METHODS

A Modified Thermodilution Method of Cardiac Output Measurements in Small Laboratory Animals

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A new simple and less traumatic modification of the thermodilution method is proposed for cardiac output measurements in small laboratory animals. In this modification, the thermistor is placed not in the major vessels, but in the esophagus at the level of the left ventricle.

Key words: *cardiac output*; *thermodilution*; *esophagus*; *small laboratory animals*

Cardiac output (CO), minute circulation volume as well as total circulation volume are the most important indices characterizing the functional state of the myocardium and peripheral vascular bed. In experiments, the thermodilution method is usually employed for measuring CO in small animals. In conventional modification of this method, an indicator is injected into the aorta, and its dilution is measured with a thermistor (TR) placed in the aorta distally to the point of injection [1]. In other modification the indicator is injected into *vena cava superior* and TR is placed in *a. pulmonaris* [2]; otherwise, indicator is injected into the right atrium or near the *ostium venae cavae* and the dilution is measured by TR in the aortic arch [5,6].

Catheterization of major vessels (aorta, *a. pulmonaris*, or their branches) and insertion of TR are a common disadvantage of all these approaches, especially in small animals. Since in rats, guinea pigs, and other experimental animals the diameter of these magistral vessels (aorta and pulmonary, carotid, and femoral arteries) does not exceed 1.5-2.5 mm, inserted catheter considerably diminishes their cross-sections and excites vascular wall interoceptors located along the catheter pathway. These factors may produce changes in the systemic hemodynamics and circulatory disturbances in the catheterized region. This can alter the cardiovascular reactions and lead to erroneous conclusions. Moreover, these methods cannot be used for repeated CO measurements in the same animal due to excessive traumatism under both repeated and long-term catheterization. It should be noted that this intervention includes traumatic surgical preparation of the major vessels lying deep inside and near the large nervous trunks.

The most close (by procedure) to our modification is the method of CO measuring by thermodilution [5], in which a small catheter with TR is inserted into the aortic arch, while the indicator (0.1 ml physiological saline at 20-24°C) is injected into the right atrium via a catheter inserted into the jugular vein. Changes in TR resistance due to cooling with physiological saline ejected from the heart into the aorta are recorded with electronic potentiometer in the form of thermodilution curves. The magnitude of CO is calculated according to the formula [6]:

$$CO=\frac{60\times M\times(T_1-T_2)\times R\times 1.146}{(F\times S)},$$

where M is injected volume, ml; T_1 — animal blood temperature, °C; T_2 — saline temperature, °C; R — recording rate, mm/sec; 1.146 is the ratio of specific heat capacities of the physiological saline and blood; F is multiplying factor for 1 mm on the plot, °C; S is area under the thermodilution curve, mm^2.

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The advantages of the proposed method are simple CO measurement, low traumatism, and prevention of hemodynamic changes.

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A small diameter catheter (0.5 mm) was inserted into the right atrium via the jugular vein. The esophageal catheter (1-2 mm) was inserted *per os* to the level of the left ventricle (LV). The indicator, 0.1-0.2 ml physiological saline at 0-20°C, was injected as a bolus into the right atrium. Physiological saline passing the LV modulates the TR resistance, which is graphically reflected on thermodilution curves recorded with a potentiometer.

In the given modification, CO calculated by formula [6] considerably differ from that obtained with usual TR location, because LV and esophageal walls reduce cooling of TR. This difference can be diminished by increasing injection volume, reducing saline temperature, or introducing a correction coefficient for the given animal species.

We compared results obtained with proposed and conventional methods and defined a correction coefficient for Wistar rats. For better accuracy, the experiments were carried out on male Wistar rats of the same age and weight (200±2 g). The standard location of TR was secured by fixing TR 1.5-2.5 cm proximally to the end of the catheter, depending on the animal size. When distal end of the catheter reaches the cardiodiaphragmatic sphincter, which can be easily defined by resistance to further thrust, TR comes very close to the LV. The visual control of TR location was performed using marks on the catheter.

RESULTS

For estimation of the correction coefficient the catheter was inserted into the aorta arch via the left carotid artery and the thermodilution curve was recorded. Then catheter with TR was removed and introduced again into the esophagus at the LV level, and thermodilution curve was recorded again. In both cases 0.15 ml physiological saline at 15°C was injected into right atrium.

A close correlation between the pairs of experimental values was found (Fig. 1), suggesting that the correction coefficient is constant for the proposed method of CO evaluation in the similar group of animals. For Wistar rats this coefficient was 0.5.

