Thank you for inviting us to comment on our recently published study “Bradycardia during targeted temperature management: an early marker of lower mortality and favorable neurologic outcome in comatose out-of-hospital cardiac arrest patients” (1).

Targeted temperature management (TTM) remains a central part of the post cardiac arrest management and accompanying sedation and neuromuscular blocking agents have been shown to make outcome prediction challenging (2). This calls for identification of early markers of the normal physiological response to the treatment and thereby physiological markers of stability and outcome after out-of-hospital cardiac arrest (OHCA). Our understanding of the physiological response to mild hypothermia is improving, and recent reports have suggested that a simple vital sign such as heart rate during the course of TTM may provide insights into the patients’ prognosis at an earlier stage than other prognostic markers.

Background

The potential beneficial effects and physiological response to mild hypothermia after cardiac arrest in the form of TTM, have gained increasingly focus following two smaller randomized controlled trials in 2002 showing favorable outcome in comatose cardiac arrest patients from an initial shockable rhythm treated with TTM at 32–34 ℃ (3,4). The International Liaison Committee on Resuscitation recommended TTM in that range (5) and the neuroprotective treatment strategy has become widely implemented since (6,7). The TTM-trial (8) was commenced in November 2010 and completed by January 2013. The study compared TTM at 33 vs. 36 ℃ and found similar outcomes in terms of mortality and neurological function in 939 patients from both shockable and non-shockable rhythm (9). The recent 2015 international resuscitation guidelines have, based on these results, uniformly recommended TTM in a broader range, with the option to choose a constant target temperature of 32 to 36 ℃ (10-12).

Bradycardia during targeted temperature management (TTM)

In the study “Bradycardia during targeted temperature management: an early marker of lower mortality and favorable neurologic outcome in comatose out-of-hospital cardiac arrest patients” published February 2016 in Critical Care Medicine we sought to assess, validate and further explore an area by which increased focus has evolved in recent years, namely a possible association between lower heart rates during TTM and a favourable prognosis following OHCA. A registry study (bradycardia <40 bpm) and a smaller retrospective study (13) (bradycardia <60 bpm) had indicated an association between lower heart rates during TTM and a favourable prognosis following OHCA. A registry study (bradycardia <40 bpm) and a smaller retrospective study (13) (bradycardia <60 bpm) had indicated an association between lower heart rates during TTM and a favourable prognosis following OHCA. A registry study (bradycardia <40 bpm) and a smaller retrospective study (13) (bradycardia <60 bpm) had indicated an association between lower heart rates during TTM and a favourable prognosis following OHCA. A registry study (bradycardia <40 bpm) and a smaller retrospective study (13) (bradycardia <60 bpm) had indicated an association between lower heart rates during TTM and a favourable prognosis following OHCA. A registry study (bradycardia <40 bpm) and a smaller retrospective study (13) (bradycardia <60 bpm) had indicated an association between lower heart rates during TTM and a favourable prognosis following OHCA.

What can a simple measure of heart rate during temperature management tell us on the physiology and prognosis of comatose cardiac arrest patients?

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potential early marker of favourable outcome (15). However, these results could not readily be extrapolated to TTM targeting 36 °C, which has been implemented in many centres following the updated resuscitation guidelines (11,12).

The TTM-trial database provided an opportunity for not only validation of the proposed association in a larger cohort of OHCA-patients treated at 33 °C (15), but also a means to extend our knowledge of lower heart rates and outcome in patients resuscitated from a non-shockable rhythm and the many patients now treated with 36 °C.

In the stratified analysis of patients treated with 33 °C (n=447) in the TTM-trial, we found that bradycardia below 50 bpm was present in 30% of patients, whereas heart rates between 50 and 59 bpm were observed in 29% of patients. The group of patients with the lowest registered heart rates also had the lowest mortality and with a step-wise increase with higher heart rates (<50 bpm, 32%; 50–59 bpm, 43%; ≥60 bpm, 60%). Higher heart rates were more often found in patients with longer time to return of spontaneous circulation (ROSC) and higher levels of lactate on admission. When using patients with no bradycardia (≥60 bpm) as reference, patients with bradycardia <50 bpm remained independently associated with lower mortality (hazard ratio =0.50; 95% CI, 0.34–0.74; P<0.001), in a multivariable model adjusted for potential confounders. Similar results were found for neurological function, with lower odds (odds ratio =0.38; 95% CI, 0.21–0.68; P<0.01) of unfavorable outcome with bradycardia.

