Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Serum tau as a predictor for neurological outcome after cardiopulmonary resuscitation

Julia Hasslacher[a], *Verena Rass*[b], *Ronny Beer*[b], *Hanno Ulmer*[c], *Christian Humpel*[d], *Alois Schiefecker*[b], *Georg Lehner*[a], *Romuald Bellmann*[a], *Michael Joannidis*[a,*], *Raimund Helbok*[b]

[a] *Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria*

[b] *Department of Neurology, Neurological Intensive Care Unit, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria*

[c] *Department of Medical Statistics, Informatics and Health Economics, Medical University Innsbruck, Schöpfstraße 41/1, 6020 Innsbruck, Austria*

[d] *Department of Psychiatry, Psychotherapy and Psychsomatics, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria*

Abstract

Aim: We evaluated serum tau protein as biomarker for poor neurological outcome over an extended observation period in patients after successful cardiopulmonary resuscitation (CPR) treated with mild therapeutic hypothermia (MTH) or normothermia (NT).

Methods: This is a retrospective analysis of a prospective observational study including 132 patients after successful CPR. Serum tau was determined in 24 h intervals for up to 168 h after CPR. Patients were treated with MTH targeting a temperature of 33 °C for 24 h or NT according to current guidelines. Neurological outcome was assessed with the Cerebral Performance Categories Scale (CPC) at hospital discharge.

Results: Forty-three percent of the patients were treated with MTH. Serial serum tau levels (pg/ml) showed a peak between 72–96 h after CPR (159 (IQR 27–625). Patients with poor neurological outcome (CPC 3–5) at hospital discharge (n = 68) had significantly higher serum tau levels compared to patients with good neurological outcome at 0–24 h (164 (48–946) vs. 69 (12–224); $p = 0.009$), at 24–48 h (414 (124–1049) vs. 74 (0–215); $p < 0.001$), at 48–72 h (456 (94–1225) vs. 69 (0–215); $p < 0.001$) and at 72–96 h (691 (197–1173) vs. 73 (0–170); $p < 0.001$). At 72–96 h the AUC to predict poor neurological outcome was 0.848 (95% CI: 0.737–0.959). Serum tau levels were not significantly different between patients with MTH and NT in multivariate analysis after adjusting for clinical relevant covariates.

Conclusion: Serum tau showed highest values and the best prognostic discrimination of poor neurological outcome at 72–96 h after CPR. Prolonged elevation may indicate ongoing axonal damage in patients with hypoxic encephalopathy.

Keywords: Cardiac arrest, Cardiopulmonary resuscitation, Biomarker, Serum tau, Outcome, Prognostication, Inflammation, Hypothermia

Introduction

Despite advances in the critical care management of patients after out-of-hospital and in-hospital cardiac arrest (CA) including targeted temperature management (TTM),[1,2] favourable long-term outcomes only range between 7 and 22%.[3–6]

Neuro-prognostication remains difficult and is currently based on a multimodal approach including clinical assessment, electroencephalography, somatosensory evoked potentials (SSEP), neuroimaging and blood derived biomarkers.[7,8] Neuron–specific enolase (NSE) is still considered as the gold standard[9,10] and is used beside S-100B,[11–14] and others including secretoneurin (SN),[15] glial fibrillary acidic protein (GFAP),[12,16] brain- derived

* Corresponding author at: Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria.

E-mail address: Michael.joannidis@i-med.ac.at (M. Joannidis).

https://doi.org/10.1016/j.resuscitation.2020.01.022

Received 21 October 2019; Received in revised form 7 January 2020; Accepted 20 January 2020

neurotrophic factor (BDNF)[12] and neurofilament light chain (NF-L).[17]

Recently serum tau levels showed a high accuracy in predicting poor outcome after out-of-hospital cardiac arrest (OHCA) independent if mild hypothermia (MTH) (33 °C) or normothermia (NT) (°36 °C) was applied.[18] In two smaller observational studies, delayed increase of serum tau was associated with poor outcome in hypothermic patients.[19,20] Tau is a microtubule-associated axonal protein with a stabilizing function under physiological conditions. Following axonal disruption, tau can be detected in brain extracellular fluid,[21] cerebrospinal fluid (CSF)[22–24] and serum.[25–28] Whereas brain extracellular tau is only elevated for 48 h after traumatic brain injury, prolonged and sustained elevated serum levels have been reported in severe subarachnoid hemorrhage (SAH) patients[21] and CA patients[19,20] with poor outcome. Because of prolonged elevated serum tau levels despite of the relatively short half-life of tau protein (115 h),[29] we speculate there is ongoing axonal injury possibly triggered by inflammatory processes. The association of tau in the brain extracellular fluid with elevated IL-6 levels in SAH patients[30] and the association of elevated tau fragments with systemic inflammatory markers[31] support our considerations.

Therefore, we hypothesized that serum tau elevation beyond 72 h may occur in patients with poor neurological outcome after successful cardiopulmonary resuscitation (CPR) possibly indicating ongoing axonal damage.

