



UPPSALA
UNIVERSITET

Department of Surgical Sciences

Annual Report 2014

Avsändare/Fastställd av Olle Nilsson 2015-04-29

Introduction

Chairman's annual address/comments

The year 2014 was another good and memorable year with numerous achievements in the areas of teaching and research by the teachers and staff of the Department of Surgical Sciences. My vision for the department is that it should provide a platform for the researchers and teachers by reducing their administrative duties and enabling them to focus on their main duties; research and teaching. We can do so by the contributions of our highly proficient and qualitative administrative staff. It is my firm belief that decisions concerning strategic research questions are best handled by the researchers themselves, while the department has an important role in providing technical and administrative support. The department should also provide research students, graduate students and staff with favorable stimulating and creative working conditions. We feel fortunate to work within a very successful university in a well-organized institution in good economic standing.

It is exciting to witness how our researchers managed to combine high quality research evidenced by top-quality research papers covering a very broad range of topics and published in the most prestigious scientific journals. The attraction of external grants has gradually increased during the last decade, this year being no exception. In addition, a vast number of scientific papers many in high-ranking journals were produced and an impressive number of Ph.D. theses defended.

Throughout 2014, our teachers have made outstanding contributions in basic education. The department has the main responsibility for several specialist education programmes in nursing within the surgical field. These programmes are of profound importance for both the University Hospital and for the nursing profession, *i.e.* intensive care, anesthesiology, surgical care and ambulance care. The new curriculum in our medicine programme is now running reasonably smoothly, but improvements are continuously implemented in order to promote the scientific and academic career of our young and capable scholars. Teachers from the department play an essential role in this development. The department is now involved in teaching during semester 1, 3, 5, 6, 7 and 11, with main responsibility for the curriculum taking place during semester 6, 7 and part of semester 11. This pedagogic involvement is an important contribution to both teaching and medicine. Other contributions within the pedagogic field include teaching in biomedicine, physiotherapy and nursing.

The task of filling the void created by the retirement of very successful senior professors is both exciting and difficult. To replace these highly successful senior researchers who accomplished so much during their prestigious and active careers is a very demanding task for the department. We have during 2014 had the privilege to welcome the new professor in surgery Peter Stålberg and Magnus Sundbom. We feel very fortunate to have been able to recruit those two highly successful researchers.

Looking forward to 2015, we can anticipate an exceptionally interesting year with numerous challenges, hard work but also a rewarding and enjoyable time to look forward to. We are excited to have the opportunity to welcome teachers, researchers and personnel from the department of Radiology and PET into our Department starting 2015, and we wish you all welcome. We are certain that this new development will be of great value to us all. I want to thank everyone at the department, including all teachers, researchers, administrators, students and laboratory personnel for their dedication and excellent work in 2014.

Olle Nilsson

Professor and Chairman

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Scientific Reports

1 Anesthesiology and intensive care medicine

Cardiac arrest-neuroprotection

Hypothermia treatment

Hypothermia treatment to 32-34 °C during 24 hours after cardiac arrest has been shown to improve survival and neurologic outcome. Forty-fifty percent of the admitted patients treated by hypothermia are now surviving. Hypothermia after global ischemia in cardiac arrest patients can be induced with both invasive and noninvasive methods with varying efficiency. Different methods have been used for early prognostification in the effort to improve treatment. Markers of brain injury that have been investigated in cardiac arrest patients treated with hypothermia are S-100 β (astroglial protein) och NSE (neuron specific enolas). Continuous EEG registration of patients during and after hypothermia treatment is of prognostic value in one study. EEG will also detect epileptic activity requiring treatment. For the cardiac arrest patient not only survival is of major importance but also how quality life will be affected.

Questions: The aim is to follow-up patients during the first six months after cardiac arrest treated by hypothermia and study quality of life, physical and psychological function, neurologic function and mortality in relation to initial levels of markers of brain injury. Finally, the aim is to describe the influence on relative's daily life.

Methods and results: Markers of brain injury are sampled directly after the patient is admitted to hospital and followed up to 108 hours after cardiac arrest. MRI of the brain is done five days after the cardiac arrest and EEG will be monitored up to 48 hours after cardiac arrest. Follow-up of the patients will be performed at discharge from the hospital and one and six months after the cardiac arrest. Next of kin will be interviewed first when the patient is discharged from hospital and at six months after the injury.

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Agencies that support the work/Funding

Institutional Grants, Uppsala University

Uppsala University Hospital (ALF)

The Laerdal Foundation for Acute Medicine

Mechanical chest compressions during cardiac arrest

Background: Every year 300,000 to 400,000 people suffer from sudden cardiac arrest outside of the hospital in Europe. Only 5-9% of these patients survives and is discharged from hospital. Lately, there is a strong emphasis on chest compressions being delivered without interruptions. Manual chest compressions during CPR result in only 20-30% of normal blood flow and are difficult to perform continuously. Mechanical chest compressions with the LUCAS device have shown increased cerebral blood flow, coronary perfusion pressure and survival in experimental studies.

Questions: Can mechanical chest compressions with the LUCAS device combined with defibrillation during ongoing chest compressions improve survival? Will treatment with the LUCAS device result in more injuries in non-surviving patients.

Methods and results: Defibrillation during ongoing mechanical compressions showed promising results with a trend in increased short time survival in out of hospital cardiac arrest in a recently completed pilot study of 149 patients. Autopsy was performed in 85 non surviving patients after being treated with either mechanical chest compressions with the LUCAS device or with manual chest compressions according to guidelines. There were no injuries in one third of the patients in both groups. The most frequent injuries found were rib fractures and sternal fractures but there was no difference between the groups. No fatal injuries were found in any of the groups. The results from this pilot studies are the foundation for a multicenter study in Europe-the LINC study of 2,500 patients with out-of hospital cardiac arrest. The study started in January 2008. Patients with cardiac arrest will be randomized to either treatment with a concept using mechanical chest compressions with the LUCAS and defibrillation during ongoing compressions or treatment according to international guidelines including manual chest compressions. In May 2011, an interim analysis was performed and resulted in allowing inclusion of the entire study population. On September 1st, 2012 the last patient was included. The database has been analyzed and first article of the ITT analysis has been published in JAMA Jan 2014. Predefined subgroup analysis has also been performed and will be submitted for possible publication. Within this study, non-surviving patients in Uppsala, Gävle and Västerås have been through autopsy. This article has been published in Resuscitation. A paper exploring health economics is under preparation

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DISCO-trial: Direct or Subacute Coronary angiography for Out-of-hospital cardiac arrest

Background: Although the majority of cardiac arrest patients with return of spontaneous circulation do not have ECG changes indicating an acute STEMI (ST-elevation myocardial infarction), registry studies have shown that about 30% of these patients have an acute occlusion, sub-occlusion or signs of recent occlusion of any coronary artery. Results from observational studies suggest that acute coronary angiography and Percutaneous Coronary Intervention (PCI) increases survival in this group of patients. Data from randomized trials are however missing.

Aim: The overall aim of this prospective, randomized pilot study is to investigate whether acute coronary angiography (within 120 minutes), with a predefined strategy for revascularization, is feasible and safe to implement in patients with out-of-hospital cardiac arrest. A further aim of the pilot study is to provide a basis for an accurate power calculation for a planned main study in which we intend to answer the important clinical question at issue; if early revascularization in this population may improve survival with good neurologic outcome.

Method: This is a national multicenter pilot study with the aim to make a larger multi-center study after the pilot phase. The pilot phase will last for about 1-2 years. The study is an open randomized trial initially with four participating hospitals: Uppsala University Hospital in Uppsala, Södersjukhuset Stockholm, Skåne University Hospital and Helsingborg hospital. The study will include a total of 120 patients including approximately 80 patients **without** STEMI and 40 patients **with** STEMI with successful resuscitation after out-of-hospital cardiac arrest. Patients included in the pilot study will also be included in the larger randomized multicenter main study since an adaptive design will be performed. The study is an open prospective randomized multicenter study with a registry follow up where out of hospital cardiac arrest without STEMI in ECG will be randomized to direct coronary angiography with possible intervention or the usual care without acute coronary angiography. Randomization takes place immediately after ECG is taken in conjunction with the first medical contact.

The study thus includes the following groups:

1. **Intervention** - Cardiac arrest where the patient regained circulation **without** STEMI randomized to acute coronary angiography within 120 minutes and possible PCI.
2. **Control** - Cardiac arrest where the patient regained circulation **without** STEMI randomized to routine care without acute coronary angiography.
3. **Observation / Control** - Cardiac arrest where the patient regained circulation **with** STEMI, will **not** be randomized but will according to routine go to acute coronary angiography. All parameters that are followed in the intervention and control group will also be noted in this group.

Acute 12-lead ECG taken in the ambulance or in the emergency department prior to randomization will be compared to the coronary angiography findings and follow-up biomarkers.

Survival and neurologic function

Follow-up at Baseline, Discharge from ICU, Discharge from hospital, one month, six months: EQ5D-5L, Cerebral Performance Category-CPC and mRS. IQCODE at baseline and at six months. Follow-up at six months: Cognitive tests: MMSE (Mini mental state examination), MoCA (Montreal Cognitive Assessment), TSQ (Two simple questions) and IQCODE (Informant questionnaire), Depression and anxiety test –HADS (Hospital anxiety depression scale). The follow up visit after six months for neurological evaluation will be performed by a person blinded for treatment.

Cardiac function endpoints

Systolic left ventricular function will be assessed by echocardiography within 24 hours, after 72 hours and after six months. Left ventricular systolic function estimated by left ventricular ejection fraction, LVEF, when patient is in the ICU. After six months, global strain will also be calculated and regional left ventricular movement estimated by the regional strain.

Feasibility and safety

In addition to parameters measured and monitored for survival, neurologic and cardiac function information from the SWEDEHEART-SCAAR registry will be included.

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The Laerdal Foundation for Acute Medicine

INTOX-A prospective measurement of serum concentrations of routine drugs in patients treated in the intensive care unit-A quality measurement/ improvement for clinical treatment and forensic assessment

Background: Patients treated in the intensive care unit (ICU) are treated with a variety of sedative and analgesic drugs to be able to undergo intensive care. The amount of drugs that each patient receives is based on standard dosages where the dose regimen is based on clinical studies with a limited number of patients included. Most patients treated in the intensive care unit have a varying degree of cardiac, renal or liver failure which affects the metabolism of the drugs administered. Possibly, the drug concentrations achieved with the standard dosages administered to these patients can vary significantly between patients. This may possibly lead to an extended hospital stay at the ICU which gives the patient an unnecessary

suffering, affects the patient's family and increases the cost of health care. Intoxications treated in the ICU is common and it is often unknown what type of medication or drugs these patients have been taken and what serum concentration it may result in. Also, there are no previous studies with reliable documentation about the drug concentrations expected to be in the blood of patients that die in the intensive care unit.

The aim: is to follow up the result of a quality measurement based on the results of a new routine for drug analysis introduced during a period of time in the intensive care unit. To ensure the quality of the dose regimen of routine drugs for sedation and analgesics. The aim is also to know if the routine analysis can give information about if the self-intoxicated patients have taken drugs that were primarily not suspected. Finally to know the serum concentrations of routine drugs in patients who died and will undergo autopsy.

Methods: Blood will be drawn according to routine procedures upon the patient's arrival at the ICU and then two times per day. Extra blood samples (one tube) will be drawn in addition to routine blood samples and the extra blood samples will be sent to the Swedish National Board of Forensic Medicine unit in Linköping, Sweden. The drugs that will be analyzed are drugs used for sedation and analgesia. There will also be a screening of unknown drugs taken by self-intoxicated patients. The administration of sedative and analgesic drugs is via infusion pumps and the amount supplied is recorded daily. Routine blood samples will be drawn to measure organ function. Sedation ratio by the RASS-scale will be evaluated and recorded 3 times per day. An assessment of the visual analogy scale (VAS) will be done for the patients who are awake and are able to cooperate. All physiological measurements will be measured and documented according to local routines. Age, sex, medical history, diagnose at admission and discharge, care burden measurement according to SAPS 3 score will be recorded. For patients who die at the CICU and will undergo autopsy, blood samples will be taken after death for analysis of routine drugs.

