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## Abstract

We studied whether a cardiopulmonary bypass (CPB) and a core-cooling technique could resuscitate an arrested heart, and whether this procedure benefited canine cadaveric heart transplantation. Donor dogs were subjected to brain death by an intracranial balloon technique, and then, to cardiac arrest conducted by cutting off ventilatory support. In the control group (Group 1; n = 8), arrested hearts were flushed with cardioplegic solution and harvested thereafter without any resuscitation technique. In the experimental group (Group 2; n = 8), arrested hearts were once resuscitated using CPB, and then harvested using a core-cooling technique and cardioplegia. These hearts were transplanted orthotopically. Seven of eight recipients in Group 1 were weaned from CPB, and five of them finally became independent of dopamine administration. All recipients in Group 2 were successfully weaned from CPB, and also became dopamine free eventually. In Group 2, all post-transplantation hemodynamic values such as cardiac output during the period of dopamine administration were equivalent to those of post-brain death period. Chemical analysis of the serum and myocardial muscle demonstrated no difference between groups. We conclude that CPB combined with a core-cooling technique makes it possible to utilize an arrested heart as a donor organ for transplantation.

**KEYWORDS:** heart transplantation, brain death, cadaver heart, core coolong, Emax

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# Transplantation of the Canine Cadaver Heart Using a Core-Cooling Technique

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**We studied whether a cardiopulmonary bypass (CPB) and a core-cooling technique could resuscitate an arrested heart, and whether this procedure benefited canine cadaveric heart transplantation. Donor dogs were subjected to brain death by an intracranial balloon technique, and then, to cardiac arrest conducted by cutting off ventilatory support. In the control group (Group 1; n = 8), arrested hearts were flushed with cardioplegic solution and harvested thereafter without any resuscitation technique. In the experimental group (Group 2; n = 8), arrested hearts were once resuscitated using CPB, and then harvested using a core-cooling technique and cardioplegia. These hearts were transplanted orthotopically. Seven of eight recipients in Group 1 were weaned from CPB, and five of them finally became independent of dopamine administration. All recipients in Group 2 were successfully weaned from CPB, and also became dopamine free eventually. In Group 2, all post-transplantation hemodynamic values such as cardiac output during the period of dopamine administration were equivalent to those of post-brain death period. Chemical analysis of the serum and myocardial muscle demonstrated no difference between groups. We conclude that CPB combined with a core-cooling technique makes it possible to utilize an arrested heart as a donor organ for transplantation.**

*Key words :* **heart transplantation, brain death, cadaver heart, core cooling, Emax**

Heart transplantation is the most advanced option in the treatment of end-stage cardiac disease, and development in immunosuppressive therapy has considerably improved the results of transplantation. However, the technique of heart transplantation has suffered from a donor shortage (1). Furthermore, successful heart transplantation has not been performed in Japan, where the cultural and religious background makes it difficult to accept the concept of brain death (2). Since the national or social consensus for brain death has not been established yet, we have examined in the present study whether resuscitation by a cardiopulmonary bypass (CPB) and core-cooling technique makes it possible to utilize an arrested heart for transplantation.

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## Materials and Methods

*Animals.* Sixteen pairs of size-matched, healthy beagle dogs weighing 9.0 to 10.8kg were used for orthotopic heart transplantation. Another 21 healthy mongrel dogs weighing 7.0 to 10.5kg were also used to measure myocardial concentrations of high energy phosphates before and after preservation. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

*Surgical procedure and experimental protocol.* The donor dogs were anesthetized with ketamine hydrochloride and sodium pentobarbital. Following endotracheal intubation, the animals were placed on a volume-cycled ventilator. Electrodes to record the electrocardiogram were inserted subcutaneously into four extremities. Intravascular catheters were placed in the femoral vessels for continuous monitoring of arterial pressure and an infusion route for

drugs. After receiving cefamandole naftate, donors underwent median sternotomy. A thermodilution catheter (Swan-Ganz catheter) was placed through the right external jugular vein into the pulmonary artery (PA). A fine catheter were inserted into the coronary sinus to measure the serum concentration of creatine phosphokinase MB isozyme (CPK-MB) in the coronary effluent. A microtipped manometer (model SPC-350, Millar Instruments, Houston, TX) and a conductance catheter (Cordis Europa NV, Roden, the Netherlands) were introduced into the left ventricle (LV) through the apex to record instantaneous changes in LV pressure and LV volume (3, 4). A multiple-holed catheter was inserted into the left atrium (LA) through the LA appendage to measure LA pressure and serve as a vent.

