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급성심근경색 쥐 모델의 심정지 후 조기 저체온 치료가 심폐소생술 결과에 미치는 효과

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Early hypothermia improves outcomes of cardiopulmonary resuscitation after cardiac arrest in acute myocardial infarction rat models

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=Abstract =

Purpose: To investigate the effect of early hypothermia on post-resuscitation myocardial recovery and survival time after cardiac arrest and resuscitation in a rat model of myocardial infarction(MI).

Methods: Thoracotomies were performed in 10 male Sprague Dawley rats weighing 450-455g. Myocardial infarction was induced by ligation of the left anterior descending coronary artery. Ninety minutes after arterial ligation, ventricular fibrillation was induced, cardiopulmonary resuscitation was subsequently performed before defibrillation was attempted. Animals were randomized to control group and experimental group(acute MI-normothermia)(32 ℃ for 4 hours). Duration of survival was recorded. Myocardial functions, including cardiac output, left ventricular ejection fraction, and myocardial performance index were measured using echocardiography.

Results: Myocardial function was significantly better in hypothermia group than the control group during the first 4 hours post-resuscitation. The survival time of the experimental group was greater than that of the control group(p<.050).

Conclusion: This study suggests that early hypothermia can attenuate post-resuscitation myocardial dysfunction after acute myocardial function, and may be a useful strategy in post-resuscitation care.

Keywords: Cardiac arrest, Cardiopulmonary resuscitation, Hypothermia, Myocardial infarction

=국문초록=

연구 목적: 본 연구에서는 심근경색 쥐 모델에서 심장정지를 유발시킨 후 심폐소생술을 수행하는 과정에서 조기 저체온 치료를 적용하여 심장근육의 기능회복과 생존율에 미치는 효과를 조사하고자 하였다.

연구 방법: 본 연구를 위하여 체중 450-550g의 수컷 Sprague Dawley 쥐 10 마리에 개흉을 실시하였다. 왼내림 심장동맥을 묶어서 심근경색을 유발시켰다. 왼내림심장동맥을 묶은 후 90분 동안 심실세동을 유도하고, 심폐소생술과 제세동을 실시하였다. 대조군(정상체온군)은 회복과정에 정상체온으로 유지한 군이며, 실험군(저체온군)은 회복과정에 32 ℃ 4시간 저체온을 유지한 군이다.

연구 결과: 심박출량, 좌심실박출률, 심근수행지수는 심폐소생술 후 첫 4시간 동안 대조군보다 실험군에서 더 양호하게 나타났다. 실험군의 생존시간은 대조군보다 더 길게 나타났다(p<.050).

결　론: 본 연구를 통하여 조기 저체온 치료의 적용이 급성심근경색의 심폐소생술 후 심장 기능을 개선하는 데 탁월한 효과가 있으며, 치료법의 새로운 기준이 될 것이다.

국문중심단어: 심정지, 심폐소생술, 저체온, 심근경색

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Ⅰ. Introduction

1. Necessity and purpose of the study

Cardiovascular disease is accountable for approximately 40% of all deaths each year in the United States[1]. Clinically, most episodes of sudden cardiac death(SCD) occur in victims with underlying heart disease, especially ischemic heart disease[2]. Accordingly, out-of-hospital coronary death is most commonly related to the early or definitive stages of myocardial infarction(MI). In survivors of cardiac arrest, coronary artery disease with vessels exhibiting more than 75% cross-sectional stenosis is found in 40% to 86% of patients, depending on age and sex of the population studied[3]. In many cases of acute MI, the initial presentation of symptoms is quickly followed by sudden death[4]. The frequency of sudden unexpected death is highest in the early post-myocardial infarction period.

Effective and rapid reperfusion is crucial in patients with acute MI after successful resuscitation. However, a large proportion of patients do not receive reperfusion therapy within the several hours after resuscitation. Koeth et al.[5] reported that 38.8% of survivors did not receive early reperfusion therapy in the pre-hospital setting of MI with resuscitation.

