

# Myocardial Protective Effect of Hypothermia during Extracorporeal Circulation—By Quantitative Measurement of Myocardial Oxygen Consumption—

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**Objective:** To evaluate the effect of systemic temperature on myocardial protection during extracorporeal circulation, we quantitatively evaluated the relationship between myocardial oxygen consumption and rectal temperature.

**Materials and Methods:** Myocardial oxygen consumption during cardiac arrest was calculated via blood gas analysis of venous blood samples collected from the coronary sinus. The rectal temperatures of the patients during extracorporeal circulation ranged from 16.0°C to 33.5°C. The patients were classified into three groups according to their rectal temperature: group I (n=10; rectal temperature: 20.3±1.80°C), group II (n=24; rectal temperature: 29.4±0.97°C), and group III (n=29; rectal temperature: 31.7±0.72°C). The myocardial oxygen consumption of each group was then compared.

**Results:** The average of the myocardial oxygen consumption of all cases was 62.5±64.0 O<sub>2</sub> ml/min/100 mm<sup>3</sup> left ventricle volume, and the averages of the individual groups were 26.9±28.8 in group I, 72.2±71.8 in group II, and 69.3±62.6 in group III. There was a significant difference in the oxygen consumption between group I and the other two groups. There was a positive correlation between the rectal temperature and myocardial oxygen consumption, as reflected in the following formula:  $Y = -0.3 \times X + 1.10 \times X^2 - 0.02 \times X^3$  (Y, myocardial oxygen consumption; X, rectal temperature; R<sup>2</sup>=0.533; P<0.0001).

**Conclusion:** This study suggested that rectal temperature below 22.5°C is advantageous due to the resultant myocardial protection such hypothermia affords. (*Ann Thorac Cardiovasc Surg* 2003; 9: 155–62)

**Key words:** myocardial oxygen consumption, hypothermia, rectal temperature

## Introduction

Hypothermia in open-heart surgery is a widely used technique for providing organ protection. There are a few reports concerning the myocardial protective effect of systemic hypothermia.<sup>1-3)</sup> We directly measured the myocar-

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dial oxygen consumption and estimated the relationship between myocardial oxygen consumption and rectal temperature during open-heart surgery in order to evaluate the protective effect of hypothermic extracorporeal circulation (ECC) on myocardial injury.

## Patients and Methods

### 1) Patients

There were a total of 63 adult study patients that were divided into three groups following the rectal temperature measurement during ECC: group I (n=10; rectal temperature, 16.0-22.5°C; average, 20.3±1.80), group II

**Table 1. Preoperative variables**

No.	Variables	Group I	Group II	Group III	G I vs G II	G I vs G III	G II vs G III
1	Number of patients	10	24	29			
2	Number of data	19	47	37			
3	Age (y.o.)	61.9±13.3	60.1±11.3	66.7±7.4	NS	NS	NS
4	CTR (%)	55.2±4.5	53.0±8.8	49.8±7.3	NS	NS	NS
5	LVH (mV) on ECG	2.8±1.1	3.4±1.14	3.05±1.14	NS	NS	NS
6	LV volume (ml)	238.8±52.5	239.3±93.7	228.2±79.7	NS	NS	NS

CTR, cardiothoracic ratio; LVH, left ventricular hypertrophy; ECG, electrocardiogram; LV, left ventricle.

G I vs G II: comparison between group I and group II; G I vs G III, comparison between group I and group III; G II vs G III, comparison between group II and group III.

(n=24; rectal temperature, 26.0-30.5°C; average, 29.4±0.97), group III (n=29; rectal temperature, 31.0-33.5°C; average, 31.7±0.72). The preoperative variables are age, cardiothoracic ratio (CTR), left ventricular hypertrophy (LVH) on electrocardiogram (ECG), and left ventricle (LV) volume measured echocardiogram (Table 1). The operative procedures for each group consisted of ascending aorta – arch graft replacement (n=8), ascending aorta – arch graft replacement + aortic valve replacement (AVR) (n=1), Bentall's operation + ascending aorta – arch graft replacement (n=1) in group I, coronary artery bypass grafting (CABG) (n=9), valve replacement (n=8), Bentall's operation + a\* (n=7) [a\*, CABG (n=1)] in group II, and CABG (n=19), valve replacement (n=8), Bentall's operation (n=1), repair of endocardial cushion defect anomaly (n=1) in group III. We adjusted the rectal temperature during the operative procedure based upon the seriousness of each patient's clinical condition or the length of ECC.