After the preliminary instrumentation, a burr hole was drilled in the right frontal area of the skull, the dura mater was incised, and a Foley catheter was introduced into the subdural space (5). The rapid injection of 20 ml of water which inflated the balloon of the catheter, produced an acute increase in intracranial pressure resulting in herniation of the brainstem. Brain death occurred within 20 min, as confirmed by neurological examination.

One hour after brain death, the donors were systemically heparinized (300 U/kg), and disconnected from the ventilator. Within 10 min, the blood pressure fell to 0 mm Hg, or cardiac arrest occurred. The donors were left still for 3 min without any manipulation.

In the control group (Group 1; n = 8), the ascending aorta was clamped, the aortic root was perfused using 15 ml/kg of cold (4°C) crystalloid cardioplegic solution (Saline 1,000 ml, 1 mEq/ml potassium chloride 20 ml, 10 % magnesium sulfate 40 ml, 2 % procaine hydrochloride 13.6 ml, 50 % glucose solution 4 ml, 8.4 % sodium bicarbonate 2 ml, 8.5 % calcium gluconate 6 ml) for 3 min, and topical cooling was initiated by pouring an ice-slush of saline into the pericardial sac. The heart was harvested and preserved in cold (4°C) saline solution (Fig. 1).

In the experimental group (Group 2; n = 8), the donors were cannulated for CPB. Before disconnecting the ventilator, an arterial cannula was inserted into the right common carotid artery as an inflow route and a two-stage venous cannula into the right atrium (RA) as an outflow route. Each was connected to a cardiopulmonary bypass unit consisting of a roller pump, a membrane oxygenator and a heat exchanger, primed with blood and dextran. Following 3 min of cardiac arrest, CPB was started at 37 °C. Fibrillation or contraction of the heart resumed within a few min, and defibrillation was performed by DC countershock for Vf. The donor heart was assisted by CPB for 30 min, then the animal was cooled using CPB. When the myocardial temperature reached 15 °C, the ascending aorta was clamped, and the aortic root was perfused with cold cardioplegic solution. The heart was harvested and immersed in the same fashion as in Group 1.

The induction of anesthesia in the recipients was performed in the same way as the donors. Following median sternotomy, each recipient was heparinized (300 U/kg), and cannulated inserting an arterial cannula into the right common carotid artery and venous cannulas into the superior and inferior venae cavae. CPB was initiated, and the recipient's native heart was excised. The hearts were transplanted as described by Lower and Shumway (6). The sequence of anastomoses was LA, PA, ascending aorta and RA. Catheters were inserted into the heart in the same manners as in the donor to measure cardiac function.

After the completion of the anastomoses, the aortic cross-clamp was released. Beating soon resumed, though all recipient dogs, except one in each group, required DC countershock. After one hour of assistance by CPB, recipient dogs were weaned from CPB. In order to maintain the systolic arterial pressure at more than 70 mm Hg in the range of an LA pressure of less than 10 mm Hg, dopamine was infused (5 $\mu$g/kg/min), as needed. Heart rate was maintained by cardiac pacing at a fixed rate of 120 beats per min.

*Hemodynamics.* Emax, cardiac output (CO), and max dP/dt were used as indices of hemodynamic function. Emax, the slope of the end-systolic pressure-volume relation (ESPVR) line, was calculated from the LV pressure and volume using software (provided by Taisho Biomedical Instruments Co., Osaka, Japan). Transient acute volume unloading was induced by 10 sec of occlusion of the inferior vena cava, and LV volume was measured with a conductance catheter and a signal converter (Sigma 5, Leycom, Ocgstgeet, the Netherlands). CO was measured using a thermodilution catheter and an output computer at a constant LA pressure. Max dP/dt, the maximum rate of rise in the LV pressure, was recorded by polygraph (San-ei polygraph 360, San-ei Inc., Tokyo, Japan).