Myocardial infarction(MI) may be classified as ST-elevation MI(STEMI) or non-ST-elevation MI(NSTEMI). The infarct related artery in STEMI was most frequently the left anterior descending coronary artery(LAD)[6]. Despite advances in the treatment of acute coronary syndromes(ACS) a large proportion of patients do not receive adequate treatment. In most cases, myocardial infarction with ST-segment elevation myocardial infarction(STEMI) is associated with thrombotic occlusion of a major coronary artery, STEMI is associated with a very high risk of mortality in 30% of cases[7].

Therapeutic hypothermia(TH) improves neurological outcomes and reduces mortality among survivors of out-of-hospital cardiac arrest[8]. Animal and human studies have also shown that TH results in improved salvage of the myocardium, reduced infarct size, reduced left ventricular(LV) remodeling and better long-term LV function[9,10]. The American Heart Association Guidelines of 2010[11] recommended therapeutic hypothermia for the treatment of neurological injury following resuscitation from out-of-hospital cardiac arrest when the initial cardiac rhythm was ventricular fibrillation(VF). A combination of TH with primary percutaneous coronary intervention(PCI) is feasible, safe, and potentially beneficial in patients after cardiac arrest due to acute MI[12]. However the effect of early application of therapeutic hypothermia still is not established.

In this present study, we investigated whether early application of hypothermia during cardiopulmonary resuscitation(CPR) reduces the severity of post-resuscitation myocardial dysfunction and improves survival after cardiac arrest and resuscitation in a rat model of MI.

Ⅱ. Methods

All animals received human 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(Washington, DC, National Academy Press, 1996).

1. Animal preparation

Ten male Sprague Dawley rats weighing 450-550g were fasted overnight except for free access to water. The animals were anesthetized by intraperitoneal injection of pentobarbital sodium(45mg/kg). Additional doses of 10 mg/kg were administered at hourly intervals but not within the 30 min preceding the onset of cardiac arrest. The trachea was orally intubated with a 14-gauge cannula mounted on a blunt-tipped needle(Abbocath-T, Abbott Hospital Products Division, North Chicago, IL) by means of the methods previously described[11]. $PETCO_2$ was measured with a side-stream infrared CO_2 analyzer (model 200; Instrumentation Laboratories, Lexington, MA). Procedures for vascular catheterization, hemodynamic measurements, blood sampling, monitoring of $PETCO_2$ are as previously described[11]. Electrocardiograph lead II is continuously recorded. A heat lamp was fixed at a location to allow maintenance of body temperature at 36.80 ± 0.20 ℃ throughout the experiment.

2. Experimental procedure

Animals were randomized into 2 groups by the closed envelope method: a) control group (acute MI - normothermia group), in which animals underwent left anterior descending coronary artery(LAD) ligation 90 min before the induction of VF and subsequent monitoring during resuscitation and the next 4 hours after return of spontaneous circulation(ROSC); b) experimental group(acute MI - hypothermia group), in which animals underwent LAD ligation 90 min before the induction of ventricular fibrillation(VF) and subsequent maintenance of low body temperature(32 ± 0.5 ℃) during resuscitation and the next 4 hours after ROSC.

A thoracotomy via the fourth left intercostal space was performed. The left atrium was elevated to expose the left coronary artery. The LAD was ligated 1-2mm below the left atrium using a 6-0 prolene suture. The chest was closed after ligation. The FIO_2 was maintained at 1.0 during the procedure. If there was an obvious change in the electrocardiogram(ECG)(ST elevation) and color(pallor) on a large area of the left ventricle observed, the rat was used for the next step.

Mechanical ventilation was initially established at a tidal volume of 0.65㎖/100 g of body weight and a frequency of 100 breaths/min. The tidal volume was adjusted to maintain $PETCO_2$ between 35 and 40mmHg. The FIO_2 was maintained at 0.21. A progressive increase in 60 Hz current to a maximum of 4mA was then delivered to the right ventricular endocardium. The current flow was continued for 3 min to preclude spontaneous reversal of VF. Mechanical ventilation was

discontinued after onset of VF. Precordial compression was then begun 6 minutes after the onset of VF with a pneumatically driven mechanical chest compressor as previously described[13]. Coincident with the start of precordial compression, mechanical ventilation was resumed. The FIO_2 was increased to 1.0. Precordial compression at a rate of 200/min was synchronized to provide a compression-ventilation ratio of 2:1 with equal compression-relaxation duration. Depth of compression was adjusted to maintain the coronary perfusion pressure(CPP) at 22.00 ± 2.00mmHg. This typically yielded a $PETCO_2$ value of 11.00 ± 2.00mmHg.

