Effect of Vagotomy on Cardiovascular Adjustment to Hyperthermia in Rats

Akira Takamata

Department of Physiology, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto, 602 Japan

Abstract To elucidate the contribution of cardiopulmonary baroreflexes on the control of total peripheral vascular conductance (TVC) during hyperthermia, α-chloralose-anesthetized rats with (VX-groups) or without (C-groups) vagotomy were subjected to body heating raising arterial blood temperature ($T_b$) at a rate of 0.1°C/min. In both the C- and VX-groups, rats were divided into normovolemia (C-NBV and VX-NBV) and furosemide-induced hypovolemia (C-LBV and VX-LBV) and cardiovascular responses to hyperthermia were compared between the four groups. Central venous pressure (CVP) decreased as $T_b$ rose to 43°C by $1.92 \pm 0.24$, $1.36 \pm 0.28$, $0.62 \pm 0.14$, and $0.35 \pm 0.23$ mmHg in the C-NBV, VX-NBV, C-LBV, and VX-LBV groups, respectively. Mean arterial pressure increased by 35–45 mmHg in the C-groups and by 25–35 mmHg in the VX-groups at $T_b$ of 42–43°C in the C-groups and 42°C in the VX-groups. Heart rate response to increased $T_b$ was not affected by vagotomy or LBV. Stroke volume correlated with CVP ($r=0.769$) and this relationship did not differ among the four groups. TVC was more highly correlated with CVP in the C-groups ($r=0.925$) than in the VX-groups ($r=0.757$). The slope of TVC vs. CVP (TVC/CVP) for the VX-groups lowered by about 40% from that for the C-groups. These results suggest that during hyperthermia, cardiopulmonary baroreflexes may partly contribute to the control of TVC, and other mechanisms related to decreased BV and increased $T_b$ play some roles in the control of TVC.

Key words: central venous pressure, cardiopulmonary baroreflex, vagal afferent, hypovolemia.

During progressive hyperthermia induced by environmental heating or exercise, decreases in central venous pressure (CVP) have been reported in many species of mammals [1–3]. This decrease in CVP may be caused by redistribution of cardiac output, and consequent displacement of blood volume from central to

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peripheral regions [3]. In addition to thermoregulatory adjustment, decreased CVP requires cardiovascular adjustment to maintain cardiac output and arterial blood pressure.

The decreased cardiac filling pressure during hyperthermia is suggested to be a limiting factor for thermoregulatory function [4]. Dehydration or hypovolemia attenuates cutaneous vasodilation in baboons [5] and exercising humans [6], by elevating the threshold core temperature for cutaneous vasodilation. In addition, expansion of blood volume improves thermal tolerance in exercising humans [7] and also in rats [8].

We previously reported a high inverse correlation between CVP and total peripheral resistance during hyperthermia in rats [9]. From those results, we suggested that the unloading of cardiopulmonary baroreceptor plays a role in the control of peripheral vascular conductance during hyperthermia, when CVP decreased.

In the present study, we performed bilateral cervical vagotomy on α-chloralose-anesthetized rats with different blood volumes and analyzed the contribution of cardiopulmonary baroreflexes to the circulatory adjustment to hyperthermia in rats.

MATERIALS AND METHODS

*Experimental animal.* Experiments were performed on male Wistar rats (209–396 g) with α-chloralose anesthesia. We used α-chloralose because of the minimal depressant effects on cardiovascular reflexes during hyperthermia in rats [10]. To clarify the contribution of cardiopulmonary baroreflexes, we divided the animals into four groups of six rats each: without vagotomy (C-groups) under normovolemia (C-NBV group) and hypovolemia (C-LBV group), and with vagotomy (VX-groups) under normovolemia (VX-NBV group) and hypovolemia (VX-LBV group). The cardiovascular responses to increased body temperature were compared among the four groups.

*Surgical procedures.* Animals were initially anesthetized with thiopental sodium (40 mg/kg body wt., i.p.), and a tracheal tube was inserted to maintain spontaneous ventilation of air. A Teflon-coated thermistor probe (OD = 1.2 mm, Takara Thermistor Instruments, Yokohama) was inserted from the left carotid artery, with the tip placed at the midthoracic aorta. Catheters for measuring arterial pressure (PE-50, Clay Adams) and central venous pressure (soft polyvinyl infant feeding tube, 3Fr, Atom, Tokyo) were inserted from the femoral artery and vein, with tips placed at the bifurcation of the iliac arteries and the thoracic inferior vena cava, respectively. Another catheter was inserted into the right atrium/inferior vena cava via the right jugular vein for injections of saline, anesthetics, and furosemide.