A data set was collected at pre-brain death, post-brain death, post-resuscitation and post-transplantation. Post-resuscitation data were obtained after the CPB and following temporary ventilation during the interval between normothermic perfusion and core-cooling. Post-transplantation data with or without dopamine was obtained 1 h after termination of CPB. Values of hemodynamic indices were calculated by the following formula: percent change in hemodynamic index = measured value/post-brain death value × 100.

*Serum CPK-MB.* CPK-MB was measured as an index of myocardial injury 30, 60, and 120 min after reperfusion in recipients. The serum CPK-MB concentration was determined by the UV-method. CPK-MB values were corrected for hemodilution using the formula: corrected concentration = measured concentration × pre-reperfusion hematocrit/hematocrit of the sample.

*Myocardial high-energy phosphate concentrations.* As an index of energy metabolism of the donor hearts, myocardial concentrations of adenosine 5′-triphosphate (ATP) and creatine phosphate (CP) were measured. Another 21 mongrel canine hearts were harvested and preserved in the same way as the hearts of beagle dogs in the main experiments of each group. Specimens were obtained from these mongrel canine hearts at following points: thoracotomy (control), harvest, and post-preservation. Post-transplantation specimens were obtained after the final hemodynamic data were acquired in the main experiments. The posterior LV wall was picked up using pliers which had been frozen in liquid nitrogen, and was excised with a knife. Specimens