The aim of our study was to investigate serum tau kinetics and predictive performance of serum tau over an extended observation period to better understand ongoing pathophysiological processes and improve prognostication, independent if MTH or NT is applied.

Methods

Study design

This is a secondary analysis of our previously published study investigating SN after successful CPR.[15] This prospective observational single centre trial included 152 consecutive adult patients (age ≥ 18 years) with an in-hospital or out-of-hospital cardiac arrest with presumed cardiac cause admitted to the medical intensive care unit (ICU) of the University Hospital of Innsbruck from September 2008 to April 2013 after successful CPR. The presence of a neuroendocrine tumor, stroke, intracranial haemorrhage or trauma as non- cardiogenic cause of CA as well as life expectancy of less than 24 h as determined by the treating physicians were considered as exclusion criteria.

Of 152 consecutive CA patients, 20 (13%) were excluded due to lost follow up (n = 4), missing values due to missing serum samples (n = 6) or death not related to hypoxic ischemic encephalopathy (HIE) (n = 10) leaving 132 patients eligible for final analysis. (ESM Fig. 1)

Measurements

Blood samples were drawn from an arterial catheter for the daily determination of all biomarkers starting at the day of CPR up to 7 days and assigned to following time intervals: 0–24 h (day 1), 24–48 h (day 2), 48–72 h (day 3), 72–96 h (day 4), 96–120 h (day 5), 120–144 h (day 6) and 144–168 h (day 7).

Description of assay methods

Blood (9 ml) was collected in EDTA tubes, immediately centrifuged for 10 min, the upper phase (serum) collected in cryovials® and stored at −80 °C. Serum tau levels were determined with a commercial ELISA (Innogenetics/Fujirebio Gent, Belgium) detecting total tau as reported previously by us.[30] The detection limit was ∼50 pg/ml for serum tau.

Additionally, serum lactate (Roche, Mannheim, Germany), as an established marker for circulatory shock was measured after admission within 24 h.

Sequential Organ Failure Assessment Score (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated at the day of ICU admission. CA data such as the rate of bystander resuscitation, time to return of spontaneous circulation (ROSC) and first monitored rhythm were collected from the emergency or heart alarm protocol according to the Utstein Style.[32]

Targeted temperature management

According to the guidelines at study initiation, MTH was routinely applied to comatose patients with an initially shockable rhythm that had received advanced life support within 15 min and showed a ROSC less than 60 min after collapse. After the change in the guidelines in 2010 recommending the use of MTH also in patients with non- shockable rhythms with a low level of evidence, we also applied MTH to comatose patients with initially non - shockable rhythms, if the event was observed and time to ROSC less than 25 min.[33] Patients that underwent MTH were maintained at a target temperature of 32–34 °C using an intravascular cooling device (Thermogard XP, Zoll®, Intravascular Temperature Management Systems) and then gradually rewarmed with a rate of 0.2–0.4 °C/h.

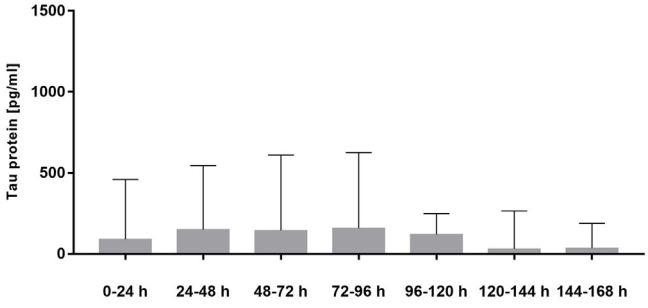

Fig. 1 – Kinetics of serum tau [pg/ml] (median + IQR) in all patients.

Core body temperature was measured in the urinary bladder using a Foley catheter.

Outcome measures

To assess neurological outcome the Cerebral Performance Categories (CPC) Scale was used[34,35] (see a detailed description in the ESM). To receive binary outcome parameters patients were classified into two groups according to their neurological outcomes: 'good outcome' (CPC 1 and 2) and 'poor outcome' (CPC 3–5). The 5 categories of CPC have been described in detail elsewhere, briefly they comprise: 1. Good cerebral performance. 2. Moderate cerebral disability. 3. Severe cerebral disability 4. Coma/vegetative state. 5. Brain death.[34]

As primary outcome measure the CPC was assessed by a physician either at death at our ICU or in survivors at discharge from hospital (also including long-term acute care facilities) following a standardized protocol. The CPCs for patients being transferred to another hospital were determined by follow-up telephone interview of the patient himself/herself, his/her family member or personnel of his/her rehabilitation facility at hospital discharge.

Ethics

The study protocol was approved by the Ethics Committee of the Medical University of Innsbruck (protocol number UN3493 272/4.31). Written informed consent was obtained from next of kin or retrospectively from patients who recovered.

