Circulatory Failure during Severe Hyperthermia in Dog

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Abstract The effect of acute hyperthermia on circulatory function was studied in 6 mongrel dogs. At a core temperature of about 40°C, central venous pressure and stroke volume were maintained at almost normal level. Cardiac output significantly increased (26 ml/(kg·min)) while systemic vascular resistance significantly decreased (1.2 mmHg·sec/ml). In addition, significant decrease in vascular compliance by 40% was observed. When body temperature was raised further (severe hyperthermia), an abrupt fall of arterial pressure was observed at the rectal temperature of about 41–42°C. Concomitant decreases in central venous pressure (3 mmHg), stroke volume (2.1 ml/beat) and cardiac output (29 ml/(kg·min)) were observed while heart rate increased (48 beats/min). These results suggest that the decrease in cardiac output during severe hyperthermia is due to the fall of central venous pressure, and the fall was attributed to the increase in unstressed vascular volume of systemic circulation due to the heat-induced cutaneous vasodilation. The observed decrease in systemic vascular compliance is considered to have a significant role in the maintenance of central venous pressure under hyperthermia.

Key Words: hyperthermia, central venous pressure, vascular compliance, dog.

Circulatory failure is known to precede death from heat stroke (Clowes and O'Donnell, 1974; Sprung, 1979). Acute hyperthermia causes peripheral vasodilation and marked redistribution of cardiac output from visceral organs to the skin (Hales and Dampney, 1975; Hales et al., 1979). Rowell (1977) showed that hyperthermia causes the shift of blood from central organs to cutaneous vessel. As the responsible mechanism of the shift of blood, he proposed increase in cutaneous vascular compliance under hyperthermia. He also suggested that the shift causes the fall in central venous pressure or filling pressure of the heart and has a
crucial role in cardiac function.

Central venous pressure is determined by total systemic blood volume and systemic vascular compliance (Gauer and Henry, 1976). Recently we developed a method to measure circulating blood volume continuously (Tanaka et al., 1981) and used the method for the determination of total systemic vascular compliance (Morimoto et al., 1981). This method was used to analyze the relationship among circulating blood volume, central venous pressure and vascular compliance during severe hyperthermia. Based on the results, the mechanism of circulatory adjustment and the cause of circulatory failure under hyperthermia were analyzed.

METHODS

Surgical procedure and measurements. Acute experiments were carried out on 6 splenectomized mongrel male dogs weighing 10–12 kg. Anesthesia was induced with thiopental sodium (25 mg/kg). Each dog was weighed, placed in the supine position on a water mat which was warmed by circulating temperature-controlled water, intubated and ventilated with 1–2% halothane in 30% O₂-70% N₂O with a volume-limited respirator. The ventilation rate was set at 10–15 times/min with tidal volume of about 300 ml. Sodium heparin was administered at an initial dose of 5 mg/kg with a maintenance dose of 2.5 mg/(kg·hr) thereafter.

Blood volume, hematocrit and plasma colloid osmotic pressure of the circulating blood were monitored continuously using the procedure previously described (Tanaka et al., 1981). Briefly, blood was led by a pump into the arterio-venous extracorporeal shunt which includes a conductivity cell for hematocrit determination, a well-type γ counter for continuous determination of blood volume using the dilution method of ⁵¹Cr-labelled erythrocytes, a needle type oncotic pressure probe for plasma colloid osmotic pressure determination and blood reservoir. The blood in the reservoir was warmed by a temperature-controlled circulating water jacket around the reservoir. 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 through the left femoral artery and vein. Body temperature was monitored with a calibrated thermocouple placed in the rectum.

Cardiac output and central blood volume (cardio-pulmonary circulating blood volume) were determined by the dye-dilution method. Indocyanine green (Cardio-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, Ltd., Tokyo) to calculate the cardiac output and the mean transit time. The blood withdrawn was reinfused into the animal through the femoral vein catheter. The central blood volume was calculated by multiplying the cardiac output by the mean transit time of the indicator. The systemic blood volume was obtained by subtracting central blood volume from 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 of the ventricle was calculated from the cardiac output and the heart rate.

The effective compliance of the systemic vascular bed was determined from the relation between changes in central venous pressure and intravascular volume induced by the loading of Ringer's solution. Details of the techniques for measurement of compliance employed in this study have been described previously (MORIMOTO et al., 1981).

Experimental protocol. The experiment was conducted under 3 conditions:

Fig. 1. The time course of rectal temperature, mean systemic arterial and central venous pressure during induced severe hyperthermia. The values are represented as the differences from those under moderate hyperthermia. The arrows on each trace of mean systemic arterial pressure indicate the point of cardiac output and central blood volume determinations. The values of severe hyperthermia were obtained at this point.
1) normothermia, 2) moderate hyperthermia and 3) severe hyperthermia.