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Agencies that support the work/Funding

Institutional Grants, Uppsala University

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Injury and critical care epidemiology

Principal investigator: Rolf Gedeberg

Injuries are the most important cause of death in the young and middle aged and a common reason for ICU admission. With the aid of unique person identification numbers to link health care registers, we have

excellent opportunities for population-based research. Each year approximately 100,000 people in Sweden are hospitalized because of injuries and 5,000 people die from their injuries.

Injury epidemiology is a collaborative effort involving several sections of the department, among them the sections for Anesthesiology and Intensive Care, Orthopedics, Vascular surgery and Forensic Medicine. A close collaboration has also been initiated with researchers at Linköping University.

During the year, the focus has been to establish collaboration with Linköping University concerning a new comprehensive data extraction from multiple health care databases, including control individuals from the normal population and data on socio-economic factors. A similarly comprehensive data extraction is underway combining data from the Swedish intensive care registry with data from the national patient registry and socio-economic data. The research objective for the critically ill population primarily aims to study the impact of comorbidity and socio-economic exposures on long-term survival.

The ability to identify and study prehospital injury deaths and consequences of prehospital management remains important for the study of the injured population. The group has published methods for the use of ICISS scores that are internationally comparable. A particular focus of our efforts is also on the ability to develop reliable estimates of comorbidity in injured patients and also applied to patients in general intensive care. We also continue to work with Bayesian models to improve injury severity estimation. In collaboration with Forensic Medicine we have develop prediction models for the outcome after violent crime. Also in collaboration with forensic medicine a study on cardiovascular outcome from exposure to androgenic anabolic steroids has been submitted for publication.

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Agencies that support the work/Funding

Uppsala University Hospital (ALF)

Lung function in anesthesia and intensive care

Principal investigator: Anders Larsson

The project is primarily aimed at improving ventilator treatment in the critically ill patient with acute respiratory failure (ARF). The secondary aim is to increase the understanding of respiratory physiology at spontaneous and mechanical ventilation during anesthesia and intensive care. The project is mainly performed at the Hedenstierna laboratory (a part of the Dept. of Surgical Sciences) and in the Central Intensive Care Unit, Uppsala University Hospital in collaboration with Professor Göran Hedenstierna as well as coworkers from Karolinska Institute, University of Bari, Politecnico di Milano University, University of Magdeburg, University of Freiburg, University of Istanbul and University of Sao Paolo, University of Helsinki and Jules Verne University, Amiens, France.

Inflammation induced by mechanical ventilation

About 3,000 patients are treated with mechanical ventilation in the Swedish intensive care units due to ARF, a condition with mortality of about 30-40%. Although mechanical ventilation saves lives, it has inherent side effects by inducing mechanical injury on the lungs, leading to local and systemic inflammation. In fact, the patients do not die of hypoxemia but of multiple organ failure caused by the inflammation. It has been shown that by decreasing the mechanical stress on the lungs by reducing the tidal volumes, mortality is reduced by ten absolute percent. In a present project we are studying in an experimental ARF model with positron emission tomography (PET) and immunohistology the inflammatory effects of two different ventilator modes; a conventional and a new, protective mode (low tidal volumes and lung recruitment i.e., opening of closed lung regions by applying high airway pressure). The results indicate that the experimental mode induces less severe inflammation. Another new, interesting finding is that the inflammation is mainly located in the “healthy” open parts of the lungs and not, as previously thought in the collapsed lung regions. Other methods of ventilation, such as variable (noisy) ventilation are under study. Furthermore, we are studying experimental ARF with synchrotron radiation computed tomography, which has a very high resolution, and have found that the ventilatory pattern on micro-level is chaotic in ARF, but not in healthy lungs.

Optimal end-expiratory pressure in ARF

Positive end-expiratory pressure (PEEP) is used to keep the lung open during the expiratory phase of the ventilator breath in ARF. Too low PEEP will induce lung collapse with hypoxemia, whereas too high PEEP might cause overdistension as well as circulatory compromise. Forced oscillation technique (FOT), a new technique that measures the mechanical properties of the respiratory system, has recently been shown by coworkers in the group to be able to indicate the amount of collapsed lung tissue. Therefore, we have studied whether FOT could be used to set “optimal” PEEP in an experimental ARF model. The results suggest that inflammation in the lungs is reduced compared with a conventional PEEP setting.

Differential lung ventilation in ARF

In the wet, heavy ARF lung the collapsed part is mainly located in the “lower” regions due to gravitation. In order to open (recruit) these collapsed lung regions (see above) and to keep it open a very high pressure is therefore sometimes needed. However, this high pressure may cause injuries in the upper “healthy” lung (see above) by overdistension and therefore the beneficial positive effect of open the lower parts of the lungs might be neutralized by the negative effect by overdistension in the upper part of the lungs. One way to overcome this problem is to put the subject in the lateral position and ventilate the lower and upper lung with different pressures (lower pressure to the upper and higher pressure the lower lung) via a double lumen tube (that makes it possible to direct ventilation separately to the right and the left lung). This new method has been studied experimentally using computed tomography, measurements of lung volume and mechanics in each lung, blood gases and electric impedance tomography (EIT) and preliminary results confirm our hypothesis.

Spontaneous breathing in ARF

Modes in which spontaneous breathing efforts are allowed have been shown, except improving the patient's comfort, to improve oxygenation in ARF. The underlying mechanism has previously been thought to be caused by recruitment of collapsed lung tissue located close to the diaphragm, but studies by us in an experimental model have shown that the explanation is that perfusion is redistributed to open and ventilated lung regions during spontaneous breathing. We are exploring the effect of spontaneous breathing further on lung perfusion in present studies. We hypothesize that the redistribution of perfusion is caused by a higher transmission of the negative alveolar pressure to the pulmonary vasculature in non-HPV regions of the lungs. Furthermore, we have started to study neuronal adjusted ventilatory assist in experimental models.

Apneic oxygenation or low tidal volume ventilation in combination with/without extracorporeal carbon dioxide removal (ECCO2R) or a proton acceptor (THAM) in ARF

As discussed above, low tidal ventilation improves survival in ARF. The ultimate ventilation would be a mode with zero tidal ventilation, i.e. apneic ventilation. We have recently shown that apneic ventilation in combination with ECCO2R gave excellent oxygenation and blood CO₂ levels in an experimental ARF model. However, to prevent alveolar nitrogen concentration/accumulation in the lungs with this technique 100% O₂ (which is toxic) is thought to be needed. We have now successfully explored a modified apneic ventilation technique in an experimental lung model, where the alveolar O₂ concentration could be kept at non-toxic levels; we have found that a THAM is a possible method keeping normal pH during apnea and that low tidal volume ventilation combined with THAM administration might be feasible.

Extracorporeal membrane oxygenation (ECMO) in ARF

ECMO treatment is an essential modality when advanced ventilator treatment fails to provide adequate oxygenation or CO₂ removal in patients with ARF. This treatment is resource intensive and is centralized in Sweden to the ECMO center at the Karolinska hospital, which treat about 50 adult patients with ECMO for ARF with a survival rate comparable with (about 60%) the normal ARF population despite these patients are more severely ill. However, the evolution of lung function during the ECMO treatment has not been studied. This is a very important issue since the optimal management of the lungs during ECMO is not known, and it is possible that a change of the handling of the lungs would further improve the results. We are planning a prospective study with lung mechanical investigations, imaging (EIT, Computed Tomography and PET) as well as inflammatory markers (TNF, IL1, IL6, IL8, IL10) from the lungs (obtained by bronchoalveolar lavage) on the patients treated at the Karolinska ECMO Centre. At present, we have studied the outcome of the H1N1 patients treated with ECMO at the ECMO center and found that except a world leading survival rate, the patients had a very good neurological outcome with a good quality of life.

Optimal ventilatory management during anesthesia

In obese patients undergoing anesthesia severe hypoxemia may develop due to rapid occurring lung collapse. We have shown that this could be ameliorated by applying a lung recruitment maneuver and continuing with PEEP (see above). Another patient group that is subjected to severe hypoxemia and compromised lung function is patients undergoing one-lung ventilation combined with pressurized capnotherax for surgical treatment of atrial fibrillation. In an experimental study we have suggested a method to optimize the lung function.

Lung function measurements using optoelectronic plethysmography during anesthesia

Optoelectronic plethysmography, in which the dimensions of thorax and abdomen are determined in real time by registration of the movement of reflective markers on the chest wall by several video cameras, is a non-invasive method to measure with high resolution the changes in thorax and abdomen induced by breathing and the anesthesia technique. The method has been used to study the ventilatory mechanical effects of propofol anesthesia and of different modes of jet ventilation. We found, very interestingly, that during emergence from anesthesia lung volume decreased due to increased activity of the expiratory muscles. The expiratory muscles are usually silent except at severe airway obstruction (e.g. asthma). We

will further explore whether this effect also occurs under inhalation anesthesia using different advanced methods.

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Dissertations 2014

João Batista Borges. Regional Lung Kinetics of Ventilator-Induced Lung Injury and Protective-Ventilation Strategies Studied by Dynamic Positron Emission Tomography

Robert Sütterlin. Jet Ventilation for Airway Surgery: The Influence of Mode and Frequency on Ventilation Efficacy

Lena Burström. Patient Safety in the Emergency Department: Culture, Waiting, and Outcomes of Efficiency and Quality

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Swedish Research Council (VR)

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University of Sao Paolo

Uppsala University Hospital (ALF)

Institutional Grants, Uppsala University

Pain research group

Principal investigator: Torsten Gordh

Search for candidate biomarkers markers relevant to pain pathophysiology

This project aims to build knowledge about the pathophysiology of chronic pain with the goal to find new diagnostic markers for early biochemical characterization of patients suffering from chronic pain (e.g. neuropathic pain, fibromyalgia, low back pain). The outcome is believed to be essential also for the development of new diagnostic and therapeutic strategies.

We also study the effects on biomarkers of various treatments such as electrical spinal cord stimulation, or pharmacological interventions. The project is a part of Uppsala Berzelii Technology Centre for Neurodiagnostics (Uppsala Berzelii Centre), with long term support by and The Swedish Research Council (VR) and VINNOVA, having access to extremely sensitive analytic methods, in cooperation with Professor Masood Kamali (the PEA method) and the group led by Professor Jonas Bergquist (mass spectrometry). It is as a PhD student project for Anne-Li Lind and Anna Jonsson.

Visualization of peripheral pain mechanisms using PET ligands relevant to inflammation

In this project we investigate some PET ligands concerning their capacity to mark for painful processes in the body. We have found markers that distinctly accumulate in painful areas in patients suffering from chronic WAD, and following wrist distortions. Experimental studies in “small animal PET scan”, as well as in vitro binding studies, is ongoing, in order to pin point to what cellular structure the relevant marker is

binding to. The project is carried out in close collaboration with Professor Fred Nyberg and post doc Anna Lesniak, and a PhD project for Dr. Mikko Aarnio.

Persistent postoperative pain

In this project, a genetic analysis of patients who have developed chronic pain after inguinal hernia surgery or hand surgery are compared with patients that had undergone the same type of surgery and not developed pain. About 2500 patients have been screened, resulting in 150 with persistent pain + 150 without pain who all have been investigated clinically. The results show that persistent postoperative pain is mainly of neuropathic, and that the presence of certain genetic HLA haplotypes seems to increase the risk for chronic pain following surgery. The project is led by Dr. Adriana Miculescu.

Strong opioids for long term treatment of pain

We are undertaking a study on long term effects, side effects, cognitive effects, and effects on quality of life, opioid receptor polymorphism as related to effect, and nerve cell culture receptor studies after chronic opioid exposure. The “problematic use of opioids” and the possibility to restore opioid induced cognitive impairment by using growth hormone therapy, is studied in experimental models and in patients. The clinical part of the project is led by Annica Rhodin, in close collaboration with Professor Fred Nyberg.

Effect of anesthetic drugs on the developing brain

Collaboration with docent Anders Fredriksson (department of neurosciences, psychiatry), docent Henrik Viberg and Per Eriksson, is ongoing, with studies on the effects of paracetamol and cannabis on the neonatal brain.

Clinical and biochemical characterization of very complex chronic pain patients

We aim to characterize a group of very complex chronic pain patients, suffering from substantial psychiatric co-morbidity in addition to their pain problem. This group, having a very low quality of life, and consuming large amounts of health care, has not been well understood, leading to consequences with poor treatment outcome. We use PRO instruments, qualitative methods, and biochemical tools. It is a PhD project for MD Eva-Britt Hysing.

