Sensitivity of Rapidly Acting Arterial Pressure Control System in Conscious Adult Rabbits at Different Ages

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Abstract Changes in sensitivity of the rapidly acting arterial pressure control (AP) system with aging were investigated. Two catheters, one for pressure measurement and the other for inducing hemorrhage from the aorta, were chronically implanted in 25 rabbits from the same colony (aged 6 to 30 months). A few days after the operations, each animal was quickly bled (2 ml/kg body weight) while it was conscious. The hemorrhage experiment was repeated 16 times and the mean arterial pressure responses were sampled with an A/D-converter and stored in a digital computer, the 16 strings of data being pooled for each animal. The overall open-loop gain (G) of the AP-system was estimated from the individually pooled responses. In the present study, aging exerted no significant effect on the value of G (7.1) as evaluated by Kruskal-Wallis' non-parametric one criterion variance analysis (p > 0.05). The reflex sensitivity of the AP-system over the pressure ranges used in this experiment thus appears to be unaffected by aging over the range from 6 to 30 months.

Key Words: aging, rapidly acting arterial pressure control system, open-loop gain, hemorrhage, conscious rabbit.

Aging has been shown to produce a variety of alterations in the cardiovascular system. Many analytical studies have been undertaken on age effects on baroreceptor reflex function. The sensitivity of the baroreceptor control of heart rate has been compared in conscious newborn lambs and adult sheep (Manders et al., 1979), and in newborn and adult rabbits (Duncan et al., 1981) using the pressor test described by Smyth et al. (1969). The results of these studies suggest that the arterial baroreceptor reflex is depressed in newborn animals with respect to control of heart rate. Several investigators (Gribbin et al., 1971; Frolikis et al., 1975; Vlachakis et al., 1976; Randall et al., 1978) have reported a decrease in baroreceptor sensitivity with aging in adult humans. Most of these studies

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examined the relationship between heart period and systolic arterial pressure changes in response to intravenous injection of pressor agents. Although the arterial baroreceptor heart rate reflex can be readily elicited by altering blood pressure simultaneously at all arterial baroreceptor sites by means of vasoactive drugs, this method does not permit examination of blood pressure as the dependent variable. Thus, due to the powerful vasoactive effects of these pressor agents, Smyth's technique cannot be used to assess the baroreflex control of peripheral circulation (Guo et al., 1982).

Vatner and Manders (1979) evaluated the responsiveness of the carotid sinus reflex by comparing the effects of bilateral carotid occlusion on the peripheral circulation in conscious newborn and adult dogs. They found that the carotid baroreceptor reflex appears to be depressed in the newborn dog as compared to the fully developed reflex in the normal adult. Lindblad (1977) reported that carotid sinus stimulation by a neck suction (=40 mmHg) induced a significantly greater reduction in mean arterial pressure in younger people (up to 30 years of age) compared to older people (above 30 years of age). However, the carotid occlusion method and the neck suction method do not allow investigation of the pressure control sensitivity of the vagally mediated baroreflex system or of the interactive system between it and the carotid sinus baroreflex system.

More precise evaluation of the effects of aging on the carotid sinus baroreceptor reflex function was conducted by Cox et al. (1981) using isolated carotid sinus of young and old greyhounds. Their results suggest that the carotid sinus baroreceptor reflex control of the systemic circulation is well maintained in older greyhounds. This technique is a theoretically straightforward method for evaluation of the carotid sinus baroreceptor reflex function. However, since the isolation of the carotid sinus inevitably eliminates the interaction between it and the vagally mediated baroreflex systems, the technique is unsuitable for evaluating the effects of aging on the overall sensitivity of the rapidly acting arterial pressure control (AP)-system.

Analytical studies on the effects of aging on baroreceptor reflex function (Bloor, 1964; Tomomatsu and Nishi, 1982) have gone further than integrative investigations. However, there is no study on the effects of aging on the normally operating overall function of the AP-system at a programmed sequence of different ages in conscious adult animals. The aim of the present study was to evaluate the overall sensitivity of the AP-system in conscious rabbits at different ages. It is particularly important to study this in conscious animals so as to exclude the complicating influences of recent surgery and general anesthesia which, however, are still in dispute (Vatner and Braunwald, 1975; Hosomi and Sagawa, 1979; Zimpfer et al., 1982). The overall sensitivity of the AP-system was evaluated as an overall open-loop gain of the system. To do this, we employed a quick mild hemorrhage method (Hosomi and Yokoyama, 1981). Since postural changes can cause fluctuations in arterial pressure, we repeated the hemorrhage experiment.
and averaged the arterial pressure responses.