Neurologic examination

Neurologic examinations were performed after complete weaning off sedation in all patients who survived including clinical examinations, neuroimaging findings, bilateral median nerve SSEP recordings and bedside electroencephalograms (EEG) with standardized auditory and noxious stimulation. A neurologist with expertise in neurocritical care performed neurological examination in accordance to the American Academy of Neurology guidelines[10] Physicians involved in primary care and prognostication of study patients were blinded to serum tau analysis.

Medical decision making

Decisions about further medical treatment were based on clinical, neurophysiological and imaging data as well as concomitant underlying diseases of the patients and were taken after completion of MTH, complete weaning off sedation and diagnostic procedures in an interdisciplinary conference of treating intensivists and neurologists.[1,10] NSE levels were available for the prognostication process and were included in the decision process. Serum tau levels were not available for the treating physicians and did not influence this critical process in any case. Patients were allocated to following subgroups: (1) Withdrawal of therapy, (2) Withholding of therapy, (3) Maximal therapy. A detailed description is given in the original publication.[15] The medical consensus was discussed with the patient's family also considering the patients' presumed will.

Statistical analysis

Categorical data are given as counts and percentages, continuous data as medians and interquartile ranges. Normal distribution of continuous data was checked by the Kolmogorov–Smirnov test. As serum tau and most other variables were not normally distributed the Mann Whitney-U-test was used for univariate comparison of continuous variables between patients. Chi-Square-test was used to compare the categorical data.

The accuracy of serum tau levels to differentiate between good and poor outcome was evaluated by the receiver operating characteristic (ROC) analysis. Overall specific ROC curves were built for serum tau at every 24 h interval up to 168 h. The 95% confidence interval for the area under the curve was calculated with

Table 1 – Characteristics of patients with good or poor neurological outcome.

Patient characteristics	Good outcome (n = 64)	Poor outcome (n = 68)	p - value
Age in years, median (IQR)	59 (50–70)	67 (57–76)	0.004
Female, n (%)	19 (29.7)	15 (22.1)	0.318
Bystander-initiated CPR, n (%)	51 (79.7)	39 (57.4)	0.006
Time to ROSC > 20 min, n (%)	23 (35.9)	48 (70.6)	<0.001
Cardiac arrest out-of-hospital, n (%)	56 (87.5)	59 (86.8)	0.900
Mild therapeutic hypothermia, n (%)	36 (56.3)	21 (30.9)	0.003
Shockable first monitored rhythm (VFib + VTac)	49 (76.6)	28 (41.2)	<0.001
First monitored rhythm			
Ventricular fibrillation (VFib), n (%)	48 (75.0)	27 (39.7)	
Asystole, n (%)	7 (10.9)	27 (39.7)	
Pulseless electrical activity (PEA), n (%)	5 (7.8)	12 (17.6)	
Ventricular tachycardia (VTac), n (%)	1 (1.6)	1 (1.5)	
Unknown, n (%)	3 (4.7)	1 (1.5)	
Outcome at hospital discharge, n (%)			
CPC 1	50 (78.1)		
CPC 2	14 (21.9)		
CPC 3		3 (4.4)	
CPC 4		2 (2.9)	
CPC 5		63 (92.6)	
SOFA score on admission	10 (8–11)	11 (9–13)	0.012
APACHE II on admission	23 (20–26)	27 (24–31)	<0.001
Lactate at 0–24 h after CPR [mg/dl]	41 (28–67)	60 (32–116)	0.010

CPR cardiopulmonary resuscitation, *ROSC* return of spontaneous circulation, *MTH* mild therapeutic hypothermia, *CPC* Cerebral Performance Categories Scale, *SOFA* Sequential Organ Failure Assessment Score, *APACHE II* Acute Physiology and Chronic Health Evaluation II.

the formula of Hanley and Mc Neil (1982).[36] The cut- off points for prediction of poor neurological outcome were determined at the specificities of 95, 96,97,98,99 and 100%, because in our clinical situation high specificity is more important than sensitivity in a predictive model.

A general estimating equation (GEE) model according to Liang and Zeger[37] was fitted in order to compare the effect of MTH and covariates on the longitudinal measurements of serum tau over 96 h. The reported model assumes an unstructured correlation structure. Furthermore, we performed a GEE model on neurological outcome as dependent variable. In univariate analysis we only assessed the effect of longitudinal tau (over 96 h) on neurological outcome. In multivariate analysis all variables, which showed statistical significance in the univariate analysis and had clinical importance, were included in the model. For the GEE modelling serum tau was logarithmically transformed to achieve normal distribution.

Values with a p-value < 0.05 were considered as statistically significant. SPSS software (SPSS Inc., Chicago, Illinois, USA) was used to analyse data.

