Prognostic value of systemic cell death biomarkers after successful cardiopulmonary resuscitation

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Background and aim

There is an increasing demand to identify new biomarkers which could provide additional information about the outcome after successful resuscitation from cardiac arrest.

Ischemia-reperfusion injury during and after resuscitation results in **increased systemic cell death**, involving apoptosis and necrosis. **Cytokeratins** are components of intracytoplasmic cytoskeleton of epithelial and parenchymal tissue. The systemic release of caspase-cleaved fragments of cytokeratin-18 (ccCK-18) has been identified as a specific biomarker of apoptotic cell death, while the level of the intact form (CK-18) reflects the total systemic cell death.

The objective of our study was to investigate **for the first time** the **prognostic value of CK-18 and ccCK-18** for mortality, neurological outcome and their association with conventionally used clinical parameters after successful cardiopulmonary resuscitation.

Patients and methods

We enrolled **40 adult patients** after **out of hospital (OHCA)** or **in-hospital cardiac arrest (IHCA)** and **successful cardiopulmonary resuscitation (CPR)** taking at least 2 minutes.

The circumstances of the cardiac arrest and CPR, laboratory and physical parameters were recorded. Plasma samples were collected **6, 24, and 72 hours** after successful CPR to determine the CK-18, ccCK-18 concentrations by **ELISA**.

The mean age of the population was **67±2 years**, **23 (57.5%)** were **female**; **29 (72.5%)** had **IHCA** and **11 (27.5%) OHCA**. We registered **short resuscitation** (≤10 min) in **18 cases (53%)**; **longer** (>10 min) in **16 cases (47%)**. The initial rhythm was **shockable** (VT, VF) in **13 cases (32.5%)**; **non-shockable** (PEA, asystolia) in **25 cases (62.5%)**.

More than a half of the patients (52.4%) had a **cardiac** (ischemic heart disease, heart failure) disease in the background. Other reasons of the cardiac arrest were mainly electrolyte disturbances (hyperkalemia), respiratory failure, severe infection, pulmonary embolism and hypothermia.

Results

Resuscitated patients had **highly elevated CK-18, ccCK-18 levels** and **decreased ccCK-18/CK-18 ratio** compared to healthy subjects, septic and postoperative patients. Values in literature [1]

	6 h values in our study	Healthy volunteer group	Postoperative group	Septic group
CK-18 (ng/l) median [IQR]	3842.5 [3047.5 – 4662.8]	241.9 [216.9 – 285.3]	558.7 [465.6 – 793.0]	1643.8 [1096.5 – 2633.5]
ccCK-18 (ng/l) median [IQR]	532.9 [378.9 – 646.9]	143.7 [134.4 – 168.1]	116.0 [106.6 – 165.1]	392.6 [258.4 – 654.5]
ccCK-18/CK-18 ratio median [IQR]	0.14 [0.11 – 0.18]	0.58 [0.55 – 0.67]	0.22 [0.18 – 0.25]	0.24 [0.14 – 0.35]

Neither the values of CK-18 and ccCK-18 nor their kinetics showed difference between survivors and non-survivors and they did not show association with the length of the resuscitation, the initial rhythm, the neurological outcome (CPC scale) or the number of the damaged organ systems either.

CK-18 showed **a declining kinetics in patients with good renal function** in contrast to patients with renal failure.

Significant **negative correlation** was observed between the **6-hour CK-18 and hemoglobin** concentrations ($r=-0.400$, $p<0.01$), suggesting that among critically slow circulation during resuscitation, higher hemoglobin and oxygen binding capacity may prevent the cell death.

Conclusion

The elevated CK-18 and ccCK-18 levels refer to a **large extent of systemic cell death** compared to other study populations. **They did not have prognostic value in a general resuscitated population.** The survival may not depend on the total cell death, but could be determined by a damage of smaller group of cells with critical function.