Mild hypothermia attenuates post-resuscitation brain injury through a V-ATPase mechanism in a rat model of cardiac arrest

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ABSTRACT. Although therapeutic hypothermia is an effective treatment for post-resuscitation brain injury after cardiac arrest (CA), the underlying mechanism remains unclear. Vacuolar H\textsuperscript{+}-ATPase (V-ATPase) plays a key role in cellular adaptation to a hypoxic environment. This study sought to evaluate the effect of mild hypothermia on V-ATPase and its involvement in neuroprotection after CA. Male Sprague-Dawley rats were subjected to a 6-min CA, resuscitated successfully, and then assigned to either the normothermia (NT) group or the hypothermia (HT) group. Rats were further divided into 2 subgroups based on the time of euthanasia, either 3 or 24 h after CA (NT-3 h, HT-3 h; NT-24 h, HT-24 h,
Mild hypothermia was induced following CA and maintained at 33°C for 2 h. Neurologic deficit scores were used to determine the status of neurological function. Brain specimens were analyzed by TUNEL assay, western blotting, and immunohistochemistry. V-ATPase activity was estimated by subtracting total ATP hydrolysis from the bafilomycin-sensitive activity. Mild hypothermia improved the neurological outcome (HT-24 h: 34.3 ± 16.4 vs NT-24 h: 50.3 ± 17.4) and significantly decreased neurocyte apoptosis 24 h after resuscitation. Mild hypothermia significantly increased V0a1 compared to NT-3 h; V0a1 expression was associated with a decrease in the cleaved caspase 3 expression. These findings suggested that mild hypothermia inhibits CA-induced apoptosis in the hippocampus, which may be associated with reduced V-ATPase impairment. These data provide new insights into the protective effects of hypothermia in vivo.

**Key words:** Cardiac arrest; Cardiopulmonary resuscitation; Electrical stimulation; Vacuolar H^+-ATPase (V-ATPase); Mild hypothermia