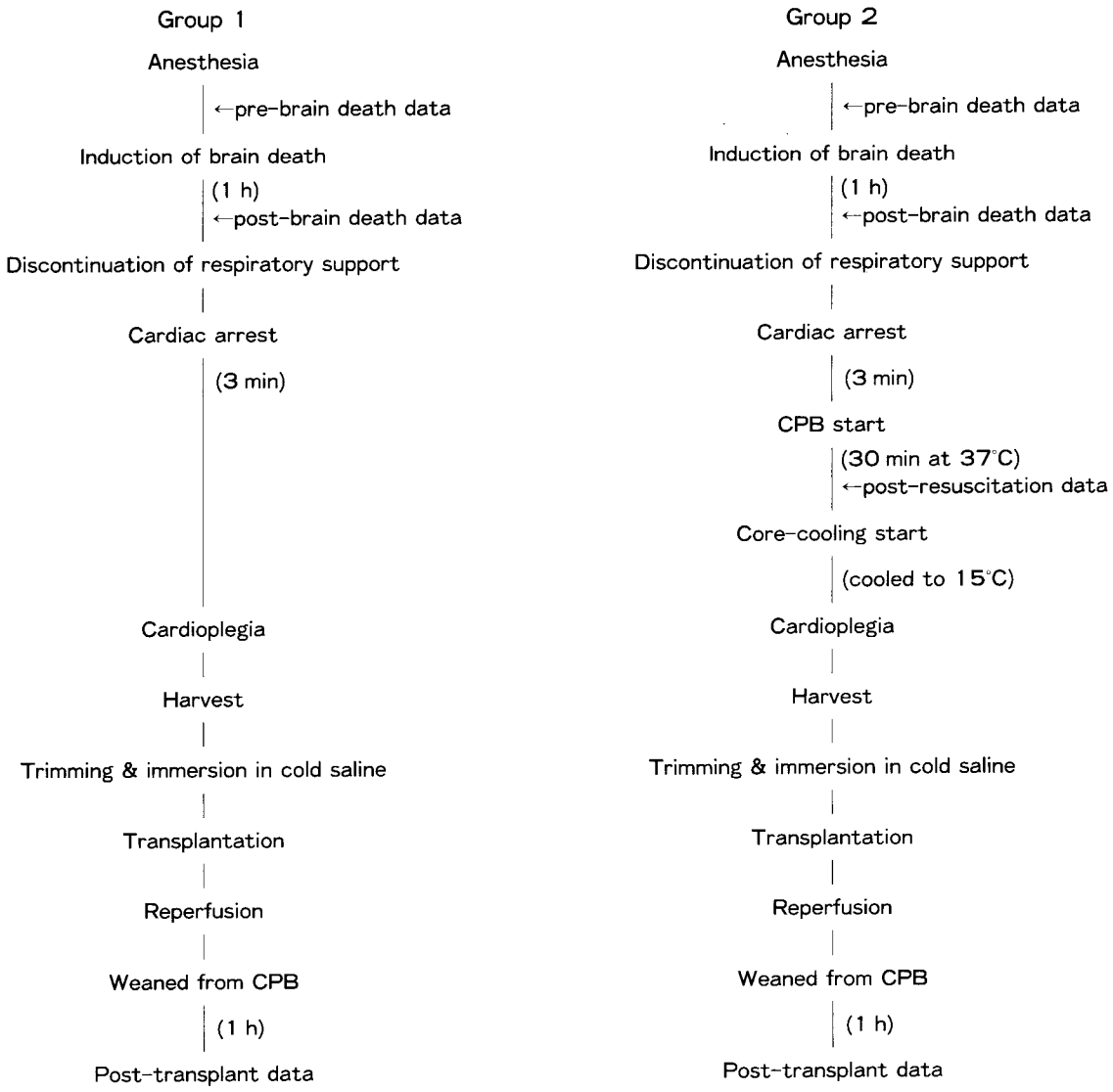


**Fig. 1** Experimental protocols in Groups 1 and 2. CPB: cardiopulmonary bypass.

were immediately preserved in liquid nitrogen. The myocardial ATP and CP concentrations were measured by the modified luciferin-luciferase method described by Bessho (7).

*Statistical analysis.* Results are expressed as the mean ± standard deviation. Analysis of variance was applied to the data, and paired or unpaired Student's $t$ test was used, as appropriate. The linear regression was calculated by the least squares method for the study of the correlation between post-resuscitation and post-transplantation hemodynamics. The $\chi^2$ test was used for weaning rates from the assistance of CPB and dopamine. A $p$-value of less than 0.05 was considered significant.

## Results

A few min following the induction of brain death, the systolic arterial pressure rose to 289.7 ± 30.3 mm Hg and heart rate to 178.1 ± 22.1 beats per min (Cushing's reflex) (8), and then decreased slowly thereafter. The mean arterial pressure began to decrease following brain death, and Ringer's lactate solution was infused in order to maintain mean arterial pressure more than 60 mm Hg. Neither Vf nor cardiac standstill occurred in any of donors after the induction of brain death in either group.

Seven of eight recipients in Group 1, and all recipients in Group 2 were weaned from CPB, though dopamine administration was necessary in all cases. Five of seven recipients in Group 1 and all recipients in Group 2 were successfully weaned from dopamine support therapy. The difference in the weaning rate from dopamine came close to statistical significance ($p = 0.051$). No significant differences existed between the two groups as far as time of hypoxia (from disconnection of the ventilator to cardiac arrest), time of ischemia (from clamping the aorta of the donor hearts to reperfusion), or time of weaning (from reperfusion to cessation of CPB) (Table 1).

*Hemodynamics.* Cardiac function was similar in both groups before brain death. Arterial pressures at weaning from CPB and from dopamine are shown in Table 2. The percentage of change of Emax, CO and max dP/dt are presented in Table 3.

The Emax of both groups measured at the post-transplantation with dopamine point was not significantly different. Neither was the post-brain death Emax value of each group significantly different. The Emax of those without dopamine also did not differ significantly from each other, but was significantly reduced from the post-brain death value in Group 2. However, this analysis excluded recipients which could not be weaned from dopamine.

The CO at post-transplantation with dopamine was significantly reduced in Group 1, but was not different in Group 2 from the post-brain death value. The CO with dopamine was significantly higher in Group 2 than Group 1.

The max dP/dt at post-transplantation with dopamine was not reduced compared with the post-brain death value in either group, and there was no difference between the groups. The max dP/dt without dopamine was significantly depressed in both groups without any difference between the groups.

*Serum CPK-MB.* The serum CPK-MB concentration increased immediately after the beginning of reperfusion in both groups. Significant difference between groups at any time point examined was not detected (Fig. 2).

*Myocardial high-energy phosphate concentrations.* The myocardial ATP level decreased in both groups of mongrel dogs over the time course of transplantation (Fig.