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Sepsis and intensive care research group

Experimental septic shock

Principal investigator: Mats Eriksson

Septic shock is secondary to bacteria, fungi or virus entering the blood, causing an extensive systemic inflammatory reaction, characterized by disturbances in cardiac performance and blood circulation, oxygenation of blood and tissues, temperature regulation, in the number of leucocytes and platelets as well as development of metabolic acidosis. Septic shock is frequently seen in ICUs all over the world. The mortality in this condition is high and may occur suddenly and unexpectedly in previously healthy people despite extensive care. MD PhD student Ewa Söderberg presented her Licentiate thesis on “Experimental Septic Shock”, 2012. The experimental part of this work takes place at the Hedenstierna laboratory, which is a part of the Department of Surgical Sciences, Uppsala University.

Steroids and endotoxemic shock

Principal investigator: Mats Eriksson

Whether or not steroids should be given in septic shock has been an issue for decades. Despite several clinical trials in which different doses and durations of treatment have been studied, the possible benefit of hydrocortisone in septic shock has not yet been clarified. Since timing of steroid treatment could be a key

to these conflicting results, we decided to examine whether hydrocortisone given at the earliest possible time point in established porcine endotoxemic shock. At the onset of endotoxemic shock, defined as the moment when the mean pulmonary arterial pressure reached the double baseline value, the pigs were randomly given a single intravenous dose of hydrocortisone at $5 \text{ mg} \times \text{kg}^{-1}$ or the corresponding volume of saline. Mean arterial pressure and systemic vascular resistance index were significantly higher and heart rate was significantly lower in the endotoxin + hydrocortisone group compared to the endotoxin + saline group. Body temperature and blood hemoglobin levels increased in the endotoxin + saline group, but not in the treatment group. Since there was no significant difference in the plasma levels of TNF-alpha or IL-6 between the groups, our results suggest that these effects are not mainly mediated by these pro-inflammatory cytokines. These results were published in *Steroids* 2012.

The next step on this topic is aiming to determine whether the expressions of neutrophil gelatinase-associated lipocalin (NGAL), a biomarker for acute renal injury as well as troponin I are modulated by steroid treatment. Preliminary data on NGAL in this aspect seem promising.

Renal function during endotoxemia

Principal investigator: Mats Eriksson

Cystatin C is increasingly used as a marker for glomerular filtration rate and acute kidney injury (AKI) in critically ill patients. We investigated cystatin C as an AKI biomarker in porcine endotoxemia. Cystatin C was not normally distributed, but appeared in two different patterns. This finding was not limited to endotoxemic challenge, but occurred also among the non-endotoxemia. Inulin x urine vs. creatinine clearance; 10Log PAH-Clearance vs. creatinine clearance; inulin x urine vs. PAH-Clearance; 10LogPAH-Clearance vs. 10Log urine all had $R > 0.6$. Cystatin C correlated poorly to any of these variables. Thus, cystatin C seems to be unpredictable in the pig and should be interpreted with care until cystatin C has been further validated. These results are in manuscript format.

Renal function in critical illness

Principal investigator: Miklos Lipcsey

Kidney function is an important risk factor for cardiovascular morbidity and mortality both in intensive care patients and in a general population. Traditionally the most important kidney markers in intensive care has been creatinine and urine production, but recently both tubular markers (e.g. U-KIM-1, U-NGAL and U-cystatin C) and glomerular damage markers (e.g. U-albumin) has emerged as interesting markers in intensive care.

During 2014 we have been involved in the development of new equations for estimating GFR (glomerular filtration rate) based on creatinine and cystatin C. The plan is now to compare cystatin C and creatinine based eGFR in intensive care patients. We have received an ethical approval for collecting laboratory data from Uppsala, Stockholm and Lund to evaluate the prognostic information of the two eGFR estimates. This project is run in collaboration with Associate Professor Johanna Helmersson-Karlqvist. We have also shown that the tubular markers U-cystatin C, U-KIM-1 and U-NGAL in general populations.

We are evaluating the performance of creatinine and cystatin C based GFR estimates in critically ill patients through clearance of vancomycin and gentamycin, antibiotics with routine plasma concentration determination. The pharmacokinetic modelling is done in collaboration with Assistant Professor Elisabet Nielsen.

Blood sampling and drug administration through intraosseous needles

Principal investigator: Mats Eriksson

In life-threatening emergencies, especially among children, it might be difficult to establish vascular access. When such access has been obtained, fluid regimen is frequently prioritized. Blood sampling is, of course, also an important part of the emergency treatment, since relevant information on the clinical

condition aids therapy and further clinical management. Intraosseous needles, most frequently inserted through the anterior tibia, have an important mission in emergencies, since they let us create a simple and fast access to the vascular system. Fluids and drugs may be administered through these needles. They may also be used for sampling of bone marrow aspirates, fairly reflecting the conditions in the peripheral blood. However, samples obtained through aspiration from intraosseous needles may contain bone marrow particles, which may harm laboratory devices. Since tools for laboratory for laboratory analyses have been improved, and handheld devices have been developed, where the aspirate is analyzed within a cartridge that is never in contact with the device itself. Utilizing an experimental model, we have compared intraosseous bone marrow aspirates analyzed by such an instrument with conventional arterial blood samples. The aims of this study were: 1) To investigate whether intraosseous samples can be used for analysis, using a handheld, cartridge-based, point-of-care analyzer, where aspirate is never in contact with the device. 2) To determine whether these values are comparable to those in arterial blood and 3) to validate the reproducibility of the method during a six hour period. There was generally a good agreement between the two intraosseous sites with Calcium and Base Excess showing the highest coefficient of variance (CV). Despite CVs were in the 20% range for calcium and base excess, we consider the results acceptable to use in this very acute situation. There was also in general a good agreement between intraosseous and arterial values but Base Excess, Lactate and especially PO₂ showed high CVs. This work was published 2012 in Resuscitation. We have also presented a report in: Scand J Lab Clin Invest on morphine analysis in samples taken from intraosseous needles compared to plasma samples. This work was the scientific presentation of a medical student, which is a part of their education. Present research focuses mainly on point-of-care analysis of blood gases during endotoxemic shock.

A study on analysis of blood gases, using a POCT device during experimental shock is published in Acta Anaesth Scand. We found systematic differences between IO and arterial/venous sample values in this setting. However, samples from tibia or humerus may give clinically useful information during initial evaluation and resuscitation. IO infusion seem to affect the results, thus sampling during infusion should probably be avoided. Cartridge based analyzers can be used to avoid possible instrument problems due to debris in IO samples.

In the patient with an acute life-threatening infection such as septic shock or meningitis, timely administration of parenteral antibiotics is paramount in order to increase the likelihood of survival. However, gaining access to the circulation could be challenging in circulatory unstable patients. A special concern is the pediatric patient, where venous access is often difficult even under stable conditions.

Thus, we aimed to investigate whether comparable antibiotic concentrations could be reached with intraosseous and intravenous administration during experimental septic shock. Cefotaxime and gentamicin were used. For both antibiotics, plasma concentrations after intraosseous and intravenous administration followed similar curves throughout the observation period, and peak concentrations were comparable. Mean concentration area under the curve (AUC mg x hr x L⁻¹) for cefotaxime was 108.1 ± 19.5 after intraosseous and 116.5 ± 11.1 after intravenous administration; ratio 0,93 (95% CI 0.71 - 1,19). Mean AUC for gentamicin was 28.1 ± 6.8 for intraosseous and 32.2 ± 3.5 for intravenous administration; ratio 0.87 (95% CI 0.62 - 1.19). These results have been published in Acta Anaesth Scand. MD PhD student Gunnar Strandberg completed his half-time dissertation 2014. Further studies will focus on blood coagulation in a trauma model of exsanguination.

Effects of Tigecycline and Doxycycline on Inflammation and Hemodynamics in Porcine Endotoxemia

Principal investigator: Miklos Lipcsey

Tigecycline is a novel antibiotic, the first in the glycylycylcline class, to be used in critically ill patients. Tigecycline is chemically related to the tetracycline class, which has anti-inflammatory properties. There are indications showing that tigecycline might have immunomodulatory properties in experimental septic shock. Using a sterile integrative porcine sepsis model, we investigated the anti-inflammatory and circulatory effects of tigecycline in comparison to doxycycline and placebo. Tigecycline did not affect

cytokine levels but counteracted hypotension and hypoperfusion. This study was recently accepted for publication in Shock.

The impact of rapid bolus administration vs. slow infusion on the extravasation of albumin

Principal investigator: Miklos Lipcsey

Albumin solutions are used for fluid resuscitation in critical illness. Recent experimental and clinical evidence suggest that extravasation of albumin could be influenced by the rate of administration in systemic inflammatory response syndromes. The aim of this project is to determine whether rapid bolus administration of albumin leads to greater extravasation compared to a slow intravenous in experimental septic shock. Endotoxemic pigs, monitored and ventilated with standard intensive care equipment, are given 5% albumin labeled with Technetium-99m either as a rapid bolus or a 2-hour infusion. Radioactivity is monitored in muscle microdialysate, plasma, and urine as well as radioactivity in liver, spleen, kidney and lung is analyzed post mortem.

Model of living bacteria and bacterial clearance by splanchnic mononuclear phagocyte system

Principal investigator: Miklos Lipcsey

In order to increase the knowledge of the interplay between bacteria and the body's immune response we have set up a model, where living E. coli bacteria are administered to the anaesthetized pig. This model may give important information on pathophysiological events and reactions, optimization of antimicrobial strategies and inflammatory markers. We have shown that during infusion of live bacteria, bacteria can be cultured despite an ongoing administration of antibiotics although termination of such an infusion causes the bacteria to disappear from the blood rapidly. The hypothesis currently investigated in this project that systemic inflammatory activation decreases the capacity of the hepatic mononuclear phagocyte system. In a porcine model, with or without inflammatory activation, bacterial clearance and endotoxin clearance trans-hepatic and trans-splenic is investigated.

Microcirculation and mitochondrial dysfunction

Principal investigator: Miklos Lipcsey

In septic shock, hypoperfusion of the organs are of crucial importance and considered to be one of the key factors in the development of this syndrome. Lack of substrate secondary to mitochondrial insufficiency seems to be, at least partly, responsible for this phenomenon. We are aiming to evaluate the rate of the occurrence of this insufficiency, and to determine whether this deficiency is due to the metabolic disturbances caused by endotoxemic shock or whether hypoperfusion per se is sufficient to explain this condition. These experiments are performed by microdialysis in anaesthetized endotoxemic pigs. Collaboration has been started with Associate Professor Robert Frithiof, to investigate the impact of experimental sepsis on the electron transport chain.

Antibiotic concentration in critical illness (ACCIS study)

Principal investigator: Miklos Lipcsey

Early and effective antibiotic therapy is of paramount importance in septic shock. Current recommendations on antibiotic dosing are mainly based on studies in healthy volunteers. In critical illness several factors change the pharmacokinetics of drugs, such as variations in total body water, plasma protein levels, and in hepatic and renal function. Initiation of renal replacement therapy can also alter elimination of antibiotics. Given the unpredictable pharmacokinetics of antibiotics, both underdosing and overdosing of these drugs is likely in the critically ill population. Our hypothesis is that antibiotic concentrations are insufficient during the first days after starting antibiotic therapy. Given that the maximum impact on outcome is probably during the first phase of the antibiotic treatment, investigating this hypothesis is of great importance. We are planning to start a multicenter study in the Uppsala-Örebro region with, currently, nine participating ICUs aiming to include 150 patients. After initiation of antibiotic therapy (with the eight most common antibiotics in this population) plasma concentrations will be followed for three days. In the

second phase of the study, based on the study data, pharmacokinetic modelling will be used to optimize dosing of the antibiotics investigated. The latter project is run in collaboration with Assistant Professor Elisabet Nielsen.

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2 Endocrine Surgery

Principal investigators: Per Hellman, Gunnar Westin, Peter Stålberg

Genetics and treatment of endocrine tumors

The Endocrine Surgical Research Group runs studies of genetics, epigenetics, diagnosis and treatment of endocrine tumors, in order to identify genes involved in tumor development and progression, and to ultimately provide possibilities for new treatment. In clinical studies genetic changes are related to the disease course of individual tumors, with the overall aim to improve diagnosis and treatment in patients with endocrine tumor disease.