METHODS

Experimental animals. Twenty-five Japanese white rabbits (average body weight ± SD, 3.9 ± 0.6 kg) from the same colony were used. The animals ranging in age from 6 to 30 months were divided equally into 5 age-groups: the 6-(6M), 12-(12M), 18-(18M), 24-(24M) and 30-(30M)-month-old groups.

Operation. The animals were anesthetized by an intravenous injection of pentobarbital sodium (27.5 mg/kg body weight). Under sterile conditions, two polyethylene catheters were chronically implanted into the animals. One (1.0 mm ID) was used for pressure measurement. One tip of this catheter was placed at the aortic arch via the left subclavian artery, and the other tip was connected to a stop-cock. The other (1.2 mm ID) was used for hemorrhage induction. One tip of this second catheter was placed at the aortic arch via the left common carotid artery (Fig. 1), and the other was connected to another stop-cock. The two stop-cocks were fixed on the rabbit's back.

Two-hour pressure recording. At the time of study a few days after the operations, all animals were in a good state of health and appetite. Around 9 o'clock in the morning, each animal was transferred from its previous hutch to an identical one in an experimental room (constant temperature, 21°C), where free access to water and food was provided. Each animal was heparinized just before beginning pressure monitoring (500 units/kg body weight) and arterial pressure was monitored with a pressure-transducer system via the pressure catheter. One hour after the arterial pressure had become stable, the mean arterial pressure was obtained using a low-pass filter with a 2 sec time constant. The data were recorded on a strip-chart, sampled with an A/D-converter at intervals of 1 sec, and stored in a digital computer.

Hemorrhage experiment. Blood (2 ml/kg body weight) was withdrawn quickly (1–2 sec) into a syringe via the stop-cock to induce hemorrhage from the aorta.

Fig. 1. Schematic illustration of the experimental setup.
The displacement of the syringe piston was converted into an electric signal by a sliding resistor attached to the piston shaft. A stopper on the shaft ensured that equal amounts of blood were withdrawn at each test. The mean arterial pressure was recorded and sampled at intervals of 100 msec for 30 sec before and 120 sec after the hemorrhage. Two min after the hemorrhage, the blood was reinfused into the aorta. The hemorrhage experiment was repeated 16 times at intervals of 10 min while the rabbits remained conscious.

**Data processing.** The percentage frequency distribution curve for the 2-hr recording of mean arterial pressure (MAP) was calculated from histograms with intervals of 1 mmHg. The standard deviation (SD) and MAP values were also calculated (7,200 sample points).

Sixteen strings of hemorrhage experiment data were averaged for each animal in order to improve the signal-to-noise (S/N)-ratio. The averaged data for each rabbit were reproduced with a D/A-converter on a strip-chart, and were designated as the individual-response. The following measurements were then performed on each individual-response. The control mean arterial pressure (CMAP) was obtained from 300 sample points for 30 sec before the hemorrhage. The maximum fall ($\Delta$AP$_t$) in mean arterial pressure after the hemorrhage was measured, and the steady-state fall ($\Delta$AP$_s$) was obtained by subtracting CMAP from the mean arterial pressure value between 60 to 120 sec after the hemorrhage. Finally, the open-loop gain ($G$) was assessed as follows (Hosomi and Yokoyama, 1981):

$$G = \frac{\Delta$AP$_t}{\Delta$AP$_s} - 1.$$  

The mean values $\pm$ standard deviation (SD) are presented. Kruskal-Wallis' non-parametric one criterion variance analysis was employed to evaluated the