Results

The median age was 64 (IQR 53–75) years, and 26% (34/132) were female. Ninety patients (68%) received bystander resuscitation and 17 patients (13%) encountered in-hospital CA. The initial rhythm was ventricular fibrillation in 75 patients (57%) (Table 1). In 68 patients (52%) poor neurological outcome (CPC 3–5) was recorded at hospital discharge, of whom 11 received the maximal ICU care, in 10 and 47 patients therapy was withheld or withdrawn, respectively. (ESM Fig. 1)

Patients with beneficial neurological outcome (64; CPC 1,2) were significantly younger ($p = 0.004$), had a higher rate of bystander-initiated CPR ($p = 0.006$), a lower rate of prolonged ROSC-time (>20 min) ($p < 0.001$), a higher rate of shockable first monitored rhythms ($p < 0.001$) and MTH treatment ($p = 0.003$). Furthermore, SOFA and APACHE II scores as well as serum lactate levels at admission were significantly lower in patients with good neurological outcome (see Table 1).

Serum tau kinetics

In all patients serum tau levels markedly increased within 24 h, reaching a plateau between 24 and 96 h and decreased thereafter (Fig. 1). Peak levels occurred between 72–96 h after CPR (159 pg/ml (27–625 pg/ml). In patients with poor neurological outcome, the same kinetics were observed whereas patients with good neurological outcome did not show an increase in the days after CPR. The number of patients analysed at each time interval is given in Table 2.

Total serum tau and hospital outcome

Patients with poor neurological outcome (CPC 3–5) had significantly higher serum tau levels when compared to patients with good neurological outcome (CPC 1–2) within the first 24 h (164 (48–946) vs. 69 (12–224) pg/ml; $p = 0.009$), at 24–48 h (414 (124–1049) vs. 74 (0–215) pg/ml; $p < 0.001$), at 48–72 h (456 (94–1225) vs. 69 (0–215) pg/ml; $p < 0.001$), at 72–96 h (691 (197–1173) vs. 73 (0–170) pg/ml; $p < 0.001$) at 96–120 h (260 (132–731) vs. (27 (0–168) pg/ml; $p = 0.001$) and 144–168 h (189 (119–603 vs. 0 (0–36); $p = 0.19$). (Fig. 2)

Table 2 – Diagnostic accuracy of serum tau at different time intervals to predict poor neurological outcome.

time interval	N	AUC [95% CI]	FPR,%	cut-off, pg/ml	Sens, %	Spec, %
0–24 h	n = 128	0.645 [0.540–0.750]	5	764	30	95
			4	937	25	96
			3	1007	21	97
			2	1109	17	98
			1	1268	2	99
			0	1274	2	100
24–48 h	n = 93	0.775 [0.679–0.870]	5	647	38	95
			4	666	38	96
			3	874	31	97
			2	913	21	98
			1	1092	21	99
			0	1102	21	100
48–72 h	n = 73	0.783 [0.671–0.894]	5	778	41	95
			4	792	41	96
			3	881	38	97
			2	1225	24	98
			1	1423	10	99
			0	1443	10	100
72–96 h	n = 53	0.848 [0.737–0.959]	5	790	50	95
			4	835	50	96
			3	880	50	97
			2	1158	25	98
			1	1167	25	99
			0	1218	20	100

TAU serum tau, *N* number of patients measured, *AUC* area under the curve, *CI* confidence interval, *FPR* false positive rate, *Sens* sensitivity, *Spec* specificity.

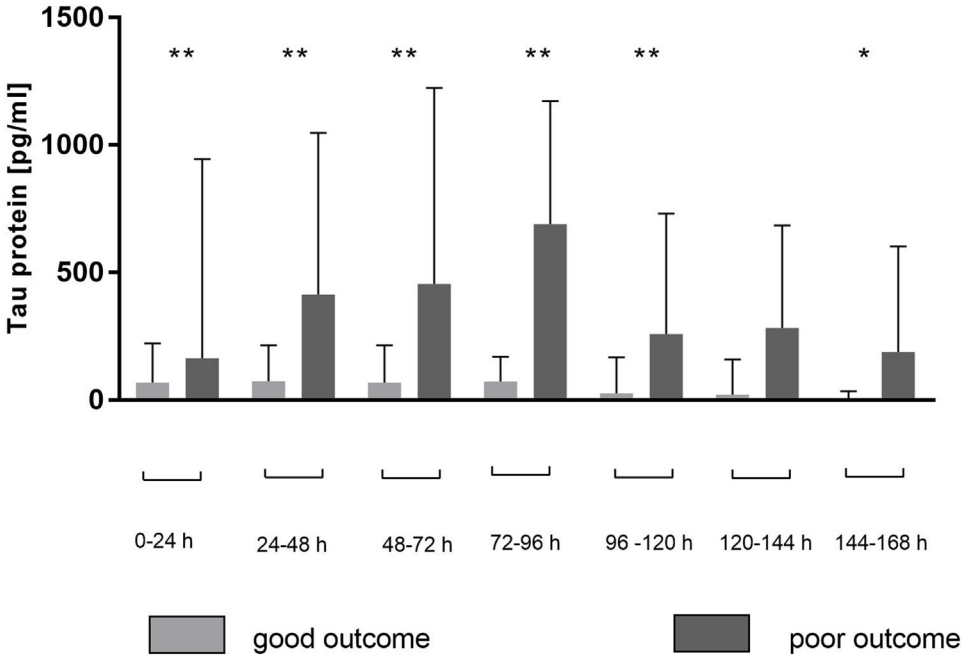

Fig. 2 – Serum tau [pg/ml] (median + IQR) in patients with good and poor neurological outcome. *p < 0.05. **p < 0.01.