## 2) Anesthetic technique

The anesthetic technique was standardized for all patients. After tracheal intubation, 3-5 µg/kg of fentanyl and propofol (3 mg/kg per hour) were infused, neuromuscular blockade was achieved by 0.1-0.15 mg/kg pancuronium bromide, and ventilation was adjusted to maintain normocapnea. Alpha stat acid-base management was adopted.

## 3) Myocardial protection and sample collection

After median sternotomy and heparinization (3 mg/kg), the standard cannulation technique was used to complete the ECC circuit. A standard ECC bypass circuit was used

in all patients including cannulation and hollow fiber membrane oxygenator (Quantum, Bard, USA). The extra corporeal circuit was primed with 1,600 ml for valve surgery and CABG or 2,000 ml for aortic arch graft replacement. The priming solution consisted of 0.5 ml/kg of bicarbonate, 1 ml/kg of mannitol, lactate ringer, heparin, plasma protein, and blood components to adjust the dilutional rate of the priming solution to the range from 20% to 25%. A non-pulsatile perfusion pump (Pemco Inc., OH, USA) was used throughout the procedure. Norepinephrine was used as necessary to maintain systemic perfusion pressure at 50-60 mmHg. For myocardial protection, cold blood cardioplegic solution, the average temperature of which ranged from 4°C to 7°C, was administered antegradely into the aortic root or directly into the coronary ostia in an intermittent fashion. Topical cooling was not used. A disposal blood cardioplegia delivery system (Gish Biomedical Inc., CA, USA) was used to mix blood from the main pump with St. Thomas solution in a ratio of one to two. After mixture, the final electric concentration of cardioplegia solution were Na (mEq/L), 134-140 (average, 136.8±1.6); K (mEq/L), 11.1-17.8 (average, 13.6±2.7); and the average hematocrit of infused cardioplegia was 10-13% (average, 11.2±1.9). It has been used after oxygenation, and the results of its blood gas analysis were saturation (Sat.) (%), 100; PO<sub>2</sub> (mmHg), 255-546 (average, 345±65.2); PCO<sub>2</sub> (mmHg), 24.1-42.6 (average, 33.0±4.5); pH, 7.418-7.642 (average, 7.535±0.054). The average interval between the cardioplegic infusions was 18.5±1.2 min, and the average dose of the cardioplegia was 492.4±98.5 ml at each infusion. The average frequency of the cardioplegia infusion per patient was 4.12±0.7 times. As shown in Table 2, there are

**Table 2. Intra- and postoperative variables in each group**

No.	Variables	Group I	Group II	Group III	G I vs G II	G I vs G III	G II vs G III
1	Range of rectal temperature (°C)	16.0-22.5	26.0-30.5	31.0-33.5			
2	Average of rectal temperature (°C)	20.3±1.8	29.4±0.97	31.7±0.72	<0.0001	<0.0001	0.0069
3	Total ECC time (min)	167.0±50.3	112.1±28.7	83.7±23.35	0.0003	<0.0001	0.00023
4	Aortic cross clamp time (min)	120.1±48.6	82.9±24.0	64.3±21.5	0.005	<0.0001	0.004
5	Interval of cardioplegia infusion (min)	23.7±6.5	17.7±5.7	16.5±4.4	0.0113	0.00036	NS
6	Frequency of cardioplegia infusion (times)	4.5±0.85	4.58±0.88	3.83±0.71	NS	<0.0001	0.0011
7	Infused volume of cardioplegia (ml)	523.1±129.2	490.5±136.5	509.2±183.3	NS	NS	NS
8	Postoperative maximum value of CPK-MB (mg/dl)	114.4±67.2	99.4±93.4	132.4±197.2	NS	NS	NS
9	Postoperative day for catecholamine support	2.42±4.2	1.65±1.5	2.47±6.8	NS	NS	NS

ECC, extracorporeal circulation; CPK-MB, creatinine phosphokinase myocardial band.

G I vs G II: comparison between group I and group II; G I vs G III, comparison between group I and group III; G II vs G III, comparison between group II and group III.

significant differences among the groups with respect to total ECC time, aortic cross clamp time, rectal temperature during cardiac arrest, interval of cardioplegic infusion, frequency of infusion of cardioplegia, and infusion volume of cardioplegia. The 13 French sized balloon catheter for retrograde infusion of cardioplegia (Terumo Cardiovascular Systems, Corp., MI, USA) was placed into the coronary sinus (CS) for collection of coronary venous blood by infusing cardioplegic solution antegradely (Fig. 1).

