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01.2018 – 12.2019

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FIELDS OF RESEARCH
› Postoperative Delirium
› Cholinergic Pathways
› Geriatric Anesthesiology

Association Between Cholinergic System Genetic Variants and Postoperative Delirium and Cognitive Dysfunction

Postoperative delirium (POD) is a common neurocognitive complication that can lead to a permanent cognitive dysfunction (POCD). Although the exact pathophysiology is not entirely clear, inflammatory processes within the brain are thought to be involved. There is evidence that a central inflammation can be inhibited by cholinergic neurons, so that any impairment in the cholinergic neurotransmission is thought to be predisposing risk factor for POD/POCD. Due to an accumulation of such predisposing and precipitating risk factors, elderly patients are at a higher risk to develop POD/POCD. In this project, we aim to investigate an association between cholinergic system genetic variants and POD/POCD by examining patients from the BioCog Study (NCT02265263/ www.biocog.eu), which included patients ≥ 65 years undergoing elective surgery. Prior to the operation, patients provided blood samples and completed baseline neurocognitive test batteries. Each patient was visited daily for the first 7 postoperative days (to detect POD via multiple validated assessment instruments), with regular follow-ups for two years (to detect POCD via neurocognitive testing). Genotyping will be performed with a commercial screening array, allowing for the identification of single nucleotide polymorphisms, insertions, deletions and copy number variations. Genes of interest include genes for cholinesterase, -transferase, -transporter and -receptors. Moreover, we will link results of genotyping to the expression profile of the corresponding genes, as well as to peripheral cholinesterase activities. The long-term objective is to verify whether genetic variants are potential predictors for POD/POCD. By identifying relevant cholinergic genes via genotyping, which can be sequenced de novo in future projects, we aim to generate new hypotheses for development of POD/POCD.

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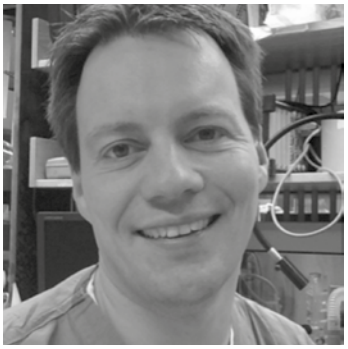

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FIELDS OF RESEARCH
› Acute Respiratory Distress Syndrome
› Hemolysis
› Blood Transfusion

Transfusion-Associated Effects of Extra-Cellular Hemoglobin on the Development and Severity of Ventilator-Induced Lung Injury

Mechanical ventilation is used to support millions of critically ill patients each year. However, despite its life-saving potential mechanical ventilation can cause injury and complications. The most important adverse effect of mechanical ventilation is the ventilator-induced lung injury (VILI). Among others, patients on the Intensive Care Unit are challenged with increased levels of circulating intravascular cell-free hemoglobin which causes vasoconstriction by depletion of endothelial nitric oxide, oxidative stress, and inflammation. Furthermore, cell-free hemoglobin contributes to tissue injuries such as renal failure and intestinal mucosa damage after cardiac surgery and is associated with an increased mortality in patients with sepsis. Recently, we demonstrated that increased plasma concentrations of cell-free hemoglobin and heme after transfusion of stored packed red blood cells potentiate a primary injury induced by prolonged hypotension. With this project, we would like to extend our knowledge and explore in more detail the mechanisms by which cell-free hemoglobin and heme might aggravate VILI. We study whether increased plasma concentrations of cell-free hemoglobin accelerate the development and increase the severity of VILI. Both, VILI and extracellular hemoglobin independently induce systemic pro-oxidant and pro-inflammatory effects. Therefore, we explore pulmonary and additional extra-pulmonary foci of inflammation and apoptosis in VILI with and without exposure to cell-free hemoglobin. Furthermore, we study whether the adverse effects caused by cell-free hemoglobin might be attenuated by therapy with the hemoglobin scavenger haptoglobin.

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FIELDS OF RESEARCH
› Immune Function in Critically ill Patients
› Immune Stimulation in Immune Suppression
› Hemophagocytic Lymphohistiocytosis in ICU

Biomarkers for Adult Hemophagocytic Lymphohistiocytosis in Critically ill Patients

Hemophagocytic Lymphohistiocytosis (HLH) is a rare life-threatening hyperinflammatory syndrome with a mortality rate of 68%. It often remains undiagnosed due to sepsis-like symptoms. Early and reliable diagnosis of HLH in the intensive care unit (ICU) is pivotal for patient outcome. It is known that adult HLH is triggered mainly by infectious diseases, malignancies, immune deficiency and autoimmune diseases, leading to an impaired function of cytotoxic T lymphocytes and natural killer cells. This results in an excessive immune activation of macrophages and T-cells with extreme cytokine production of interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α) – the so-called cytokine storm. These highly activated macrophages and the »cytokine storm« infiltrate lymphoid and non-lymphatic tissues and lead to hemophagocytosis and multiple organ failures. Within this project, we plan to build up a biobank and systematically investigate this life-threatening hyperinflammatory syndrome in the ICU in order to detect biomarkers for an early diagnosis. The project aims to find a highly sensitive and highly specific biomarker panel to significantly improve the currently available diagnostic possibilities, to get further insights into its pathophysiology, and subsequently to reduce mortality. In particular and driven by previous studies, we analyze CRP, PCT, IL-1β, IL-6, IL-8, IL-10, TNF-α, IFN-γ, SIL-2R, ferritin, glyco-sylated ferritin, EBV and CMV viral load, the microRNAs miR-205-5p, miR-194-5p and miR-30c-5p, perforin and CD107a.