The predictive performance of serum tau increased over time reaching a maximum at 72–96 h after CPR and then decreasing again. The AUC at 72–96 h was 0.848 (95% CI: 0.737–0.959). At a specificity of 97% (FPR 3%) with a sensitivity of 50% the cut-off for poor outcome was 880 pg/ml. (Fig. 3,Table 2).

In a GEE model with neurological outcome as dependent variable, serum tau was significantly associated with poor outcome in univariate analysis (Wald Chi -Square (95% CI): 14.758 (−5.689E-7 - (−1.845E-7); p < 0.001). Tau remained a significant predictor also in multivariate analysis (Wald Chi-Square (95% CI): 14.651 (0.000- (−5.473E-5)); p < 0.001) when adjusting for the covariates age, shockable rhythm, time to ROSC > 20 min and MTH (Table 3).

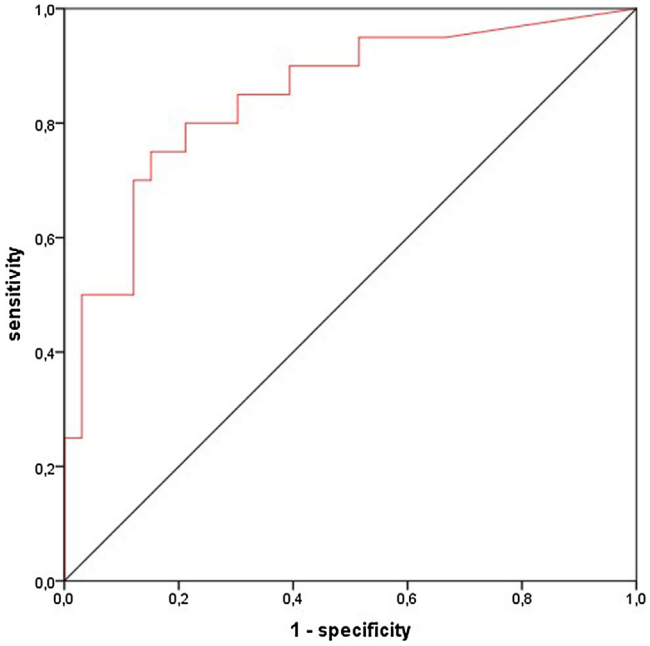

Fig. 3 – ROC curve at 72–96 h after cardiopulmonary resuscitation.

Serum tau and targeted temperature management

Fifty-seven patients (43%) were treated with MTH. The majority (49 patients, 86%) initially presented with a shockable rhythm and tended to have lower SOFA scores. APACHE II scores where even significantly lower in this subgroup (MTH vs. NT: 24 (IQR 20–27) vs. 27 (IQR 23–31); p < 0.001). Serum tau tended to be lower and showed a markedly lower variability in patients treated with MTH, but the differences reached statistical significance only at 0–24 h and 72–96 h after CPR (ESM Fig. 2). In patients with poor neurological outcome statistical significance was reached only at 0–24 h (ESM Fig. 3) and in patients with good neurological outcome at 72–96 h (ESM Figure 4). In the GEE model we could observe a statistically significant effect of MTH on serum tau levels

Table 3 – Generalized estimating equation model with outcome as dependent variable.

	Wald Chi-Square (95% CI)	p-value
Age	6.793 (−0.65 to (−0.009))	0.009
Shockable rhythm	10.621 (−2.656 to (−0.661))	0.001
Time to ROSC > 20 min	12.557 (0.711 to 2.470)	<0.001
MTH	0.427 (−1.270 to 0.635)	0.514
TAU	**14.651 (0.000 to (−5.473E-5))**	**<0.001**

CI confidence interval, *ROSC* return of spontaneous circulation, *MTH* mild therapeutic hypothermia, *CPR* cardiopulmonary resuscitation, *TAU* serum tau over 96 h.

over 96 h after CPR (Wald Chi-Square (95% CI): 5.034 (27.751−411.117); p = 0.025). After adjustment for clinical relevant covariates (age, first monitored rhythm, time to ROSC > 20 min, bystander initiated CPR, lactate and MTH) the effect of MTH was not statistically significant anymore (Wald Chi-Square (95% CI): 2.294 (−47.098 to 367.324); p = 0.130). (ESM Table 1)

CPC assessment at hospital discharge

The median follow up time was 11 (IQR 4−24) days for all patients, 20 (IQR 11−38) days for patients with good and four (IQR 2−9) days with poor neurological outcome. 62,5% of the survivors with good neurological outcome (n = 64) were discharged from our hospital to home, 37,5% patients were transferred to a secondary hospital or rehabilitation institution. Survivors with poor neurological outcome (n = 5) were all discharged to a secondary hospital.