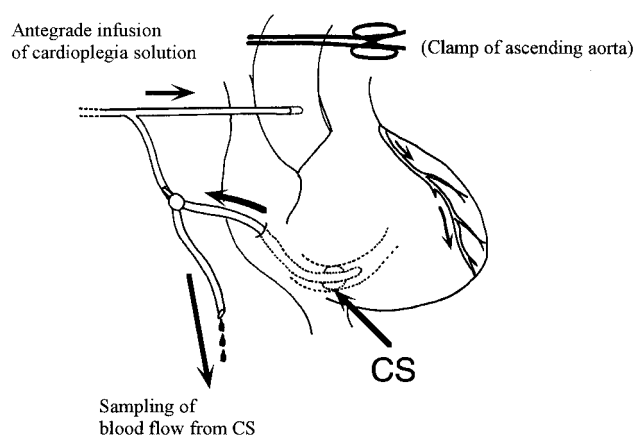
#### 4) Myocardial oxygen consumption

The oxygen content of the collected blood was measured with an ABL 330 blood gas analyzer (8 Radiometer A/S, Copenhagen, Denmark) at two points, when the infused cardioplegic volume reached 100 ml and just before the finishing of infusion of cardioplegia. From the difference of these oxygen contents, the myocardial oxygen consumption between the periods of the cardioplegia infusion was calculated according to formula-1 (Fig. 2).

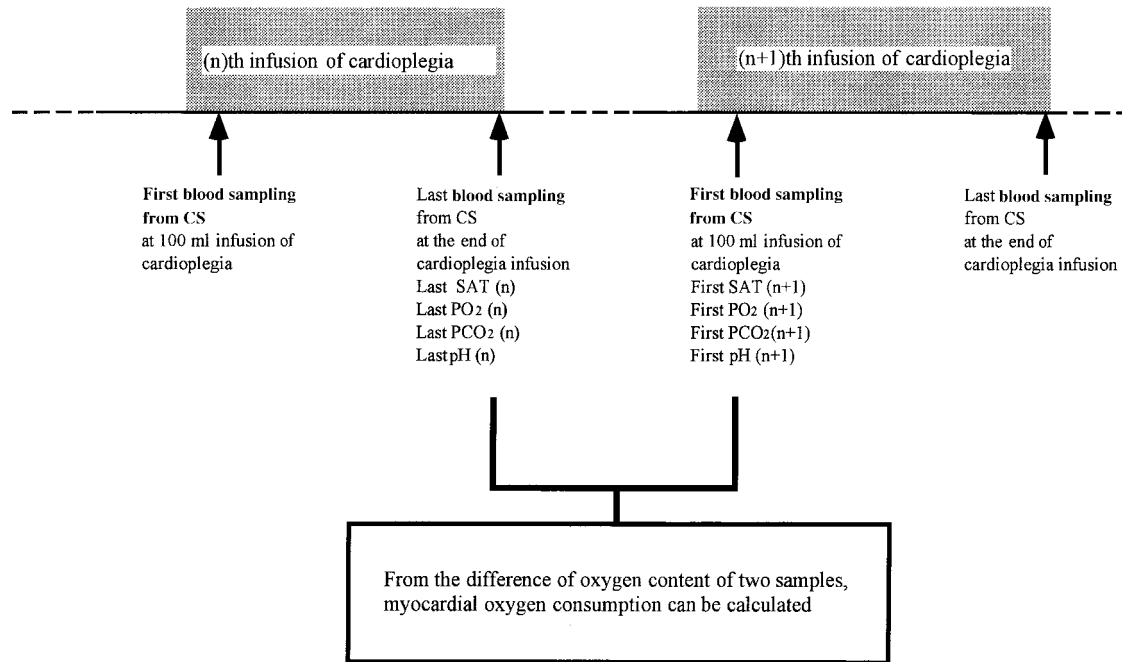
##### Formula-1

Myocardial oxygen consumption volume (O<sub>2</sub> ml)

$$= 1.34 \times 4 \times [(last\ SAT_n - first\ SAT_{n+1}) + 0.003 \times (last\ PO_{2n} - first\ PO_{2n+1})] \times \text{infused volume of cardioplegia (dl)}$$



**Fig. 1.** Schema of our cardioplegia delivery system, and sampling from coronary sinus. The balloon cannula was placed in the coronary sinus, from which the flowing blood was collected for measurement of myocardial oxygen consumption. CS, coronary sinus.



