
**Rapid Head Cooling Initiated Coincident With Cardiopulmonary Resuscitation Improves Success of Defibrillation and Post-Resuscitation Myocardial Function in a Porcine Model of Prolonged Cardiac Arrest**

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# Rapid Head Cooling Initiated Coincident With Cardiopulmonary Resuscitation Improves Success of Defibrillation and Post-Resuscitation Myocardial Function in a Porcine Model of Prolonged Cardiac Arrest

**To the Editor:** In cardiac arrest, systemic hypothermia initiated after resuscitation has been shown to improve survival and long-term neurologic outcome (1,2). Systemic hypothermia established before cardiac arrest improved the defibrillation success and resuscitation outcome in a porcine model (3), and intra-arrest systemic hypothermia has also been shown to reduce mortality rates in rats (4). In the present study, we sought to investigate the effect of preferential head cooling initiated at the start of cardiopulmonary resuscitation (CPR) on success of resuscitation and on post-resuscitation myocardial function and survival.

Sixteen male domestic pigs were randomized to hypothermia (n = 8) or control (n = 8). After 10 min of electrically induced and untreated ventricular fibrillation (VF), CPR was started. After 2 min of chest compression, 1 dose of epinephrine (30 μg/kg) was injected into the right atrium. Repeat doses of epinephrine were given at the 7th, 10th, and 12th min after the start of CPR. After a total 5 min of chest compression, 1 150-J biphasic electrical shock was delivered. Return of spontaneous circulation (ROSC) was established if an organized cardiac rhythm with mean aortic pressure of more than 60 mm Hg persisted for an interval of 5 min or more. If ROSC was not achieved, CPR was resumed for 1 min before the next defibrillation attempts. This sequence was repeated until the animal was either successfully resuscitated or pronounced dead after a total of 15 min of CPR.

Coronary perfusion pressure (CPP), the difference of diastolic pressure of the aorta and the right atrium, was used as a surrogate for coronary blood flow during CPR. Total electrical shocks were defined as the total number of the electrical shocks required to attain ROSC. Successful electrical shock was defined as return of organized cardiac rhythm with minimal mean aortic pressure >60 mm Hg.

Before the onset of cardiac arrest, the core temperature of all the animals was kept at 38°C. The hypothermia group was cooled with evaporative perfluorochemical through the nasal cavity by the Rhinochill (Benechill Inc., San Diego, California) device, coincident with starting CPR. The cooling was continued for 4 h or until core temperature reached 34°C. Within 4 h after resuscitation, the cooling was restarted when the core temperature went up to 34.5°C. Rewarming was passive. The temperature of the control group was not controlled after VF was induced.

Thoracic echocardiographic measurements were obtained hourly during the first 4 h and repeated at 96 h after ROSC. Neurological outcome was evaluated every 24 h by using neurological deficit score (NDS), which means no neurological deficit at 0 and death at 400.

Differences among the groups were assessed by the Fisher exact test for the comparison of the categorical variables and by the Mann-Whitney 2-sample rank sum test for continuous variables. A value of $p < 0.05$ was considered significant.

Baseline myocardial function and hemodynamic status did not differ significantly. Of the 8 animals in the hypothermia group, 7 achieved a core temperature of 34°C within the 4-h period. The average time to target core temperature was 155.4 ± 73.8 min (n = 7).

Fewer, but not a significant number of defibrillation shocks were required to achieve ROSC in the hypothermia group (9.5 vs. 16.5, p = 0.07). The hypothermia group had a higher success rate than the control group for the total number of shocks (97% vs. 70%, p = 0.03) but not initial shocks (75% vs. 38%, p = 0.315). The total dose of epinephrine required was also lower in this group (30 μg/kg vs. 60 μg/kg, p = 0.01), as was the duration of CPR (350 s vs. 568 s, p = 0.046) (Table 1). At the time these observations were made, the head temperature was approximately 4°C below baseline in the hypothermia group (p = 0.03) but unchanged in the control group. Meanwhile, the core temperature was at baseline value in both groups (Fig. 1).