Discussion

In the present study, we analysed serum tau in patients after successful CPR treated with MTH or NT over an extended observation period of 168 h. Serum tau showed significantly higher levels in patients with poor (vs. good) neurological outcome with a peak at 72−96 h. Best performance for prognostication could be also demonstrated at 72−96 h. Application of MTH seemed to have minor influence on serum tau levels.

In patients with poor neurological outcome serum tau levels peaked at 72−96 h after CPR, whereas patients with good neurological outcome did not develop a relevant increase. Our results are consistent with two small studies including 22 and 25 hypothermic CA patients, respectively: the first showed peaking serum tau levels at 96 h[19] and the second two peaks within an observation time of up to 108 h (within 24 h and after 24−48 h after CPR) in patients with poor neurological outcome.[20] In the study of Mattsson et al.[18] a significant increase of serum tau occurred between 24 and 48 h in patients with poor outcome. However, one could speculate that a delayed potentially more pronounced peak was not detected due to the limited observation period of 72 h.

Direct comparisons of absolute values and cut-off points have to be drawn with caution, because each study with CA patients used a different analysis method.[18–20] The two small studies reported about serum tau levels from zero to 600 pg/ml[19] and 700 pg/ml,[20] respectively, which is similar to our study (0−1500 pg/ml). Mattsson et al.[18] do not provide ranges but showed generally lower serum tau levels at several timepoints. The reference value of serum tau in healthy volunteers is 4.5 pg/ml.[38]

Although serum tau has only a relatively short half-life in serum,[20] we found prolonged high levels at later timepoints after CPR. This supports the hypothesis, that there is a continuous release of tau from injured neurons.[18] Tau is normally secreted from injured neurons to the CSF. Under hypoxic conditions, it may pass the blood brain barrier secondary to disruption and is consequently detectable in blood.[39] According to serum kinetics with prolonged elevation beyond the initial injury, we speculate that further release of tau is resulting from secondary brain damage in hypoxic encephalopathy promoted by inflammatory processes. This is in line with the findings of a previous study of our group, which show sustained elevated cerebral microdialysis (CMD)-tau protein concentrations in the extracellular brain tissue in SAH patients.[21] Furthermore, we found an association between tau levels and IL-6 suggesting neuroinflammation asunderlying mechanism for ongoing axonal damage.[30] Recently it was also shown, that tau fragments, although not capable of predicting neurological outcome, are associated with elevated levels of systemic inflammation in CA patients.[31] Unfortunately, we did not have the opportunity to compare tau levels with other inflammatory markers such as IL-6, but it would be interesting to address this topic in further studies.

Tau is a microtubule-binding protein responsible for axonal stability and integrity.[40] Axonal injury might thus be an explanation for raising axonal biomarkers such as NF-L and tau. A recent MR- diffusion tensor imaging study suggests that both hemispheres are predominantly affected by axonal injury after CA.[41] Recently, serum NF-L showed better predictive performance than tau in a large cohort of comatose resuscitated patients.[17] Both markers seem to be very specific for the brain. Although tau is also expressed in other organs than the brain (Courtesy of Human Protein Atlas, www.proteinatlas.org),[42] there is no data available that any extracerebral pathology leads to a significant increase in serum tau.

In our study, accuracy in terms of poor neurological outcome was increasing over time achieving a maximum at 72−96 h after CPR, independent whether MTH or NT was applied. We would have expected a further improvement of predictive performance after 96 h, but due to a diminished sample size after death and patient transfer reliable prediction was not maintainable (data not shown). Cut-off points with a high specificity for poor outcome were combined with an acceptable sensitivity, but in general, it is rare to have a low FPR with a high sensitivity in CA studies.[43,44] Tau was significantly associated with poor outcome in univariate and multivariate analysis after adjusting for clinically relevant covariates.

In the TTM trial[18] the prognostic accuracy of serum tau for poor neurological outcome was increasing over time reaching a maximum at 72 h after CPR (AUC of 0.91), but it remains unclear if there would have been further improvement later in the course due to the limited observation period. Compared to our study, the TTM trial[18] included a higher number of patients and yielded better results in outcome prediction, but focused on the first 72 h. The two studies mentioned above also investigating serum tau in CA patients were limited because of their small sample size, but had a prolonged observation time. They reported about an association between delayed serum tau peaks after 24−48 h and poor 6-month outcome[20] and best prediction at 96 h after CPR in hypothermic patients.[19]

Based on existing data, we believe that there is an additional value of prognostication in the late phase beyond 72 h after CPR. Our findings support current recommendations for neuro-prognostication after CA suggesting prolonged evaluation of biomarkers, especially if MTH is applied.[8]

We observed slightly lower serum tau levels in patients treated with MTH. The influence of MTH on serum tau levels was significant in univariate analysis, but did not remain significant in multivariate analysis when adjusting for clinically relevant covariates. Patients treated with MTH tended to be less severely ill reflected by lower APACHE II scores at ICU admission. In conclusion, the application of MTH might have a minor influence on serum tau levels. Similar findings were reported in the large TTM trial.[18]

Limitations

The limitations of the study are consistent with those of the original study.[15] Thus, the study is designed as a single – centre study and patients were not randomized to the MTH or NT group.