**Fig. 2.** Schema of the timing of blood sampling in each cardioplegic infusion by two points of sampling. Myocardial oxygen consumption could be calculated from oxygen contents at two points. CS, coronary sinus.

1.34\*: Oxygen volume (ml) fully saturated with 1 g of hemoglobin

4\*\*\*: Average hemoglobin concentration of the cardioplegia solution (g/dl)

0.003\*\*\*: Solubility coefficient for oxygen: oxygen volume (ml) of dissolution in 100 ml of blood per 1 mmHg of oxygen tension

Last SAT<sub>n</sub>: Oxygen saturation of the collected blood from the CS just before finishing (n)th infusion of cardioplegia

First SAT<sub>n+1</sub>: Oxygen saturation of the collected blood from the CS at initial 100 ml of (n+1)th infusion of cardioplegia

Last PO<sub>2n</sub>: Partial pressure of oxygen of the collected blood from the CS just before finishing (n)th infusion of cardioplegia

First PO<sub>2n+1</sub>: Partial pressure of oxygen of the collected blood from the CS at initial 100 ml of (n+1)th infusion of cardioplegia

The myocardial oxygen consumption per minute and per 100 mm<sup>3</sup> left ventricle (LV) volume (O<sub>2</sub> ml/min/100 mm<sup>3</sup> LV volume) was calculated by dividing the myocardial oxygen consumption volume with the interval period of the cardioplegia infusions and LV myocardial volume according to formula-2.

#### Formula-2

LV oxygen consumption (O<sub>2</sub> ml/dl/min/100 mm<sup>3</sup> LV volume) = [myocardial oxygen consumption volume / interval period of cardioplegia infusions (min) / LV myocardial volume (mm<sup>3</sup>)]

LV myocardial volume was measured with a preoperative echocardiogram according to the formula; LV mass (mm<sup>3</sup>) = 1.04 × [(IVSd + LVDd + PWTd)<sup>3</sup> - LVDd<sup>3</sup>].

IVSd (mm): interventricular septum

LVDd (mm): dimension of left ventricular diameter in the diastolic phase

PWTd: thickness of the posterior wall of the LV in the diastolic phase<sup>4)</sup>

The estimated LV myocardial volume ranged from 65.3 to 534.6 mm<sup>3</sup> with an average of 244.1 ± 108.2 mm<sup>3</sup>. From the second infusion of cardioplegia, the calculation of the myocardial oxygen consumption was carried out because the rectal temperature reached the targeted temperature and stabilized. The total number of the data obtained from all of the study patients was 103, which consisted of 19 data from group I, 47 data from group II and 37 data from group III.