**Table 1** Asphyxiating, ischemic and weaning time

| Group | Asphyxiating time[a] (min) | Ischemic time[b] (min) | Weaning time[c] (min) |
|---|---|---|---|
| 1 | 10.2 ± 2.1 (n = 8) | 296.4 ± 12.8 (n = 8) | 64.7 ± 9.3 (n = 7)[d] |
| 2 | 10.2 ± 1.5 (n = 8) | 281.0 ± 17.6 (n = 8) | 60.8 ± 8.6 (n = 8) |

*a* : Time from ventilator disconnection to cardiac arrest
*b* : Time from clamping donor heart aorta to reperfusion
*c* : Time from reperfusion to cessation of cardiopulmonary bypass
*d* : One was not weaned in Group 1.
There were no significant differences between Groups 1 and 2.

**Table 2** Arterial pressure at weaning from cardiopulmonary bypass and from dopamine

| Group | Weaning from CPB[a] | | Weaning from dopamine[b] | |
|---|---|---|---|---|
| | sys. SAP (mm Hg) | m. PAP (mm Hg) | sys. SAP (mm Hg) | m. PAP (mm Hg) |
| 1 | 87.7 ± 17.0 (n=7) | 17.7 ± 2.4 (n=7) | 73.0 ± 12.0 (n=5) | 87.7 ± 17.0 (n=5) |
| 2 | 92.8 ± 12.9 (n=8) | 16.4 ± 3.2 (n=8) | 83.4 ± 25.2 (n=8) | 92.8 ± 12.9 (n=8) |

CPB: cardiopulmonary bypass; sys. SAP: systolic systemic arterial pressure; m. PAP: mean pulmonary arterial pressure.
*a* : Seven of 8 recipients in Group 1 and all recipients in Group 2 were weaned from CPB. *b* : Five of 7 recipients in Group 1 and all recipients in Group 2 were weaned from dopamine support therapy.
There were no significant differences between Groups 1 and 2.

3). The concentration at the post-preservation and post-transplantation was significantly lower in Group 1 but not in Group 2 compared with the control group. However, no significant difference in myocardial ATP levels among the groups was detected at any time point.

The CP concentration of Group 1 was significantly lower at harvest compared with Group 2, and returned to the control level after transplantation (Fig. 4).

**Table 3** Comparison of percent changes in cardiac function

| | pre-BD[a] (%) | post-BD[b] (%) | RES[c] (%) | Tx-DOA[d] (%) | Tx[e] (%) |
|---|---|---|---|---|---|
| Emax[f] | | | | | |
| Group 1 | 135 ± 36 | 100 | | 105 ± 42 | 62 ± 32 |
| Group 2 | 126 ± 39 | 100 | 69 ± 15** | 121 ± 47 | 71 ± 21** |
| Group 1 *vs.* 2 | N.S. | | | N.S. | N.S. |
| CO[g] | | | | | |
| Group 1 | 118 ± 22 | 100 | | 52 ± 34* | 46 ± 37* |
| Group 2 | 144 ± 31 | 100 | 113 ± 24 | 85 ± 25 | 77 ± 20* |
| Group 1 *vs.* 2 | N.S. | | | $p < 0.05$ | N.S. |
| max dP/dt[h] | | | | | |
| Group 1 | 142 ± 39 | 100 | | 93 ± 48 | 52 ± 18** |
| Group 2 | 184 ± 50 | 100 | 81 ± 29 | 110 ± 15 | 69 ± 14** |
| Group 1 *vs.* 2 | N.S. | | | N.S. | N.S. |

Data are presented as percent change from the post-brain death values; * $p < 0.05$, ** $p < 0.01$ *versus* (*vs*) post-brain death data.
*a:* Pre-brain death. *b:* Post-brain death. *c:* Post-resuscitation. *d:* Post-transplantation with dopamine. *e:* Post-transplantation without dopamine.
*f:* Slope of end-systolic pressure-volume relation line. *g:* Cardiac output. *h:* Maximum rate of rise in the left ventricular pressure. N.S.: Not significant.