During normothermia, total systemic vascular compliance was measured. After 1–2 hr of allowance for recovery from blood volume modification, compliance, cardiac output and central blood volume were measured. Soon after the measurement, the dog was heated by increasing the temperature of water circulating around the blood reservoir and water mat under the animal. When rectal temperature was increased by about 1.6°C over a period of about 90 min, water temperature was adjusted to maintain the level. The cardiac output and central blood volume were measured after the body temperature reached a steady state at about 40°C (moderate hyperthermia), and then the total systemic vascular compliance under moderate hyperthermia was measured. Before the second heating pro-

Fig. 2. Changes in cardiac output, heart rate and stroke volume are shown as the difference from the values under normothermia. Values are means ± S.E. of 6 dogs.
Fig. 3. Changes in mean systemic arterial and central venous pressure and systemic flow resistance are shown as the difference from the values under normothermia. Values are means ± S.E. of 6 dogs.

procedure was commenced, cardiac output and central blood volume were measured again to assess the effect of the measurement of compliance. Therefore, two measurements were made under moderate hyperthermia (Figs. 2, 3 and 4). Here, the dog was heated again (the second heating) in the same way as the first heating, and an abrupt fall in systemic arterial pressure was observed when the rectal temperature reached about 41–42°C (Fig. 1). At this point (severe hyperthermia), cardiac output and central blood volume were measured.

Throughout the experiment, changes in systemic arterial pressure, central venous pressure, plasma oncotic pressure, hematocrit and blood volume were determined continuously.

The results are presented as means and standard error. The effects of acute
hyperthermia on each of the variables was compared on the basis of paired analysis and null hypothesis was rejected at 5% level.

RESULTS

Circulatory failure during severe hyperthermia

The time course of rectal temperature and mean systemic arterial and central venous pressures during the second heating period are shown as the difference from values under moderate hyperthermia. Rectal temperature increased linearly due to the continuous heating, while mean systemic arterial pressure was maintained at a constant level (101.4 ± 5.7 mmHg) until rectal temperature reached about 41–42°C, when the pressure showed a sharp drop. In only one case did mean systemic arterial pressure show a gradual drop from what it was at the onset of the second heating. Central venous pressure gradually decreased from the start of second heating. There was no significant change in plasma volume and plasma oncotic pressure even in the face of the circulatory failure.

Fig. 4. Changes in total blood volume, central blood volume (blood volume in cardiopulmonary circulation) and systemic blood volume are shown as the difference from the values under normothermia. Values are means ± S.E. of 6 dogs.
Changes in hemodynamic function under different levels of body temperature

The changes in cardiovascular functions (Figs. 2 and 3) and blood volume (Fig. 4) under different levels of body temperature are shown as the difference from the values under normothermia. The mean rectal temperature during normothermia, moderate and severe hyperthermia was 38.7±0.3°C, 40.3±0.2°C and 42.0±0.1°C (mean±S.E.), respectively.

Figure 2 shows the changes in cardiac output, heart rate and stroke volume as a function of rectal temperature. The average values of cardiac output, heart rate and stroke volume during normothermia were 108.4±4.7 ml/(kg·min), 178±9 beats/min and 6.5±0.3 ml/beat. During moderate hyperthermia, the cardiac output increased significantly by about 20% from the control value. The heart rate and stroke volume showed a tendency to increase during moderate hyperthermia compared with the control value. On the other hand, severe hyperthermia caused reduction in cardiac output, marked increase in heart rate and decrease in stroke volume.

Figure 3 shows the changes in mean systemic arterial pressure, central venous pressure and systemic vascular resistance from the values under normothermia. The mean and standard error of the mean systemic arterial pressure, central venous pressure and systemic vascular resistance during normothermia was 117.5±5.6 mmHg, 1.50±0.47 mmHg and 6.2±0.5 mmHg·sec/ml, respectively. Mean systemic arterial pressure decreased by about 10 mmHg during moderate hyperthermia and by about 60 mmHg during severe hyperthermia. Central venous pressure remained constant during moderate hyperthermia, but decreased significantly by 3 mmHg during severe hyperthermia. The systemic vascular resistance decreased linearly with the rise in core temperature, and the differences were significant both under moderate hyperthermia and severe hyperthermia. Figure 4 shows the changes in total, central and systemic blood volume. The respective values during normothermia was 70.1±2.4 ml/kg, 26.8±1.6 ml/kg, and 43.3±3.4 ml/kg. The total blood volume determined by 51Cr-RBC dilution method did not change during moderate and severe hyperthermia. The central blood volume, which was determined by indicator mean-transit-time method, did not change during moderate hyperthermia, while significant decrease of 5.1 ml/kg from the control value was observed during severe hyperthermia. The systemic blood volume, which was obtained by subtracting the central blood volume from the total blood volume, increased significantly by 6.6 ml/kg during severe hyperthermia.