Endocrine tumors are of special interest in tumor biology because of a common extended disease course, and often presence of only few specific genetic changes, which can be related to variable tumor biology. For many endocrine tumors histopathology can often not distinguish tumors with more malignant biological features, and there is a general hope that genetic differences will provide better means of discrimination. Genetic studies are expected to become of great importance for the clinical management by predicting prognosis, and genetic defects may be used as targets for new treatment. The overall aim of the studies is to identify tumor genes and other prognostic markers of importance for the development and progression of endocrine tumors, reveal gene changes with new technology, and investigate new possibilities of treatment against tumor progression, all in order to offer personalized care for each patient.

Parathyroid

In parathyroid tumors overexpression of β -catenin has been demonstrated due to a truncating mutation of the Wnt receptor LRP5. The mutation has been shown to stimulate cell proliferation in an own established parathyroid cell line, and tumor growth in SCID mice, supporting our identification of a new important receptor for Wnt-mediated tumorigenesis. The same mutation has been revealed and found to influence tumor growth in breast cancer. Accumulation of active non-phosphorylated β -catenin also occurs in parathyroid carcinomas, but due to aberrant CpG methylation and lost expression of the tumor suppressor gene APC. Therefore, adjuvant epigenetic therapy should be considered as an additional option in the treatment of patients with recurrent or metastatic parathyroid carcinoma. A genome-wide analysis of parathyroid tumor DNA methylome has revealed several epigenetically deregulated genes of putative importance to benign and malignant parathyroid tumorigenesis. The HIC1 tumor suppressor gene plays a growth-regulatory role in the parathyroid glands and reduced HIC1 expression by repressive histone modification H3K27me3 rather than by CpG methylation was observed in parathyroid tumors regardless of the hyperparathyroid disease state.

Carcinoids

Small intestinal neuroendocrine tumors (SI-NETs) have been studied with molecular methods. We have as the first group revealed presence of a suspect tumor suppressor gene for SI-NETs on chromosome 18q. Chromosome 18q was also shown to be involved in familial tumors in collaboration with Professor E Tiensuu-Janson. A candidate tumor suppressor gene at 18q, Elongin, has been thoroughly studied. Expression array has identified different clusters of tumors, and methylation as well as single nucleotide polymorphism arrays have continued the search for molecular deficits in these tumors. We have demonstrated mutations in the CDKN1B gene in 8.5% of our cohort. The large local cohort in Uppsala, but also nationally, are identified clinically and tumor markers and prognostic variables are being identified to subgroup the patients.

Endocrine pancreatic tumors

Several previous studies have investigated gene changes associated with endocrine pancreatic tumors. In an ongoing study, we have by exome sequencing identified a gene involved in the development of insulinoma; and further studies in other tumors are being performed.

Adrenocortical tumors

We have in collaboration with researchers at Yale University and the Experimental Surgery group at Uppsala University identified novel mutation in *KCNJ5* and *CACNA1D* (publications in *Science* and *Nature Genetics*, respectively) in aldosterone-producing adenomas in primary aldosteronism. Germline mutation of *KCNJ5* was demonstrated in familial hyperaldosteronism. We have continued the search for mutations in these tumors to cover the majority of the tumors. In continued studies, *PRKACA* was found mutated in a subset of cortisol-producing adenomas (published in *Nature Genetics*). Analysis of DNA CpG methylation genome-wide has revealed genes with putative importance to benign and malignant adrenocortical tumor development.

Graves' disease

In a translational study, also in collaboration with the Experimental Surgery Group, reasons for postoperative hypocalcemia after surgery for Grave's disease is being studied. SNP array, calcium-citrate clamping and immunological studies are performed.

Clinical studies

Clinical studies of primary hyperparathyroidism (HPT) focus on relations between calcium, aldosterone and/or parathyroid hormone (PTH), and increased mortality in cardiovascular disease, serum lipid dysregulation, insulin resistance, coagulation abnormalities, endothelial cell malfunction, which all have been linked to the metabolic syndrome. These studies are performed on patients with primary HPT, and normal individuals (from the PIVUS cohort).

Continuous studies are ongoing for studying of parathyroid function, vitamin D and mineral status in obesity, and after gastric by-pass surgery.

Efforts are being made to investigate possible new tracers for PET, specifically targeting the adrenal cortex, in order to simplify diagnosis of primary aldosteronism and cortisol-producing adenomas.

Endocrine tumors have variable and extended disease course, and often few specific genetic aberrations possible to relate to tumor type and tumor biology. A large collected tissue bank is used to study genes of importance for endocrine tumors using various molecular methods including RNA expression arrays, SNP arrays, exome sequencing, and concomitant studies of epigenetics. Clinical investigations study epidemiology and survival in endocrine tumors, relating gene abnormalities to prognosis of patients with endocrine tumors, with the aim to develop prognostic markers and individually designed therapy based on genetic and epigenetic aberrations.

Members of the group during 2014

Per Hellman, Professor

Gunnar Westin, Professor

Peter Stålberg, Associate Professor

Ola Hessman, MD, PhD

Hella Hultin, MD, PhD

Olov Norlen, MD, PhD

Göran Åkerström, Professor

Research students 2014

Katarina Edfeldt, Genetics in small intestinal NETs

John Eriksson, Epidemiological studies of small intestinal neuroendocrine tumors

Tommy Ahlström, Effects of calcium and parathyroid hormone in the population

Elham Barazeghi, Epigenetic derangements in parathyroid tumors

Maria Annerbo, Hypocalcemia in Grave's disease

Kosmas Daskalakis, Translational studies of small intestinal NETs

Agencies that support the work/Funding

Cancerfonden

Vetenskapsrådet

Uppsala University Hospital (ALF)

Lions Cancerfond

Selanders Foundation

Bergholms Foundation

Erikssons Foundation

Dissertations 2014

Katarina Edfeldt. Small Intestinal Neuroendocrine Tumors: Genetic and Epigenetic Studies and Novel Serum Biomarkers

Experimental Surgery

Principal investigators: Peyman Björklund and Per Hellman

The group of Experimental Surgery did started as an independent research group in January 2012, supported by a Young Investigator Award and project grants from Swedish Cancer Society.

We utilize state of the art methods such as Next Generation Sequencing (NGS), high throughput array technologies and drug screening of viable primary tumor cells.

Personalized medicine, Precision Medicine

In partnership with SciLifeLab, clinical diagnostics platform and utilizing high density SNP array technology and Next Generation Sequencing, we aim to develop a fast and affordable diagnostic tool to identify genetic and epigenetic aberration in each individual tumor. Viable tumor cells are then subjected to screening for druggable targets.

Adrenal tumors; genetics, epigenetics and new therapeutic strategies

In pheochromocytoma tumors we have identified mutations in *H-RAS*. This finding introduces possibilities for targeted therapy in non-resectable tumors. In parallel we have developed an NGS based mutation screening method to identify patients with hereditary pheochromocytoma and paragangliomas.

Screening of viable primary tumor cells for candidate drugs have shown induction of apoptosis by somatostatin analogues and other agents affecting the methylation activity.

In cortisol producing tumors we have identified recurrent mutations in *PRKACA* and are performing drug screening tests on primary tumor cell cultures.

Complicated Graves' disease

Even though Grave's thyrotoxicosis is a common disease, complications such as disrupted calcium homeostasis and ophthalmopathy are rare. We aim to identify genetic determinants predisposing for complications.

Rare Mendelian inherited conditions

In collaboration with several international and national groups we are utilizing NGS to identify genes responsible for rare syndromes.

Endocrine disrupting chemicals and adrenal disorders

As a part of an international consortium led by associate Professor Monica Lind UU and Professor Bruce Blumberg University of California, Irvine, we aim to determine physiological effects of Bisfenol A on adrenals and kidneys.

Clinical studies

In collaboration with other groups, we are evaluating a new target for positron-emission-tomography (PET) for diagnosis of adrenal tumors, aiming at improved diagnostic imaging procedure.

Members of the group during 2014

Joakim Crona, MD, PhD student (Genetics of Pheochromocytoma and Paragangliomas)

Alberto Delgado Verdugo, MD, PhD student (Methylation and Wnt regulation in Endocrine Tumours)

Maria Annerbo, MD, PhD student (Calcium Metabolism in Grave's disease)

Tobias Åkerström, MD, PhD student (Genetics of Aldosterone producing Adrenal tumors)

Rajani Maharjan, MS PhD student (Genetics of Adrenocortical Cancer)

Lee Starker, MD, PhD (Rare Mendelian Inherited Conditions)

Dissertations 2014

Joakim Crona. Charting the Genetic Landscape and Clonal Architecture of Pheochromocytoma

Alberto Delgado Verdugo. Genetic Aspects of Endocrine Tumorigenesis: A Hunt for the Endocrine Neoplasia Gene

Tobias Åkerström. Genetic Alterations in Aldosterone Producing Adenomas

Agencies that support the work/Funding

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Selander Foundation

Lions Cancerfond

Uppsala University Medical Faculty Starting Grant

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Clinical cancer epidemiology

Principal investigator: Lars Holmberg

The group is based at the Regional Cancer Centre in the Uppsala Örebro region. Professor Holmberg also has an affiliation with Division of Cancer Studies, Medical School, King's College London. The group collaborates within an EU network with Sweden, UK, Ireland and Italy. Researchers at the Dana-Farber Cancer Institute at Harvard Medical School, Boston, USA, collaborate with the group in translational research. Several of the projects involve collaborations with networks for clinical data bases in cancer in Sweden and the AMORIS group which governs a large cohort for studies of serum biomarkers and their relation to cancer.

Clinical trials

The group has participated with main functions or lead several clinical trials, among them the Scandinavian Prostate Cancer Group Study no. 4 (SPCG4), the SWEDCIS trial of breast conservation ± radiotherapy in ductal cancers in situ of the breast, the CW1 trial of breast cancer conservation ± radiotherapy in invasive breast cancer and the HABITS study, which tested if hormonal replacement therapy in women with a previous breast cancer is safe. In a network with other researchers, the group is currently preparing a large randomized study in active surveillance for prostate cancer.

Translational research

In collaboration with the Karolinska Institute and the Department of Immunology, Genetics and Pathology at the Uppsala University Hospital the group is conducting a study of the reasons for a worse prognosis among very young women with breast cancer. The study involves utilization of a large number of bio samples. In the AMORIS cohort the group collaborates with the principal investigators of the cohort in studies on serum biomarkers and later risk and natural history of several types of cancer. One of the primary focuses is on perturbed lipid metabolism and risk of cancer progression.

Register-based research

In collaboration with steering groups for large clinical data bases at the Regional Cancer Centre and at King's College London, the group has conducted research on different aspects of treatment for prostate and breast cancer, among them side-effects of radiotherapy and hormonal treatment. The group has also studied the impact of local recurrence and metachronous contralateral breast cancer on breast cancer prognosis.

Methodological developments

The group participates in methodological development in advanced biostatistical tools. One main interest has been to disentangle cohort heterogeneity and its impact on long-term disease specific outcomes such as outcomes measured together with competing risks.

Members of the group during 2014

Lars Holmberg, Professor, Head of Regional Cancer Centre, Uppsala-Örebro Region

Sonja Eaker, Senior researcher, Head of Regional Biobank Centre, Uppsala-Örebro Health Care Region

Hans Garmo, PhD, Senior Biostatistician

Birgitta Grundmark, PhD, Clinical Assessor, Department of Drug Safety, Medical Products Agency, Uppsala

Mieke Van Hemelrijck, PhD, Lecturer, Division of Cancer Studies, Medical School, King's College London

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3 Gastrointestinal Surgery

The report is presented in two main parts – upper abdominal surgery and colorectal surgery. Both main parts are further subdivided into sections and research fields. Since more than one year the gastrointestinal research group has common seminars in which research projects are presented and discussed.

Upper Abdominal Surgery

The research in Upper abdominal surgery is divided in four main areas; Bariatric surgery, Esophageal- and gastric cancer, Hepatic surgery, and Biliary- and pancreatic surgery.

Bariatric surgery

In bariatric surgery, we have focused on surgical technique, postoperative changes in gastrointestinal physiology and long term results. Our research is clinical and based on operated patients with the aim to improve surgical technique and understand the altered physiology. We perform Duodenal Switch (DS) in patients with super obesity, i.e. BMI > 50 kg/m², and laparoscopic gastric bypass (GBP) routinely. Almost all patients are potential research subjects, as we have many ongoing projects.