#### 5) Intra- and postoperative data

Intraoperative variables included rectal temperature, to-

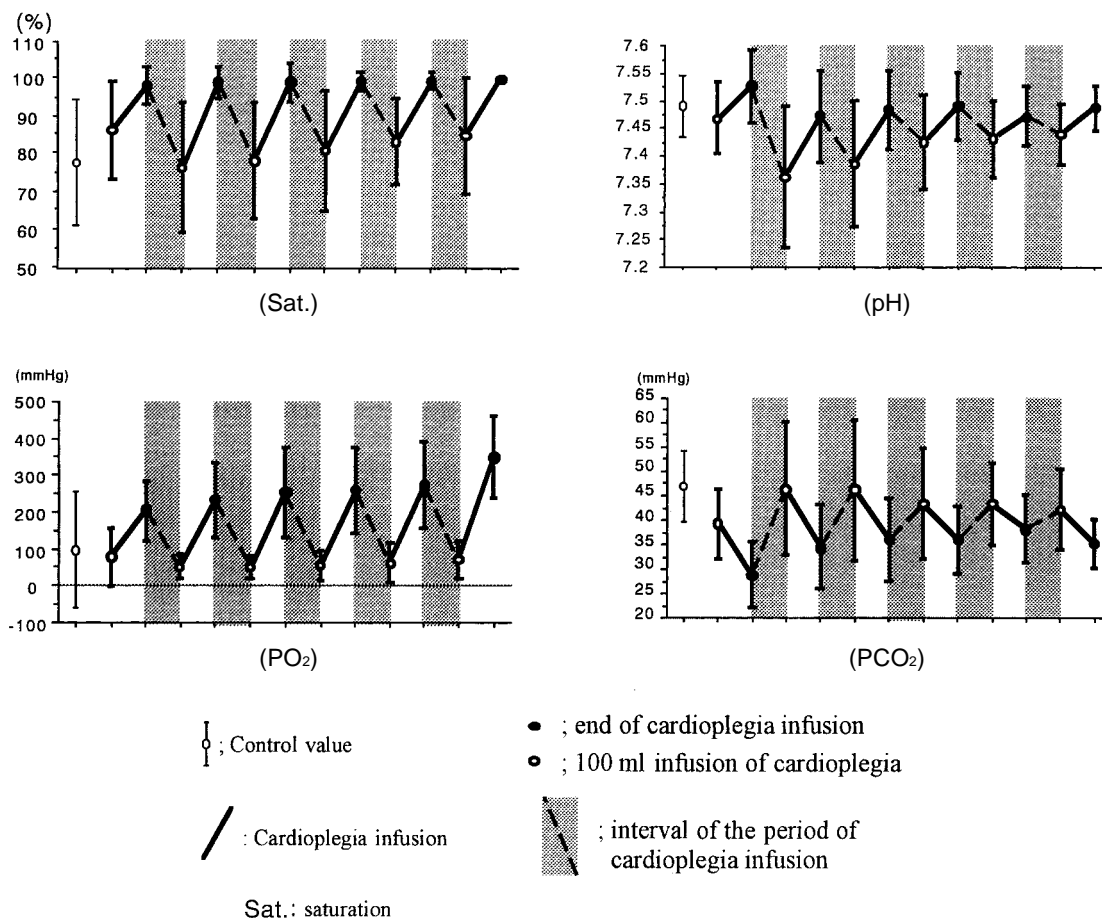


Fig. 3. Graphs showing three values of the collected blood: Sat., pH, PO<sub>2</sub>, and PCO<sub>2</sub>.

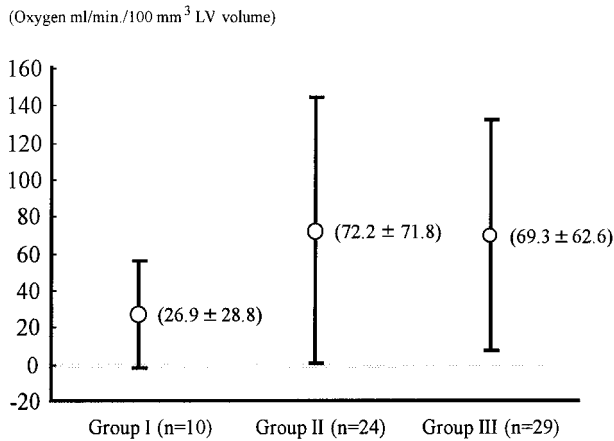
tal ECC time, aortic cross clamp time, interval of cardioplegia infusion, frequency of cardioplegia infusion, and the infused volume of cardioplegia. In the postoperative period, the following parameters were analyzed and compared: max value of postoperative value of creatinine phosphokinase myocardial band (CPK-MB) and dates of catecholamine administration.

#### Statistical analysis

The data in this study are expressed as means  $\pm$  standard deviations (SD). The differences between variables including the myocardial oxygen consumption in three groups were determined by the Tukey-Kramer test. The correlation between rectal temperature and myocardial oxygen consumption was estimated by simple regression testing. All computations were performed using Stat View 5.0 (SAS Institute, Cary, NC, USA) statistical software packages.

#### Results

- 1) The groups had no differences with respect to preoperative characteristics such as age, CTR, LVH on ECG, and LV volume measured by echocardiogram (Table 1).
- 2) In terms of intra- and postoperative variables, there are significant differences between the total ECC time, aortic cross clamp time, the interval of cardioplegic infusion, and the frequency of cardioplegic infusion. The differences were predominantly attributable to the length of the operative procedure during aortic cross clamping. Group III, consisting of almost all CABG cases, had a shorter interval of cardioplegic infusion of every completion of coronary anastomosis (Table 2). However, there was no difference between the postoperative max CPK-MB and the postoperative date of required catecholamine support.
- 3) The courses of Sat., pH, PO<sub>2</sub>, PCO<sub>2</sub>, and of the col-



**Fig. 4.** In group I, significantly lower oxygen consumption occurred compared to the other two groups.

lected coronary sinus blood (Fig. 3)

The collected blood at the time of the 100 ml cardioplegic infusion showed hypoxemia, hypercarboxemia, and acidosis. The collected blood just before finishing of infusion of cardioplegia showed normal values for pH, PCO<sub>2</sub> with good oxygenation.

