaxation were determined from the changes in CVP and CBV of each group using the simulation analysis.

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Fig. 2. Changes in circulating blood volume (ΔBlood Volume, upper trace) and central venous pressure (ΔCVP, lower trace) before, during, and after infusion of lactated Ringer’s solution. Mean values of each group are illustrated with S.E.

4.3±0.4 ml·kg⁻¹ in the TSA group, which was significantly higher than 2.8±0.4 ml·kg⁻¹ in the control group and 2.0±0.8 ml·kg⁻¹ in the MTX group. The changes in CVP for each condition are shown in the lower panel in Fig. 2. At the end of the infusion, changes in CVP were +2.7±0.3 mmHg in the MTX group, which was significantly higher than +1.3±0.1 mmHg in the control group and +0.9±0.2 mmHg in the TSA group. During the recovery period, CVP returned toward the control level by +0.3±0.3 (MTX group), +0.2±0.1 (TSA group), and +0.1±0.1 mmHg (control group), and no significance was found.

Figure 3 shows the relationship between changes in CVP and CBV replotted for each group. In each of experimental conditions, both CVP and CBV increased linearly. However, the slope in the TSA group was higher and the slope in the MTX group was lower, suggesting a high effective vascular compliance in the TSA group and a low effective vascular compliance in the MTX group. During the period of recovery from the infusion (the parts of the downward arrows in each
hysteresis in Fig. 3), CBV decreased due to transcapillary fluid shift, while CVP was lower at the same level of CBV during the infusion period (the parts of the upward arrows) due to stress relaxation or delayed compliance of the vascular bed.

In order to quantify changes in effective vascular compliance, simulation analysis was performed using the values of changes in CBV and CVP. The effective vascular compliance was calculated to be $5.6 \pm 0.3 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$ in the control group. It significantly increased to $13.3 \pm 3.2 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$ in the TSA group and significantly decreased to $2.6 \pm 0.2 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{kg}^{-1}$ in the MTX group. Time constants of stress relaxation in the MTX (92±25 min) and TSA (74±12 min) groups were twice as long as those of the control group (39±7 min).

To assess the effect of changes in vascular compliance and stress relaxation, the obtained values were used to calculate CVP response to stepwise increases of CBV by 10 ml·kg⁻¹, maintaining the value for 60 min. As shown in Fig. 4, the initial rise in CVP was $1.8 \pm 0.1 \text{ mmHg}$ in the control group, $0.8 \pm 0.2 \text{ mmHg}$ in the TSA group, and $3.9 \pm 0.3 \text{ mmHg}$ in the MTX group. After 60 min, CVP became $0.4 \pm 0.1 \text{ mmHg}$ in the control group and $0.3 \pm 0.1 \text{ mmHg}$ in the TSA group, and $2.0 \pm 0.5 \text{ mmHg}$ in MTX group.

We also calculated the change in CBV required to maintain a stepwise increase of CVP by 1 mmHg for 60 min (Fig. 5). The initial amount of CBV necessary for
Fig. 4. Simulated responses in central venous pressure to the stepwise change in circulating blood volume by 10 ml/kg body wt. The responses were calculated using obtained values of effective vascular compliance and stress relaxation. The results are shown as mean values and S.E. (hatched area).

a stepwise rise in CVP by 1 mmHg was 5.6±0.3 ml·kg⁻¹ in the control group, 13.3±3.2 ml·kg⁻¹ in the TSA group, and 2.6±0.2 ml·kg⁻¹ in the MTX group. The additional volume of CBV for maintaining increased CVP was 0.20±0.03 ml·mmHg⁻¹·kg⁻¹·min⁻¹ in the control group, 0.17±0.06 ml·mmHg⁻¹·kg⁻¹·min⁻¹ in the TSA group, and 0.02±0.01 ml·mmHg⁻¹·kg⁻¹·min⁻¹ in the MTX group.

DISCUSSION

In this experiment, the effect of sympathetic nerve activity on effective vascular compliance and stress relaxation was studied. Total spinal anesthesia and administration of methoxamine were used to modify the control of vessels by the sympathetic nervous system. Results obtained from animals with these treatments were compared with the results obtained from animals with halothane anesthesia. The changes in circulatory responses in the preinfusion phase of each experimental group (Table 1) indicate sufficient effects of blockade and stimulation of the autonomic nervous system. Although halothane has a slightly inhibitory effect on the autonomic nervous system, a group under 1.5% halothane anesthesia was used as the control in this study.