At present, we are studying operative technique in DS, comparing laparoscopy to open surgery. We are evaluating changes in appetite-regulation and gastrointestinal physiology in operated patients (DS and GBP) and controls as well as calcium homeostasis and vitamin-D levels. The effects of bariatric surgery on colorectal - and anal sphincter function are evaluated in a PhD project using manometry and validated questionnaires.

In collaboration with Örebro, we have finished a ten year follow-up of 880 GBP-operated patients, demonstrating good long-term weight results and high quality of life in generally satisfied patients. We have started detailed studies of long-term results in super obese patients, to clarify differences between DS and GBP concerning glucose homeostasis, gastrointestinal symptoms, patient satisfaction, and of cause weight result.

Bariatric research is expanding and the number of projects performed in collaboration with other units in the hospital, e.g. the Metabolic unit, Department of Endocrinology and Gastroenterology, or departments at the University, are increasing continuously.

Esophageal- and gastric cancer

In the field of esophageal- and gastric cancer, we participate in the international CRITICS-study on adjuvant chemo-radiation in gastric cancer and perform vitro evaluation of chemotherapy for gastric- and oesophageal cancer.

At present, we are evaluating the gastric tube with continuous pHi-measurements in esophageal resections to identify early ischemia. We are also working on detailed loco-regional evaluation of esophageal cancer with PET/MRI.

Patient outcome on a national level is studied in a PhD project in collaboration with the national quality register, NREV. Locally, we are studying the effect of value-based care on outcome and patient satisfaction.

Members of the Esophageal- and Gastric Surgery Group 2014

The research group is headed by Professor Magnus Sundbom.

Jakob Hedberg, Associate Professor of Surgery

David Edholm, MD, PhD

PhD students

Zakaria Abdulla, MD

Eduardo Sima, MD

Gustav Linder, MD

Martin Skogar, MD

Eladio Cabrera, MD

Dissertations 2014

David Edholm. Gastric Bypass - Facilitating the Procedure and Long-term Results

External Founding 2014

Bergholms fond, 100,000 SEK

Bergholms fond, 100,000 SEK

Liver surgery

Principal investigator: Agneta Norén

Liver surgery for colorectal liver metastases (CRLM) has become standard treatment for patients with resectable disease. The treatment is multimodal with chemotherapy and also ablative methods as a complement to surgery. In liver surgery we have focused on defining the possible risk following liver resection induced by preoperative chemotherapy. More than half (60-70%) of the patients receive preoperative chemotherapy and some patients develop sinusoidal injury (SI) due to oxaliplatinbased chemotherapy. SI is associated with preoperative bleeding and morbidity after liver surgery. SI was initially described as simple sinusoidal dilatation, but further research revealed a full spectrum of histopathological changes including congestion in sinusoids, hemorrhage in perisinusoidal space leading to hepatocyte loss, perisinusoidal and centrilobular fibrosis, sinusoidal obstruction, nodular regenerative hyperplasia and veno-occlusive lesions

MRI studies

In an attempt to diagnose SI noninvasively a project using pre-operative 3T MR we have studied patients with and with-out pre-operative chemotherapy the day before surgery with 83 special techniques to reveal and grade steatosis, steatohepatitis, SI and portal flow. The results are related to the histopathological evaluation and to the clinical outcome. Two of the studies are recently published (see publication list) and further MR studies are planned.

Local registry of liver surgery

We have also studied the clinical outcome in the patient material from our institution of approximately 500 resected patients with liver metastasis from CRLM during the last twelve years with focus on liver specific complications related to chemotherapy (manuscript).

Liver tissue and cultured cells

In collaboration with prof. Per Artursson, department of pharmacy, we have studies aimed at developing a model using cultured human liver cells, obtained from waste liver tissue after resection for liver metastases from colorectal cancer. The cultured cells will be used to study membrane transport function, the influence

of preoperative chemotherapy as well as the influence of cytostatic drugs on this function. On aim is to enlighten the effect of oxaliplatin treatment for CRLM on non-tumorous liver tissue, using label-free global proteome analysis to quantify changes in proteins, associated biological process and pathways (manuscript).

Ablative methods with IRE

A safety and effect study on irreversible electroporation (IRE) for liver tumors are running. IRE is a new non-thermal tissue ablation technique, using short duration electrical fields to permanently defect the cell membrane leading to cell death.

Members of the liver surgery group 2014

Ulf Haglund, MD, PhD, Professor Emeritus of Surgery

Agneta Norén, MD, PhD

Frans Duraj, MD

Jozef Urdzik, MD, Ph D

Petter Fruhling, MD

Dissertations 2014

Josef Urdzik. Colorectal Cancer Liver Metastases: Effects of Chemotherapy on Liver Parenchyma and Resection.

Biliary surgery

Principal investigator: Britt-Marie Karlson

The biliary group has focused on surgery for gall stones and ERCP. Long term results after endoscopic sphincterotomy, particularly in patients with gall stone-related pancreatitis, are under evaluation and a prospective study on Gallbladder in situ after papillotomy is ongoing. We have also investigating the need of antibiotics before cholecystectomy and are starting a prospective randomized study to evaluate Tissel after cholangiotomy.

In collaboration with Per Sangfelt and Fredrik Rorsman, department of Medical Sciences, studies in primary sclerosing cholangitis are ongoing and a consecutive patient material with this disease is accumulated with endoscopic cholangiographic data.

Members of the group during 2014

Britt-Marie Karlson, MD, PhD (she is on the board of National Registry of Pancreatic Cancer)

Ann Langerth, MD

Stefan Linder MD, PhD

Christopher Månsson, MD

Bahman Darkahi, MD

Agencies that support the work/Funding

The research is funded by "ALF-medel".

Pancreatic cancer

Principal investigator: Britt-Marie Karlson

A project on irreversible electroporation (IRE) in patients with inoperable pancreatic cancer has started and the first phase 1 study is finished. Several (phase 2) studies are ongoing with different groups of patients, treated before or after chemotherapy, with local recurrence after pancreatic surgery

In collaboration with prof. Peter Nygren, department of oncology, ongoing studies on chemotherapy resistance for pancreatic, duodenal and cholangiocellular cancer.

Members of the group during 2014

Britt-Marie Karlson, MD, PhD (she is on the board of National Registry of Pancreatic Cancer)

Ann Langerth, MD

Stefan Linder MD, PhD

Christopher Månsson, MD

Bahman Darkahi, MD

Agencies that support the work/Funding

The research is funded by "ALF-medel".

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Colorectal surgery

The research in this field is divided into colorectal cancer, peritoneal carcinomatosis, functional bowel disorders (including proctology), and inflammatory bowel disease.

Colorectal cancer

We are continuing the effort to find prognostic markers in order to individualize surgical and oncological treatment. Analyses of the influence of genetic aspects is also performed as well as studies to improve the knowledge on the interaction between heredity and various biomarkers, like tryptophanyl-tRNAsynthetase, microsatellite instability and mismatch repair genes. We also perform several studies on the effects of several surgical and perioperative factors, like preoperative bowel preparation, intraoperative antibiotics, adhesion prophylaxis, and the importance of the patients position during abdominoperineal resections, supine versus prone for the oncological outcome. Other ongoing studies are the influence of surgical complications on recurrence and survival as well as the impact of a diverting stoma and laparoscopic surgery on outcome. We participate in a national trial exploring the effects of a nationwide colon cancer screening project with regards to compliance, polyp detection rate, complications, and disease rate reduction.

Peritoneal carcinomatosis

We have one of the largest patients cohorts treated with cytoreductive surgery and intraoperative chemotherapy worldwide. Since 2001 more than 500 patients have been treated and this large series is analyzed concerning various outcomes. One project aims at evaluating the histopathological specimens, and we have observed that neoplastic cells are absent in 15%. In a recent study we observed that appendiceal neoplasms, low levels of tumor markers, and no preoperative chemotherapy increased the likelihood of negative histopathology. We are also studying the morbidity after surgery and HIPEC, its effect on outcome and predictors of morbidity. A study exploring the dose – efficacy relationship is also performed. A project analyzing risk factors for appendiceal neoplasms has started as well as a study exploring risk factors for development of peritoneal carcinomatosis. We have together with the other Swedish centers formed a network and a national registry as well as national multicenter studies is planned.

Functional bowel disorders and proctology

In depth analyses of bowel motility has since long been a focus of the group. We have analyzed the effect of electrical stimulation of sacral nerve roots in 42 constipated subjects. Totally 15 patients had more than 50% symptom relief and received a permanent implant. Out of these only five (12% on an ITT basis) had sustained benefit. Further studies will be performed aiming at characterizing the subgroup with treatment response.

We have also a long tradition in incontinence research and have contributed substantially to the concept of injectable bulking treatment for fecal incontinence. The active treatment group in a previously published randomized multicenter study comparing submucous injection of dextranomer in stabilized hyaluronic acid against placebo has been followed up after 3 years and the effect was essentially unchanged. We have also analyzed the long term morbidity and stability of a response. In a study of patients with systemic sclerosis,

we observed that the external sphincter was affected and mainly responsible for incontinence. A randomized trial comparing injectable treatment versus sacral nerve stimulation for fecal incontinence has recently started.

A comprehensive project concerning functional outcome and secondary treatment of patients treated for anorectal malformations in childhood have been performed in collaboration with the Department of Pediatric Surgery. Approximately 40% of the cohort of 136 subjects reported either that they had a stoma or fecal incontinence. Several treatments have been developed for this patient category.

In order to prevent iatrogenic incontinence we have investigated sphincter saving surgery for anal fistulas and observed a healing rate after intersphincteric ligation of the fistula tract in 9/15 patients with recurrent anal fistula after a median follow up of 13 months. We participate in a national randomized trial comparing plug closure versus advancement flap closure of anal fistula.

A previous study of anal sphincter function after excisional haemorrhoidectomy found fecal incontinence in 40/418 which was related to surgery. An extended anatomical and physiological analysis of this subgroup found definite signs of external sphincter injuries, reduced anal pressures and impaired sealing capacity indicating iatrogenic injuries. We are currently performing a long term follow up of 200 patients who participated in a randomized trial about twelve years ago comparing two forms of surgical technique. Another research focus is minimal invasive haemorrhoid surgery and the importance a Doppler guidance during transanal haemorrhoidal dearterialisation is explored in a randomized trial.

Inflammatory bowel disease

We have participated in the population based IBD cohort ICURE study focusing on epidemiology in Ulcerative colitis and Crohns disease headed by the Department of gastroenterology. Incident cases of pediatric Crohns disease are biopsied for evidence of enteral viral infections an etiological factor. This project is performed together with The Pediatric gastroenterologists. We participate in the research network: Swedish organization for inflammatory bowel disease.

Members of the group during 2014

Wilhelm Graf, Professor, Director

Helgi Birgisson, Ass Professor

Urban Karlbom, Ass Professor

Lars Pählman, Professor Emeritus

Joakim Folkesson, MD, PhD

Helene Silliin, MD, PhD

Filip Sköldberg, MD, PhD

Peter Cashin, MD, PhD

Helgi Johansson, MD, PhD

Åsa Collin, MD

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Torbjörn Zackari, MD

Dissertations 2014

Lana Ghanipour. Colorectal Cancer: Aspects of Heredity, Prognosis and Tumour Markers.

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4 Forensic medicine

The research at the Division of Forensic Medicine during 2014 were in four main areas; consequences of abuse of anabolic androgenic steroids (AAS), injury epidemiology/injury interpretation, infant abuse, and determination of post-mortem interval in decomposed bodies found indoors.

Consequences of abuse of anabolic androgenic steroids (AAS)

Principal investigator Ingemar Thiblin

During 2014 there have been two projects, both currently continuing. One is a larger PhD project aiming to identify cardiovascular lesions and testicular lesions in deceased AAS users and the other is a wide epidemiological study on the morbidity and mortality among users of AAS. The heart and testes were chosen because clinical experience suggests that the heart and reproductive organs are strongly affected by AAS. There are currently a number of clinical studies and some case reports/case series regarding deceased AAS users. There have been no previous large-scale surveys of organ pathology of the kind we currently conduct. The project is run in close cooperation with the National Board of Forensic Medicine's Forensic Medicine Department in Uppsala.

The epidemiological survey is conducted in cooperation with epidemiological expertise at the Uppsala Clinical Research Center (UCR) and it is based on everyone who tested positive for AAS when tested at the Doping Control Laboratory at the Karolinska University Hospital in Huddinge during the period 2002 to 2009. In part the study is a follow-up on a previous similar study that we presented a few years ago, which showed an excess mortality of around 20 times in AAS users compared to the expected mortality of the total population.

