Institutional report - Experimental

The effects of cardiac cooling under surface-induced hypothermia on the cardiac function in the in situ heart

Yoshiharu Nishimura*, Yasuaki Naito, Takehiko Nishioka, Yoshitaka Okamura

Department of Thoracic and Cardiovascular Surgery, Wakayama Medical University, Wakayama City, Wakayama, Japan

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Abstract

It has been reported that in the excised cross-circulated dog heart model, cardiac cooling increases Emax (contractility index) and the external work (EW) of the left ventricle without affecting the systolic pressure volume area (PVA)-independent myocardial oxygen consumption (VO2). However, it remains unclear whether this cooling inotropism and oxygen-saving effect can also be demonstrated in an in situ heart. In the present study, we investigated the effect of cardiac cooling under surface-induced hypothermia in the in situ heart to assess the practical application of this method. Adult mongrel dogs were examined under surface-induced hypothermia with or without vasodilator. Using conductance catheter, pressure–volume relationship were obtained and mechanoenergetical parameters were measured. Optimal temperature for cardiac cooling was also examined. Simple hypothermia increased Emax compared with normothermia without affecting PVA-independent VO2, but EW did not increase. However, with concurrent vasodilator administration, cardiac cooling increased not only Emax but also EW without affecting PVA-independent VO2 compared with normothermia. However, at temperature below 32 °C, Tau increased significantly and diastolic dysfunction was noted. Cardiac cooling with concurrent vasodilator administration in the in situ heart has inotropic and oxygen-saving effects and optimal temperature for cardiac cooling is thought to be 34 °C.

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Keywords: Cardiac cooling; In situ heart; Pressure–volume relationship

1. Introduction

Induced hypothermia has been used clinically to lower whole-body and myocardial oxygen demand after cardiac surgery [1]. Moreover, it has been reported that cardiac cooling increases its contractility [2].

From mechanoenergetical approach, Suga et al. found that cardiac cooling increased contractility index (Emax) without affecting relation between O2 consumption per beat (VO2) and systolic pressure–volume area (PVA) and they proved that cooling inotropism has an oxygen-saving effect compared to catecholamines in the excised cross-circulated dog heart preparation [3]. If this oxygen-saving effect of cooling inotropism can be applied for the in situ heart, it could contribute to postoperative management for failing heart in cardiac surgery.

Unlike the excised cross-circulated heart preparation, the change in preload and afterload directly affects cardiac pump function in the in situ heart. Therefore, it is not clear whether the cooling inotropic effect in the excised heart preparation can also be demonstrated in the in situ heart.

*Corresponding author: Department of Thoracic and Cardiovascular Surgery, Wakayama Medical University, Kimiidera 811-1, Wakayama city, Wakayama, Japan.
Tel.: +81-073-447-2300; fax: +81-073-446-4761.
E-mail address: nishim-y@wakayama-med.ac.jp (Y. Nishimura).
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This study assessed the effect of cardiac cooling in the in situ heart under surface-induced hypothermia using pressure–volume relationship as well as the optimal temperature for cardiac cooling in the in situ heart to evaluate the clinical application of this method.

2. Subjects and methods

2.1. Experimental settings

The experiment was conducted on adult mongrel dogs. All of the animals involved in this experiment were treated according to guidelines recommended by the Japanese Association of Experimental Animals. Under anesthesia with intramuscular administration of 7 mg/kg of Ketamine hydrochloride and continuous intravenous administration of 0.08 mg/kg/min of pentobarbital sodium, the animals were placed under artificial ventilation Then, 0.7 μg/kg/min of atropine sulfate and 3 μg/kg/min propranolol hydrochloride were administered continuously throughout the experiment to block the autonomic reflex and the effect of endogenous catecholamines [4]. Following left thoracotomy, a pulse Doppler blood flowmeter (VF-1, Crystal Biotec Inc.) was applied proximal to the circumflex branch of the left coronary artery. A micro-manometer (8 Fr, Sentron Inc.) and a conductance catheter (7 Fr, LEYCOM Inc.) were inserted from the cardiac apex into the left ventricle to
continuously measure the left ventricular pressure and left ventricular volume, while simultaneously examining the left ventricular pressure-volume relationship. The conductances were summed and converted to volume using the computer system Sigma 5 (LEYCOM Inc.) [5]. The dogs were gradually cooled in the bath-tub filled by water and ice bag especially constructed for this purpose. Blood temperature was continuously monitored and the ice bags were placed in such a manner that a given degree of cooling temperature was maintained for about 30 min as a steady condition.