To assess the accuracy of the proposed method, CO was determined in three groups of Wistar rats. In the first group the thermodilution curves were recorded in the aorta, and in groups 2 and 3 in the esophagus. In groups 1 and 2, an MT-54 thermistor was used, and CO was calculated according to [6] (multiplied by 0.5

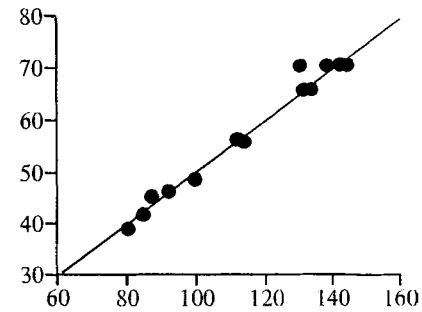

Fig. 1. Cardiac output (ml/min) obtained by conventional (ordinate) and modified (abscissa) methods. Each point corresponds to individual rat. The data fit to linear regression equation (straight line): $y=(0.49711\pm 0.00257)x$, $R=0.996$, $p<0.00001$.

in the second group). In group 3, a Baltherm catheter for thermodilution was used. CO was calculated using a Nihon Kohden RM-6000 polygraph built-in processor and then corrected by a factor of 0.5. The obtained values differed insignificantly (Table 1, Fig. 2). These values did not differ from cardiac indices (264±10 ml/min/kg) determined by conventional technique [3,4].

It should be noted that changes in the volume and temperature of saline did not affect the accuracy of repeated measurements in the same animal with an interval of 1 min. Therefore, our method allows to repeat measurements in the same animal. Figure 3 shows the dynamics of CO during hypovolemic shock. At the same time, in repeated measurements cooling the indicator below 10°C allows to diminish considerably the injected volume, although it leads to overcooling of the animal during repetitive thermodilution recordings. On the contrary, a higher temperature (above 15°C) of the indicator requires larger injection volumes, which increases the circulation volume. Both the volume and temperature depend on the TR and sensitivity of the recording system.

If the rat weights are in the range of 170 to 230 g, it is not necessary to recalculate the correction coefficient. Special experimental series showed that CO variations due to minor differences in the thickness of LV and esophageal walls did not exceed the standard error, and the obtained values corresponded to normal.

The advantage of our method in comparison with the conventional ones is its simplicity. It does not

TABLE 1. Cardiac Output (CO) and Cardiac Index Obtained by Various Methods ($M\pm m$)

Group	CO, ml/min	Cardiac index, ml/min/kg
Aorta (MT-54)	54.0±3.7	270.1±18.5
Esophagus (MT-54)	57.8±3.4	289.0±16.9
Esophagus (Baltherm)	60.5±4.2	302.5±21.2

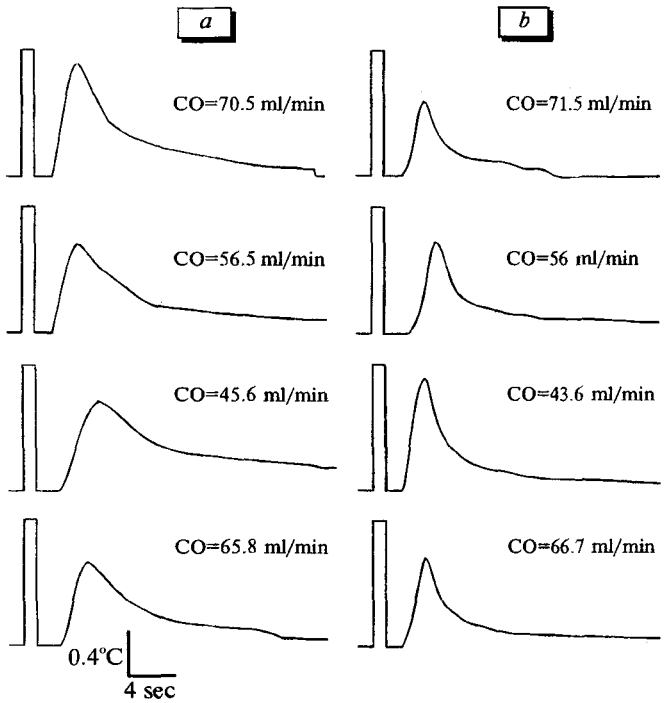

Fig. 2. Thermodilution curves and cardiac output (CO) obtained with conventional (a) and modified (b) location of a thermistor. Here and in Fig. 3: recording velocity 2.5 mm/sec, blood temperature 38°C, indicator — physiological saline (0.15 ml, 15°C).

require special skills in catheterization of major vessel and animal surgery. Only a little transcutaneous incision in the supraclavicular region should be done for jugular vein preparation and introduction of a catheter into the right atrium. Introduction of a TR in the esophagus is also an easy procedure.

