

# Department of Anesthesiology

## Chair of Anesthesiology

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### Director

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### Research focus

- Clinical and experimental pharmacology of anesthesia
- Experimental pain research: Pathomechanisms of cold hyperalgesia and cold allodynia, pain models for rare pain syndromes
- Clinical research in perioperative medicine
- Medical technology of diagnostic and therapeutic procedures
- Research projects furthering the medical education

### Structure of the Chair

Professorships: 2

Personnel: 450

- Doctors (of Medicine): 141
- Scientists: 8 (thereof funded externally: 3)
- Graduate students: 8

### Clinical focus areas

- Clinical anesthesiology
- Operative intensive care medicine
- Pain management center
- Emergency medicine
- Palliative medicine

### Special structural features

- 50 anesthesia workplaces
- Anesthesia outpatient department
- Pain outpatient department, pain ward (four hospital beds)
- Two intensive care units (35 critical care beds)
- Pain management unit (in cooperation with the Department of Neurology)
- Medical management of the emergency service (Erlangen, administrative district Erlangen-Höchstadt, Herzogenaurach)
- Medical care in air rescue services and in transport within UK Erlangen

### Research

Research at the Department of Anesthesiology is focused on the clinical and experimental pharmacology of anesthesia and on the experimental and clinical pain research. In addition, innovative techniques for drug administration and patient monitoring are investigated, and projects dealing with the quality improvement of teaching and training are part of the Department's research program.

#### Clinical and experimental pharmacology of anesthesia

This research is focused on the quantitative mathematical modeling of the pharmacokinetics and pharmacodynamics of anesthetic drugs with respect to model identification, computer simulation to improve study design and for educational purposes, and model based dosing strategies for therapeutic optimization.

During the reporting period, the pharmacokinetics of the opioid hydromorphone was investigated during postoperative pain therapy in cardiac surgery patients. The main focus of these investigations was the external validation of a pharmacokinetic model of hydromorphone that has been developed in previous studies. Further, a new pharmacokinetic model for dexmedetomidine in Chinese children, aged between 1 and 9 years, was developed within the framework of a research cooperation with the Department of Anesthesiology, Wenzhou Medical University, China.

#### Experimental pain research: Pathomechanisms of cold hyperalgesia and cold allodynia, pain models for rare pain syndromes

In the area of experimental pain research, the Heisenberg professorship, which has been existing since May 2014, was extended by the DFG for additional two years. The research topics of this program are the pathomechanisms of cold hyperalgesia and cold allodynia, which are investigated in the somatic and trigeminal system.

To improve the study of trigeminal sensory neurons that innervate teeth, a new method has been developed that allows to identify this particular subpopulation of cells in the trigeminal ganglion. This method made it possible to identify, to quantify the expression, and to study the function of ion channels and receptors characteristic for tooth innervation by immunohistochemistry and in live cell cultures.

Another translational project, in cooperation with the Department of Medicine 1, deals with heritable polymorphisms that lead to a heightened susceptibility for acute and chronic pruritus. Here, differences between a large body of inbred strains are quantified and analyzed for the respective differences in genetic haplotypes. Another research area deals with the analysis of rare hereditary pain syndromes using human induced pluripotent stem cells (hiPSC) generated from skin biopsies. In cooperation with the Division of Stem Cell Biology, we differentiate hiPSC-derived pain sensing neurons (nociceptors) from affected pain patients, which otherwise are not available for analysis. This disease model improves our understanding of the pathophysiology of hereditary pain syndromes and enables us to develop individual therapeutic approaches, which we can then transfer to the patient. Pain sensing neurons (C-fibers) of the patients *in vivo* display pathological activity that can only be assessed with non-routine special examinations (microneurography). In our disease model we could show that also patient-derived nociceptors show pathological hyperactivity *in vitro* and therefore mimic the disease of the patient.

Further, new therapeutic concepts for chronic pain syndrome after traumatic brain injury have been developed and tested in preclinical studies in cooperation with the Department of Anesthesia, Pain, and Perioperative Medicine of the Stanford University, USA. The promising results achieved with these studies build the platform for further confirmatory investigations.

#### Clinical research in perioperative pain

The molecular basis for the interindividual variability of pain sensation in healthy volunteers was the main focus of the investigations. The genome-wide methylation analysis results support the hypothesis that epigenetic regulation of TRPA1 seems to regulate thermal and mechanical pain sensitivities.