2.2. Measurement parameters

2.2.1. Systolic elastance (Emax; mmHg/ml)
The Emax has been reported to be obtained as the slope of the systolic pressure-volume relation (straight line) and to be an index of the left ventricular contractility that does not depend on the loading conditions of the heart [6,7]. A pressure-volume curve was drawn by changing the preload via transient occlusion of the inferior vena cava, and Emax was calculated as the slope of a regression line (Fig. 1A, B).

2.2.2. External work (EW; mmHg/ml)
EW, represented by the area surrounded by the pressure-volume loop, is the work of the left ventricle per beat to eject blood against the aortic pressure.

2.2.3. Stroke volume (SV; ml)
SV is represented as the length of the volume axis of the pressure-volume-area loop.

2.2.4. Pressure-volume area (PVA; mmHg/ml)
PVA is the area in the pressure-volume diagram that is circumscribed by end-systolic and end-diastolic pressure-volume relation curves and the systolic segment of the pressure-volume loop trajectory. It consists of EW and potential energy (PE), and shows the total mechanical energy produced by one heart beat [8] (Fig. 1A).

2.2.5. Myocardial oxygen consumption volume (VO2; ml O2/min)
The left circumflex area VO2 (CxVO2) was used as an index of VO2. The CxVO2 was calculated from the product of the blood volume in the circumflex branch of the left coronary artery (VO2; ml O2/min) and the coronary arteriovenous oxygen difference (Vol%) (CxVO2 per min) divided by 100. The blood flow in the circumflex branch of the left coronary artery was measured with a pulse Doppler flow meter.

2.2.6. VO2-PVA relationship per beat
The relationship between VO2 and PVA per beat obtained by alternately changing the preload and afterload is represented as a straight line, shown in Fig. 2A and Fig. 2B. The VO2 axis intercept represents the oxygen consumption required for the myocardial basal metabolism and calcium handling in excitation contraction coupling, i.e., PVA independent VO2.

2.2.7. Cardiac output (CO; l/min)
CO was obtained from the product of heart rate (HR) by SV.

2.2.8. Systemic vascular resistance (SVR; N·sec·m⁻²·10⁵)
SVR was calculated using standard formula [9].

3. Experiment protocol

3.1. Experiment 1 (simple hypothermia)
Five adult mongrel dogs weighing 12.3 ± 1.6 kg were used in this experiment. At first, mBP, CVP, HR, left ventricular pressure, volume, coronary blood flow, and coronary arteriovenous oxygen difference were measured under steady-state hemodynamic condition under normothermia (37–39 °C), and Emax, EW, PVA, CxVO2, VO2-PVA relation, CO, and SVR were calculated under normothermia. Surface hypothermia was then induced in the same adult dogs under the same conditions to decrease the blood temperature to 32 °C. After stabilizing the hemodynamics, the same measurements as those obtained under normothermia were then obtained under hypothermic conditions (hypothermia).
Table 1
Hemodynamic indices in the experiment 1 (simple hypothermia experiment)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normo</th>
<th>Hypo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>148.2 ± 28.0</td>
<td>114.6 ± 9.1*</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>76.6 ± 17.9</td>
<td>79.4 ± 22.1</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml O₂/min)</td>
<td>1.8 ± 1.0</td>
<td>1.3 ± 0.7*</td>
</tr>
<tr>
<td>Emax (mmHg/ml)</td>
<td>3.4 ± 1.5</td>
<td>4.4 ± 1.9*</td>
</tr>
<tr>
<td>PVA-independent VO₂ (ml O₂/beat-100 g LV)</td>
<td>0.6 ± 0.5</td>
<td>0.5 ± 0.4</td>
</tr>
<tr>
<td>External work (mmHg·ml)</td>
<td>887.9 ± 254.1</td>
<td>814.3 ± 260.8</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>13.5 ± 3.6</td>
<td>12.5 ± 4.1</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>2.0 ± 0.7</td>
<td>1.5 ± 0.5*</td>
</tr>
<tr>
<td>Systemic vascular resistance (N·sec·m⁻²·10⁶)</td>
<td>3281.2 ± 1785.7</td>
<td>4646.6 ± 2392.7</td>
</tr>
</tbody>
</table>

Normo: Normothermic run, Hypo: Hypothermic run.
*: P < 0.05, **: P < 0.01

3.2. Experiment 2 (hypothermia using vasodilator)

Five adult mongrel dogs weighing 15.4 ± 3.2 kg were used in this experiment. To examine the effect of the vasodilator, each parameter described above was measured under normothermia (37–38 °C). Following intravenous administration of 15 μg/kg/min of the ganglion blocking agent trimetaphan camsylate (Arfonad®, Nippon Roche) as a vasodilator, each parameter was measured again (normothermia with trimetaphan). Then, the blood temperature was lowered to 32 °C by surface hypothermia under administration of trimetaphan (hypothermia with trimetaphan).