#### 4) Myocardial oxygen consumption (Fig. 4)

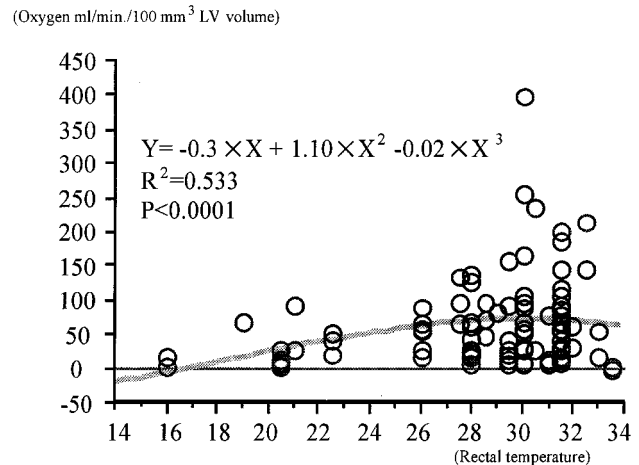
The overall average of the myocardial oxygen consumption rate was 62.5±64.0 O<sub>2</sub> ml/min/100 mm<sup>3</sup> LV volume, and the rates of the individual groups were 26.9±28.8 in group I, 72.2±71.8 in group II, and 69.3±62.6 in group III. Among the three groups, there were significant differences between group I and group II (P<0.05) and between group I and group III (P<0.05). There was no significant difference between group II and group III.

#### 5) The correlation between rectal temperature and myocardial oxygen consumption

There was a positive correlation between rectal temperature and the myocardial oxygen consumption rate, as described by the correlation formula of  $Y = -0.3 \times X + 1.10 \times X^2 - 0.02 \times X^3$  (Y, myocardial oxygen consumption rate; X, rectal temperature; R<sup>2</sup>=0.533; P<0.0001) (Fig. 5).

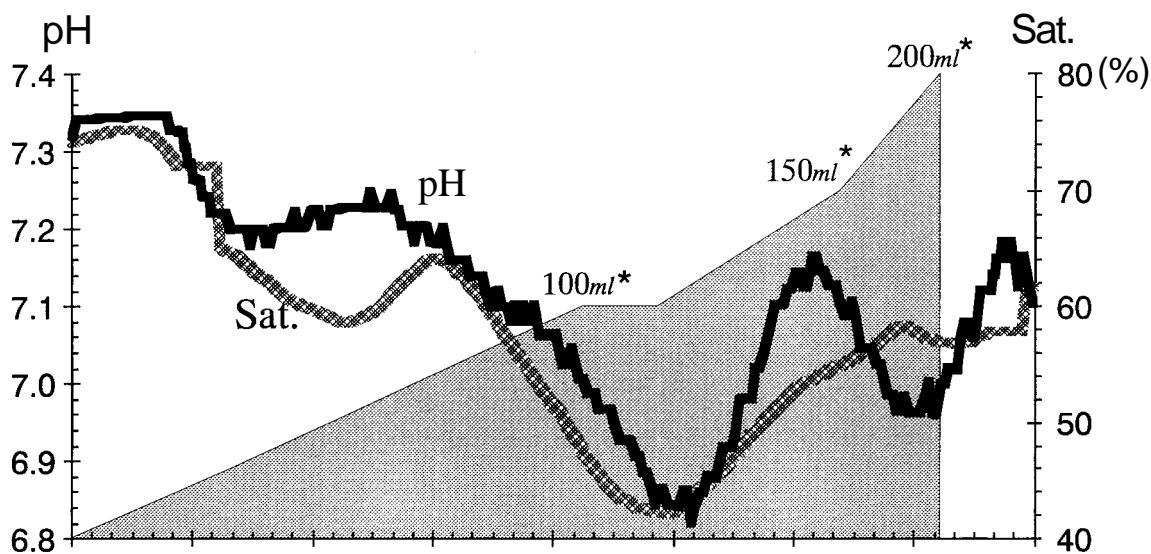
## Discussion

The object of hypothermia during ECC is to prevent ischemic injury of the organs, which can be induced by a relative insufficiency of perfusion for organ metabolism. However, the optimal temperature of hypothermia for each disease is not yet clear, and the temperature setting of