In experimental group, rapid cooling was performed externally with the aid of ice packs and an electrical fan[14], coincident with the start of compression. Resuscitation was attempted with up to three 3-J biphasic waveform countershocks(CodeMaster XL, Heartstream Operation, Philips, Seattle, WA) after 6 minutes of cardiac arrest and 8 minutes after the start of precordial compression. In unsuccessfully resuscitated animals, precordial compression was restarted and maintained for 30 seconds before a second sequence of electrical shocks. ROSC was defined as the return of supraventricular rhythm with a mean aortic pressure of 50mmHg for a minimum of 5 minutes.

Animals were monitored for both of 90 minutes after LAD ligation and 4 hours after resuscitation. After the panel of 4 hours post resuscitation measurements and cooling procedures were completed, intravascular catheters were removed and wounds surgically sutured. The animals were then rewarmed passively and observed for an additional 44 hours. Post-operation pain was controlled by subcutaneous injection of the analgesic, ketorolac(0.4 mg/kg), which was based on a pain scoring system that included assessment of heart rate, respiratory rate and overall performance level. To prevent infection in the wound site, antibiotics were injected intramuscularly. After the total of 48 hours the animals were euthanized with an intraperitoneal injection of pentobarbital sodium(150mg/kg).

3. Measurements

Aortic and right atrial pressures, electrocardiogram, and $PETCO_2$ values were continuously recorded on a personal computer-based data-acquisition system supported by WinDaq hardware and software(Data Q, Akron, OH). Coronary perfussion pressure(CPR) was calculated as the difference between aortic and time-coincident right atrial pressures in the interval between chest compressions. Myocardial functions, including ejection fraction(EF) and cardiac output(CO), were measured by echocardiography(Model HD11XE, Philips Medical Systems, Andover, MA). The myocardial performance index(MPI), which combined time intervals related to systolic and diastolic functions and reflecting the global cardiac function was also calculated using the formula $(a - b)/b$, where a = mitral closure-to-opening interval(time interval from cessation to onset of mitral inflow) and b = ET(aortic flow ejection time, obtained at the LV outflow tract)[15].

4. Statistical analysis

Normal distribution was confirmed with the Kolmogorov-Smirnov test. For measurements between groups, independent samples t test were employed for scale variables. Comparisons between time-based measurements within each group were performed with repeated-measurement analysis of variance. Measurements were reported as means ± SD values. All the statistical analyses were performed with the use of SPSS version 15.0(SPSS, Chicago, IL). For all statistical analyses, a value of $p<.050$ was considered significant.

Ⅲ. Results

For induction of MI, the LAD was ligated after exposure of the heart. The ST segment elevation in the ECG occurred just after ligation of the LAD and was a strong indication of induction of MI〈Fig. 1〉. And the change in color on a large area of the left ventricle was observed(Data is not shown).

No differences in the first(before LAD ligation) and second baseline(75 minutes after LAD ligation) in hemodynamics, myocardial function, and arterial lactate were observed among the two groups〈Table 1〉. However, CO and EF were decreased in both groups after ligation of the LAD($p<.010$). The CPP was 21.60 ± 0.90 mmHg in control group and 22.20 ± 2.10mmHg in the experimental group with no statistical difference at 4 minutes after CPR(Data is not shown). All of the animals were successfully resuscitated. The average number of defibrillation shocks given to achieve ROSC was 0.90 ± 0.30(range, 0 to 1) and did not differ significantly between the two groups.

In most of animals, there were no significant differences in the incidences of VF and subsequent defibrillation shocks before cardiac arrest, before and after ROSC and between the two groups〈Table 2〉.