The planning of this study together with the power calculation was originally targeted on SN. Serum-tau was considered as secondary end-point in the originally protocol.

The assessment of long – term outcome was not part of the original study protocol. Median follow-up time for patient with good neurological outcome at hospital discharge was 20 (IQR 11–38) days. Although this is a quite long observation period, we can't rule out later improvement or worsening of neurological outcome. Little data exist about the recovery trajectory after hospital discharge in CA patients, but CPC at hospital discharge has shown to be a good predictor of long-term outcome.[45]

In our study we had 10 (7,5%) drop-outs because of death not related to HIE. Thereby we wanted to avoid misclassification to a "neurological death" and confounding of outcome assessment. This sensitive topic was recently addressed by Taccone et al.[46] reporting about 4,2% of death after awakening in non-survivors of CA.

Neuro-prognostication was performed according to the AAN guidelines.[10] This may have influenced the decision to withdraw care in individual patients when compared to the current recommendations given by ESC and ESICM.[47] On major difference is the change in NSE cut–offs and the time to neuro-prognostication. However, neuro-prognostication was always performed by independent neuro-intensivists based on a multifaceted approach and did not change over time.

In our study we included both, IHCA and OHCA patients. However, the proportion of IHCA patients was only 13% and we only found significant differences in the rate of bystander CPR and application of MTH, but not in severity of illness scores (SOFA and APACHE II) and outcome.

Conclusions

In our study, we could show that peak levels and best prognostication of serum tau is achieved at 72–96 h after CPR in a population consisting of hypothermic and normothermic patients. Sustained elevations beyond 72 h after CPR might be a sign of ongoing neuroinflammatory processes in hypoxic ischemic injury. The influence of MTH seems to be negligible. Further studies are needed to support repeated biomarker assessment beyond 72 h after cardiac arrest.

Conflicts of interest

None.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2020.01.022.

REFERENCES

1. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 2013;369:2197–206.
2. Rittenberger JC, Callaway CW. Temperature management and modern post-cardiac arrest care. N Engl J Med 2013;369:2262–3.
3. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010;81:1479–87.
4. Girotra S, Nallamothu BK, Spertus JA, et al. Trends in survival after in-hospital cardiac arrest. N Engl J Med 2012;367:1912–20.
5. Kudenchuk PJ, Redshaw JD, Stubbs BA, et al. Impact of changes in resuscitation practice on survival and neurological outcome after out-of-hospital cardiac arrest resulting from nonshockable arrhythmias. Circulation 2012;125:1787–94.
6. Nolan JP. Optimizing outcome after cardiac arrest. Curr Opin Crit Care 2011;17:520–6.
7. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation 2014;85:1779–89.
8. Sandroni C, Geocadin RG. Neurological prognostication after cardiac arrest. Curr Opin Crit Care 2015;21:209–14.
9. Shinozaki K, Oda S, Sadahiro T, et al. S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review. Crit Care 2009;13:R121.
10. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Quality Standards Subcommittee of the American Academy of N. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;67:203–10.
11. Bottiger BW, Mobes S, Glatzer R, et al. Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. Circulation 2001;103:2694–8.
12. Mortberg E, Zetterberg H, Nordmark J, Blennow K, Rosengren L, Rubertsson S. S-100B is superior to NSE, BDNF and GFAP in predicting outcome of resuscitation from cardiac arrest with hypothermia treatment. Resuscitation 2011;82:26–31.
13. Rosen H, Sunnerhagen KS, Herlitz J, Blomstrand C, Rosengren L. Serum levels of the brain-derived proteins S-100 and NSE predict long-term outcome after cardiac arrest. Resuscitation 2001;49:183–91.
14. Tiainen M, Roine RO, Pettila V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003;34:2881–6.
15. Hasslacher J, Lehner GF, Harler U, et al. Secretoneurin as a marker for hypoxic brain injury after cardiopulmonary resuscitation. Intensive Care Med 2014;40:1518–27.
16. Hayashida H, Kaneko T, Kasaoka S, et al. Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. Neurocrit Care 2010;12:252–7.
17. Moseby-Knappe M, Mattsson N, Nielsen N, et al. Serum neurofilament light chain for prognosis of outcome after cardiac arrest. JAMA Neurol 2018;76:64–71.
18. Mattsson N, Zetterberg H, Nielsen N, et al. Serum tau and neurological outcome in cardiac arrest. Ann Neurol 2017;82:665–75.
19. Mortberg E, Zetterberg H, Nordmark J, et al. Plasma tau protein in comatose patients after cardiac arrest treated with therapeutic hypothermia. Acta Anaesthesiol Scand. 2011;55:1132–8.
20. Randall J, Mortberg E, Provuncher GK, et al. Tau proteins in serum predict neurological outcome after hypoxic brain injury from cardiac arrest: results of a pilot study. Resuscitation 2013;84:351–6.
21. Helbok R, Schiefecker A, Delazer M, et al. Cerebral tau is elevated after aneurysmal subarachnoid haemorrhage and associated with brain metabolic distress and poor functional and cognitive long-term outcome. J Neurol Neurosurg Psychiatry 2015;86:79–86.
22. Franz G, Beer R, Kampfl A, et al. Amyloid beta 1-42 and tau in cerebrospinal fluid after severe traumatic brain injury. Neurology 2003;60:1457–61.