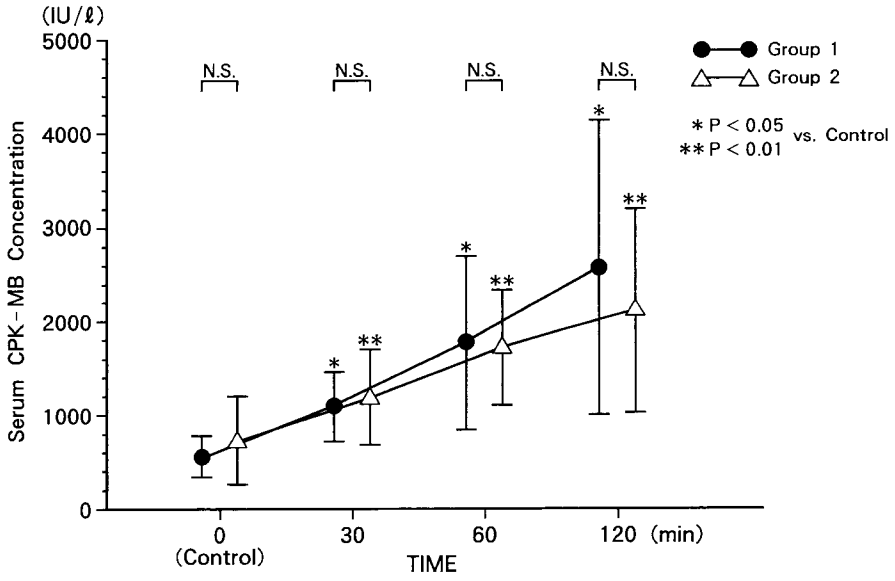


**Fig. 2** Comparison of serum CPK-MB concentrations in Groups 1 and 2 prior to and following reperfusion. CPK-MB: creatine phosphokinase MB isozyme. N.S.: not significant.

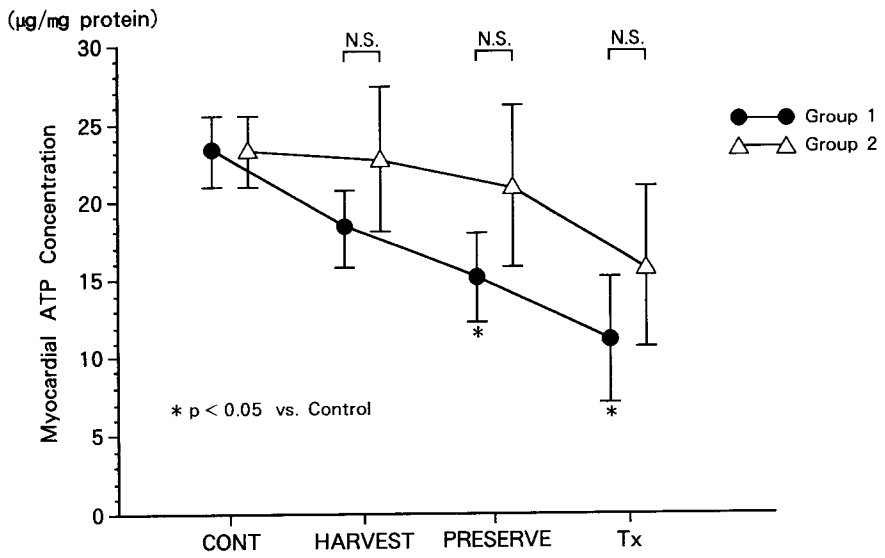


**Fig. 3** Myocardial ATP concentrations during the experimental procedure. ATP: adenosine 5′-triphosphate. CONT: control at thoracotomy. HARVEST: immediately prior to harvest. PRESERVE: immediately following preservation. Tx: following transplantation. N.S.: not significant.

