

**First results from a prospective clinical trial measuring effects of hypothermia for organprotection during cardiac surgery- A new biomarker: Cold response protein RBM3 is upregulated after mild-to-moderate hypothermia during cardiopulmonary bypass**

Rosenthal L.M. (1,2), Tong G. (1) Wowro S. (1) Pfitzer C. (1,2,3) Berger F. (1,3,4), Schmitt K.R. (1,3)  
(1) Department of Congenital Heart Disease and Paediatric Cardiology, Deutsches Herzzentrum Berlin, Germany  
(2) Berlin Institute of Health (BIH), Berlin, Germany  
(3) DHZK (German Centre for Cardiovascular Research), partner site Berlin, Germany  
(4) Department of Paediatric Cardiology, Charité  
– Universitaetsmedizin Berlin, Germany

#### Introduction

Therapeutic hypothermia during cardiac surgery has been widely used for neuroprotection and to attenuate the systemic inflammatory response to cardiopulmonary bypass (CPB). Whereas global protein synthesis is repressed when the body temperature is decreased, a small group of RNA-binding proteins such as RNA-binding motif 3 (RBM3) is induced in response to hypothermia. Experimental data suggests that RBM3 plays a key role in hypothermia-induced neuroprotection. To date all research on RBM3 was performed in vitro or in animal models. Detection and regulation of RBM3 expression in human blood has not been investigated until now. The aim of this study was to investigate RBM3-regulation and cytokine dynamics in patient's blood in response to CPB and hypothermia.

#### Methods

A single-center prospective trial with 23 patients undergoing cardiac surgery at German Heart Institute Berlin, Germany was performed. Blood samples were collected from the central venous line during the induction of anesthesia, after weaning from CPB and 24 hours later. RBM3 protein was quantified in blood samples of patients and from 14 healthy individuals employing an Enzyme-linked Immunosorbant Assay (ELISA). Cytokine levels were analysed via Dry Blood Spot Sample collection (DBS) and enzyme immunoassay (EIA).

#### Results

RBM3 protein was detectable in human blood of healthy individuals and patient's with congenital heart disease (CHD). Hereby, RBM3 was significantly upregulated in response to CPB and application of mild-to-moderate hypothermia (32 – 34 °C) after weaning from CPB. A complex immune reaction with significant induction of proinflammatory cytokines and molecules (IL-1 beta, IL-6, IL-8, IL-12p40, IL-16, IL-18, MCP-1, CCL3, CCL4, ICAM-1) in response to CPB and activation of neutrophil cells was detected. Additionally significant elevated VEGF-levels reflecting ischemia-reperfusion-injury and significant reduced coagulation factors due to consumption coagulopathy were observed 24 hours after weaning of CPB.

#### Conclusions

Despite many technological improvements cardiac surgery with application of CPB remains associated with severe inflammatory response. Cold response protein RBM3 protein can be measured in human blood and is up-regulated after application of mild-to-moderate hypothermia during cardiac surgery employing CPB. RBM3 is therefore a promising new biomarker for hypothermia treatment and a possible new therapeutic target for interventional strategies during CPB.