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Clinical paper

MIF reflects tissue damage rather than inflammation in post-cardiac arrest syndrome in a real life cohort☆

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ABSTRACT

Introduction: Following successful resuscitation from cardiac arrest (CA), neurological impairment and other types of organ dysfunction cause significant morbidity and mortality—a condition termed post-cardiac arrest syndrome. Whole-body ischemia/reperfusion with oxygen debt activates immunologic and coagulation pathways increasing the risk of multiple organ failure and infection. We here examined the role of the pro-inflammatory cytokine *macrophage migration inhibitory factor* (MIF) in post-cardiac arrest syndrome.
Methods: MIF plasma levels of $n = 16$ patients with return of spontaneous circulation (ROSC) after CA were assessed with a previously validated method and compared to markers of systemic inflammation and cellular damage. ICU patients without former CA and healthy volunteers served as controls.
Results: MIF levels in patients after ROSC were higher compared to those in healthy volunteers and ICU patients without CA. Kaplan–Meyer analysis revealed a distinctly elevated mortality since day one that further increased towards an elevated 60-days-mortality in patients with high plasma MIF. ROC curve identified plasma MIF as a predictor for mortality in patients after CA. Correlation with inflammatory parameters revealed that high MIF levels did not mirror post CA inflammatory syndrome, but distinctive cellular damage after ROSC as there were strong correlations with markers of cellular damage like LDH and GOT/GPT.
Conclusion: High MIF levels were associated with elevated 60-days-mortality and high MIF predicted mortality after CA. We found a close relation between circulating MIF levels and cellular damage, but not with an inflammatory syndrome.

Introduction

In patients with return of spontaneous circulation (ROSC) after cardiac arrest (CA), subsequent mortality and morbidity are caused by cerebral and cardiac dysfunction that accompanies prolonged whole-body ischemia/reperfusion [1]. This syndrome is called post-cardiac arrest syndrome. According to the consensus statement of the *International Liaison Committee on Resuscitation* (ILCOR), the post-cardiac arrest syndrome can be divided into four phases [2]. The immediate post-arrest phase (phase I) occurs in the first 20 min following return of spontaneous circulation (ROSC). The early post-arrest phase (phase II) occurs between 20 min and 6–12 h after ROSC. Early interventions may be effective in this window of time. The intermediate phase (phase III) is between 6–12 h and 72 h when injury pathways are still active, and extended intensive care treatment can be initiated. The recovery phase (phase IV) extends from 3 days and beyond. The most mandatory measure is rapid treatment of the underlying disease responsible for the initial event like adequate ventilation or percutaneous coronary intervention during phases I and II [3]. Thereafter, phase III is characterized by myocardial dysfunction, anoxic brain injury and a systemic inflammatory response with plasma cytokine elevation [4,5]. To date, just few therapeutic interventions can be recommended to treat this 3rd phase after CA [2]. This is a consequence of the multifarious parameters that take place in this phase and that shares many of the features, which are frequently seen in patients with severe sepsis or septic shock. This led to the synonym "sepsis-like syndrome" [4]. High mortality rates can be further attributed to multiple organ

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failure due to ischemia, reperfusion and hypoxia during or after CPR leading to generalized tissue damage [6]. *Macrophage migration inhibitory factor* (MIF) is a key mediator of the inflammatory response to bacterial infections including an aggravating role septic shock [7–9]. MIF is quasi-ubiquitously expressed and stored in numerous cell types, while specifically secreted from the pituitary gland upon endotoxaemia, from immune cells upon inflammatory stimulation, and from selected endothelial and parenchymal cells upon hypoxic, hyperoxic, and other stress stimuli [10–12]. Although many stimuli are known to release MIF from intact cells, there have been discussions about increased levels of circulating MIF due to release from damaged cells. However, until today it is unclear, whether elevated MIF levels after CA reflect the post-cardiac arrest systemic inflammatory response or a distinct cellular damage after global ischemia and reperfusion injury.

Since post-cardiac arrest syndrome constitutes a challenge for the ICU physician and the complex interplay of cytokines after global ischemia is far from being understood yet, it is of great interest to investigate the role of MIF in this context.

We here provide first reliable and reproducible MIF values in patients after cardiac arrest applying a previously validated protocol and investigate, whether MIF plasma level might reflect the inflammatory response in post-cardiac arrest syndrome.