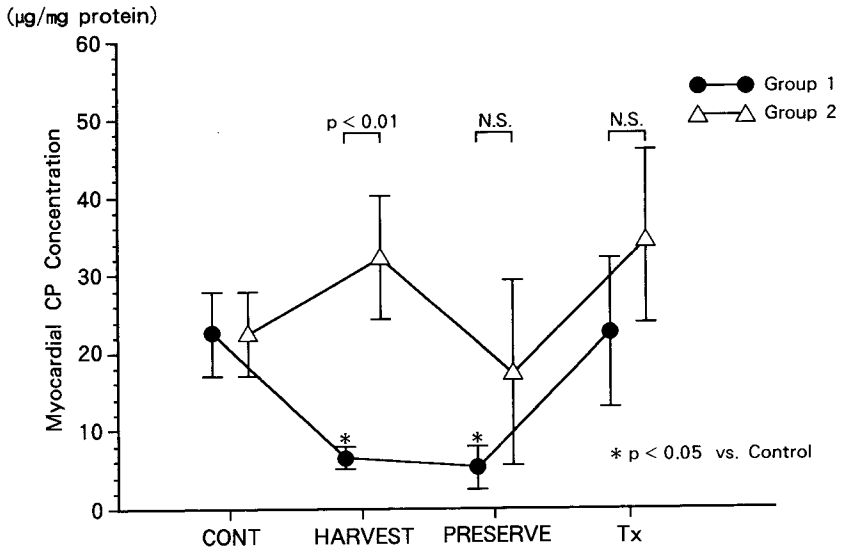


**Fig. 4** Myocardial CP concentration during the experimental procedure. CP: creatine phosphate. See footnotes to Fig. 3.

## Discussion

Donor shortage has been a problem for heart transplantation, due to an increase in medical contraindications to organ harvesting and a high rate of refusal for donation of organs (9).

Once brain death has been confirmed, three choices are proposed to the bereaved family: a) to continue life-support until spontaneous cardiac arrest, b) to discontinue life-support, and c) to offer patient's organs for

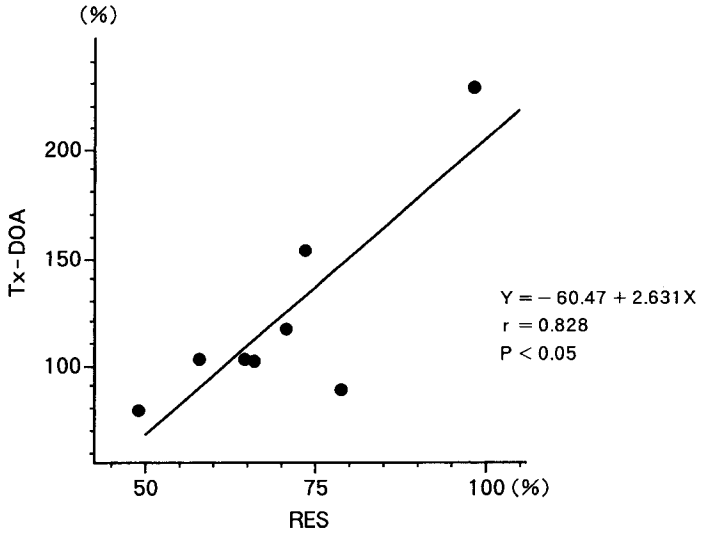


**Fig. 5** Correlation in Emax in Group 2 between post-resuscitation and post-transplantation during dopamine administration. Tx-DOA: post-transplantation with dopamine. RES: post-resuscitation.

transplantation ante-mortem (10). If the heart can be used for transplantation after cessation of its beating, the donor pool might be expanded.

In the late 1960's, Wuerflein and Shumway resuscitated the heart-lung preparation, which was removed en bloc from a cadaver donor dog and transferred to a constant temperature Ringer's lactate bath, using a ventilator and a rotary pump (11, 12). They mentioned that the heart must be removed from a cadaver under conditions that will allow it to assume full function immediately after orthotopic placement. However, further studies were suspended during the 1970's, because organs were procured from brain-dead donors.

In order to use cadaver hearts, Shirakura *et al.* perfused the cadaver donor heart with warm blood and subsequent cold crystalloid cardioplegia using a balloon-double-lumen catheter placed in the ascending aorta and a drainage tube placed in the right atrium (13, 14). Recently, they described a new method using a percutaneous cardiopulmonary support (PCPS) machine by which damaged organs are cooled below 20°C for 2 h before excision (15). Gundry *et al.* perfused the donor heart 30 min after death with 250 ml of cold cardioplegic solution containing 200,000 units of streptokinase which dissolve intravascular clots, but resuscitation of the heart was not performed in their experiments (16).