Injury epidemiology/injury interpretation

Principal investigator Ingemar Thiblin

In Sweden, nearly 100,000 persons per annum receive hospital care for injuries, 3,000 die before receiving hospital care, and 1,500 die after receiving hospital care. Injuries are the main cause of death and disability below the age of 60. At present, the feedback to the public bodies responsible for injury prevention on injury-related death and complications is highly deficient. To overcome these shortcomings, we intend to cooperate with the UCR to establish an injury database that will provide a constantly updated current picture of regional injury incidence, an improved standard analysis and registration of causes of injury and injury mechanisms within the health care services and forensic medicine, methods for the reliable assessment of the causes of injuries and their levels of severity, and a data source for research within various disciplines such as medicine, law, and criminology.

So far, we (the UCR and the Division of Forensic Medicine) have focused on creating a model for the assessment of the level of severity for injuries caused by assault. This has resulted in a very sturdy model that predicts with almost 100% accuracy (AUC 0.98) whether an injury or a combination of injuries is life threatening, which is central to forensic medicine assessments. The model is based on the so-called Bayesian regression, and an extension of the model is expanded to include injuries caused by means other than assault. An adaptation into a web-based application is also planned.

The project further includes the development of new advanced methods of damage analysis. These are intended for use in forensic medicine assessments and for the indirect improvement of the quality of the injury database. The project is conducted in cooperation with Dr. Svein Kleiven's research team at the KTH Royal Institute of Technology. In short, it concerns the simulation of injuries with the help of Finite Element Analysis based on information on the injured body part (e.g. skull thickness) as well as observations made at the scene (documentation of drop heights, the shape of hard objects in the environment, etc.). This simulated image of the injury can then be compared to the true image of the injury,

which allows conclusions to be drawn regarding the stated or assumed course of events. Among other things, this is central to the assessment of causes of injury (whether accident, self-inflicted, or inflicted by someone else) and to injury preventive work (e.g. the development of improved motorcycle helmets). Conducted in close cooperation with the National Board of Forensic Medicine, the project has been going on for several years.

An on-going PhD project aims at A) develop an easy-to use and valid model for scoring the level of violence (brutality score) in homicides and B) examine the level of violence in homicides in a longitudinal perspective by employing the model. This project is done in collaboration with sociologists at the Department of Forensic Psychiatry, Stockholm.

Infant abuse

Principal investigator Ingemar Thiblin

A new Ph.D. project concerning infant abuse was started in 2014. The project is based on registry data from the National Board of Forensic Medicine and The National Board of Health and Welfare. The previously widely accepted conception of certain findings (e.g. retinodural bleeding or metaphyseal lesions) and circumstances (e.g. no history of trauma in the presence of retinodural bleeding) in infants are virtually pathognomonic for infant abuse has been increasingly questioned during the latest years. Several alternative hypotheses have been presented. All hypotheses, both those in favor of abuse and those questioning abuse have in common that empirical verification has been hard to obtain. One major limitation of previous studies is circular reasoning, since the explanatory variables often are more or less identical to the criteria for defining cases as abuse cases. Our aim is to perform large registry based studies that test the different proposed hypothesis in a uniform manner, avoiding methodology involving circularity.

Post mortem interval

Principal investigator Ingemar Thiblin

An important but difficult task is to determine the post mortem interval (PMI) in decomposed bodies. So far most research in this area has focused on bodies found out doors. This new Ph.D. project aims at developing a method for PMI determination by combining classical decomposing scoring models with entomological data employing Bayesian network software.

Members of the group during 2014

Ingemar Thiblin, Professor

Håkan Sandler, MD, PhD

Greta Ågren, Ass. Professor

Hamid Mobini-Far, PhD student

Fredrik Tamsen, PhD student

Jacob Andersson, PhD student

Ann-Sofie Pålsson

Collaborations

Rolf Gedeberg, Ass Professor UCR, Uppsala University

Svein Kleiven, Ass. Professor Dept. of Neuronics, KTH Royal Institute of Technology

Joakim Sturup, Ph.D. Sociologist, Swedish Board of Forensic Medicine

Anders Lindström, PhD, Entomologist, SLU

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5 Hand Surgery

Principal investigator: Monica Wiig

1A) Flexor tendons - prevention of adhesion formations

The main objective of our research is to improve the results after tendon surgery. We want to develop new drugs and find strategies for the prevention of post-surgical adhesion formation and decrease the formation of ruptures after trauma, inflammatory processes and tendon surgery. To do that we need to understand the mechanism of how adhesions develop and in parallel work with the development of new drugs to prevent adhesion formation as well as identify risk factors for ruptures of the tendons.

Adhesions comprise scar-tissue that connects anatomic structures that should not normally be connected. Such adhesions develop when the body's repair mechanisms respond to tissue injury as the result of surgery, trauma or infection. Adhesions form after almost any type of surgery and are a significant source of post-surgical complications. In addition, adhesions prolong subsequent surgery and constitute a considerable burden on the healthcare systems.

In a rabbit model of flexor tendon injury, we have identified tissue- and temporal-specific aspects to the flexor tendon healing process for factors involved in remodeling, inflammatory response and fibrosis. We have also looked at changes in mRNA expression of neuropeptides and factors involved in angiogenesis.

A new therapeutic option has emerged in the form of a synthetic peptide (PXL01) structurally derived from human lactoferrin. PXL01 exhibits broad-spectrum antimicrobial properties and is shown to down-regulate inflammatory cytokines. PXL01 also inhibits plasminogen activator inhibitor type 1 (PAI-1), which is expected to increase the fibrinolytic activity after surgery and is suggested to be an additional mechanism for these peptides to reduce excessive scarring. It is presently unclear, though, which of these activities that are important for the observed anti-adhesion effect *in vivo*.

Nonclinical efficacy studies in the rabbit model demonstrate a significant effect of PXL01 in HA in adhesion prevention without any negative consequences on tendon healing.

We have performed a prospective, randomized, double-blind, multicenter trial including 138 patients admitted for flexor tendon repair surgery. PXL01 in HA, or placebo was administered locally around the repaired tendon. The study suggests that treatment with the peptide PXL01, formulated with native sodium hyaluronate carrier, in connection to the surgical flexor tendon repair after hand injury, improves the clinical outcome in terms of mobility of the affected finger. A potential for a favorable role of PXL01 to stimulate nerve regeneration is also raised. Published in Plos One Oct 2014.

In a mechanism of action study we observed significantly higher levels of *PRG4* mRNA in rabPXL01 in HA treated tendons, but not in tendon sheaths, at all-time points, which subsequently may lead to increased lubrication of the injury site and inhibition of peritendinous adhesion formations. In addition, coordinated repression of the expression of several pro-inflammatory mediators was observed in tendon sheaths. Taken together, our results indicate that adjuvant treatment with rabPXL01 in HA will increase lubricin levels and inhibit the inflammatory response. This would lead to reduced gliding resistance and adhesion formations as well as increased tendon excursion after tendon injury and repair, and could explain the results seen in the previously reported clinical study.

1B) Tissue engineering

We are starting a project on tissue engineering, to characterize and compare the *in vivo* result after reconstruction of tendons after injury and diseases. In an animal model we plan to investigate what happens with "tissue engineered tendons" (allografts) and different tendon grafts after transplantation. Focus will be on different factors included in the healing process and of importance for strength and the undesirable scar tissue. Adhesions contribute to decreased mobility and we want to avoid adhesion formations as much as possible.

2) Trigger finger study

The overall purpose of the program is to develop a new, better treatment of trigger finger, one of the most common conditions seen in the clinical practice of hand surgery. Triggering occurs as a result of a disproportion between the flexor tendons and the A-1 pulley and includes thickening of the pulley and tendon, but the pathogenesis of these changes is not clearly understood. Several factors, including inflammation, trauma, degeneration and heredity, that may initiate the pathologic process also are poorly defined in the current literature. Besides surgery, corticosteroid injections are currently used to treat trigger finger, suggesting an inflammatory response.

The first goal is to try to understand the mechanism behind the origin of trigger finger. Through histological and transcript analyses of affected fingers and control material we aim to analyze cellular and molecular changes in affected tendons, tendon sheaths and the A-1 pulley. In particular we will address cells and transcripts known to be important for inflammatory and fibrotic responses. We have started to include patients in this study.

Based on this first part, the second goal is to initiate a clinical study in which one or several compounds will be evaluated for the treatment of trigger finger. Two such potential compounds are Hyaluronic acid and the lactoferrin peptide PLX01, which currently are employed as combination therapy in a clinical study aiming to prevent adhesions after flexor tendon surgery.

Members of the group during 2014

Monica Wiig, principal investigator

Sara Edsfeldt, PhD student

Björn Holm, PhD student

David Hart, Professor, Calgary Canada

Simon Farnebo, Linköping

Eva Nordin

Ylva Petterson

Ylva Gollbo Foucard

Elisabeth Källman

Publications 2012-2014

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6 Nursing

Nursing research is currently a group of nurse researchers and nurse PhD students within the department rather than a research group. The nurse researchers and PhD students are members of the department's different research groups and the nursing research concerns a diversity of topics. We are just in the beginning of creating an inter-professional nurse research network within the department.

Intensive care of the ventilator treated patient

Nursing perspectives on patient safety in the ICU with special reference to ventilator treated patients. The aim is to improve safety of the nursing procedures in the severely ill ventilator treated patients.

The studies can be divided into three specific projects:

- Reducing the risk of hypoxemia in connection with endotracheal intubation
- Reducing the risk of lung complications when changing ventilator filters – a procedure, which is done daily.
- Reducing the risk of circulatory and respiratory compromise at specific nursing procedures (e.g. turning and washing) in the ventilator treated patient.

Members of the group during 2014

Joakim Engström, RN, PhD student

Camilla Fröjd, RN, PhD

Henrik Reinius, MD, PhD student

Anders Larsson, MD, Professor

Collaborations

Göran Hedenstierna, Professor

Filip Fredén, MD, PhD

João Batista Borges, MD, PhD student

Neurological assessment and six-month follow-up for patients treated with induced hypothermia after cardiac arrest

Observes patients during the first six months after cardiac arrest treated with induced hypothermia to investigate quality of life, physical and psychological function, neurological function and mortality. This is related to the initial levels of biochemical markers, findings of EEG, neurological investigation, Sensory Evoked Potential (SEP) and Magnetic resonance imaging (MRI).

We compare quality of life and function over time and relationship between quality of life and function. Another aim is to describe the relatives experience when someone they care for survived a cardiac arrest and how the incident has affected their daily life.

Members of the group during 2014

Ing-Marie Larsson, RN, PhD student

Ewa Wallin, RN, PhD student

Marie Sellert-Rydberg, RN, PhD student, Intensive Care Unit, Falun Hospital

Sten Rubertsson, MD, Professor, Principal Investigator

Marja-Leena Kristofferzon, RN, FD, Dept. of Health and Caring Sciences University of Gävle

Patient safety in intensive care

The intensive care unit (ICU) work system (as all high risk organizations) consists of five elements: Technology and tools, Tasks, Environment, organization and at the center the individuals, being providers and patients. The characteristics of these elements and their interactions will determine the performance of the processes, e.g. compliance to evidence-based guidelines and ward routines, which in turn may affect patient safety. The five elements co-exist and interact. To achieve patient safety, the entire work system should be well designed.

The *hypothesis* is that there is a cognitive overload in intensive care making it difficult for intensive care nurses to catch up with, and prioritize/utilize important information. Furthermore, when adding the large amount of impressions that the nurses constantly are subjected to bedside, coming from technical devices, equipment and patients' vital signs, there is a risk for cognitive overload, which may influence compliance to evidence-based guidelines and ward routines and this in turn may harm patient safety.

The study explores the nature and extent of the ICU nurses' cognitive work load and how this compromises patient safety. The aim is also to improve patient safety by interventions in the ICU work system.

Since there exists very few observational studies of the intensive care work systems from a high risk organization perspective, and rarely none in which interventions have been done to improve the intensive care work systems with regard to technology, cognitive work load and patient safety, this project will, to some extent be shaped along with the results from the study above. However, the overall intention of the project is to test which technical and environmental interventions will create a firm intensive care work system with optimal patient safety, regardless of which people are working within the system.