Material and methods

Study setting and population

After approval of the institutional review board (Ethics commission University Hospital Duesseldorf), 16 patients admitted to an academic, interdisciplinary, internist-neurologic intensive care unit (ICU) due to cardiac arrest were enrolled. Written informed consent was obtained from all patients after regaining consciousness or their next of kin. As a control population we analyzed MIF levels in 10 healthy volunteers and in 16 patients admitted to the ICU due to other reasons than cardiac arrest.

Treatment of patients

All patients received standardized intensive care treatment including mechanical ventilation, fluid substitution, antibiotic, SIRS/sepsis and vasopressor treatment according to the European Resuscitation Council Guidelines for Resuscitation 2010 [13]. Patients were sedated using midazolam or propofol and received adequate analgesia with sufentanil. Percutaneous coronary intervention was performed if cardiac disease was the underlying cause for CA. Mild therapeutic hypothermia (MTH) was induced in patients with CA due to VF and was induced using ice bags [3,13]. Tracheal extubation was performed when standard extubation criteria were fulfilled. Patients were discharged from the ICU after fulfillment of standardized clinical discharge criteria.

Blood sample collection

The first blood samples were drawn within the first hours after ROSC and every following 24 h at the same time of day for maximal 5 days or until discharge from ICU and death, respectively. Blood samples for MIF measurements were drawn *via* an arterial catheter into heparinized tubes. Samples from healthy volunteers were drawn just once *via* venous punction of the antecubital vein.

MIF measurements

Blood samples for determining MIF plasma levels were immediately centrifuged at 1000*g* for 15 min at 4 °C. Plasma was obtained and frozen at −20 °C until measurement. MIF levels were determined using an enzyme-linked immunosorbent assay (ELISA, R&D, Minneapolis, USA) as described previously [14–16].

Data collection

Baseline characteristics regarding demographic and CPR related parameters were collected immediately after hospital admission and 24, 48, 72 and 96 h after admission. Besides the data relative to the CA characteristics, biological parameters, severity scores on admission, ICU management and outcome were also recorded prospectively.

Statistical analysis

Data are given as mean and standard error of the mean unless indicated otherwise. The D'Agostino & Pearson omnibus normality test was used to test all data for normal distribution. We used the Student t test or one-way-ANOVA with post-hoc Tukey-adjustment for multiple measurements to compare normally distributed results and the Mann–Whitney U test to compare non-normally distributed data. Proportions were compared using Fisher's exact test. Survival analysis was done by the Kaplan–Meier method and compared by the log rank test. ROC curve was constructed to assess the ability of MIF levels at baseline to predict ICU-death. All tests were two sided, and P values less than 0.05 were considered statistically significant. All data were analyzed with a commercially available software package (GraphPad Prism 6, La Jolla, CA, USA).

Results

Characteristics of the study population enrolled at the intensive care unit

Sixteen patients with ROSC after CA were included in this prospective study. Overall duration of mechanical resuscitation varied from 5 to 50 min (mean 20 ± 13 min). The presenting initial rhythm was ventricular fibrillation in 25% and asystole or pulseless electrical activity (PEA) in 75%. Patients' characteristics and cardiac arrest-related data about treatment and outcome are presented in Table 1.

High MIF levels are associated with increased mortality in patients after cardiac arrest

In patients after ROSC, MIF plasma levels at admission to the ICU were higher compared to those in healthy volunteers (172.9 ± 45.3 ng/l *vs.* 18.2 ± 1.7 ng/l, n = 10–16, P < 0.01, Fig. 1A) and compared to patients admitted to the ICU due to other reasons than CA (172.9 ± 45.3 ng/l *vs.* 54.5 ± 4.8 ng/l, n = 16, P < 0.05, Fig. 1A).

Mean MIF level after ROSC was 120.9 ng/ml. After dividing the group of patients in one group with high MIF (beyond median, >120.9 ng/ml) and one group with low MIF (below median, ≤120.9 ng/ml), 60-days mortality analyzed with Kaplan–Meyer surviving curves showed increased mortality in patients with high MIF (P = 0.041, log-rank = 3.81, Fig. 1C).

To determine the discriminatory power of plasma MIF after ROSC, we calculated the AUC for the prediction of ICU mortality with 0.873 (95% CI 0.699–1.05, P = 0.013, Fig. 1B). The MIF level with the highest specificity and sensitivity was 136.3 ng/l (sensitivity 71% [95% CI 0.3–0.96], specificity 89% [95% CI 0.52–0.99].