

# Hypothermia Improves Outcome From Cardiac Arrest

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## ABSTRACT

*Out-of-hospital cardiac arrest is common and patients who are initially resuscitated by ambulance officers and transported to hospital are usually admitted to the intensive care unit (ICU). In the past, the treatment in the ICU consisted of supportive care only, and most patients remained unconscious due to the severe anoxic neurological injury. It was this neurological injury rather than cardiac complications that caused the high rate of morbidity and mortality.*

*However, in the early 1990's, a series of animal experiments demonstrated convincingly that mild hypothermia induced after return of spontaneous circulation and maintained for several hours dramatically reduced the severity of the anoxic neurological injury. In the mid-1990's, preliminary human studies suggested that mild hypothermia could be induced and maintained in post-cardiac arrest patients without an increase in the rate of cardiac or other complications. In the late 1990's, two prospective, randomised, controlled trials were conducted and the results confirmed the animal data that mild hypothermia induced after resuscitation and maintained for 12 - 24 hours dramatically improved neurological and overall outcomes. On the basis of these studies, mild hypothermia was endorsed in 2003 by the International Liaison Committee on Resuscitation as a recommended treatment for comatose patients with an initial cardiac rhythm of ventricular fibrillation.*

*However, the application of this therapy into routine clinical critical care practice has been slow. The reasons for this are uncertain, but may relate to the relative complexity of the treatment, unfamiliarity with the pathophysiology of hypothermia, lack of clear protocols and/or uncertainty of benefit in particular patients. Therefore, recent research in this area has focused on the development of feasible, inexpensive techniques for the early, rapid induction of mild hypothermia after cardiac arrest. Currently, the most promising strategy is a rapid infusion of large-volume (40 mL/kg) ice cold intravenous fluid. Also, newer automated surface cooling/warming devices have been developed which allow tight control of body temperature in the ICU.*

*On the other hand, a number of questions remain. The benefit of hypothermia in non-ventricular fibrillation cardiac arrest remains uncertain. Also, the best timing of induction and the duration of hypothermia after cardiac arrest are uncertain. Clinical trials are currently underway to assess these issues. (Critical Care and Resuscitation 2005; 7: 325-327)*

**Key words:** Cardiac arrest, therapeutic hypothermia, review

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Out-of-hospital cardiac arrest occurs in approximately 1:1500 adults each year<sup>1</sup> and is likely to increase in incidence as the population grows older. Patients who are initially resuscitated and transported to hospital are usually admitted to the intensive care unit (ICU). In the past, the treatment in the ICU largely

consisted of supportive care only, and most patients remained unconscious due to the severe anoxic neurological injury.<sup>2</sup> Although there are considerable differences in the published outcomes around the world, in Australia, where the average time between collapse and defibrillation by ambulance officers is approxim-

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ately 12 minutes, about 8% of patients with an initial cardiac rhythm of ventricular fibrillation survive to hospital discharge.<sup>1</sup> In a study of 850 out-of-hospital cardiac arrest patients who had an initial cardiac rhythm of asystole, there were no patients with good neurological outcome at hospital discharge.<sup>3</sup>

However, there is now an effective treatment for the anoxic neurological injury following cardiac arrest. In the early 1990's, animal studies of cardiac arrest demonstrated convincingly that mild hypothermia induced after return of spontaneous circulation and maintained for several hours dramatically reduced the severity of the post-arrest anoxic neurological injury.<sup>4</sup> In the mid-1990's, preliminary human studies suggested that mild hypothermia could be induced and maintained in post-cardiac arrest patients without an increase in the rate of cardiac or other complications.<sup>5,6</sup>

Between 1997 and 1999, two prospective, randomised, controlled trials were conducted which compared post arrest hypothermia with patients maintained at normothermia. The results of these studies confirmed the animal data and demonstrated that mild hypothermia induced after resuscitation and maintained for 12 - 24 hours dramatically improved neurological and overall outcomes.<sup>7,8</sup> A third smaller trial compared post arrest hypothermia with normothermia in patients with non-VF arrest.<sup>9</sup> A meta-analysis of these three clinical trials has found that the number needed to treat for one additional patient to leave hospital neurologically intact is 7 (95% confidence interval 4 - 16).<sup>10</sup> On the basis of these studies, mild hypothermia was endorsed in 2003 by the International Liaison Committee on Resuscitation as a recommended treatment for comatose patients with an initial cardiac rhythm of ventricular fibrillation.<sup>11</sup>

However, the application of this therapy into routine clinical critical care practice has been very slow. The reasons for this are uncertain, but may relate to the relative complexity of the treatment, unfamiliarity with the pathophysiology of hypothermia, lack of clear protocols and/or uncertainty of benefit in particular patients. Therefore, recent research in this area has focused on the development of feasible, inexpensive techniques for the early, rapid induction of mild hypothermia after cardiac arrest.

Currently, the most promising strategy for the induction of hypothermia is a rapid infusion of large-volume (40 mL/kg) ice-cold intravenous crystalloid fluid. This has been shown in an emergency department study of post-arrest patients to rapidly decrease core temperature by 1.8°C and improve blood pressure, acid base and renal function.<sup>12</sup> There were no adverse events due to pulmonary oedema. Also, this approach was noted to be much more convenient than the use of ice-

packs for medical and nursing staff.

There are animal data which suggests that the effect of hypothermia is time dependant.<sup>13</sup> Since there is often a considerable time period between resuscitation in the home and induction of hypothermia in the hospital, we recently studied a protocol for rapid cooling immediately post-arrest by ambulance paramedics. The paramedic cooling protocol consisted of administration of a muscle relaxant (pancuronium) and the rapid infusion of 2000 mL of ice-cold Hartmann's Solution. We concluded from this pilot study that the pre-hospital cooling was feasible and not associated with adverse effects.

However, it is uncertain whether this very early cooling post resuscitation by paramedics is of significant additional benefit compared with delayed hospital cooling. Pre-hospital cooling requires a large additional commitment in resources, equipment and paramedic training. Therefore, an improvement in outcome with paramedic cooling compared with hospital cooling needs to be demonstrated before this protocol becomes widely adopted.

To answer this question, we are conducting a randomised, controlled trial comparing out-of-hospital cooling and hospital cooling in patients who have been resuscitated from out-of-hospital cardiac arrest. In the treatment arm, paramedics undertake immediate cooling after resuscitation from out-of-hospital cardiac arrest, using a muscle-relaxant and large volume, ice-cold fluid. In the control arm, patients receive standard paramedic advance life-support care, and are cooled only after arrival at the hospital.

Since post-ventricular fibrillation arrest patients have significantly different outcomes to other (non-ventricular fibrillation) cardiac arrest patients, we are also conducting a parallel clinical trial in non-ventricular fibrillation arrest patients.

Other recent developments in the application of hypothermia after cardiac arrest are the introduction of automated surface cooling/warming devices which allow tight control of body temperature in the ICU. These non-invasive devices should improve the control of body temperature, particularly during the rewarming phase. Whilst intravascular cooling devices have been developed, these are very expensive and require additional training for insertion by medical staff.

A number of important research questions remain. The benefit of hypothermia in non-ventricular fibrillation cardiac arrest or asphyxial cardiac arrest remains uncertain. Also, the best timing of induction and the duration of hypothermia after cardiac arrest are uncertain. Hopefully, the current clinical trials described above should provide answers to these questions.

In summary, there is convincing evidence that mild

hypothermia for 12 to 24 hours improves outcome after cardiac arrest due to ventricular fibrillation. Given this data and the lack of apparent significant adverse side-effects, this therapy should now be considered "standard of care" in this patient population.

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