<table>
<thead>
<tr>
<th></th>
<th>6M</th>
<th>12M</th>
<th>18M</th>
<th>24M</th>
<th>30M</th>
<th>All</th>
<th>$r$</th>
</tr>
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<tbody>
<tr>
<td>MAP</td>
<td>94</td>
<td>92</td>
<td>99</td>
<td>95</td>
<td>94</td>
<td>95</td>
<td>0.056</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
<td>4</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>-0.322</td>
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<tr>
<td>$\Delta$AP$_t$</td>
<td>10.2</td>
<td>15.5</td>
<td>10.2</td>
<td>13.0</td>
<td>16.2</td>
<td>13.0</td>
<td>0.337</td>
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<tr>
<td>$\Delta$AP$_s$</td>
<td>1.3</td>
<td>2.0</td>
<td>1.2</td>
<td>1.6</td>
<td>1.9</td>
<td>1.6</td>
<td>0.237</td>
</tr>
<tr>
<td>G</td>
<td>6.7</td>
<td>6.7</td>
<td>7.6</td>
<td>7.1</td>
<td>7.4</td>
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<td>0.22</td>
<td>0.17</td>
<td>0.12</td>
<td>0.12</td>
<td>0.18</td>
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<tr>
<td>BW$\pm$SD</td>
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<td>3.7$\pm$0.7</td>
<td>4.0$\pm$0.8</td>
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<td>4.0$\pm$0.3</td>
<td>3.9$\pm$0.6</td>
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</tr>
</tbody>
</table>

The number of experimental animals is indicated in parentheses. BW$\pm$SD: the mean values $\pm$ SD of body weight. Statistical tests (see RESULTS).
aging effect on MAP, SD, ΔAP₁, ΔAPₛ, and G. We also compared the significance between the variables of any two of the 5 age-groups by Steel-Dwass' method. The correlation coefficients of MAP, SD, ΔAP₁, ΔAPₛ, and G to age were calculated and are listed in the right-hand column (r) of Table 1. MAP, SD, ΔAP₁, ΔAPₛ, and G were pooled in each age-group and are shown in the first 5 rows of Table 1.

The 5 individual-responses in each age-group were again pooled to obtain the group-response. The standard deviation (CSD) in mean arterial pressure 30 sec before hemorrhage for each group-response was calculated and is shown in the bottom row of Table 1.

MAP, SD, ΔSP₁, ΔAPₛ, and G from the 25 individual-responses were pooled and are tabulated as means in the second column from the right in Table 1.

RESULTS

The pressure fluctuations were caused mainly by postural changes, i.e., wandering, eating, drinking, and defecation. As a result of these fluctuations, i.e., noise, the S/N-ratio in each original-response was very low. Figure 2 shows

Fig. 2. Original-responses of mean arterial pressure to quick mild hemorrhage in an 18-month-old conscious rabbit (3rd to 10th tracings). Upper tracing, time; 2nd tracing, change in volume of blood removed.

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8 out of 16 original-responses to the hemorrhage in an 18M conscious rabbit. The individual-response shown in Fig. 3 is derived from the 16 original-responses from which the 8 responses in Fig. 2 were taken. CMAP, ΔAP₁, and ΔAP₈ in this case were 109, 11.1, and 1.3 mmHg, respectively, and the estimated G value was 7.5. The correlation coefficients of MAP and SD to age were not significant ($p>0.05$) (Table 1). Thus, the arterial pressure and its stability were unaffected by aging. The correlation coefficients of ΔAP₁, ΔAP₈, and G to age were also not significant (Table 1), indicating that the overall sensitivity of the AP-system is not affected by aging. There was no significant effect of aging on MAP, SD, ΔAP₁, ΔAP₈, and G by Kruskal-Wallis' multi-sample test ($p>0.05$), and also no significant difference between the variables of any 2 of 5 age-groups by Steel-Dwass' multiple comparison ($p>0.05$).

**DISCUSSION**

The present experimental results show that the overall G of the AP-system in rabbits does not change with aging from 6 to 30 months.

To demonstrate the changes in sensitivity of the AP-system, we evaluated ΔAP₁ as a measure of the stimulus to the baroreceptors, ΔAP₈ as a measure of the integrated output from the AP-system, and G estimated from ΔAP₁ and ΔAP₈ as a measure of the overall sensitivity of the system. The techniques used are based on the assumption that the nadir of pressure immediately after withdrawal represents the passive response of the system without compensation by the AP-