*Measurements.* Cardiac output (CO, ml·kg⁻¹·min⁻¹) was measured by the thermodilution method [11]: infusing 0.9% NaCl solution at room temperature
(0.2 ml) into the right atrium through the jugular vein catheter and recording the transient change in arterial blood temperature \(T_b\) with the aortic thermistor probe. The value was calculated from the volume (ml) and the temperature (°C) of injectate and the area under the trace of the change in \(T_b\) (°C·s), correcting by the specific heats and specific gravities of injectate and blood.

Mean arterial pressure (MAP, mmHg) and central venous pressure (CVP, mmHg) were measured with the pressure transducers (Statham-Gould P23 ID and Nihon Kohden TP-400T, Tokyo) connected to catheters from the femoral artery and thoracic inferior vena cava, respectively, with the zero reference level at two-thirds of the chest thickness from the back. Heart rate (HR, beats·min⁻¹) was counted from the arterial pulsations of the pressure recording.

Stroke volume (SV, ml·kg⁻¹·beat⁻¹) was determined from CO and HR. Total peripheral vascular conductance (TVC, ml·kg⁻¹·min⁻¹·mmHg⁻¹) was calculated by the equation of \(\text{TVC} = \text{CO}/(\text{MAP} - \text{CVP})\).

Percent change in blood volume (BV) was calculated from hematocrit [12], because during isotonic fluid modifications, BV change calculated from hematocrit was highly correlated with the values determined by the dilution method with \(^{51}\)Cr-labeled erythrocyte [13].

**Experimental protocol.** After surgical operation, \(a\)-chloralose (50 mg·kg body wt⁻¹; i.v.) was injected through the jugular vein catheter, and rats were placed in the supine position maintaining \(T_b\) at 37°C with an infrared lamp (150 W, Toshiba, Tokyo). Before heating experiment, \(a\)-chloralose (10–20 mg·kg body wt⁻¹; i.v.) was supplemented as required to maintain stable blood pressure and heart rate.

Vagotomy: Bilateral cervical vagotomy was performed in the VX-groups. The cervical vagi were carefully isolated from the carotid arteries and cervical sympathetic nerves, and the vagi were then ligated and cut after 2% lidocaine hydrochloride jelly was carefully applied to them. We performed measurements 60 min after cervical vagotomy, by which time the transient increase in MAP had returned to the pre-vagotomy level.

**BV modification.** To modify the level of CVP, we decreased BV inducing diuresis by intravenous injection of furosemide (3 mg·kg body wt⁻¹) in the C-LBV and VX-LBV groups. The measurements were started 60–90 min after the administration of furosemide. In preliminary experiments, urinary output (determined with a bladder catheter) returned almost to the control level of 0.01–0.02 ml·100 g body wt⁻¹ in 60 min and plasma volume decreased by 16.3±1.5% of premodified level, and the level was maintained within the time span of the experiment.

Body heating: After the measurements at \(T_b\) of 37°C, body surface heating with an infrared lamp was performed. \(T_b\) was raised linearly at a rate of 0.1°C/min by adjusting the distance between the lamp and the body surface of the rat. We finished the experiment by an intravenous infusion of a lethal dose of pentobarbital sodium when \(T_b\) rose to 43.5°C, at which \(T_b\), MAP abruptly fell.

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Statistics. Two-way analysis of variance (ANOVA) with replication was used to determine the effect of vagotomy or BV on the cardiovascular functions at various $T_b$s, and one-way ANOVA with repeated measurements was used to determine the effect of $T_b$ in each group. Tukey post hoc test was performed to determine the difference between groups or $T_b$s. The null hypothesis was rejected when $p < 0.05$. Values were represented as mean±SE of six rats. Regression equation was determined by Brace's method [14].

RESULTS

Effects of vagotomy and BV modification on the cardiovascular functions before body heating

Table 1 shows the hematocrit and measured cardiovascular variables in each group before heating. Hematocrit values were not significantly different between the C-NBV and VX-NBV groups but significantly different between the C-LBV and VX-LBV groups. Percent decrease in plasma volume induced by the administration of furosemide was 16.3±1.5% in the C-groups and 15.8±1.6% in the VX-groups, and the decreases were not different between the C- and VX-groups. Neither LBV nor vagotomy significantly affected MAP or HR at the $T_b$s of 37.0°C. In the rats under NBV, vagotomy decreased CVP by 0.97 mmHg and TVC by 0.606 ml·kg$^{-1}$·min$^{-1}$·mmHg$^{-1}$, but vagotomy induced no significant differences in measured variables except hematocrit value in the rats under LBV. In the C-LBV group, CVP decreased by 1.03 mmHg, CO by 125.4 ml·kg$^{-1}$·min$^{-1}$, SV by 0.274 ml·kg$^{-1}$·beat$^{-1}$, and TVC by 0.904 ml·kg$^{-1}$·min$^{-1}$·mmHg$^{-1}$ with respect to the C-NBV group, whereas no significant differences were observed between LBV and NBV in the VX-groups.