The ROSC was achieved in 8 of 8 (100%) of the hypothermic animals and in 7 of 8 of the control subjects (88%) (p = NS). The CPP before initial defibrillation was 21.3 ± 9.6 mm Hg in the hypothermia group and 17.7 ± 5.6 mm Hg in the control subjects (p = NS). Throughout the CPR process, CPP was not significantly different between these 2 groups and was above the threshold of 15 mm Hg.

Myocardial systolic function and specifically ejection fraction and fractional area change together with diastolic function and specifically isovolumetric relaxation time (IVRT) and spectral tissue Doppler echocardiography (E/E′ ratio) were significantly higher after hypothermia when compared with control animals (Table 1).

All 8 hypothermic but only 2 control animals survived to 96 h (100% vs. 29%, p = 0.003). The neurological deficit scores of the hypothermic animals at 48 h after ROSC were significantly different from those of the control subjects (0 vs. 400, p = 0.005) (Table 1).

The beneficial effect of hypothermia on successful defibrillation in the present study could not be attributed to a direct effect of cooling on the myocardium, because the initial defibrillation occurred 15 min after arrest, at which point head temperature in the hypothermic animals was 4°C below baseline, whereas core temperature was no lower than baseline.

In this study, we demonstrated that head cooling initiated at the same time as CPR significantly improves survival and highlighted the importance of initiating hypothermia as early as possible after

**Table 1** Comparison of Events and Measurements in Each Group

| | Weight (kg) | Blood pH Before CPR | Blood pH After CPR | Arterial $PaO_2$ Before CPR (mm Hg) | Arterial $PaO_2$ After CPR (mm Hg) | CPR Duration (s) |
|---|---|---|---|---|---|---|
| Hypothermia (n = 8) | 40.5 (39–41) | 7.53 (7.47–7.57) | 7.42 (7.33–7.47) | 99 (94–116) | 458 (249–514) | 350 (321–437)* |
| Control (n = 8) | 40.5 (39–45) | 7.51 (7.43–7.56) | 7.35 (7.19–7.47) | 97 (88–135) | 386 (237–487) | 568 (294–909) |

| | CPP Before Initial ES (mm Hg) | No. of ES | Initial ES Success (%) | Total ES Success (%) | Epinephrine (μg/kg) | NDS at 48 h After ROSC |
|---|---|---|---|---|---|---|
| Hypothermia (n = 8) | 18.4 (11.3–36.4) | 9.5 (2–14) | 75 | 97 (60–100)* | 30 (30)* | 0 (0–75)* |
| Control (n = 8) | 17.6 (10.0–28.4) | 16.5 (2–28) | 38 | 70 (33–94) | 60 (30–120) | 400 (0–400) |