Members of the group during 2014

Project Leader: Camilla Fröjd, PhD, Specialist Nurse in Intensive Care, Senior Lecturer

Anders Larsson, MD, Professor Intensive Care Specialist

Johann Valtysson, MD, PhD Head of the Intensive Care Department at Uppsala University Hospital

Anders Jansson, Associate Professor, Dept. of Information Technology

Marcus Arvidsson, MTO Security, Stockholm

Burn care

Resuscitation in acute burn care

Evaluates how routines for adjustment of the resuscitation fluid in acute burn care were carried out in practice and to develop a burn resuscitation protocol for improving procedures to ensure patient safety.

Members of the group during 2014

Björn Wikehult, RN, PhD

Linda Yngvesdotter, RN, MSc Burn Center Uppsala University Hospital

Bengt Gerdin, MD, Professor

Reference

Yngvesdotter, Linda, Vätskebehandling inom brännskadevård (2012) Självständigt arbete på avancerad nivå (magisterexamen), 10 poäng/15 hp Degree project)

Patient satisfaction with care

Evaluation of patients' experiences of care. At present the focus is on patients treated on the Burn Center.

Members of the group during 2014

Björn Wikehult, RN, PhD,

Mimmie Willebrand, Professor (Dept of Neuroscience)

Working hours, sleep quality and health among intensive care unit personnel

The aims of this cross-sectional study were to examine how ICU personnel experience their sleep quality and possible links between working hours, sleep quality and perceived health. An additional aim was to study if demographic variables such as age, gender, profession, and years in the profession are associated with the experience of altered sleep quality?

Members of the group during 2014

Björn Wikehult, RN PhD

Caisa Öster, RN PhD (dept of Neuroscience)

Surgical care

Patient-centered care in surgical care and competence development among surgical nurses

Research investigator: Eva Jangland

The need for a more patient-centered care has been highlighted in international and national research. The overall aim in the thesis (Jangland 2011) was to describe patient-health-professional interactions in a hospital setting, with a specific focus on the surgical care unit.

In an analysis of complaints to a local Patients' Advisory Committee patients and relatives reported a range of concerns and impacts including increased anxiety and reduced confidence in health care after negative patient-health professional interactions. In an intervention study, when the patients were asked to express their daily questions and concerns in writing, showed improved patient participation in the surgical care units. However, some patients also reported that no one in the health-care team paid attention to their concerns.

In a phenomenographic analysis four qualitatively different ways of understanding the nurse-patient relationship were identified among surgical nurses. In a most restricted understanding the nurses focus on the work task, whereas in the others nurses demonstrate increasing degree of patient-centeredness. The result has pedagogical implications indicating that to be able to develop competence development in this area the nurses need to have time at ward meetings or in supervision to discuss, and there through in a reflective process, become aware of different ways of understanding their role.

A number of projects targeting to evaluate and improve nursing care, patient participation, continuity of care, as well as to evaluate the implementation of Nurse Practitioner in surgical care has been outlined during 2012. Several data collections and analysis of data has been carried out in collaboration with national and international researchers.

Collaborations

Claes Juhlin, MD, Associate Professor

Department of Medicine and Health, Faculty of Health Sciences, Linköping University:

Pia Yngman Uhlin, RN, PhD

Susanne Börjesson, RN, Associate Professor

Madeleine Abrandt Dahlgren, Professor in medical education

AnnaKarin Johansson, RN, PhD

Deborah Becker, PhD ACNP practice ass Professor of Nursing, School of Nursing, University of Pennsylvania, Philadelphia, USA

Camilla Fröjd, RN, PhD

Åsa Muntlin-Athlin, RN, PhD, Dept. of Medical Sciences, Uppsala University; School of Nursing, University of Adelaide, Australia

Patient-Health professional interactions - studies on patient interactions and participation in a hospital setting

Aims to describe patients' and relatives' complaints to the local Patients' Advisory Committee about encounters and communication in health care, and to identify and describe different ways surgical nurses understand their roles and interactions with patients and their families in a surgical care setting.

Patients and relatives reported a range of concerns and impacts including increased anxiety and reduced confidence in health care after negative patient-health professional interactions. Health professionals need to understand the patient's perspective and the consequences of a negative interaction for the individual patient or relative.

In the phenomenographic analysis four qualitatively different ways of understanding the nurse-patient relationship were identified among surgical nurses. The understandings represent a hierarchy of increasing complexity and comprehensiveness. In the most restricted understanding, nurses focus on the work task, whereas in the others nurses demonstrate increasing degrees of patient-centeredness. To realize patient-centered care in surgical care, nurses should incorporate all four understandings of their interactions with the patient and their role in the nurse-patient relationship, including the most comprehensive one, where the patient is seen as a person, with weaknesses and strengths, individual needs and personal resources.

Members of the group during 2014

Eva Jangland, RN, PhD

Lena Gunningberg, RN, Associate Professor

Maria Carlsson, RN, Associate Professor

Ewa Lundgren, MD, Associate Professor

Jan Larsson MD, PhD

Adequate nutritional treatment and cranberry capsules to prevent hospital acquired postoperative complications in hip fracture patients

Investigates:

- Whether there were any differences between patients receiving nutritional intervention preoperatively and for five days postoperatively and patients who did not, in terms of postoperative complications, rehabilitation, length of stay and food and liquid intake.
- Whether the biochemical markers S-IGF-1, S-Transthyretin and S-Albumin are affected by patients' energy intake.
- If cranberry capsules given preoperatively and postoperatively will decrease the incidence of bacteria's in the urine in female hip fracture patients receiving urine catheter. A Randomized Control Study.

Members of the group during 2014

Anna-Karin Gunnarsson, RN, PhD student

Lena Gunningberg, RN, Associate Professor

Kenneth B Jonsson, MD, Associate Professor

Sune Larsson, MD, Professor

Torbjörn Åkerfeldt, MD, PhD student

Dissertations 2014

Anna-Karin Gunnarsson. Patients with Hip Fracture: Various aspects of patient safety

Operating room care

Work environmental considerations in the operating room during major surgery – Aspects on CRS and HIPEC.

Aims to analyze the amount of airborne and UFP generated during peritonectomy and to compare it with standard colorectal (CRC) surgery, and to determine the prevalence of platinum and risk of exposure for the two main people handling and administering the cytotoxic agent during HIPEC.

Members of the group during 2014

Sara Näslund Andréasson, RN (OR) MSN, PhD student

Haile Mahteme, MD, ass Professor Supervisor

Helena Anundi, 1st Occupational Hygienist PhD Supervisor

Christine Leo Swenne, RN (OR) PhD Supervisor

Lars Pählman, MD, Professor Supervisor

Anesthesia Care

Aspects of the surgical team's and patients' perception of efficiency, and the recovery process after major abdominal surgery

Aims to:

- Explore variations in how staff and leadership working in a non- team organization within an operating department understand and experience operating room efficiency.
- Explore how organized surgical team members (Peritoneal Carcinomatosis team) and their leaders understand operating room efficiency.

Members of the research group

Erebouni Arakelian, RN, MSc, PhD student

Haile Mahtheme, MD, Associate Professor

Lena Gunningberg, RN, Associate Professor

Jan Larsson, MD, PhD

Karin Norlén, MD, PhD

Endocrine surgery

Genetics of midgut carcinoids

Wants to clarify the gene expression pattern in midgut carcinoid tumors, with emphasis on genes involved in progression and aggressiveness.

Search for new diagnostic and prognostic markers.

Members of the group during 2014

Katarina Edfeldt, RN, MSc PhD student

Per Hellman, MD, Professor Supervisor

Peter Ståhlberg, MD, Associate Professor Supervisor

Gunnar Westin, Professor Supervisor

Publications 2012-2014

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7 Oral & Maxillofacial Surgery

Oral and Maxillofacial Surgery at Uppsala University Hospital connects odontology with medicine and within our field we perform research in several areas and collaborations.

Oral cancer – tobacco, virus, alcohol and malignant cell transformation

Principle investigators Lars Sand and Jan Hirsch

The overall aim is to study clinical, immunological, genetic and viral parameters of importance for malignant cell transformation in a global network covering the spectrum from low to high socioeconomic standards.

We will elucidate the presence of Human papilloma virus (HPV) plus quantitative gene expression of viral DNA, differential expression of apoptosis, cell cycle regulation and intermediate genes, in patients with benign and malignant oral lesions in retrospective and prospective studies locally and in a national network. Utilizing human gDNA (genomic deoxyribonucleic acid) extracted from blood- and tissue samples which are phenotyped as normal respectively malignant, a high-resolution array-based comparative genomic hybridization (HR-aCGH) approach will be conducted. The aim is to generate genetic profiles, which may distinguish different phenotypes from each other in order to develop informative diagnostic and prognostic tools.

Surgery in the Cranio-maxillofacial complex

Principle investigators Andreas Thor, Jan Hirsch and Lars Sand

A longstanding goal in cranio-maxillofacial (CMF) surgery is to develop new approaches to surgery planning and evaluation which will reduce morbidity and increase precision, leading to better function and aesthetics and ultimately to better quality of life for patients with serious congenital and acquired conditions. With a computer system that allows the surgeon to plan the surgical procedure, test alternative surgical solutions, move bone segments, and design patient-specific implants and plates, the improved patient outcome can be achieved while at the same time the costs of surgery and follow-up care can be reduced considerably. Our goal is to produce a system where the surgeon can plan a complex procedure in less than one hour, leading to a drastically reduction of time in the operating room for complex cases. In-house production of the system-designed, patient-specific devices will lead to considerable additional cost savings, and allow surgery on trauma patients within hours, rather than days that out-sourced planning and production require today. The ultimate goal is of course custom-made solutions/implants with optimal load-bearing properties that contain bone or bone substitutes and have surfaces that can work as delivery systems to promote bone regeneration and that will yield surgical results superior to what is currently achievable.

Image-Guided Planning of Cranio-Maxillofacial Surgery using Haptics and 3D Visualization, computer assisted surgery, bone regeneration and patient specific implants

Principle investigators Andreas Thor and Jan Hirsch

With development of a haptic system that allows for virtual planning and training of difficult surgery of skeletal congenital or acquired defects, it further includes virtual design and fitting of patient specific biomaterials. The algorithms for the biomaterial can be transferred for Free Form Fabrication using Electron Beam Melting techniques. The implants will be manufactured with properties fulfilling the biomechanical requirements of a specific anatomical site and with surface properties to stimulate healing, and ultimately incorporation even during non-privileged conditions. The new technologies will be

evaluated using molecular methods and PET/CT technology for in vivo study of the biology of bone formation and integration. Imaging for planning and for evaluating healing are important areas of our research. In addition we will make use of in vitro immunological data from early interaction between blood and blood derivatives with a variety of implant surface candidates. Osseointegrated implants, intra- as well as extra-oral, require a sufficient bone volume and the need for “every-day” reconstructive therapies for lost bone is immense. We are involved in long-term follow-up studies on implant and bone regenerative therapies. Furthermore we are involved in establishing a hands-on digital workflow for planning of maxillofacial surgery where computerized tomography of the face is combined by scanning technologies of the teeth and jaws. Alloplastic reconstruction of the temporo-mandibular joint is another area where we focus and are investigating the Swedish experience in a retrospective as well as prospective fashion.

Functional outcome, quality of life

Principle investigator Jan Hirsch and Andreas Thor

The aim is to conduct in-depth analyses of skull and facial fractures and their ramifications and to create a structure for research and quality assurance. The project uses computerized fracture classification systems that define fractures in great detail to facilitate documentation and web-based communication. We apply a newly developed semi-automatic system for segmenting bone structures, in particular the orbit, evaluating the precision of outcome after surgery. The system will be integrated in our haptic planning console for CMF surgery.

Experiences made from treating total edentulous patients with fixed restorations and evaluating the oral health impact the therapies have on quality of life is also studied in our group.

Members of the group during 2014

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Gunnar Antoni, Jens Sörensen; Pet-centre Uppsala University

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Uppsala University Hospital (ALF)

Folktandvården, Uppsala

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Publications 2012-2014

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8 Orthopedics

Medical epidemiology

Principal investigator: Karl Michaëlsson

The epidemiology research group is based at the Uppsala Clinical Research Center (UCR, www.ucr.uu.se). This facilitates fruitful interaction with the biostatisticians and data managers at UCR. We also collaborate with external epidemiological, nutritional, genetic, cardiovascular, injury, osteoporosis and bone density expertise. Our main research topics are osteoporotic fractures but we are involved in other areas of epidemiological research such as injuries, outcome in intensive care, cardiovascular diseases, nutrition and the impact of physical activity on disease and mortality. We also administrate a multidisciplinary network of epidemiologists at Uppsala University (www.ucr.uu.se/epinet). A one-week long course in medical epidemiology is each year held by us, normally during week 43.