The aortic temperature decreased to 32.00 ± 0.30 ℃ in the experimental group vs. 37.10 ± 0.10 ℃ in the control group at 15 minutes

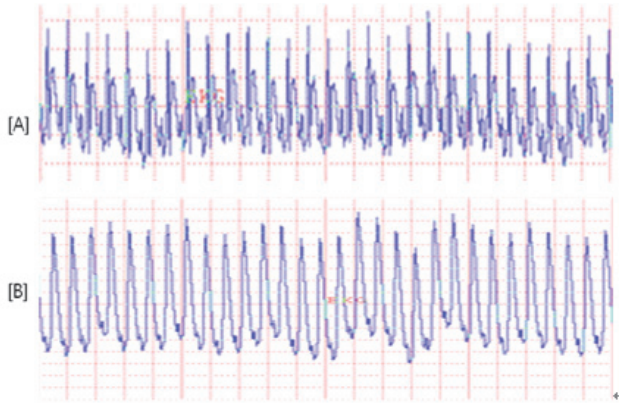

Fig. 1. Limb lead electrocardiogram(ECG) before [A] and after the ligation of left anterior descending coronary artery [B]. ST elevation after ligation is shown(lower panel).

Table 1. Characteristics at 1st and 2nd baseline

	Myocardial infarction		p
	Normothermia (n=5)	Hypothermia (n=5)	
1st Baseline(before left anterior descending coronary artery ligation)			
Body weight, kg	520.00 ± 19.00	518 ± 18.00	.910
Heart rate, beats/min	377.00 ± 29.00	371 ± 44	.790
Mean aortic pressure, mmHg	143.00 ± 9.00	137 ± 9	.370
Central venous pressure, mmHg	1.60 ± 0.10	1.7 ± 0.4	.790
Arterial temperature, ℃	36.90 ± 0.20	37.0 ± 0.1	.210
Cardiac output, mℓ/min	116.00 ± 5.00	114 ± 13	.820
Left ventricular ejection fraction, %	71.00 ± 3.80	74.4 ± 2.9	.160
Myocardial performance index	0.54 ± 0.07	0.57 ± 0.09	.510
Lactate, mg/L	0.78 ± 0.60	0.67 ± 0.27	.830
2nd Baseline(75 min after left anterior descending coronary artery ligation)			
Heart rate, beats/min	410.00 ± 21.00	399 ± 34	.560
Mean aortic pressure, mmHg	110.00 ± 7.00	118 ± 8	.110
Central venous pressure, mmHg	3.30 ± 1.90	4.4 ± 2.0	.590
Arterial temperature, ℃	36.90 ± 0.30	36.8 ± 0.1	.520
Cardiac output, mℓ/min	83.00 ± 11.00	92 ± 5	.130
Left ventricular ejection fraction, %	48.90 ± 3.30	53.5 ± 7.0	.220
Myocardial performance index	0.96 ± 0.04	0.85 ± 0.14	.160
Lactate, mg/L	1.15 ± 0.29	0.78 ± 0.32	.210

Values are expressed as mean ± SD.

after ROSC〈Fig. 2〉.

The post resuscitation myocardial dysfunctions such as decreased CO and LVEF, and increased myocardial performance index(MPI) were observed at 60 and 240 minutes after resuscitation. The experimental group

Table 2. Incidence of ventricular fibrillation and defibrillation in the time points before cardiac arrest, before and after ROSC

	Myocardial infarction		p
	Control group (n=5)	Experimental group (n=5)	
Before cardiac arrest			
Ventricular fibrillation	3.40 ± 4.30	1.20 ± 1.10	.300
Defibrillation	4.80 ± 6.30	0.80 ± 0.80	.200
Before return of spontaneous circulation (ROSC)			
Defibrillation	1.00 ± 0.00	0.80 ± 0.40	.910
After return of spontaneous circulation (ROSC)			
Ventricular fibrillation	1.20 ± 1.30	0.20 ± 0.40	.140
Defibrillation	0.80 ± 0.80	0.40 ± 0.90	.490