We found no interaction suggesting a different association of lower heart rates and outcome in patients treated with 36 °C (n=430), however the heart rate lowering effect was less pronounced and patients treated with 36 °C had approximately 10 bpm higher resting heart rate during TTM compared to the 33 °C group (Figure 1). Only 8% of the patients had bradycardia <50 bpm during TTM. In an explorative analysis of quartiles of minimum heart rates in the 36 °C group, we found that patients with heart rate below ≤57 bpm were independently associated with lower mortality (hazard ratio =0.63; 95% CI, 0.40–0.98; P=0.04) and lower odds of unfavourable neurological outcome (odds ratio =0.41; 95% CI, 0.21–0.83; P=0.01), compared to patients with heart rates ≥79 bpm (1).

**Mechanisms behind the heart rate lowering effect**

Hypothermia may affect the resting heart rate in various ways, including suppression of the sympathetic activity (16,17) or elevation of parasympathetic activity (16). Others have proposed that the heart rate lowering effect is mainly due to effects on the cardiac pacemaker cell, with a decrease in spontaneous depolarization (18) as discussed in our paper (1). What is known is that the heart rate lowering effect of hypothermia is present in healthy subjects immersed into cold water (16) and the markedly reduction in heart rate seen in a large proportion of comatose cardiac arrest patients during TTM may be perceived as an early marker of the physiological response to the treatment and thereby a favourable prognosis, represented by lower mortality and less neurological damage.

Comatose survivors of OHCA predominantly die from either cerebral or cardiovascular causes (19), and based on the possible causal mechanisms mentioned above of the heart rate lowering effects of mild hypothermia, it is reasonable to deduct that lower heart rates seen during TTM in post cardiac arrest care may represent a marker of both cardiac and cerebral stability with intact autonomic regulation of the heart.

In a recently published editorial regarding the importance of heart rate and its relation to the post cardiac arrest syndrome, the authors correctly point out that residual confounding may be present in the multivariable models used in our and other studies, simply due to the fact that they have not been conceptualized or due to unavailability (20). One of the important limitations to our studies is the lack of pre-arrest medication including beta-blockers, though patients with pre-arrest indications for such medications had a trend towards higher and not lower mortality.
Perspectives

So, to answer and discuss the question raised by the title of this commentary, “What can a simple measure of heart rate during temperature management tell us on the physiology and prognosis of comatose cardiac arrest patients?” Lower heart rates are seemingly a strong early physiological marker of favourable outcome in post cardiac arrest care, independent of cardiac arrest characteristics, comorbidity, vasopressor need and chosen temperature.

It can be speculated, based on the findings in this study, that lowering of the heart rate could be a specific therapeutic target in post cardiac arrest care for example by administering beta-blockers or ivabradine. The authors do, however, believe higher resting heart rates during TTM and a lack of bradycardic response is a physiological marker of incipient cardiac instability and/or higher degree of cerebral injury. Treating the heart rate alone would most likely be equivalent of shooting the messenger, and more benefit may be achieved by tracking down potentially reversible causes of the instability causing the higher heart rates instead. As of now, no treatment modalities other than TTM are supported for post-conditioning of the anoxic brain injury caused by the arrest, but the cardiovascular mortality seen in these patients may be reduced by early recognition of the cause of relative tachycardia. This may be facilitated by increased understanding of the physiological and pathophysiological responses to the treatment, e.g., exemplified by otherwise normal persistent heart rates above 60 bpm being associated with increased mortality during TTM at 33 °C.

The findings further provide prognostic information to the treating physician and thereby a higher level of information to base their clinical decision-making on and this information is available earlier in the course than other established prognostic markers. This further enables more information of the patient’s physiological state to be shared with the relatives, which are often eager to be informed of the patients’ chances of a favourable outcome. It should however be noted that final neurological prognostication should only be made using a multimodal approach no earlier than 72 h after ROSC (2), and only when normothermia have been reached and sedation has been completely tapered.

A lack of bradycardic response in a patient during TTM, even though the heart rate may be within the normal range for a normothermic patient, could encourage the treating physician to reassess the patient for potential emerging complications or unrecognized differential diagnoses. However, whether managing these complications will lead to an improved prognosis remains to be proven.

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Footnote

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