Table 1. Cardiovascular parameters before heating.

<table>
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<tr>
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<th>C-groups</th>
<th>VX-groups</th>
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<tr>
<td></td>
<td>C-NBV</td>
<td>C-LBV</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>46.1±2.1</td>
<td>51.9±1.4*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>118.8±6.7</td>
<td>110.0±6.2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>421.7±10.5</td>
<td>405.8±23.0</td>
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<tr>
<td>CVP (mmHg)</td>
<td>-0.41±0.10</td>
<td>-1.44±0.22*</td>
</tr>
<tr>
<td>CO (ml/(kg·min))</td>
<td>364.3±14.4</td>
<td>238.9±14.3*</td>
</tr>
<tr>
<td>SV (ml/(kg·beat))</td>
<td>0.868±0.041</td>
<td>0.594±0.036*</td>
</tr>
<tr>
<td>TVC (ml/(kg·min·mmHg))</td>
<td>3.100±0.18</td>
<td>2.196±0.158*</td>
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Hct, hematocrit; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; CO, cardiac output; SV, stroke volume; TVC, total systemic vascular conductance. Values are shown as mean±SE of 6 rats. *Significantly different from C-groups. †Significantly different from NBV.

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Effects of vagotomy and BV modification on the cardiovascular response to the elevation of $T_b$

Figure 1 shows the cardiovascular responses as a function of $T_b$ in the C- (Fig. 1A) and VX-groups (Fig. 1B). Mean arterial pressure increased as $T_b$ rose in all groups. In the C-groups, MAP did not change initially and started to increase sharply at $T_b$ of around 41°C and continued to increase until $T_b$ reached 43°C, whereas MAP in the VX-groups started to increase gradually from $T_b$ of 39°C, peaked at $T_b$ of 42°C, and abruptly fell thereafter. The responses of MAP to increased $T_b$ were not affected significantly by LBV in either the C- or VX-groups, although values in the rats under LBV showed lower tendencies than those under NBV. In the C-groups, the maximal increases in MAP from preheating levels were 43.9±3.4 mmHg in NBV and 34.5±12.0 mmHg in LBV at 43.0°C, and in the VX-groups the increases were 25.7±3.8 mmHg in NBV and 28.9±9.9 mmHg in LBV at 42°C.

Cardiac output in the C-NBV group was almost constant throughout heating, whereas in the VX-NBV group, CO started to decrease at $T_b$ of 40.5°C and was significantly lower than in the C-NBV group at $T_b$ higher than 41°C. On the other hand, CO in the C-LBV group was lower than in the VX-LBV group at $T_b$s between 40.0 to 41.5°C. In the C-groups, CO in LBV was significantly lower than in NBV throughout the experiment, while no significant difference was observed in CO between NBV and LBV in the VX-groups throughout the heating.

Heart rate increased as $T_b$ rose in a similar manner in all groups, without any significant difference except those at $T_b$ of 41.5 and 42.0°C between the C-NBV and VX-NBV groups. At the end of heating ($T_b=43°C$), HR increased by 208±19 beats·min⁻¹ in C-NBV, 219±21 beats·min⁻¹ in C-LBV, 175±20 beats·min⁻¹ in VX-NBV, and 195±6 beats·min⁻¹ in VX-LBV.

In the C-NBV group, CVP was maintained at the initial level up to $T_b$ of 40°C, and then decreased from preheating level by 1.91±0.24 mmHg at $T_b$ of 43°C. In the VX-NBV group, CVP at $T_b$ of 37°C was lower by 0.97 mmHg from the value observed in the C-NBV group, and this level was maintained up to $T_b$ of 40°C, and decreased from the preheating value by 1.36±0.28 mmHg at $T_b$ of 43°C. CVP in the C-LBV group was lower than in the C-NBV group by about 1 mmHg at 37°C, and the level was maintained up to $T_b$ of 42°C, and then decreased at $T_b$ of 43°C from the preheating level by 0.62±0.14 mmHg. CVP in the VX-LBV group remained constant throughout the heating experiment, without any significant difference from the C-LBV group. In the C-groups, CVP in NBV was higher than in LBV at $T_b$ between 37 and 41.5°C, while the effect of LBV was not observed in VX-groups except at $T_b$ of 43°C.