| | Baseline | PR 1 h | PR 2 h | PR 3 h | PR 4 h | PR 96 h |
|---|---|---|---|---|---|---|
| Cardiac output (l/min) | | | | | | |
| Hypothermia (n = 8) | 7.2 (6.3–11.0) | 5.2 (2.6–7.7) | 4.6 (2.8–6.9) | 4.6 (2.6–5.7) | 4.5 (2.3–6.1) | NA |
| Control (n = 8) | 6.61 (4.0–9.4) | 5.3 (3.0–7.3) | 4.8 (3.8–6.7) | 5.4 (3.4–7.2) | 4.9 (3.8–12.2) | NA |
| LVEF (%) | | | | | | |
| Hypothermia (n = 8) | 65.4 (59.1–69.4) | 56.7 (50.6–60.9)* | 60.4 (54.4–68.9)* | 62.6 (54.7–69)* | 63.3 (59.7–67.1)† | 65.4 (62.5–68.5)* |
| Control (n = 8) | 64 (56.7–68.2) | 50.7 (42–53.1) | 50.9 (40.8–54.8) | 51.4 (39.8–56.2) | 52.9 (41.2–55) | 57.6 (56.5–58.7) |
| Fractional area change (%) | | | | | | |
| Hypothermia (n = 8) | 50.0 (44.6–56.0) | 41.9 (35.0–45.6)* | 44.5 (36.6–54.8)* | 48.1 (40.6–54.0) | 48.6 (45.2–52.7) | 49.6 (44.4–52.6)* |
| Control (n = 8) | 49.1 (43.6–54.4) | 40.0 (24.5–37.9) | 32.3 (23.5–40.7) | 36.7 (25.1–39.2)† | 36.7 (29.4–41.7)† | 39.9 (39.3–40.6) |
| Isovolumetric relaxation time (s) | | | | | | |
| Hypothermia (n = 8) | 1.0 (0.9–1.2) | 0.7 (0.6–1.3)* | 1.0 (0.8–1.4)† | 1.1 (1.1–1.2)† | 1.2 (1.1–1.2)† | 1.1 (1.0–1.2)* |
| Control (n = 8) | 1.1 (0.9–1.2) | 0.6 (0.4–0.7) | 0.6 (0.5–0.8) | 0.6 (0.6–0.7) | 0.7 (0.6–0.8) | 0.8 (0.7–0.9) |
| E/E′ | | | | | | |
| Hypothermia (n = 8) | 10.1 (7.2–10.7) | 12.0 (10.7–14.8) | 9.1 (8.2–10.0)* | 9.1 (7.6–9.7)* | 8.7 (8.0–9.9)* | 8.9 (7.2–10.4) |
| Control (n = 8) | 10.4 (9.0–11.0) | 12.8 (11.7–16.2) | 11.7 (10.3–14.4) | 11.3 (10.1–13) | 10.2 (10.0–10.5) | 11.5 (10.0–13.1) |

Continuous variables are presented as median and range. *$p < 0.05$; †$p < 0.001$.

CPP = coronary perfusion pressure; CPR = cardiopulmonary resuscitation; E/E′ = spectral tissue Doppler echocardiography ratio; ES = electric shock; LVEF = left ventricular ejection fraction; NDS = neurological deficit score; $PaO_2$ = partial pressure of oxygen in arterial blood; PC = precordial compression; PR = post-resuscitation; ROSC = return of spontaneous circulation.

the arrest. Apparently, the beneficial effect of cooling initiated during cardiac arrest was not lost in the current study by delaying cooling until the beginning of the resuscitative effort, a model more closely simulating the real-life situation.

Unlike the beneficial effect on success of defibrillation, however, the improvement in myocardial function cannot be attributed to head cooling alone, because the core temperature was reduced (−0.7°C) at the time these data were obtained. Several mechanisms might have contributed to the observed improvement in myocardial performance. First, resuscitation in the hypothermia group was easier and faster. Fewer electrical shocks were needed to resuscitate, epinephrine dosage was lower, and CPR duration was shorter in the hypothermic animals. All of these factors have previously been shown to affect myocardial function. Second, therapeutic hypothermia decreases metabolic demand in the myocardium at risk. It would be interesting to see whether the same degree of myocardial improvement could be obtained with less head cooling and no systemic cooling at all. Conversely, we will also need to determine the effect on myocardial performance of post-resuscitation hyperthermia observed in the control animals. It is not inconceivable that some if not all of the benefit of "hypothermia" is in fact attributable to prevention of hyperthermia rather than to induction of hypothermia. The very significant benefit of intra-arrest head cooling observed in this study now needs to be confirmed and extended in other studies.