Although the estimation of vascular compliance is more commonly measured by the mean circulatory filling pressure, we used the CVP-CBV relationship in a beating heart to measure effective vascular compliance in this study. Under this
Fig. 5. Circulating blood volume necessary to maintain a stepwise increase in central venous pressure by 1 mmHg. The responses were calculated using the results in Table 1. The results are shown as mean values and S.E. (hatched area).

Physiological condition, a change in cardiac output might effect the value of effective vascular compliance, while in the experimental conditions used in this study, sympathetic activity was blocked or stimulated maximally. In addition, the real value of CBV monitored continuously was used for the calculation of effective vascular compliance. Thus, effective vascular compliance as determined here was larger than that reported by other investigators who measured mean circulatory filling pressure (Guyton et al., 1975; Rothe, 1983; Green, 1987). A possible explanation for the higher value found here is that changes in CVP and CBV during 10 min of infusion were used for our analysis. Thus, the effective vascular compliance in our present analysis includes the overall effect of the regulatory mechanism of vascular compliance, including the redistribution of blood within the body and change in unstressed blood volume.

The effective vascular compliance under total spinal anesthesia was twice as large, and with metoxamine the value was less than a half of the value obtained with halothane anesthesia. The larger effective vascular compliance found in animals with total spinal anesthesia suggests the onset of vasodilation. The decrease in the effective vascular compliance after the administration of metoxamine suggests vasoconstriction and decreased vascular capacity.

A change in blood distribution was found to be one of the causes of altered
vascular capacity. As shown in Table 1, in halothane anesthesia, the blood volume in the central circulation was 24.1% of the total blood volume. In total spinal anesthesia, it was reduced to 15.9%, indicating a shift of blood to peripheral circulation. The blood volume in the central circulation after the administration of methoxamine was 15.5%. These findings suggest that the effect of methoxamine on cardiopulmonary circulation is greater than that on the peripheral circulation (Duke et al., 1963). In this experiment, dogs were splenectomized to obtain stable values of circulating blood volume. The dog has a large spleen, the size of which is known to vary with sympathetic activity. Thus, there is a possibility that the TSA group will show a higher value and the MTX group a lower value of vascular compliance when measurements are performed on dogs that have not been splenectomized.

Another advantage of the present analysis is that it is possible to numerically analyze the time constant of stress relaxation or delayed compliance. The time constants shown in Table 1 indicate that under total spinal anesthesia and under administration of methoxamine, time constants were twice as large (74 and 92 min) compared with that under halothane anesthesia (39 min). Thus, the autonomic nervous system regulates vascular compliance and stress relaxation to reduce CVP when CBV is increased under halothane anesthesia. Under autonomic nervous system blockade with total spinal anesthesia, it takes much longer to regulate CVP with the change in vascular compliance and stress relaxation. In contrast, vessels are constricted maximally with the administration of methoxamine to regulate vascular compliance and stress relaxation.

To visualize the change in stress relaxation, blood volume change in response to the stepwise increase in CVP was simulated using the effective vascular compliance and the time constant of stress relaxation obtained. As shown in Fig. 5, under total spinal anesthesia the initial blood volume required to maintain increased CVP by +1 mmHg is larger and the volume required to maintain the CVP is less than under halothane anesthesia. This suggests that effective vascular compliance is greater and the speed of increase in the maintenance volume is slower when intravascular blood volume is increased in animals with total spinal anesthesia. Under the administration of methoxamine, the initial volume is less and the maintenance volume is also less than under halothane anesthesia. This suggests that effective vascular compliance is less and the speed of increase in stress relaxation is slower when intravascular blood volume is increased under the administration of methoxamine.

These results suggest that the autonomic nervous system regulates not only effective vascular compliance but also the speed of regulation of stress relaxation. The range of the regulation of effective vascular compliance was from 2.6 to 13.3 ml·mmHg$^{-1}$·kg$^{-1}$. The time constant of stress relaxation was altered by the autonomic nervous system in the range of 39–92 min.

In summary, we have shown that autonomic nervous system plays an important role in the maintenance of CVP regulating effective vascular compliance and
stress relaxation.

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