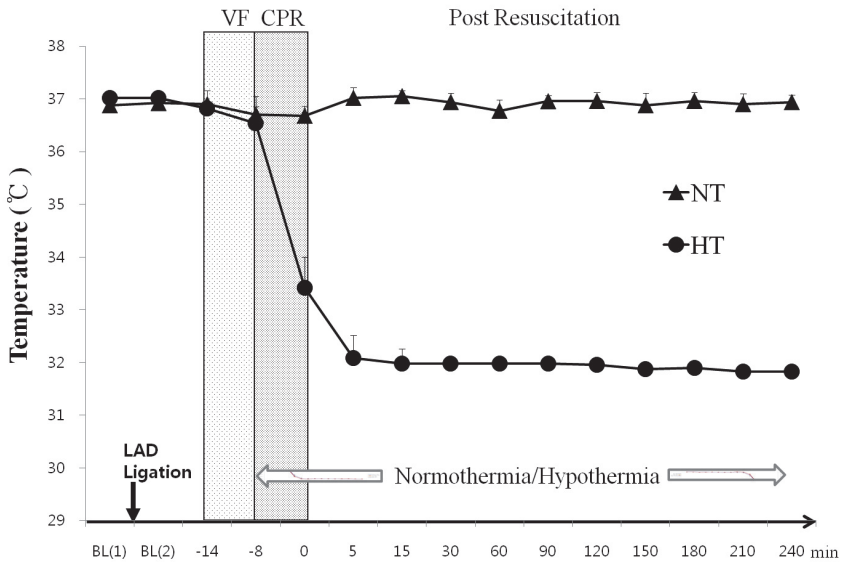

Fig. 2. Experimental procedure and arterial temperature during 6 minutes of untreated ventricular fibrillation(VF) was followed by 8 minutes of cardiopulmonary resuscitation(CPR). Hypothermia was initiated at precordial compression(PC) 0 min. NT, normothermia; HT, hypothermia.

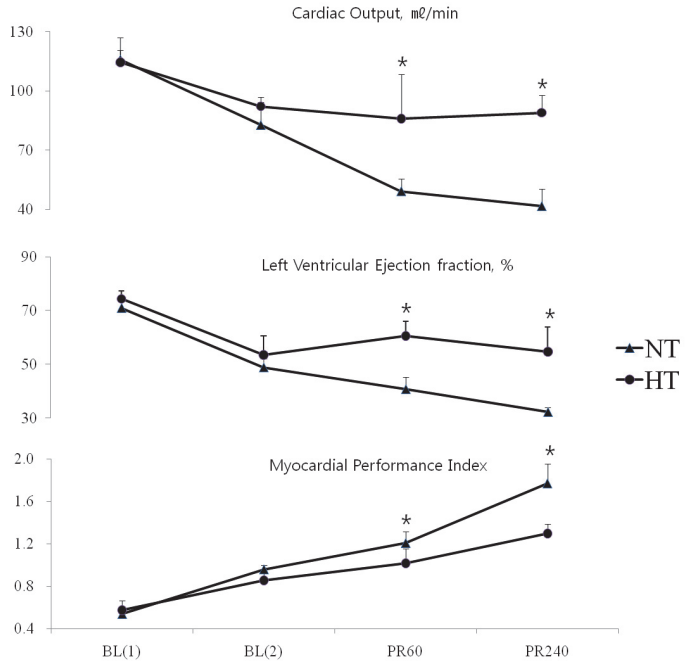

Fig. 3. Comparison of the cardiac output, left ventricular ejection fraction and myocardial performance index values in both groups of acute myocardial infarction during 4 hours after resuscitation. * $p < .05$. NT, normothermia; HT, hypothermia; PR, post-resuscitation.