**Fig. 5.** There was a linear correlation between rectal temperature and the oxygen consumption rate of the myocardium.

ECC currently tends to be higher than before in order to avoid side effects of hypothermia such as postoperative coagulation problems.<sup>5,6)</sup> There are a few reports concerning the effects of systemic temperature during ECC on myocardial metabolism.<sup>2,3)</sup> There are few reports that quantitatively study myocardial oxygen consumption in the clinical setting during ECC. We directly measured the myocardial oxygen consumption during cardiac arrest by using blood gas analysis of the blood flowing from the CS in an antegrade infusion of cardioplegia. Prior to this study, we carried out the basic experiment by using three porcine models (weighting 30-40 kg) for the timing of blood sampling from CS. Figure 6 shows the continuous record of pH and Sat. of the blood flowing from the CS with antegrade infusion of cardioplegic solution from the aortic root. The lowest values of pH and Sat. occurred when the approximately 100 ml of cardioplegia was infused antegradely, which means that part of blood contains the metabolites reflecting myocardial metabolism during the period between the cardioplegic infusions. Clinically, the blood flowing from the CS during the 100 ml infusion of cardioplegia is the darkest, which suggests deoxygenated blood, and is an indicator of the timing of the blood sampling. At the time just before finishing cardioplegia infusion, the environment of the myocardium is thought to be refreshed because any myocardial metabolites should have been washed out. We collected the blood samples at 100 ml infusion of cardioplegia and at the time just before finishing cardioplegia infusion. From the difference in oxygen contents between these two samples, the myocardial oxygen consumption during the



**Fig. 6.** In porcine models, the blood pH, PO<sub>2</sub> and PCO<sub>2</sub> of the sampling blood from CS were measured continuously by using Paratrend 7 system (PT 7) (Biomedical Sensors, High Wycombe, UK). The Sat. of sample blood was calculated from the PO<sub>2</sub> value. Under the condition of total ECC, these measurements were carried out at the three levels of rectal temperature, which were 20°C, 25°C, and 30°C. The lowest value of pH and Sat. at each rectal temperature were observed at the 100 ml of initial infusion of cardioplegia solution as shown in Fig.

\*, infusion volume of cardioplegia antegradely; Sat., saturation.

period of cardioplegia infusions could be calculated. There are a few reports of myocardial metabolism assessments in the clinical setting of open-heart surgery.<sup>7)</sup> Our method reported herein seems to be one of the simplest and most useful methods for intraoperative monitoring whether myocardial protection is effective. In our hospital, we determined the required dosage of cardioplegic solution based upon the result of the analysis of coronary venous blood because the myocardial oxygen consumption rate is fundamentally different depending upon the type and severity of the disease or the systemic temperature. As the patients in this study are of a heterogeneous population, there is a limitation on this paper from this view point.

It is clear that myocardial metabolism is suppressed as myocardial temperature decreases.<sup>2,8,9)</sup> In this study, the suppression of myocardial oxygen consumption via systemic hypothermia is considered to be secondary to cardiac hypothermia, which was induced by lower systemic temperatures. In an animal study, Grover and colleagues also showed that a systemic temperature of 23°C enhances cardioplegic myocardial protection compared to systemic temperatures of 30°C and 37°C, and the mechanism of

this hypothermic effect on myocardial protection was hypothesized to be attributable to lower myocardial temperature.<sup>2)</sup> Hypothermia is still advantageous for protecting the myocardium, which is the focus of postoperative recovery. In particular, myocardial protection in the operations that require longer ECC such as aortic arch graft replacement is more important.

For collection of CS blood, the balloon catheter was placed in the CS. For good fixation of the balloon cannula in CS, the tip of the balloon cannula was located somewhat deeply in the CS, where the collected blood could be derived almost entirely from the LV. Therefore, the calculated myocardial oxygen consumption rate in this paper might not reflect that of the whole heart, and thus, there is a limitation in this paper in attempting to describe the metabolism of the entire heart.

In conclusion, we demonstrated that myocardial oxygen consumption was suppressed when rectal temperature is below 22.5°C, and there was a positive correlation between myocardial oxygen consumption in ECC and rectal temperature, which ranged from 16°C to 33.5°C.

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