Figure 5 shows the relationship between the change in blood volume and central venous pressure during normothermia and moderate hyperthermia. The slope of the linear regression line between central venous pressure and blood volume indicates the whole body vascular compliance, which was 4.49 ml/(kg·mmHg) and 2.82 ml/(kg·mmHg) under normothermia and moderate hyperthermia, respectively. The decrease of whole body vascular compliance by 40% from normothermia to moderate hyperthermia was statistically significant.
In more than 80 per cent of deaths from heat stroke, acute circulatory failure has been observed (O’DONNELL and CLOWES, 1972). In this experiment, changes in cardiovascular function and blood volume were measured under acute hyperthermia in the dog and the cause of circulatory failure due to severe hyperthermia was analyzed.

During the moderate hyperthermia up to 40.3°C of body temperature, systemic arterial pressure was maintained rather well with increased cardiac output. The increase was mainly due to the increase in heart rate. On the other hand, when body temperature was elevated up to 41–42°C, an abrupt fall in systemic arterial pressure was observed.

**DISCUSSION**

Fig. 5. The relation between changes in blood volume and central venous pressure in response to the infusion of Ringer’s solution. Results of 6 dogs are used. The slope of regression line represents the systemic vascular compliance. The difference between the slopes of the two regression lines was statistically significant.

![Graph](image.png)
arterial blood pressure was observed. At this point, cardiac output was lowered by 29 ml/(kg·min), and stroke volume was reduced by 2.1 ml/beat. The increase in heart rate by 48 beats/min was unable to compensate for the fall of cardiac output. Simultaneously, central venous pressure or right ventricular filling pressure decreased by about 3 mmHg. In other words, the central venous pressure plays a key role in maintaining the circulatory function under hyperthermia.

To analyze the cause of decline in central venous pressure, circulating blood volume and central venous pressure were monitored continuously and systemic vascular compliance was determined by means of the infusion of Ringer's solution. The amount of blood held by the systemic vascular bed depends both on the vascular compliance and on unstressed vascular volume (Shoukas and Sagawa, 1971; Tripodo, 1981). When central venous pressure is chosen as the reference parameter of the pressure-volume relationship of systemic circulation (Gauer and Henry, 1976), the relationship among central venous pressure, systemic vascular compliance and systemic vascular volume is represented as follows:

Total systemic blood volume = systemic vascular compliance × central venous pressure + unstressed systemic vascular volume,  
(Eq. 1)

where unstressed vascular volume stands for the volume which does not contribute to the increase of pressure. From this relationship central venous pressure can be represented as,

central venous pressure = (total systemic blood volume − unstressed systemic vascular volume)/systemic vascular compliance.  
(Eq. 2)

During moderate hyperthermia in this experiment, central venous pressure and blood volume were well maintained at a constant level (Figs. 3 and 4), although systemic vascular compliance decreased by about 40% (Fig. 5). These data suggest the increase in unstressed blood volume during moderate hyperthermia (Eq. 1). In other words, the decrease in systemic vascular compliance plays a significant role in the maintenance of central venous pressure and preventricular pressure under moderate hyperthermia. As the body temperature was elevated further, a progressive decrease in systemic vascular resistance and an abrupt fall of arterial pressure were observed. This fall suggests the existence of a critical point at which this balance is broken. The increase in cutaneous circulation under heat stress has been observed using the microsphere method by Hales and Dampney (1975) and Hales et al. (1979). Hyperthermia causes cutaneous vasodilation for heat dissipation, and the increase in heat induced pooling of blood in cutaneous vein (Rowell, 1977). During severe hyperthermia in this experiment, central venous pressure decreased by 3 mmHg although systemic blood volume increased by 5 ml/kg. From these results, the cause of the decline in central venous pressure can be attributed to the further increase in unstressed systemic vascular volume under severe hyperthermia.

The decrease in systemic vascular compliance observed during moderate hyperthermia might also be explained by the redistribution of blood volume due
to heat stress. The vascular compliances of visceral organs are higher than those for the extremities. For example, the vascular compliance of the liver is about 20 ml/(kg·mmHg) (GREENWAY, 1981), while the compliance of the cutaneous vein of forearm is about 0.63 ml/(kg·mmHg) (ECHT et al., 1974). Therefore, the redistribution of blood flow and volume from splanchnic to cutaneous region causes the decrease of systemic vascular compliance. ROWELL (1982) suggested in his review that the redistribution of blood flow can alter what might be called a "weighted effective compliance" of the vasculature without any active venomotor changes. We have determined the systemic vascular compliance under different levels of body temperature and showed that the compliance decreases as body temperature increases. The decrease in systemic vascular compliance has a significant role in maintaining central venous pressure or preventricular pressure and cardiac output.

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REFERENCES


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