Hypothermia Improves Outcomes of Cardiopulmonary Resuscitation After Cardiac Arrest In a Rat Model of Myocardial Infarction

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심근경색에 의한 심정지 후 치료적 저체온증으로 호전된 쥐의 심폐소생술 모델

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요 약

Therapeutic hypothermia(TH) improves neurological outcomes and reduces mortality among survivors of out-of-hospital cardiac arrest. Animal and human studies have shown that TH results in improved salvage of the myocardium, reduced infarct size, reduced left ventricular remodeling and better long-term left ventricular function in settings of regional myocardial ischemia. This study is to investigate the effect of TH on post-resuscitation myocardial dysfunction and survival time after cardiac arrest and resuscitation in a rat model of myocardial infarction (MI). Thoracotomies were performed in 10 Male Sprague-Dawley rats weighing 450-550 g. MI was induced by ligation of the left anterior descending coronary artery (LAD). Ninety min after LAD ligation, ventricular fibrillation induction and subsequent cardiopulmonary resuscitation was performed before defibrillation attempts. Animals were randomized to two groups: a) Acute MI-Normothermia b) Acute MI - Hypothermia (32 °C for 4 h). Myocardial functions, including cardiac output, left ventricular ejection fraction, and myocardial performance index were measured echocardiographically together with duration of survival. Ejection fraction, cardiac output and myocardial performance index were 54.74 ± 9.16, 89.00 ± 8.89, 1.30 ± 0.09 respectively and significantly better in the TH group than those of the normothermic group at the first 4 h after resuscitation(32.20±1.85,41.60±8.62,1.77±0.19)(p=0.00). The survival time of the hypothermic group (31.8 ± 14.8 h) was greater than that of the normothermic group(12.3 ± 6.5 h, p<0.05). This study suggested that TH attenuated post resuscitation myocardial dysfunction in acute MI and would be a potential strategy in post resuscitation care.

[3]

1. Introduction

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..[3] 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). 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[4].

Therapeutic hypothermia (TH) improves neurological outcomes and reduces mortality among survivors of out-of-hospital cardiac arrest[5]. 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. The American Heart Association Guidelines of 2010[1] recommended therapeutic hypothermia for the treatment of neurological injury following resuscitation from out-of-hospital cardiac arrest when the initial cardiac rhythm was 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[3].

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

2. Material and Method

2.1. Animal preparation and experimental procedure

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 (45 mg/kg).

Animals were randomized into 2 groups by the closed envelope method: a) 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 h after ROSC; b) acuteMI-hypothermia group, in which animals underwent LAD ligation 90 min before the induction of VF and subsequent maintenance of low body temperature (32±0.5°C) during resuscitation and the next 4 h 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 1-2 mm 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 ECG (ST elevation) and pallor 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 ml/100 g of body weight and a frequency of 100 breaths/min. The tidal volume was adjusted to maintain $PetCO_2$ between 35 and 40 mmHg. The FIO_2 was maintained at 0.21. A progressive increase in 60 Hz current to a maximum of 4 mA 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 min 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±2 mmHg. This typically yielded a $P_{ET}CO_2$ value of 11±2 mmHg.

2.2. Measurement

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). CPP 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).

2.3. Statistical analysis

Normal distribution was confirmed with the Kolmogorov-Smirnov test. For measurements between groups, independent samples t test were employed for scale variables. 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 $p<.05$ was considered significant.

3. Result

Table 1. Incidence of ventricular fibrillation and defibrillation before cardiac arrest and after ROSC.

	Myocardial infarction		*p*
	Normothermia (n=5)	Hypothermia (n=5)	
Before cardiac arrest			
Ventricular fibrillation	3.4 ± 4.3	1.2 ± 1.1	0.30
Defibrillation	4.8 ± 6.3	0.8 ± 0.8	0.20
Before ROSC			
Defibrillation	1.0 ± 0.0	0.8 ± 0.4	0.91
After ROSC			
Ventricular fibrillation	1.2 ± 1.3	0.2 ± 0.4	0.14
Defibrillation	0.8 ± 0.8	0.4 ± 0.9	0.49

Table 2. Characteristics at 1st(before LAD ligation) and 2ndbaseline (75 min after LAD ligation).

	Myocardial infarction		*p*
	Normothermia (n=5)	Hypothermia (n=5)	
1stBaseline			
Body weight, kg	520 ± 19	518 ± 18	0.91
Heart rate, beats/min	377 ± 29	371 ± 44	0.79
Mean aortic pressure,mmHg	143 ± 9	137 ± 9	0.37
Central venous pressure,mmHg	1.6 ± 0.1	1.7 ± 0.4	0.79
Arterial temperature, °C	36.9 ± 0.2	37.0 ± 0.1	0.21
Cardiac output,mL/min	116 ± 5	114 ± 13	0.82
Lef ventricular ejection fraction, %	71.0 ± 3.8	74.4 ± 2.9	0.16
Myocardial performance index	0.54 ± 0.07	0.57 ± 0.09	0.51
Lactate, mg/L	0.78 ± 0.60	0.67 ± 0.27	0.83
2nd Baseline (VF-15)			
Heart rate, beats/min	410 ± 21	399 ± 34	0.56
Mean aortic pressure, mmHg	110 ± 7	118 ± 8	0.11
Central venous pressure, mmHg	3.3 ± 1.9	4.4 ± 2.0	0.59
Arterial temperature, °C	36.9 ± 0.3	36.8 ± 0.1	0.52
Cardiac output, mL/min	83 ± 11	92 ± 5	0.13
Left ventricular ejection fraction, %	48.9 ± 3.3	53.5 ± 7.0	0.22
Myocardial performance index	0.96 ± 0.04	0.85 ± 0.14	0.16
Lactate, mg/L	1.15 ± 0.29	0.78 ± 0.32	0.21

4. 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, hypothermic group showed improvement of myocardial function as measured by CO, LVEF, and MPI at 60 and 240 min 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. Mild therapeutic hypothermia reduces acute mortality, improves hemodynamic parameters and reduces metabolic acidosis in a pig model of ischemic cardiogenic shock. Wolfrum and colleagues[6] 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. 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. also emphasized that efforts to shorten the time from ROSC to hypothermic target temperature may significantly improve survival and neurologic outcome (32 to 34 °C). 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 °C) in our study.

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 h post resuscitation. Third, we did not measure the infracted 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 be not same.

References

[1] American Heart Association. Heart Disease and Stroke Statistics-2004 Update. Dallas, Texas: American Heart Association 2003.

[2] Gonzales L, Langlois J, Parker C, Yost D. Combined interventions may improve success when treating sudden cardiac arrest. 2010;14:222-8.

[3] Koeth O, Zahn R, Bauer T, etal. Primary percutaneous coronary intervention and thrombolysis improve survival in patients with ST-elevation myocardial infarction and pre-hospital resuscitation. 2010;81(11):1505-8.

[4] Rott D, Nowatzky J, Teddy Weiss A, et al. ST deviation pattern and infarct related artery in acute myocardial infarction. 2009; 32(11):E29-32.

[5] Manari A, Albiero R, De Servi S. High-risk non-ST-segment elevation myocardial infarction versus ST-segment elevation myocardial infarction: same behaviour and outcome? 2009; 10 Suppl 1:S13-6.

[6] Wolfrum S, Pierau C, Radke PW, Schunkert H, Kurowski V. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. 2008; 36:1780-6.