23. Kay A, Petzold A, Kerr M, Keir G, Thompson E, Nicoll J. Temporal alterations in cerebrospinal fluid amyloid beta-protein and apolipoprotein E after subarachnoid hemorrhage. Stroke 2003;34:e240–3.
24. Zanier ER, Zoerle T, Fiorini M, et al. Heart-fatty acid-binding and tau proteins relate to brain injury severity and long-term outcome in subarachnoid haemorrhage patients. Br J Anaesth 2013;111:424–32.
25. Liliang PC, Liang CL, Weng HC, et al. Tau proteins in serum predict outcome after severe traumatic brain injury. J Surg Res 2010;160:302–7.
26. Shaw GJ, Jauch EC, Zemlan FP. Serum cleaved tau protein levels and clinical outcome in adult patients with closed head injury. Ann Emerg Med 2002;39:254–7.
27. Teunissen CE, Dijkstra C, Polman C. Biological markers in CSF and blood for axonal degeneration in multiple sclerosis. Lancet Neurol 2005;4:32–41.
28. Zheng YK, Dong XQ, Du Q, et al. Comparison of plasma copeptin and multiple biomarkers for assessing prognosis of patients with aneurysmal subarachnoid hemorrhage. Clin Chim Acta 2017;475:64–9.
29. Li J, Li XY, Feng DF, Pan DC. Biomarkers associated with diffuse traumatic axonal injury: exploring pathogenesis, early diagnosis, and prognosis. J Trauma 2010;69:1610–8.
30. Schiefecker AJ, Dietmann A, Beer R, et al. Neuroinflammation is associated with brain extracellular TAU-Protein release after spontaneous subarachnoid hemorrhage. Curr Drug Targets 2017;18:1408–16.
31. Grand J, Kjaergaard J, Nielsen N, et al. Serum tau fragments as predictors of death or poor neurological outcome after out-of-hospital cardiac arrest. Biomarkers 2019;24:584–91.
32. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, Inter American Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation 2004;63:233–49.
33. Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. Resuscitation 2010;81:1219–76.
34. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. Lancet 1994;343:1055–9.
35. Stiell IG, Nesbitt LP, Nichol G, et al. Comparison of the cerebral performance category score and the health utilities index for survivors of cardiac arrest. Ann Emerg Med 2009;53:241–8.
36. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.
37. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121–30.
38. Zetterberg H, Wilson D, Andreasson U, et al. Plasma tau levels in Alzheimer's disease. Alzheimers Res Ther 2013;5:9.
39. Sharma HS, Miclescu A, Wiklund L. Cardiac arrest-induced regional blood-brain barrier breakdown, edema formation and brain pathology: a light and electron microscopic study on a new model for neurodegeneration and neuroprotection in porcine brain. J Neural Transm (Vienna) 2011;118:87–114.
40. Guo T, Noble W, Hanger DP. Roles of tau protein in health and disease. Acta Neuropathol 2017;133:665–704.
41. van der Eerden AW, Khalilzadeh O, Perlbarg V, et al. White matter changes in comatose survivors of anoxic ischemic encephalopathy and traumatic brain injury: comparative diffusion-tensor imaging study. Radiology 2014;270:506–16.
42. Uhlen M, Fagerberg L, Hallstrom BM, et al. Proteomics. Tissue-based map of the human proteome. Science 2015;347:1260419.
43. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. Resuscitation 2013;84:1324–38.
44. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 1: patients not treated with therapeutic hypothermia. Resuscitation 2013;84:1310–23.
45. Phelps R, Dumas F, Maynard C, Silver J, Rea T. Cerebral performance category and long-term prognosis following out-of-hospital cardiac arrest. Crit Care Med 2013;41:1252–7.
46. Taccone FS, Horn J, Storm C, et al. Death after awakening from post-anoxic coma: the "Best CPC" project. Crit Care 2019;23:107.
47. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:202–22.