An ongoing further project investigates huge data amounts recorded during anesthesia procedures. This work is performed in cooperation with the Chair of Medical Informatics and deals with the identification and selection of mathematical derivatives that allow an accurate description of the time course of monitoring parameters like blood pressure, heart rate, and oxygen saturation in more than 400,000 anesthesia protocols. These parameters will be applied to automatically identify risk profiles for clinical outcome parameters like mortality and cardiac morbidity.

### Medical technology of diagnostic and therapeutic procedures

The development of innovative dosing algorithms for intravenous drug therapy and the biosignal analysis for anesthesia control are the main research tasks.

During the reporting period, we investigated the impact of the cardiovascular function on the pharmacokinetics of anesthetic drugs with high hepatic metabolism. The implementation of the monitoring variable cardiac output as a covariate of the pharmacokinetic model may lead to a relevant improvement of anesthesia control through a more precise prediction of the dose-concentration relationship, as demonstrated in a preclinical study for the opioid sufentanil as an example.

On the basis of the gathered experience from earlier investigations, a new software solution for an individual effect related dosing of anesthetic drugs was implemented and *in silico* tests successfully validated.

In addition, the software interfaces for the import of cardiorespiratory variables as anesthesia control parameters were also implemented and successfully tested.

### Research projects furthering the medical education

An emphasis of the scientific work during the reporting period is the development of curricula. Using a six steps' approach for curriculum development, several curricula for the management of emergencies and a sample curriculum for the specialization in anesthesiology have been implemented on behalf of the German Association for Anesthesiology and Intensive Care (DGAI).

Furthermore, several human factors have been researched in virtual reality scenarios in acute medicine. In this context the influence of hierarchies and checklists on strategies of decision making and actions in an operative setting have been analyzed.

In cooperation with industrial partners, the usability and practicability of medical products are regularly tested in the simulation and training center.

### Teaching

The Department of Anesthesiology is committed in mandatory and elective courses in the field of Medicine and Dentistry. It has to be pointed out that the Department takes responsibility for a number of interdisciplinary course formats, including pain medicine, emergency

care medicine and rehabilitation/physical medicine / naturopathic treatment as well as emergency medicine for dentists in cooperation with the Department of Oral and Maxillofacial Surgery. The elective course "rescue medicine" bridges into multiprofessional teaching.

Furthermore the Department of Anesthesiology is one of the hosts for the written and oral examination for the European Diploma of Anesthesiology and Intensive Care (EDAIC).

For the training in education new teaching concepts could be implemented, including virtual situative learning in the simulation and training center.

The Department of Anesthesiology supervises MD and PhD theses.

### Selected publications

St Pierre M, Breuer G, Strembski D, Schmitt C, Luetcke B. Does an electronic cognitive aid have an effect on the management of severe gynaecological TURP syndrome? A prospective, randomised simulation study. *BMC Anesthesiol* 2017; 17(1): 17-72

Eberhardt MJ, Schillers F, Eberhardt EM, Risser L, de la Roche J, Herzog C, Echtermeyer F, Leffler A. Reactive metabolites of acetaminophen activate and sensitize the capsaicin receptor TRPV1. *Science Report* 2017 Oct 6;7(1):12775

Eisenried A, Meidahl ACN, Klukinov M, Tzabazis AZ, Sabadini RA, Clark JD, Yeomans DC. Nervous system delivery of antilyso-phosphatidic acid antibody by nasal application attenuates mechanical allodynia after traumatic brain injury in rats. *Pain* 2017 158(11): 2181-2188

Gombert S, Rhein M, Eberhardt M, Münster T, Bleich S, Leffler A, Frieling H. Epigenetic divergence in the TRPA1 promoter correlates with pressure pain thresholds in healthy individuals. *Pain* 2017 158(4): 698-704

Touska F, Turnquist B, Vlachova V, Reeh PW, Leffler A, Zimmermann K. Heat-resistant action potentials require TTX-resistant sodium channels Nav1.8 and Nav1.9. *J Gen Physiol*. 2018 Aug 6;150(8):1125-1144

Birkholz T, Leuthold C, Schmidt J, Ihmsen H, Schüttler J, Jeleazcov C. Influence of Cardiac Output on the Pharmacokinetics of Sufentanil in Anesthetized Pigs. *Anesthesiology* 2018; 128(5): 912-920

### International cooperations

Prof. E. Jørum, Department of Neurology, Oslo University Hospital-Rikshospitalet, Oslo: Norway

Prof. G. Peltz, Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, Stanford: USA

Prof. V. Vlachová, Czech Academy of Sciences, Prag: Czech Republic

Prof. D.C. Yeomans, Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, Stanford: USA

Prof. M. Kurrek, Department of Anesthesiology, University of Toronto, Toronto: Canada