Pretto *et al.* have reperfused arrested hearts with CPB, and reported increased resuscitability of the heart and prolonged survival of the recipients, compared with standard cardiopulmonary resuscitation (17). Mooney *et al.* have reported on emergency cardiopulmonary bypass support in patients with cardiac arrest, and that percutaneous cardiopulmonary bypass support was an interim treatment which could be instituted within min and was a powerful resuscitative tool which stabilized the condition of patients with cardiac arrest (18). One advantage of our method is that the donor heart can be profoundly cooled with cardiopulmonary bypass after resuscitation of the heart.

Donor hearts are injured by hemodynamic change following brain death (8), but the cardiac function is restored within a week after orthotopic heart transplantation (19). In this study, the Emax, CO, and max dP/dt were used as indices of cardiac function. The Emax is a global index of ventricular contractility, and is independent of preload and afterload (20). Cardiac function in Group 2 was restored to the post-brain death level, at least when dopamine was administered.

Measurement of the left ventricular pressure-volume relationship prior to procurement appears to be a clinically useful predictor of donor-heart performance after transplantation (21). It may be possible to predict post-transplantation cardiac function based on the post-resuscitation function, because a close correlation existed for the Emax and CO between both points (Figs. 5, 6). Further studies regarding the assessment of chronic

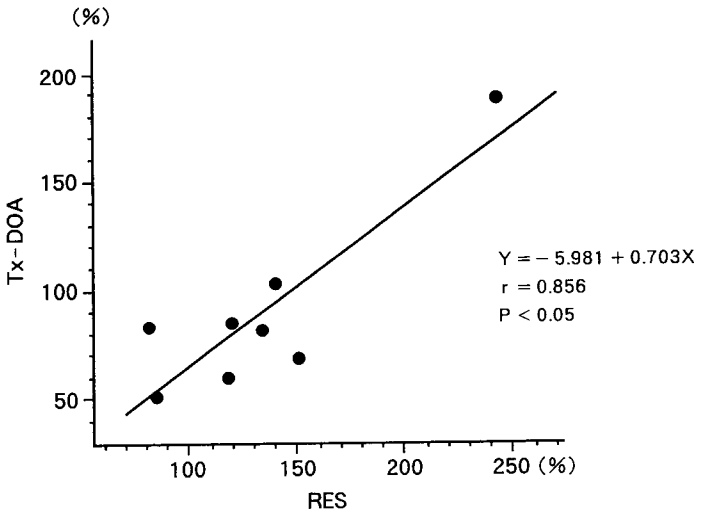


**Fig. 6** Correlation in cardiac output in Group 2 between post-resuscitation and post-transplantation during dopamine administration. See footnotes to Fig. 5.

cardiac function after transplantation are required. Cadaver donors should be selected prior to procurement, according to cardiac function at post-resuscitation period.

The serum CPK-MB concentration reflects the extent of myocardial injury. In our study, the serum concentration of CPK-MB steeply elevated after reperfusion in each group with or without resuscitation. It is difficult to distinguish reperfusion injury from ischemic injury on the basis of changes in the serum concentration of CPK-MB (22). Myocardial concentrations of ATP and CP seem to reflect cardiac metabolism. In this study, the post-transplant levels of both indices had no significant difference between the groups, suggesting that the myocardium was severely damaged. The working heart is damaged by regional ischemia irreversibly after 40 min (23). In spite of reperfusion with normal blood, global ischemia of 15 min leads to depression of left ventricular metabolic and mechanical function (24). Although donor hearts in Group 2 suffered ischemia twice and reperfusion twice, the cardiac function after transplantation returned at least to the post-brain death level by the administration of dopamine. The myocardium is certainly restored from damage by resuscitation, and hemodynamic indices are more sensitive than chemical.

Although further studies on the preserving solutions, and free radical scavengers are necessary in order to minimize ischemic and reperfusion injury and to improve the post-transplant myocardial function, we consider that the heart resuscitated from cardiac arrest by cardiopulmonary bypass using a core-cooling technique could be used for heart transplantation.

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