This modification does not require extensive surgery and manipulations on arteries or near nerve trunks, which allows to minimize trauma and to avoid changes in the systemic hemodynamics. This improves the accuracy and reliability of experimental results. In addition, this modification may be used for repeated measurements, because catheterization of the jugular vein and its branches is not very traumatic. It is important that our modification does not require miniature TR, since the size of TR is limited only by the diameter of the esophagus, which is 3-4-fold larger than that of the aorta. However, the catheter should be flexible enough when working on guinea pigs because of esophagus dorsal flexure at the cervicothoracic level.

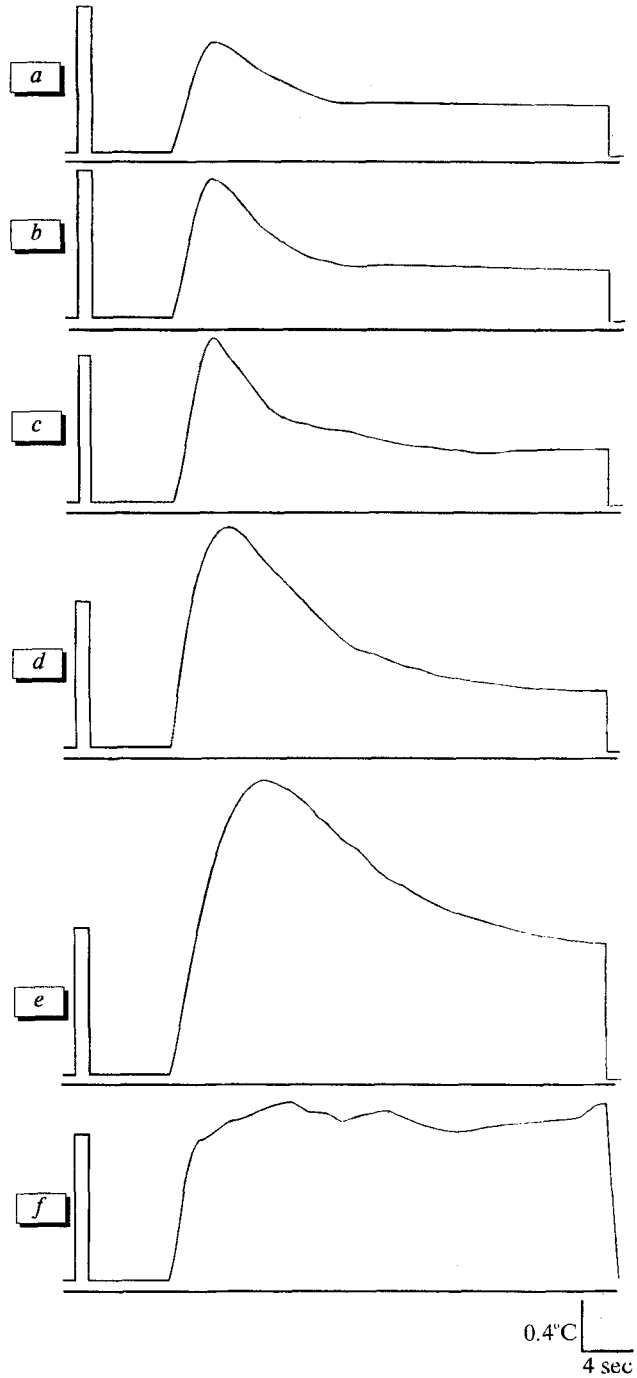

Fig. 3. Thermodilution curves and cardiac output (CO) in the dynamics of hypovolemic shock caused by hyperthermia. *a*) initial indices: rectal temperature (T_{rect}) 38°C, heart rate (HR) 400 beat/min, CO=62.7 ml/min, stroke volume (SV) 0.156 ml; *b*) hyperthermia: T_{rect}=41°C, HR=461 beat/min, CO=68.2 ml/min, SV=0.148 ml; *c*) hyperthermia: T_{rect}=43°C, HR=571 beat/min, CO=47.9 ml/min, SV=0.084 ml; *d*) 1 min after hyperthermia: T_{rect}=44°C, HR=545 beat/min, CO=29.7 ml/min, SV=0.054 ml; *e*) 10 min after hyperthermia: T_{rect}=43°C, HR=400 beat/min, CO=10.9 ml/min, SV=0.027 ml; *f*) cardiac arrest.

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