Total peripheral vascular conductance in the VX-NBV group was about 0.6–0.7 ml·kg⁻¹·min⁻¹·mmHg⁻¹ lower than in the C-NBV group throughout the heating period, which was a significant difference, but the responses to increased $T_b$ were similar between the C-NBV and VX-NBV groups: increased up to $T_b$ of 39–40°C and decreased thereafter. On the other hand, no significant difference in TVC
was observed between the C-LBV and VX-LBV groups throughout the experiment, except at $T_b$ of 43°C. In the C-groups, TVC in LBV was significantly lower than in NBV throughout the heating, but in the VX-groups a significant difference was not observed between NBV and LBV.

Figure 2 shows the relationship between CVP and SV expressed by using mean values of 6 rats in each group at each measured $T_b$. Open circles represent C-groups and closed circles, VX-groups. Because no difference was found among regression
equations of 4 groups, we pooled the data of all groups and obtained a regression equation of

$$SV = 0.305 \times CVP + 1.132 \quad (r = 0.769).$$

Fig. 1. Cardiovascular responses to the elevation of body temperature ($T_b$) in non-vagotomized control groups (C-groups; A) and vagotomized groups (VX-groups; B). ○, normal blood volume (NBV); ●, low blood volume (LBV). MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; CVP, central venous pressure; TVC, total peripheral vascular conductance.

*Indicates significant difference between NBV and LBV, ‡ indicates significant difference from the values at $T_b$ of 37°C in NBV and §, in LBV; ‡ indicates significant difference of VX-NBV from C-NBV and #, VX-LBV from C-LBV. HRs at $T_b \geq 41°C$ in the C-NBV group were significantly different from that at $T_b = 37°C$ and that at $T_b \geq 40°C$ in the C-LBV group. HRs at $T_b \geq 40°C$ in VX-NBV were significantly different from those at $T_b = 37°C$ and those at $T_b \geq 39°C$ in VX-LBV.
Fig. 3. Relationship between CVP and TVC in C-groups (○) and VX-groups (●). Each point represents mean value of six rats at each $T_b$. The regression equations are TVC = 1.051 × CVP + 3.944 in the C-groups and TVC = 0.638 × CVP + 3.626 in the VX-groups. The slope in the VX-groups is 39.3% smaller than in the C-groups.

Figure 3 shows the relationship between CVP and TVC, using mean values of C- (open circle) and VX-groups (closed circle) at each $T_b$ below 43°C. TVC was linearly correlated with CVP in both C- ($r = 0.925$) and VX-groups ($r = 0.757$). The regression equations calculated from mean values at each $T_b$ were TVC = 1.051 × CVP + 3.944 in the C-groups and TVC = 0.638 × CVP + 3.626 in the VX-groups. The slope of the CVP-TVC relationship in the VX-groups was 39.3% smaller than that in the C-groups, with a significant difference ($p < 0.05$).

DISCUSSION

Decreased cardiac filling pressure during hyperthermia is caused by displacement of BV from central to peripheral regions, and can be a threat to both cardiovascular and thermoregulatory functions [4]. In the present experiment, we...
compared the cardiovascular responses to progressively increased $T_b$ between control and vagotomized rats in the different blood volume in order to clarify the involvement of cardiopulmonary baroreflexes. The major finding of the present study is that the cardiopulmonary baroreflexes partly contribute to the control of TVC. The involvement of $T_b$- and/or BV-dependent mechanisms on the control of peripheral vascular response was also suggested because vagotomy did not completely abolish decrease in TVC during progressive hyperthermia.

During progressive hyperthermia, both CVP and TVC decreased at $T_b$ above 40–41°C (Fig. 1). The correlation between CVP and TVC was significant, with a higher coefficient in the C-groups ($r=0.925$) than in the VX-groups ($r=0.757$). The slope of the CVP vs. TVC relationship for the VX-groups was about 40% smaller than for the C-groups, with a significant difference (Fig. 3). The range of CVP observed in the VX-groups was lower than in the C-groups and the large majority of the data clustered between $-1.25$ and $-1.75$ mmHg. However, the slope in the VX-groups (TVC/CVP; 0.638) was smaller compared to the slope in the C-LBV group (TVC/CVP; 1.111) even when the data from the same range of CVP were used for the analysis. These results suggest that the smaller slope of CVP vs. TVC relationship in VX-groups may not be a result of the smaller CVP range in the VX-group. The afferent nerves from aortic arch arterial baroreceptor were also denervated by vagotomy. However, denervation of aortic arch arterial baroreceptor might attenuate increase in TVC, because MAP during progressive hyperthermia increased significantly. The effect of denervation of aortic arch baroreceptor afferent is opposite to the effect of cardiopulmonary baroreceptor afferent denervation which might attenuate decrease in TVC. These results suggest that the attenuation of decrease in TVC in response to the decreased CVP was mainly by the effect of denervation of the afferent nerves from the cardiopulmonary mecano-receptor and the cardiopulmonary baroreflexes partly contribute to the control of TVC during hyperthermia.

