Mild therapeutic hypothermia attenuates post-resuscitation myocardial dysfunction caused by epinephrine through inhibiting ß-adrenergic receptor signaling

W. Wang[1,5], T. Hua[1], H. Li[1], X. Wu[1], M. Peberdy[1,2], J. Ornato[1,3] and W. Tang[1,3,4]

[1]Weil Institute of Emergency and Critical Care Research at VCU,VA [2]Department of Internal Medicine and Emergency Medicine, VCU, VA [3]Department of Emergency Medicine, VCU, VA [4] Sun Yat-sen Memorial Hospital, SunYat-sen University, Guangzhou, China, [5]Department of Emergency Surgery, The Second Affiliated Hospital, Anhui Medical University

Background

Epinephrine administered during cardiopulmonary resuscitation (CPR) is associated with severe post-resuscitation myocardial dysfunction. β-adrenergic actions of epinephrine increase myocardial oxygen consumption during global myocardial ischemia and contribute to myocardial dysfunction. In our previous study, we demonstrated that therapeutic hypothermia reduced the severity of post-resuscitation myocardial dysfunction caused by epinephrine[1]. The mechanism of this myocardial protective effect of hypothermia remains unclear.

Methods

Animal Model

Animals were anesthetized and intubated. Catheters were then inserted at the femoral vein, femoral artery, and external jugular vein. A guidewire was advanced into the right ventricle to induce ventricular fibrillation (VF) via electrical stimulation. Precordial compression and ventilation were started after onset of untreated VF. Resuscitation was attempted with up to three 2-J counter shocks after CPR.

Experimental Protocol

Thirty two male Sprague-Dawley rats weighing between 450–550 g were randomized to four groups: 1) normothermic placebo control; 2) normothermic epinephrine; 3) hypothermic placebo control; and 4) hypothermic epinephrine. Ventricular fibrillation was induced electrically and untreated for 8 minutes. Hypothermia was initiated coincident with the start of CPR and maintained at 33 ± 0.2° C for 4 hours after resuscitation, after which the animals were euthanized. Normothermia groups maintained core temperature at 37 ± 0.2° C throughout the study. Either placebo or epinephrine was administered 5 minutes after the start of CPR and 3 mins before defibrillation. Post-resuscitation ejection fraction (EF) was measured hourly for 4 hours. The hearts were then harvested for cyclic Adenosine monophosphate (cAMP) and Inositol 1,4,5-trisphosphate (IP3) assay analysis.

Results

Figure 1. . There was an improvement in left ventricular ejection fraction within 4 hours of post-resuscitation in animals treated with hypothermia therapy at the beginning of CPR when compared with animals treated with normothermia.

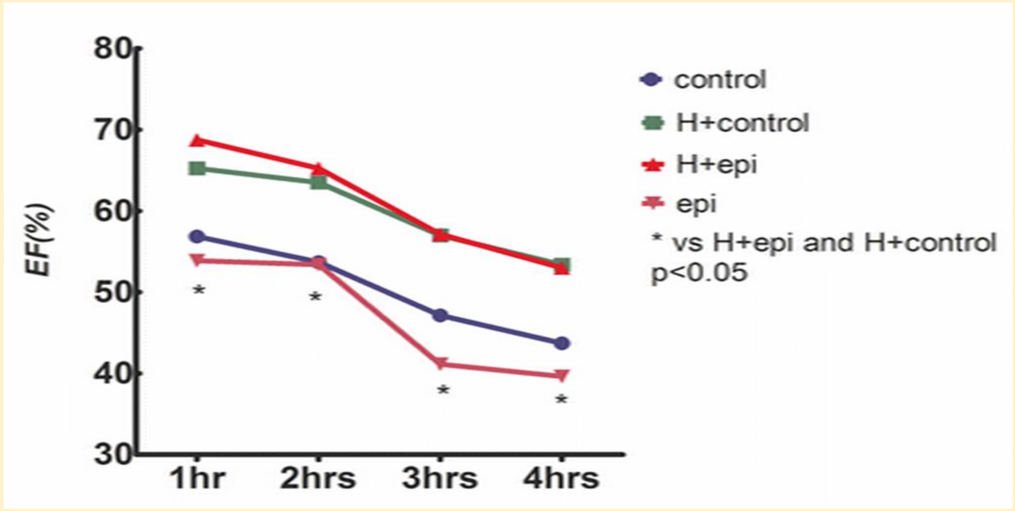
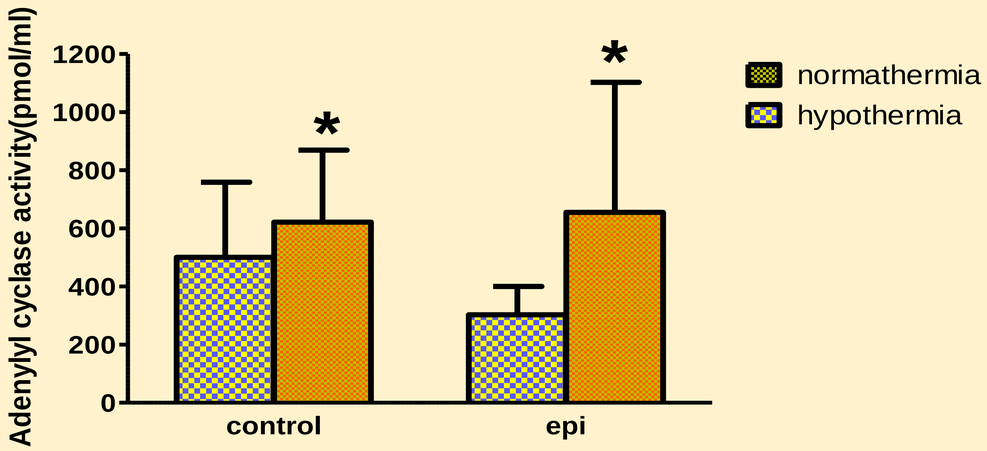


Figure2 . There was a significant decrease in myocardial cAMP concentration in the animals treated with both epi and hypothermia during CPR. * means vs h+epi p<0.05



Discussion

In the present study, we found that mild hypothermia at 32°C sustained post-resuscitation inotropic effects of β-adrenoceptor, recognized by higher EF, despite reduced cAMP in cardiac tissue. The preferred theory to explain such a result is that reduced cAMP leads to low influx of calcium from the extracellular space, thus preventing cytosolic calcium overload[2]and myofilament hyper-contracture and preserving myocardial compliance. In addition, elevated catecholamine levels during the early post-resuscitation period reduce β-adrenoceptor response to further stimulation by β-adrenoceptor desensitization and down-regulation, which will affect cardiac cAMP levels[3].

Conclusions

Epinephrine, when administered during normothermic cardiopulmonary resuscitation, significantly increases severity of postresuscitation myocardial dysfunction. This adverse effect was inhibited by hypothermia. The potential mechanism may involve reduced activity of β-receptors after hypothermia.

References

1. Sun S, Tang W, Song F, et al. The effects of epinephrine on outcomes of normothermic and therapeutic hypothermic cardiopulmonary resuscitation. Critical care medicine. 2010;38(11):2175-2180.
2. Schiffmann H1 GJ, von Hirscheydt A et al. Effects of epinephrine on the myocardial performance and haemodynamics of the isolated rat heart during moderate hypothermia--importance of calcium homeostasis. Resuscitation. 2001;50(3):309-317.
3. Ji XF, Shuo W, Yang L, et al. Impaired beta-adrenergic receptor signalling in post-resuscitation myocardial dysfunction. Resuscitation. 2012;83(5):640-644

Disclosure

None