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FIELDS OF RESEARCH
› Pathophysiology and Preventive Strategies of Neuromuscular Organ Failure in Critically ill Patients
› Metabolism in Critically ill Patients

Prevention of Neuromuscular Organ Failure in Critically ill Patients

My research focus as a Clinician Scientist is the prevention of ICU-acquired muscle weakness via advanced, muscle activating physiotherapy methods. The current therapeutic options allow for the survival of severe diseases. Serious neuromuscular sequelae are an increasing problem that significantly worsens the acute and long-term outcomes in terms of reduced physical functional, reduced quality of life, and increased mortality. We have shown that systemic inflammation and immobilization are major risk factors, inducing pathophysiological processes that lead to an ICU-acquired weakness. Decreased protein synthesis, increased protein degradation, and metabolic dysregulation in the form of a pronounced insulin resistance are detected very early in the course of critical illness. We could recently show that a daily exercise program with electric muscle stimulation can maintain muscle mass, as well as improve glucose metabolism in skeletal muscle. However, these successes are inconsistent and patient-specific, so that a broad application is not yet recommended. From the data of earlier investigations, we could determine the key factors influencing the effectiveness of enhanced physiotherapy options in the prevention of neuromuscular organ failure. Considering these findings, a specific therapy will be further developed under standardized conditions using an established sepsis-mouse-model. Furthermore, recent investigations lead us to the point that neuromuscular failure already occurs during perioperative setting. Therefore, we just initiated an observational trial to confirm these findings of the first description of Perioperative Acquired Weakness (POAW). My work is embedded within the BIH Twinning Research Grant project »Inflammation-induced skeletal muscle atrophy in critically ill patients«. Additional research interests: glucose metabolism, glucose monitoring, insulin therapy, nutritional support, caloric needs, indirect calorimetry, extracorporeal membrane oxygenation.

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FIELDS OF RESEARCH
› Anesthetics
› Neurophysiology
› Neurometabolism

Impact of Anesthetics on Cerebral Energy Metabolism During Light and Deep Anesthesia: Possible Implications for Postoperative Neurological Complications

IAnesthesia is a state of pharmacologically induced unconsciousness, amnesia, and analgesia that allows surgery and intensive care treatment – undoubtedly a key element of modern medicine. However, deep anesthesia is associated with postoperative delirium and lasting cognitive decline. The underlying mechanisms of these postoperative complications are largely unknown. The depth of anesthesia can be classified by typical EEG patterns. Burst suppression (BS) and isoelectricity characterize deep anesthesia and correlate with hypometabolism in the brain. Similar EEG-patterns also occur during situations with energy mismatch such as hypoxia or traumatic brain injury, suggesting similar but reversible effects of anesthetics on cerebral metabolism. In the clinical routine, the use of deep anesthesia to reduce metabolism and evoke neuroprotection is controversial as anesthetics impair mitochondrial function. Importantly, the relationship between mitochondrial dysfunction and depth of anesthesia was not yet systematically studied. In my work, my colleagues and I aim to characterize the effects of anesthetics on the oxidative phosphorylation and function of neurons during different anesthetic regimes in vitro (i.e. brain slices) and in vivo in rats. Combining oxygen-measurements, electrophysiology and flavin adenine dinucleotide (FAD)-imaging with computational modeling, we want to predict possible targets of anesthetics in the mitochondrial enzymatic system. Understanding mitochondrial function during deep anesthesia will increase our knowledge on the pathophysiology of postoperative neurological complications. Furthermore, comparing gaseous and intravenous anesthetics has clinical relevance for appropriate therapeutic choice. Last, the use of multiparametric measurements and computational modeling could lead to find new biomarkers and improve monitoring during surgery and clinical situations in which deep anesthesia is performed such as status epilepticus or high intracranial pressure.

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FIELDS OF RESEARCH
› Clinical Neurophysiology in Anesthesiology
› Clinical Pain Research
› Medical Information Systems

Absence of Clinical Responses to Noxious Stimulation Under General Anesthesia is Not Indicative of an Absence of Nociception

In current clinical practice, dosing of analgesics during general anesthesia is performed based on the patient's responsiveness to noxious stimulation. If a patient moves or exhibits an increase in blood pressure or heart rate in response to a surgical stimulus, the analgesic dose is increased as the clinical responses are considered signs of a neuronal processing of the painful sensory input, which is termed nociception. Accordingly, if a patient shows no clinical responses to noxious stimulation, the analgesic dose is considered sufficient, as the absence of responses is considered indicative of absent nociception. However, we were able to demonstrate in an experimental setting using functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and spinal pain reflexes (NFR) during general anesthesia that nociception persists in the spinal cord and the brain throughout the common clinical doses of anesthetics (von Dincklage et al., Neuroimage 2018). Furthermore, we showed that the assumption that absence of clinical responses is a sure sign of a sufficient analgesic dose is not valid as we demonstrated a persistence of nociception in spinal cord and brain even though the subjects showed no clinical responses to the stimuli (von Dincklage et al., British Journal of Anaesthesia 2018). Also, we showed in a clinical study that higher analgesic doses during general anesthesia seem to be associated with lower rates of chronic pain, which might be explained by a better suppression of pain sensitization processes that might be triggered through intraoperative nociception (von Dincklage et al., European Journal of Pain 2018). Thus, if future studies confirm this connection between persistent nociception during general anesthesia and triggering of chronic pain, the current clinical practice of dosing analgesics according to clinical responsiveness might have to be changed and alternative surrogate measures for nociception during general anesthesia might be required.

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