The fact that the decrease in TVC during hyperthermia was not completely abolished after vagotomy indicates that some factor or factors other than the cardiopulmonary baroreflex are involved in the control of TVC during hyperthermia. Possible mechanisms of the vasoconstriction during progressive hyperthermia, in addition to cardiopulmonary baroreflex, are as follows: 1) Increased plasma concentration of catecholamines induced by increased $T_b$ causing vasoconstriction. In the present study, we did not measure plasma catecholamine concentrations, but increased catecholamines during progressive hyperthermia has been reported in many species [1, 15]. 2) Direct local effect of heat on cutaneous circulation should be considered. An extreme increase in skin temperature has been reported to induce local vasoconstriction or heat-induced vasoconstriction which occurs especially in AVA-existing regions including the extremities of sheep [16], the fingers of humans [17], and the tail of rats [18]. Decreased TVC during heating might be partly caused by increased skin temperature, especially in the tail, because we used body surface heating with an infrared lamp to increase $T_b$. 3)
Resetting of arterial baroreflex response might cause peripheral vasoconstriction during hyperthermia. Gorman and Proppe [19] reported that the HR response to changed MAP was not altered, but HR at the same MAP increased by about 30 beats/min during hyperthermia in the baboon. Although they did not examine the arterial baroreflex control of TVC to changed MAP, arterial baroreflex control of TVC at increased \( T_b \) might be involved [9].

4) Blood gases and plasma electrolyte were not determined in this experiment, but increased respiratory rate during progressive hyperthermia causes hypocapnia [20], which might be related to the peripheral vasoconstriction during hyperthermia.

5) Relative peripheral vasoconstriction with the decrease in BV has also been reported during increased \( T_b \) by Proppe and his colleagues [5,21].

Although CVP decreased as \( T_b \) rose (Fig. 1), the magnitude of the decrease in CVP varied with BV levels and vagal denervation. Decreases in CVP from \( T_b \) of 37 to 43°C were 1.92 ± 0.24, 1.36 ± 0.28, 0.62 ± 0.14, and 0.35 ± 0.23 mmHg (N.S.) in the C-NBV, VX-NBV, C-LBV, and VX-LBV groups, respectively. Attenuation of the decrease in CVP with vagotomy suggests that the cardiopulmonary baroreflex has some role in the control of systemic vascular compliance. Decreased BV also attenuated the decrease in CVP during heating in both the C- and VX-groups, and the effect of BV modification was more significant in the C-groups. These results suggest that unloading of the cardiopulmonary baroreceptor by decreased BV or vagotomy may decrease the systemic vascular compliance, together with other BV-dependent mechanisms, to maintain cardiac filling pressure during hyperthermia [22–24].

SV showed significant correlation with CVP (Fig. 2) and the relationship was not influenced by initial BV or vagotomy, which indicates that SV was primarily controlled by cardiac filling pressure under the present experimental conditions.

Heart rate during heating showed similar responses among the four groups, irrelevant to initial BV level or vagotomy (Fig. 1). We previously reported that HR response during hyperthermia did not depend on initial BV levels [9]. In addition, the present study showed that this response was not affected by vagotomy. These facts illustrate that the change in HR during hyperthermia may be primarily influenced by increased \( T_b \), not by cardiopulmonary baroreflex. The increase in HR might be caused by an increasing sinus node discharge rate due to the direct effect of \( T_b \) [25], and/or resetting of arterial baroreflex control of HR [19] with the increased intravascular concentrations of catecholamines [3].

The hematocrit in the VX-LBV group was significantly smaller than that in the C-LBV group and the same tendency was observed in the VX-NBV group (Table 1). Increased renal sympathetic nerve activity, plasma renin activity, and AVP by removal of afferent signals from cardiac mechanoreceptor could be speculated as a possible mechanism [26], but further study is required as to the mechanism of plasma volume increase after vagotomy.

In summary, the cardiopulmonary baroreflex may partly contribute to the control of peripheral vasoconstriction together with \( T_b \) and/or BV-dependent
mechanisms during progressive hyperthermia.

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