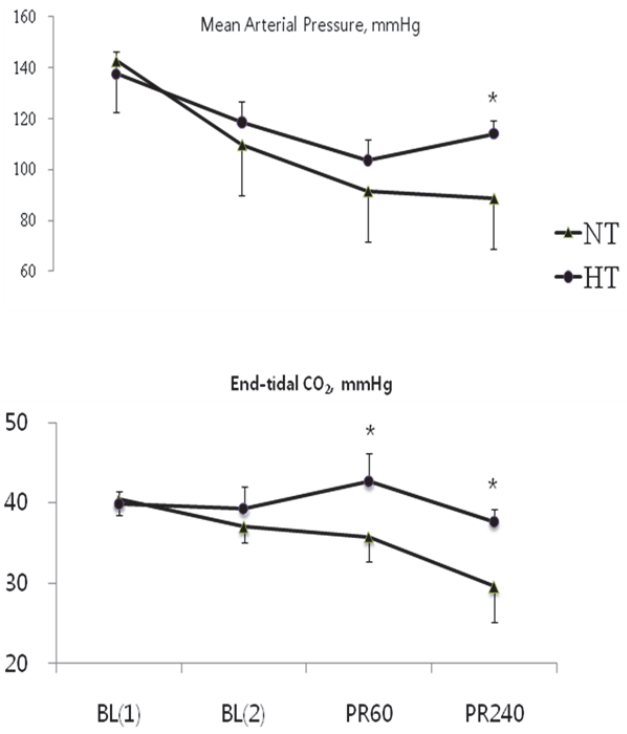

Fig. 4. Effects of hypothermia on mean arterial pressure and end-tidal CO_2 before onset of cardiac arrest and after resuscitation in rat model of acute myocardial infarction. * $p < .05$. NT, normothermia; HT, hypothermia.

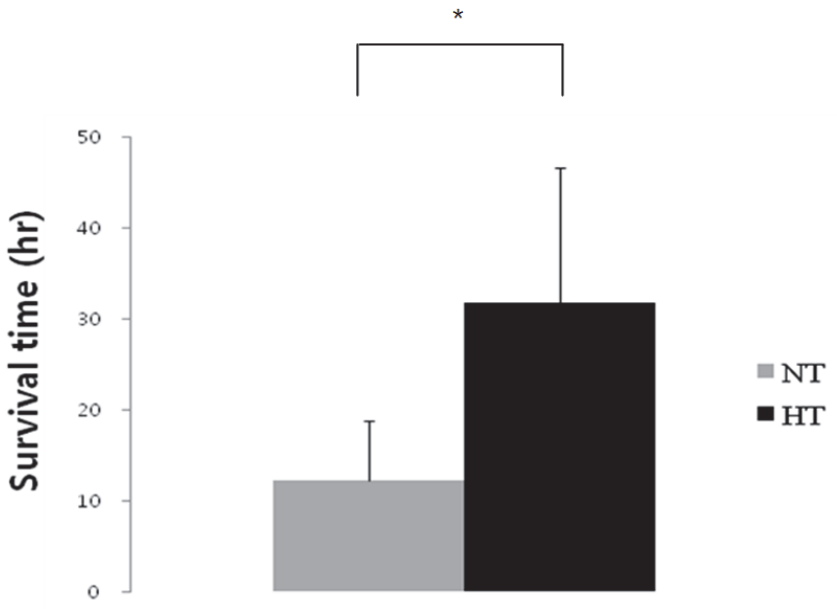

Fig. 5. Comparison of survival time following cardiopulmonary resuscitation. Significant differences were observed in both groups of acute myocardial infarction. * $p < .05$. NT, normothermia; HT, hypothermia.

showed significantly improved myocardial function than the control group(p< .050)〈Fig. 3〉. Mean arterial pressures of the animals in the experimental group were higher than in the control group at 240 minutes post resuscitation(p = .010)〈Fig. 4〉. The end-tidal CO_2 values after resuscitation were significantly different between the two groups(p= .010)〈Fig. 4〉. There were no significant differences in arterial lactate concentration between the two groups.

The average survival time of the experimental group was 31.80 ± 14.80 hours, which was greater than that of the control group(12.30 ± 6.50 hours, p< .050)〈Fig. 5〉. At autopsy, pallor of the wall of left ventricle, mostly the anterior wall, confirmed LAD ligation. Except for the MI area, no gross abnormalities in the study groups were observed at necropsy.