3.2.1. Experiment 3 (optimal temperature for cardiac cooling in the in situ heart)

Five adult mongrel dogs weighing 15.6 ± 3.0 kg were used in this experiment. As the vasodilator, Chlorpromazine hydrochloride (CPZ; Contomine®, Yoshitomi) was used in this experiment, m BP, HR, Emax, EW, Work efficiency (WE; defined as EW/PVA), CO was measured. To access the parameter of diastolic function, the time constant (Tau) of isovolumic left ventricular pressure decline was also calculated. Following intravenous administration of 5 μg/kg/min of CPZ, each parameter was measured (normothermia with CPZ). The blood temperature was lowered to 34 °C by surface hypothermia under administration of CPZ (34 °C with CPZ) and each parameter was measured. Then, the temperature was lowered to 32 °C (32 °C with CPZ) and each parameter was measured.

The measured values are expressed as mean ± S.D. and the measured values under the respective conditions were compared using paired t-test and one way analysis of variance (ANOVA) with a significance level of P < 0.05.

4. Results

4.1. Experiment 1 (simple hypothermia)

Experimental data from five animals are shown in Table 1. Emax significantly increased under hypothermia (P < 0.01). However, EW did not show any significant difference under normothermia and hypothermia. CO decreased significantly under hypothermia, as HR reduced (P < 0.05). SVR showed a significant increase under hypothermia (P < 0.05). VO₂ axis intercept showed nearly equivalent values under normothermia and hypothermia.

4.2. Experiment 2 (hypothermia using vasodilator)

Experimental data from five animals are shown in Table 2. Emax did not change with or without the use of trimetaphan under normothermia, while Emax increased significantly under hypothermia with trimetaphan (P < 0.05). Like Emax, EW did not exhibit any significant difference with or without the use of trimetaphan under normothermia, and compared with those values, EW increased significantly under hypothermia with trimetaphan.

Table 2
Hemodynamic indices in the experiment 2 (hypothermia using vasodilator)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normo</th>
<th>Normo + Tr</th>
<th>Hypo + Tr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>152.6 ± 14.8</td>
<td>138.8 ± 18.2</td>
<td>103.8 ± 18.2*</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>109.8 ± 20.1</td>
<td>85.4 ± 17.1*</td>
<td>79.0 ± 14.3*</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml O₂/min)</td>
<td>2.7 ± 0.9</td>
<td>2.5 ± 0.9</td>
<td>1.9 ± 0.5*</td>
</tr>
<tr>
<td>Emax (mmHg/ml)</td>
<td>6.1 ± 1.4</td>
<td>5.5 ± 1.9</td>
<td>8.8 ± 2.2*</td>
</tr>
<tr>
<td>PVA-independent VO₂ (ml O₂/beat-100 g LV)</td>
<td>1.4 ± 0.5</td>
<td>1.8 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>External work (mmHg·ml)</td>
<td>421.7 ± 144.6</td>
<td>461.4 ± 196.6</td>
<td>585.7 ± 201.4*</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>5.2 ± 2.1</td>
<td>6.6 ± 2.1</td>
<td>8.0 ± 2.6*</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>0.8 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>Systemic vascular resistance (N·sec·m⁻²·10⁶)</td>
<td>12087.4 ± 5425.8</td>
<td>8039.0 ± 2914.1*</td>
<td>8147.4 ± 1261.9*</td>
</tr>
</tbody>
</table>

*: P < 0.05 vs. Normo, #: P < 0.05 vs. Normo + Tr.
Table 3
Hemodynamic indices in the experiment 3 (optimal temperature for cardiac cooling in the in situ heart)

<table>
<thead>
<tr>
<th></th>
<th>Norm + CPZ</th>
<th>34 °C + CPZ</th>
<th>32 °C + CPZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>133.2 ± 15.8</td>
<td>123.8 ± 6.3</td>
<td>109.4 ± 5.6*</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>108.2 ± 21.7</td>
<td>105.4 ± 31.6</td>
<td>105.6 ± 19.0</td>
</tr>
<tr>
<td>Emax (mmHg/ml)</td>
<td>6.6 ± 1.1</td>
<td>8.0 ± 1.0*</td>
<td>9.5 ± 1.0*</td>
</tr>
<tr>
<td>External work (mmHg·ml)</td>
<td>604.8 ± 140.5</td>
<td>766.0 ± 197.4</td>
<td>744.2 ± 223.8</td>
</tr>
<tr>
<td>Work efficiency (%)</td>
<td>37.0 ± 9.5</td>
<td>48.5 ± 8.2*</td>
<td>54.1 ± 6.1*</td>
</tr>
<tr>
<td>Cardiac output (/min)</td>
<td>1.0 ± 0.4</td>
<td>1.2 ± 0.3*</td>
<td>1.0 ± 0.3*</td>
</tr>
<tr>
<td>Tau (msec)</td>
<td>30.1 ± 8.9</td>
<td>36.6 ± 10.7</td>
<td>66.1 ± 17.3*</td>
</tr>
</tbody>
</table>

Norm + CPZ: Normothermic run using Chlorpromazine, 34 °C + CPZ: 34 °C using Chlorpromazine, 32 °C + CPZ: 32 °C using Chlorpromazine.
* P < 0.05 vs. Norm + CPZ, #: P < 0.05 vs. 34 °C + CPZ.

