The complement lectin pathway protein MAp19 and out-of-hospital cardiac arrest: Insights from two randomised clinical trials of targeted temperature management

Authors:
J Bro-Jeppesen¹, AN Jeppesen², SF Haugaard³, A Troldborg⁴, C Hassager¹, J Kjaergaard¹, H Kirkegaard⁵, M Wanscher⁶, AM Hvas³, S Thiel⁴, ¹Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Cardiology - Copenhagen - Denmark, ²Aarhus University Hospital, Department of Anaesthesiology and Intensive Care Medicine - Aarhus - Denmark, ³Aarhus University Hospital, Centre for Hemophilia and Thrombosis, Department of Clinical Biochemistry - Aarhus - Denmark, ⁴Aarhus University, Department of Biomedicine - Aarhus - Denmark, ⁵Aarhus University Hospital, Research Center for Emergency Medicine and Department of Anesthesiology and Intensive Care Medicine - Aarhus - Denmark, ⁶Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Anaesthesia - Copenhagen - Denmark.

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Background/Introduction:
Activation of the complement system is known to be a potent inducer of systemic inflammation, which is an important component of post-cardiac arrest syndrome. Mannan-binding-lectin associated serine protease-2 (MASP-2) is responsible for activation of the lectin pathway of the complement system. MAp19 is suggested to be a competitive inhibitor of MASP-2 associated complement activation.

Purpose:
This study describes serial levels of MAp19 protein in comatose survivors of out-of-hospital cardiac arrest (OHCA), evaluates the effect of two different regimes of targeted temperature management and investigates the possible association between levels of MAp19 and mortality.

Methods:
In this post-hoc study, we analysed data from two larger randomised controlled studies, "Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest" (TTM) and "Targeted temperature management for 48 versus 24 hours and Neurological Outcome after out-of-hospital cardiac arrest" trial (TTH). We measured serial levels of MAp19 in 240 patients (TTM-trial; n=158, TTH-trial; n=82) at admission (TTM-trial only), 24h, 48h and 72h after OHCA and in 82 healthy controls. The effect of targeted temperature management on MAp19 levels was analysed according to temperature allocation in main trials. Serial MAp19 levels was evaluated by repeated measures mixed model. We reported 30-day mortality and.

Results:
MAP19 levels were significant lower in OHCA patients within 72h after OHCA (p-values <0.001) compared with healthy controls. A target temperature at 33°C compared to 36°C for 24 hours was associated with significant lower levels of MAp19 (-57 ng/mL [95%CI: -97- -16 mg/mL], p=0.006), Figure, left panel. Target temperature at 33°C for 48 h compared with 24 h in the TTH cohort was not associated with a difference in MAp19 levels (-31 ng/mL [95%CI: -120-60 mg/mL], p=0.57), Figure, right panel. MAp19 levels below the median at admission in the TTM cohort were associated with higher mortality (17% vs. 42%, plog-rank =0.0005), even in multivariable analysis adjusting for witnessed arrest, bystander CPR, initial rhythm, sex, age, time to ROSC and lactate level at admission (two-fold higher MAp19, HR=0.48 (95%CI: 0.31-0.75), p=0.001). Analysis of MAp19 levels at 24-72h in the merged cohort was not associated with mortality (all p-values > 0.38).

Conclusions:
Survivors after OHCA display lower levels of MAp19 protein compared with healthy controls. A targeted temperature management at 33°C compared with 36°C was significantly associated with lower MAp19 protein levels, whereas target temperature at 33°C for 48 h compared with 24 h did not influence MAp19 protein levels. High levels of MAp19 protein at admission were independently associated with lower mortality.
Conclusions:
Survivors after OHCA display lower levels of MAp19 protein compared with healthy controls. A targeted temperature management at 33°C compared with 36°C was significantly associated with lower MAp19 protein levels, whereas target temperature at 33°C for 48 h compared with 24 h did not influence MAp19 protein levels. High levels of MAp19 protein at admission were independently associated with lower mortality.