Ⅳ. Discussion

The present study demonstrated the therapeutic effect of hypothermia on post resuscitation myocardial dysfunction and survival after cardiac arrest and resuscitation in a rat model of MI. In the present study, experimental group showed improvement of myocardial function as measured by CO, left ventricular ejection fraction(LVEF), and MPI at 60 and 240 minutes after resuscitation. Our results were consistent with previous studies which indicated that the severity of myocardial damage and dysfunction after CPR were reduced when hypothermia was applied[16,17]. Götberg et al.[18] also reported that mild therapeutic hypothermia reduces acute mortality, improves hemodynamic parameters and reduces metabolic acidosis in a pig model of ischemic cardiogenic shock. Wolfrum and colleagues[12] suggested that mild therapeutic hypothermia in combination with primary percutaneous coronary intervention(PCI) is feasible and safe in patients resuscitated after cardiac arrest due to acute MI. However, our results confirmed that even though hypothermia improves post resuscitation myocardial function and survival in acute MI when compared with normothermia, the duration of survival was not optimal. Therefore, hypothermia is not a replacement for reperfusion therapy but rather expanding the window for the definitive treatment.

Therapeutic hypothermia has become an accepted part of post resuscitation care. Tissier et al.[19] reported that rapid cooling reduces infarct size as well as other sequelae of ischemia, such as post-ischemic contractile and mitochondrial dysfunction. Howes et al.[20] also emphasized that efforts to shorten the time from ROSC to hypothermic target temperature may significantly improve survival and neurologic outcome(32 to 34 ℃). Therefore, using ice packs and a fan, we started the cool down at the beginning of CPR. Thirteen min were needed to reach the target temperature(32 ℃) in our study.

Although it is currently possible to improve post resuscitation myocardial function and duration of survival, hypothermia does not improve animal's ultimate survival compared with no MI rats. In our study, the average

survival time of the experimental group was 31.8 ± 14.8 hours, which was greater than that of the control group(12.30 ± 6.50 hours, $p<.05$). However, Sun et al.[16] observed longer durations of survival in pharmacologically induced hypothermia animals than MI-hypothermia rats after CPR. Logue et al.[21] also found that all of rats cooled to 33 ℃ survived for 14 days after cardiac arrest in rats.

We had previously demonstrated that both CPP and $PETCO_2$ are extremely important predictors for ROSC[22]. In our present study, both CPP and $PETCO_2$ remained constant, and no differences were observed in both groups. All the animals were resuscitated. Based on these observations, we concluded that the previous surgical injury on the chest caused by the thoracotomy did not affect the efficiency of chest compression during CPR. Furthermore, we demonstrated that the severe myocardial dysfunction in both of groups was caused solely by the LAD ligation, because the possible variables, including CPP and $PETCO_2$, were identically controlled, and total energy required for successful defibrillation before ROSC in both groups had no significant differences. Also, the fact that significant differences in both post resuscitation myocardial function and duration of survival between normothermic and hypothermic animals further confirmed that the thoracotomy did not affect the post resuscitation outcome.

In the previous study, we investigated the possibility of ROSC and post resuscitation myocardial dysfunction in a rat model of chronic myocardial ischemia, 4 weeks after coronary artery constriction. Even with significantly impaired post resuscitation myocardial function, the duration of post resuscitation survival in coronary artery constriction animals did not differ from those in the sham-operated and LAD-ligated animals[23]. However, this study found that the total numbers of shocks for resuscitation in acute MI was less than that of chronic myocardial ischemia in spite of worse myocardial function, and survival time was shorter. This was the first study in which we evaluated post resuscitation myocardial dysfunction and survival time after cardiac arrest and CPR in the rat model of acute MI, therefore, further study is needed.

We recognize important limitations in the experimental method and interpretation of our findings. First, this study was conducted on only two groups of five animals and data were obtained on only ten animals. Second, we could not confirm the association of survival and myocardial function because the measurements of these functions were limited to only 4 hours post resuscitation. Third, we did not measure the infarction area of the myocardium using special staining. Even if we had tried to occlude the same site in the LAD, severity and the area of MI might not be same.

Ⅴ. Conclusion

This study suggests that early application of TH attenuated post resuscitation myocardial dysfunction in acute MI would be a potential strategy in post resuscitation care in the clinical setting.

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