![Fig. 4. Responses of arterial pressure (AP) and mean arterial pressure (MAP) to quick mild hemorrhage under intact (INTACT) and baroreceptor deafferentated (CS+Au+V) conditions in an anesthetized rabbit. MAP was derived from AP with a low-pass filter with a 2 sec time constant.](image-url)
system. Approximately, 75% of the compensation (Fig. 3) was completed within 5 to 10 sec. This might seem to be effects of stress-relaxation and volume redistribution. If so, we should consider a pressure fall 5 to 10 sec after the hemorrhage as the input, i.e., ΔAP₂, and we could obtain a smaller gain value. In order to validate the present study, we carried out the hemorrhage experiments on an anesthetized rabbit under intact and afferent nerves (carotid sinus, aortic, and vagi) sectioned conditions. The arterial pressure responses to the hemorrhage were processed with the low-pass filter with a 2 sec time constant (Fig. 4). Under the deafferented condition, removal of this amount of blood caused a maintained fall in pressure. This fact shows that the filter could cut the effects of stress-relaxation and volume redistribution. HOSOMI and YOKOYAMA (1981) showed that a filter with a 2 sec time constant was the most suitable.

Since the quick mild hemorrhage used to obtain these parameters would represent a commonly occurring disturbance to the system, the AP-system was able to demonstrate its pressure control ability at the pressure at which the experiment was performed. Although we were unable to estimate G over a wide range of pressures, the value obtained by this method appears to reflect the pressure control ability of the AP-system operating at normal pressure. This could be the reason why we estimated a fairly large G value (7.1) in conscious rabbits.

VATNER and BRAUNWALD (1975) and ZIMPFER et al. (1982) demonstrated that pentobarbital anesthesia impairs a buffer function of the baroreflex system to restore hypotension caused by hemorrhage from the inferior vena cava. HOSOMI and SAGAWA (1979), however, found that it does not impair the buffer function of the baroreflex system to restore hypotension caused by hemorrhage from the aorta. Thus, the effect of pentobarbital anesthesia on the baroreflex system is still in dispute. HOSOMI et al. (1983) reported the G value (7.3) estimated from arterial pressure response to quick mild hemorrhage from the aorta in anesthetized rabbits. This value is within the range of the G value (7.1±0.3) estimated in the present study. Therefore, pentobarbital anesthesia does not seem to affect the G value.

The results of this study differ from the general assumption found in the literature that baroreceptor sensitivity declines with aging (GRIBBIN et al., 1971; FROLKIS et al., 1975; DUKE et al., 1976; VLACHAKIS et al., 1976; RANDALL et al., 1978). Earlier studies, however, were based on the relationship between heart period and systolic arterial pressure changes in response to intravenous injection of pressor agents. Therefore, the overall open-loop gain calculated in the present study differs considerably from those previously defined. The effect of aging on the AP-system appears to be different from that on the baroreceptor-heart rate reflex. COX et al. (1981) found that carotid sinus baroreceptor reflex control of the systemic circulation is well preserved in older greyhounds. They estimated the open-loop gain of the baroreflex using vascularity isolated carotid sinuses. Bloor's finding (BLOOR, 1964) that the sensitivity of the aortic baroreceptor does

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not change with aging was based on the relation between the peak discharge frequency in the aortic nerve and mean arterial pressure. Our results indicate that the overall $G$ of the AP-system does not change with aging within the range of 6 to 30 months.

Vatner and Manders (1979) found that the sensitivity of the carotid baroreceptor reflex appears to increase with aging from birth to maturity. Similar findings were reported by Manders et al. (1979) and by Duncan et al. (1981). These authors, however, did not demonstrate the age at which this sensitivity or the baroreceptor-heart rate response reached its maximum. The present results show that the AP-system of the 6-month-old rabbit has the same gain as that of the adult. As a result, the sensitivity of the AP-system reached its maximum by the age of 6 months.

Bloor (1964) investigating anesthetized rabbits demonstrated clearly that mean arterial pressure increases during the first 17 days of life, reaching about 106 mmHg at 4 months of age. We monitored the mean arterial pressure for 2 hr in conscious rabbits at various ages and calculated the MAP. The value of MAP did not show any significant change with aging. The mean value of MAP in 25 conscious rabbits was 95 mmHg. This difference in data may be related to the presence or absence of anesthesia.

We calculated the SD value from the pressure as recorded over a 2-hr period. Since SD is one measure of the variability in mean arterial pressure (Cowley et al., 1973; Ito and Scher, 1978; Ito and Scher, 1979), an increase or decrease in this value reflects a decrease or increase in $G$. In the present study, no significant change in SD was noted with aging, suggesting that the sensitivity of the AP-system over the pressure range used in this experiment does not change with aging from 6 to 30 months.

REFERENCES


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