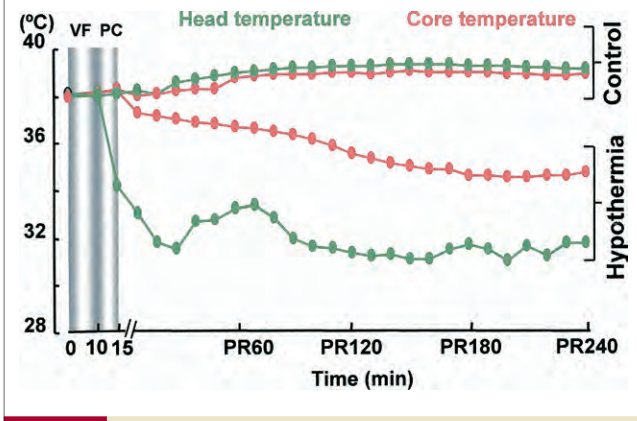


**Figure 1** Head and Core Temperatures of Experimental Groups

PC = precordial compression; PR = post-resuscitation; VF = ventricular fibrillation.

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## Letters to the Editor

# Depression, Inflammation, and Cardiovascular Disease

## Is 5-Lipoxygenase the Missing Link?

In a study recently published in the *Journal*, Vaccarino et al. (1) concluded that despite the significant comorbidity of depression with inflammation and of depression with cardiovascular disease (CVD), the inflammatory biomarkers C-reactive protein (CRP) and interleukin (IL)-6 could account for only a small portion of the association between depression and CVD. Therefore, using these 2 biomarkers of inflammation, the study found that, for the most part, depression and inflammation influence CVD risk through independent pathways. The authors contrasted the multifactorial link between depression and CVD to the robust and prognostic association of these 2 inflammatory biomarkers with depression as a possible reason that there is only a weak link of these biomarkers to CVD associated with depression. We would like to suggest an alternative explanation.

Recently, it was proposed that 5-lipoxygenase (5-LOX) provides a biologic link between depressive symptoms and atherosclerosis (2). 5-Lipoxygenase is an inflammatory enzyme responsible for the synthesis of arachidonic acid metabolites, that is, leukotrienes. Increased activity of the 5-LOX pathway, which includes another protein termed FLAP (5-lipoxygenase–activating protein), is strongly associated with atherosclerosis and elevated CVD risks, including that for stroke (3). In addition to its presence in the cardiovascular system, 5-LOX is expressed in the brain (4), where its functioning may be independent of cardiovascular activity. In the brain, 5-LOX participates in the regulation of neurotransmitter receptors, e.g., glutamate (2), and influences amyloid-beta deposition (5). Pharmacologic 5-LOX inhibition is being considered as therapy for atherosclerosis and CVD. Interestingly, in an animal model of depression, 5-LOX inhibition produces antidepressant-like effects (6). Therefore, it was proposed that 5-LOX may be a common biologic mechanism involved in both atherosclerosis and depression (2).

C-reactive protein and (IL-6 are only 2 of the numerous molecules that may be associated with inflammation. It is possible that their abundance in peripheral samples such as the plasma is not proportionally or equally related to the severity and progression of various pathobiologic processes, for example, inflammation, CVD, and depression. Moreover, whereas the mechanistic association of these 2 molecules with inflammation and atherosclerosis appears straightforward, it is unclear how they might modify neuronal functioning, suggesting that in depression they are not a direct biologic marker. In fact, currently there are no reliable direct biologic markers for depression.

Nevertheless, it could be that when up-regulated, a common biologic pathway participates in inflammation, atherosclerosis, and depression, albeit by recruiting different effectors. For example, activation of cardiovascular 5-LOX may lead to inflammation of the blood vessel wall and consequent atherosclerosis. In the brain, activation of 5-LOX may contribute to lower phosphorylation and membrane insertion of glutamate receptors type 1 (GluR1); decreasing 5-LOX activity and increasing GluR1 phosphorylation may be antidepressant. If a common mechanism, such as proposed here for 5-LOX, is indeed operative, one would expect that subtle changes in such a mechanism, for example, due to genetic variability (3), may influence blood vessels and brain functioning even in the absence of major alterations of biomarkers such as CRP and IL-6. Supporting this possibility is the observation of an association between depressive symptoms in clinically nondepressed subjects and the progression of subclinical atherosclerosis (7). By excluding CRP and IL-6 as common biologic markers, the report by Vaccarino et al. (1) provides impetus for new directions in research on the association between CVD and depression.

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