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Moving Beyond One-Size-Fits-All Treatment for Patients After Cardiac Arrest

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Post–cardiac arrest syndrome is a heterogeneous entity that involves multiple organ systems and causes substantial morbidity and mortality after successful cardiopulmonary resuscitation.[1] Several clinical trials have shown that targeted temperature management (TTM) for comatose survivors of cardiac arrest improves survival and enhances the quality of life of survivors.[1] Practice guidelines vary in recommendations of temperature target.[2,3] The initial clinical trials using 33 °C led to some adaptation of TTM in clinical practice. Still, another clinical trial using 36 °C as a target showing similar outcomes has led to some confusion on the temperature target for TTM.[4] The TTM trials have made brain injury a significant inclusion criteria with patients who are comatose after successful CPR. While comatose patients may appear similar clinically, the severity of brain injury varies widely. The TTM regimen studied did not account for the severity of brain injury.[2,3] Currently, practice guideline recommendations vary. One guideline has different levels of recommendation based on target temperatures 33 °C vs 36 °C,[2] and another guideline provides a range from 32 °C to 36 °C.[3]

There is a growing realization that in patients with critical care illness, brain injury, whether from a primary brain pathology or a systemic insult, is a significant determinant of functional outcome.[5] In patients following cardiac arrest, brain injury accounts for a substantial proportion of in-hospital morbidity and death.[1] In survivors, it has a significant impact on the quality of life.[6] A study by Callaway and colleagues,[7] published in *JAMA Network Open*, attempted to provide some insights on the brain and systemic injury biomarkers as a possible basis for the choice of temperature target in TTM for comatose survivors of cardiac arrest. The authors used a quality improvement database to track the use of TTM and compared the populations in which the managing clinician chose either 33 °C or 36 °C. The primary outcome was survival to discharge, but the study also characterized the quality of survival using the modified Rankin Score and cerebral performance category. Based on their previous published works, Callaway et al categorized patient severity by the presence of early severe cerebral edema on head CT scan and "highly malignant EEG."[7] In the subgroup of patients who did not have severe cerebral edema or highly malignant EEG, the researchers tested the interaction of the Pittsburgh Cardiac Arrest Category and TTM strategy. They performed 2 sensitivity analyses: calculation of the relative risk for characteristics that were likely associated with the outcome or choice of TTM target and creation a propensity score for the likelihood of the decision of temperature target.

The study by Callaway et al[7] included 1319 patients from 2010 to 2018.[7] The key finding was that in patients without severe cerebral edema or highly malignant EEG, TTM at 33 °C was associated with better survival than TTM at 36 °C for patients with the most severe post–cardiac arrest illness. TTM at 36 °C was associated with better survival in mild to moderate severity of illness. Patients with severe cerebral edema or highly malignant EEG had poor outcomes regardless of the TTM strategy.

This study has several important limitations. The study is a retrospective review of a cohort that was initiated as a quality improvement database, in which clinician decisions on choice of target temperature were based on their assessment of the clinical situation. The authors are transparent about this major limitation and took steps to address it in the analysis. They appropriately cautioned readers not to "infer a causal connection based on these observational cohort data."[7] The mode of death in association with the withdrawal of life-sustaining therapy was highest in those with severe cerebral edema (49.7%) and in those with highly malignant EEG (74%). The proportion of deaths associated with withdrawal of life-sustaining therapy with neurologic prognosis in the TTM 33 °C group was 59.5% and in the TTM 36 °C group was 43.3%. Another significant limitation is related to

the low quality of existing neurologic prognostication studies,[8] which added bias to the study that was difficult to control.

Despite these limitations, the study by Callaway and colleagues[7] is an encouraging step forward from the status quo. It provides supporting evidence that brain injury in patients who experience cardiac arrest is a significant target and beneficiary of TTM. The study demonstrates a potential direction that may transform much of the current neurologic assessment of patients after cardiac arrest that is mostly focused neurologic prognostication. Currently, neurologic prognostication focuses on identifying patients who are likely to have unfavorable outcomes, which may become the basis for the withdrawal of life-sustaining therapies.[8] This practice was common and acceptable in an era where we did not have effective treatment for brain injury after cardiac arrest. With the ability of TTM to improve survival and outcome, we need to identify biomarkers to help us use TTM to its fullest. We need to develop reliable brain and systemic biomarkers that are capable of early detection and stratification of injury. With these biomarkers, we can match the "dose" of TTM, either the depth of cooling or the duration of cooling.

While it is apparent that the one-size-fits-all approach to any therapy is imprecise, there has been little attempt to surmount this problem in post–cardiac arrest care. It may appear evident that patients with different severities of brain injury require different types of therapy. This idea may be further complicated when we consider the effects of the systemic injury on brain recovery. How will we approach patients with minimal brain injury and severe cardiac injury vs those with severe brain injuries and preserved cardiovascular function? The brain does not exist in isolation in patients who have experienced cardiac arrest.[1] Systemic physiology is closely linked to brain injury and recovery. The effects of systemic cardiopulmonary changes need to be linked to changes in neurobiology. The Pittsburgh Cardiac Arrest Category score that Callaway et al developed attempts to address these concerns by combining neurologic parameters (assessed via the Full Outline of UnResponsiveness [FOUR] score) and cardiopulmonary function (assessed via the Sequential Organ Failure Assessment [SOFA] cardiovascular plus pulmonary score).[7] Neurologic prognostication directly influences clinical decisions. As such, better-designed neurologic prognostication studies are also strongly encouraged.[8]

After the studies by Callaway and colleagues are prospectively validated, we need to look beyond injury detection and clinical stratification to guide therapies. We need to encourage the development of brain-specific biomarkers that can detect not only ongoing brain injury, but also its recovery. It should provide actionable information to clinicians about treatment response of the brain in real time. These brain-specific biomarkers should allow clinicians not only to define the appropriate initial therapy but also to titrate ongoing therapies or modify treatments based on the response of the brain. This dynamic interaction of real-time brain injury detection and treatment titration will be undertaken with the ultimate goal to improve long-term outcomes in this very challenging population.

ARTICLE INFORMATION

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