(P < 0.05). CO was nearly equivalent in the three groups with no reduction even under hypothermia. When the VO2-PVA relation under normothermia was compared with that under hypothermia with trimethaphan, the VO2 axis intercept under normothermia and hypothermia with trimethaphan showed almost equivalent values.

4.2.1. Experiment 3 (optimal temperature for cardiac cooling in the in situ heart)

Experimental data from five animals are shown in Table 3. Emax increased significantly under 34 °C with CPZ, as compared with Emax under normothermia with CPZ (P < 0.05); and Emax further increased significantly under 32 °C with CPZ, compared with Emax under the two conditions described above (P < 0.05). EW significantly increased under hypothermia (P < 0.05), but did not differ under 34 °C and 32 °C. WE (Work efficiency) increased significantly under 34 °C with CPZ, compared with WE under normothermia with CPZ (P < 0.05), but did not differ under 34 °C and 32 °C. Tau did not significantly differ between normothermia with CPZ and 34 °C with CPZ, but Tau significantly increased under 32 °C with CPZ compared to that under 34 °C with CPZ (P < 0.05).

5. Discussion

The mechanism of cooling inotropism as described in the previous reports include a decreased reaction rate of contractile protein and calcium ion, prolonged duration of excitation and contraction time, and slowing of cross bridge cycling [10–13]. Suga et al. reported that cardiac cooling increased Emax without affecting PVA-independent VO2 and has energetically more advantages in saving myocardial oxygen consumption compared to catecholamine in cross-circulated dog heart preparations [3].

The new findings in the present study are that in the in situ heart, cardiac cooling under surface-induced hypothermia with concurrent vasodilator administration has an inotropic effect and an oxygen-saving effect. The difference in the experimental model between the excised heart as described by Suga et al and the in situ heart examined in this study was the presence of peripheral vascular resistance. In the simple hypothermia experiment, cardiac contractility (Emax) increased, however, the external work of the left ventricle did not change. We hypothesized that the increased peripheral vascular resistance had an harmful effect on left ventricular afterload. Then, in the second experiment of this study, we use Trimethaphan Camysylate as a vasodilator. Consequently, with concurrent vasodilator administration, cardiac cooling increased Emax and external work, and did not change the VO2 axis intercept which was equivalent to the basal metabolism and calcium handling in the excitation–contraction coupling. However, cardiac output did not increase, probably due to the decreased heart rate caused by hypothermia.

We verified that Chlorpromazine hydrochloride had the same vasodilator effect as Trimethaphan Camysylate during cardiac cooling in the in situ heart. This result suggests that other vasodilators could be used in the same situation. Chlorpromazine hydrochloride is often used as a vasodilator during cardiopulmonary bypass in the cardiac surgery. We used Chlorpromazine hydrochloride to examine the practical application of this method.

Furthermore, we investigated the optimal temperature of cardiac cooling in the in situ heart. It is well known that one of the harmful effects of cardiac cooling is to induce ventricular fibrillation. Thinking of this harmful effect, we set up the temperature as normothermia, 34 °C and 32 °C in the experiment 3. We found that 34 °C was the optimal temperature for cardiac cooling in the in situ heart for the following reason. Although Emax increased the most under 32 °C, External work did not differ between 34 and 32 °C. Furthermore, Tau which is an index of ventricular relaxation or diastolic function significantly increased under 32 °C. These results suggest that under 32 °C reinforcement of systolic function was demonstrated. However, diastolic dysfunction was also demonstrated. Though the mechanism of diastolic dysfunction by cardiac cooling is not clearly understood, this side effect should be noted in therapeutic hypothermia.

The importance of peripheral vascular factor should be discussed not only hemodynamically but also metabolically, because, it would affect the cardiac function. In the present experiments metabolic abnormalities during hypothermia such as acidosis and electrolyte imbalance were corrected. However, in the clinical setting, rewarming process would produce the increased metabolic oxygen demand of the peripheral organs to the failing heart. Further evaluation will be necessary in the mehano-energetics of the rewarming heart.

References


