CHEST

We Must Keep Our Cool Regarding the Effect of Therapeutic Hypothermia After In-Hospital Cardiac Arrest

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Therapeutic hypothermia and targeted temperature management (TTM) have been studied extensively in patients at risk of hypoxic brain injury after cardiac arrest.[1] In animal studies, rapid induction of therapeutic hypothermia is possible and appears to have neuroprotective effects.[2] In 2002, a landmark trial suggested lower mortality rates and better functional outcome with the induction of hypothermia targeting 33 °C in patients resuscitated from out-of-hospital cardiac arrest (OHCA).[3] This had an immense impact on post-cardiac arrest management, because for the first time a therapy was suggested that might reduce the risk of hypoxic brain injury in patients with OHCA. Therapeutic hypothermia was adopted quickly and was included in international recommendations. At the same time, more focus was placed on the treatment of these patients, which included prolonged care in the ICU.[4] Retrospective studies suggested improved outcomes with the use of therapeutic hypothermia in a wide range of patients with cardiac arrest.[4] Further randomized controlled trials tried to refine this therapy by inducing therapeutic hypothermia earlier after return of spontaneous circulation and prolonging it for up to 48 h, but without any clear signs of clinical benefit.[5,6]

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The results of two large trials by the TTM investigators have questioned the benefit of therapeutic hypothermia.[7,8] The recent TTM2 trial is the largest thus far and conclusively showed that, in 1,850 patients who were treated at multiple experienced centers, therapeutic hypothermia compared with targeting normothermia neither decreased mortality rates nor improved functional outcome.[7] However, TTM2 focused mainly on patients with a presumed cardiac cause of the arrest and included only patients with OHCA.

The Therapeutic Hypothermia After Cardiac Arrest With Nonshockable Rhythm (HYPERION) study, published in 2019 (before TTM2), compared therapeutic hypothermia targeting 33 °C with normothermia in patients who had been resuscitated from a nonshockable out-of-hospital or in-hospital cardiac arrest (IHCA).[9] The study found no difference in mortality rates but found a statistically significant difference in the proportion of patients with good functional outcome that was defined as a cerebral performance category of 1 or 2. Interestingly, when looking at the subgroups, therapeutic hypothermia appeared to be much more effective in the patients with IHCA compared with the patients with OHCA. In this issue of *CHEST*, the HYPERION investigators explore these findings further in a post hoc analysis that compared the approximately 150 patients with IHCA included.[10] Because the HYPERION study did not stratify for whether the arrest occurred in or out of hospital, the chance of significant differences in baseline characteristics could be a likely explanation for the quite dramatic difference in efficacy. The current study showed no baseline imbalance between the two intervention groups, for example, with regards to location of the arrest, initial rhythm, cause, or time to return of spontaneous circulation, which are known factors associated with outcome after IHCA. In contrast, there were differences in the proportions of immediate CPR and circulatory shock that favored the hypothermia group. In crude numbers, there was an 11% absolute difference in the proportion of patients

with good functional outcome at 90 days, with a wide 95% CI of 1% to 20%, which suggests uncertainty about the effect. With one patient changing group from good outcome to poor outcome in the group with therapeutic hypothermia or vice versa, the difference would not be statistically significant. In addition, patients were lost to follow-up, rendering even more uncertainty, as shown in the best- and worst-case scenarios in the article's appendix. Thus, it is clear that this study is too small to allow for any definite conclusions and must be seen as hypothesis-generating only. Furthermore, only patients with an initial nonshockable rhythm were included in the HYPERION trial, so the results of the current post hoc analysis cannot be extrapolated to other patient groups.

Nonetheless, if the findings are replicable and therapeutic hypothermia works much better in IHCA with a nonshockable initial cardiac rhythm compared with patients with OHCA, is there any possible explanation among these new data presented? The most obvious explanation would be whether it is quicker to start treatment and thus reach 33 °C after IHCA. In experimental studies, the target temperature can be reached within 30 min after return of spontaneous circulation.[2] However, as shown in this post hoc analysis, the target temperature was not achieved dramatically faster in the IHCA group compared with the OHCA group and compared with most other therapeutic hypothermia trials.[6,10] Alternatively, could there be some difference in the pathophysiologic process behind the patients' death after IHCA compared with OHCA? Indeed, the cause of death is more commonly multiorgan failure after IHCA than with OHCA.[11] Conversely, in the HYPERION trial and in this post hoc analysis, there was no difference when assessing mortality rates, only in functional outcome.

We believe that this article is important but that it should not influence clinical practice. We are awaiting the results of other larger trials that are not yet published. Currently, the overall evidence is that therapeutic hypothermia does not convey benefit compared with normothermia after cardiac arrest; the current guidelines of the European Resuscitation Council and the European Society of Intensive Care Medicine recommend targeting temperatures below 37.8 °C.[12] However, the effects of therapeutic hypothermia in patients with IHCA warrant further research. Alexiane Blanc et al[10] should be congratulated for presenting these preliminary findings.[10] Nevertheless, we must keep our cool and stick to the current recommendations on temperature management after cardiac arrest and target normothermia and the avoidance of fever.[12]

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