We use different internationally unique cohort designs with the main overall aim to study the etiology and prevention of osteoporotic fractures:

1. The Uppsala Longitudinal Study of Adult Men (ULSAM)
2. Screening Across the Lifespan Twin study (SALT)
3. The Swedish Mammography Cohort (SMC)
4. The Swedish Mammography Cohort Clinical (SMCC)
5. Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)
6. The Cohort of Swedish Men (COSM)
7. Lifegene
8. EpiHealth
9. Uppsala Family Study
10. Uppsala Birth Cohort Multi-generational Study (UBCoSmultigen)
11. Mapping of the hip fracture event circumstances

Brief descriptions of the cohorts can be found at: <http://www.surgsci.uu.se/Forskning/>

Members of the group during 2014

Head Karl Michaëlsson, Professor

Liisa Byberg, PhD, Associate Professor

Carina Fredriksson, Research Nurse

Breiffni Leavy, Research Physiotherapist

PhD students during 2014

Breiffni Leavy (Principal Adviser Liisa Byberg)

Björn Knutsson (Principal Adviser Karl Michaëlsson)

Mohammad Kharazmi (Principal Adviser Karl Michaëlsson)

Agencies that support the work/Funding

Swedish Research Council, 2012-2015, VR 2011-2427, Påverkan av genetik och livsstil för osteoporos och osteoporosfrakturer 4,900 SEK

ALF, during 2014, 1,700 SEK

The Swedish Council for Health, Working Life and Welfare FORTE/FAS, 3,000 + 2,800 SEK, 2012-2017 (two different projects)

Biomaterials

Principal investigator: Sune Larsson

Our main interest is to develop new cell free bone substitutes for clinical use whenever there is need for building new bone due to bone loss caused by injury or disease. A substantial part of our work is done in collaboration with the departments of polymer chemistry and material science at the Ångström laboratory, Uppsala University. Over the past years a lot of effort has been put into the development, refinement and evaluation of various hydrogel compounds intended for use as a new carrier for bone morphogenetic protein (BMP). With this new carrier the release of the BMP molecule seems much more efficient than with previously used carriers based on bovine collagen, which means that the BMP dosage can be lowered dramatically while still gets the same amount of bone being formed. During the last years we have done studies using PET technique. By using different tracers where one binds to the BMP molecule and the other to osteoblasts it is possible to follow not only the release of BMP but also the bone formation. By the use of PET technique we can over time correlate the release profile of BMP with bone formation, with the aim to define the most efficient release profile for BMP from a bone forming perspective. The first manuscript where this novel technique has been used has recently been submitted for publication.

A second research line is to optimize calcium phosphate compounds with respect to injectability, mechanical properties, carrier ability and resorption characteristics when used as bone substitutes for filling of bone defects. This work has been ongoing for several years using both in vivo and in vitro models. Over the last years the first preclinical studies have been completed and evaluation of a number of different implants has been done. By the use of our micro-CT equipment formation of bone tissue and the in vivo behavior of implants can now be assessed not only ex vivo but also in living animals. The equipment allows not only more precise assessment of the bone tissue but also a substantial reduction in the number of animals needed to address a number of the questions that have to be answered.

Members of the group during 2014

Sune Larsson, Professor

Richard Marsell, MD, PhD

PhD students

Anders Westermark

Gry Hulsart Billström

Agencies that support the work/Funding 2014

4,800,000 SEK from EU for the project Bidesign (funding for five years)

500,000 SEK ALF funding from Uppsala University Hospital

400,000 SEK from the Thureus fund

Spinal Surgery

Principal investigator: Claes Olerud

The Spinal Surgery Research Group consists of members involved in the clinical management of patients with spine pathology which facilitates clinical research and registry based research with clinical implications. There are several different research lines where cervical spine research may be the most prominent with three ongoing PhD projects, and lumbar spinal stenosis with two PhD projects.

The cervical spine projects comprise studies on artificial disks, dysphagia in relation to anterior cervical spine surgery, non-invasive CT-based motion analysis, complications in relation to bone graft harvesting, artificial disk fixation, degeneration of the segment adjacent to a fusion, and validation of various pain measurement instruments for cervical spine research. Another project deals with Odontoid fractures in the elderly with a clinical multi-center RCT and registry studies on epidemiology and survival as main components, but also consisting of studies on health economics and the significance of osteoporosis.

The project on lumbar spinal stenosis evaluates results of different surgical methods in a multi-center RCT with the Spinal Surgery Research Group as the coordinating center. The effects of fusion in lumbar spinal stenosis are studied, and the influence of obesity and smoking on outcome after surgical treatment. The follow-up includes generic and condition-specific outcome measures as well as radiological studies. Also this project analyses registry data in epidemiological and outcome studies. This is in cooperation with the Epidemiology Group.

Another research lines is on traumatology of the cranio-cervical junction, CCJ. Suspected acute ligament injuries of the cranio-cervical junction are evaluated with a specific MRI technique and compared to CT – data. In another arm of this project chronic WAD-patients are investigated with both the specific MRI technique and dynamic MRI to evaluate cranio-cervical ligament insufficiency. Patients with detected injuries are treated with fusion surgery in a prospective study. Some anatomical work on the soft tissues in the CCJ is also performed.

Fractures in Anchylosing Spondylitis are studied in clinical and registry studies and the mechanical behavior of spinal fixation in the ankylosed spine is evaluated with finite element analysis in collaboration with KTH, Stockholm.

The Spine Surgery Unit at Uppsala University Hospital was 2012 as the first unit in Sweden appointed as an AOSpine Center of Excellence. Apart from being prestigious this allows the unit to accept clinical and research fellows with financial support from AOSpine.

Members of the group during 2014

Claes Olerud, Professor

Anders Bjurholm, Associate Professor

Håkan Jonsson, Associate Professor

Yohan Robinson, Associate Professor

Bengt Sandén, Associate Professor

Martin Skeppholm, MD, Stockholm Spine Center

PhD students

Peter Försth, MD, Stockholm Spine Center

Thomas Karlsson, MD

Björn Knutsson, MD, Sundsvall

Anna MacDowall, MD

Anna-Lena Robinson, MD

Caroline Sköld, MD, resident, PhD student

Christian Carrwik, MD, resident, PhD student

Jan Triebel, MD, MBA, resident, PhD student

SpineLab

Principal investigator: Nils Hailer

Spinal cord injury is an incurable condition with devastating impact on the life of mostly young adults. The pathophysiology of spinal cord injury is characterized by two phases: In the acute phase, endogenous CNS macrophages (i.e., microglial cells) contribute to secondary neuronal damage: They release neurotoxic factors, aggravate excitotoxic damage, and induce neuronal apoptosis. In the chronic phase, microglial cells and astrocytes take part in the formation of glial scar tissue and prevent axonal regeneration.

We believe 1) that the pivotal role of inflammation after spinal cord injury has not been adequately addressed by current experimental strategies, 2) local application of neuroprotective substances allows for controlled and sustained release of high concentrations of endogenous neuroprotective substances that cannot be reached by systemic application. We thus investigate the possibility of encapsulating the neuroprotective substances in different carriers.

Several immunomodulatory substances have been investigated for their capacity to inhibit microglial activation and to enhance neuronal survival following spinal cord injury, and some substances exert distinct glia-inhibitory and neuroprotective effects. We have previously shown that immunomodulatory substances potently suppress microglial activation and proliferation, and they have the capacity to promote both neuronal survival and preservation of a myelinated axon projection.

Different carrier compounds such as hyaluronic acid hydrogels and collagen matrices are developed together with chemists at the Ångström lab in order to be able to encapsulate and release immunomodulatory substances. We recently found enhanced survival of motoneurons in spinal cord cultures sustained on hyaluronic acid hydrogels.

The experiments are undertaken in close collaboration with the groups of Jöns Hilborn, the Ångström lab, and Elena Kozlova, Department of Neuroscience, Uppsala University.

Key findings:

1. Spinal cord slice cultures (SCSCs) cultured on a collagen-based biomaterial or on PET inserts degenerated dramatically after a four-day *in vitro* incubation compared to SCSCs maintained on a HA-based hydrogel. The use of HA-based hydrogel was associated with unique motoneuron survival and suppressed micro- and astroglial activation. HA-based hydrogel had a considerably higher elastic modulus compared to collagen-based hydrogel whereas the presence of soluble HA in culture media had no protective effects on SCSCs.
2. After eight days of *in vitro* incubation a combination of interleukin-1 receptor antagonist (IL1RA) and trophic support with neurotrophin (NT)-3 preserved neurons in the ventral horns and prevented degenerative loss of neurons. Release of IL-1 β was detected from SCSCs and the kinetics of IL-1 β release was similar to those described after *in vivo* SCI. Thus, antagonization of IL-1 by IL-1RA seems a reasonable mechanistic explanation for the observed phenomenon.
3. Excitotoxic injury to SCSCs with NMDA vastly decreased the number of neurons within the ventral horns but not in the dorsal horns. NMDA-induced injury was associated with an increased number of apoptotic cells, an increased number of activated microglial cells and astrocytic activation. Treatment with IL1RA counteracted the neuronal loss observed in the ventral horns, suppressed the increase in the number of apoptotic cells and activated microglial cells and reduced astroglial activation. Renshaw cells, a subpopulation of ventral horn interneurons, degenerated

even in SCSCs not subjected to excitotoxicity, and this subpopulation of neurons did not respond to IL1RA treatment.

4. Transplantation of NCSCs onto excitotoxically injured SCSCs counteracted the neuronal loss observed in the ventral horns, reduced the proportion of apoptotic cells among neurons and suppressed the number of activated microglial cells and astrocytes. NCSCs migrated across the surface of the cultures but not into them, suggesting that NCSCs exert neuroprotective actions through the release of soluble mediators.

Members of the group during 2014

Nils Hailer, Associate Professor

Nikos Schizas, PhD student

Britt-Marie Andersson, Laboratory Assistant

Esther Söderlund, Bachelor of Sciences, Project student

Bioimplantat

Principal investigator: Hans Mallmin/Jan Milbrink

The Bioimplant research group evaluates new knee and hip implants through prospective and longitudinal studies, often in form of randomized, controlled trials, RCT. We have focused on the stability of fixation of uncemented implants with roentgen stereogrammetry, RSA, effects on bone mineral density, BMD, adjacent to the femoral implant with dual energy X-ray absorptiometry, positron emission tomography (PET), clinical score systems, and gait analysis. Two regimes for weight-bearing have been evaluated in a RCT with outcome variables stability and BMD. The stability evaluated with RSA for an uncemented versus cemented natural knee II-prosthesis has been subject for a RCT-study with two year follow-up. Bone metabolic response to biological implants, especially endoprostheses of the hip, has been investigated using PET. An uncemented short-stemmed hip prosthesis, CFP®, leading to a very restricted collum osteotomy, is subject for a prospective and longitudinal study of stability and bone mineral density with an extension to five years of follow-up. A validation of computed tomography in comparison to RSA for implant stability is performed in cooperation with the researchers at Karolinska Sjukhuset, Solna

A single center an academic non commercially sponsored Randomised Clinical Trial, phase 2, "Uncemented total hip implant and subcutaneous injections of Denosumab for patients with osteoarthritis of the hip. A randomized double blind placebo controlled study on the effects on bone evaluated with DXA, PET/CT, and biochemical markers" has been approved by the Medical Product Agency and the Regional Ethical Committee. The effect on bone metabolism and density of two subcutaneous injections of a human monoclonal antibody, Denosumab, with an osteoprotegrin-like action will be studied and followed for two years. The inclusion of the 64 study persons were completed in January 2015.

Members of the group during 2014

Hans Mallmin, Professor

Jan Milbrink, Associate Professor, MD

Nils Hailer, Associate Professor, MD

Olof Nilsson, Professor, MD

Per Mattsson, Associate Professor, MD

Stergios Lazarinis, MD

Asgeir Gudnason, PhD student

Andreas Nyström, MD, PhD student

Demostenis Kirirtopoulos, PhD student

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Skofonden 400,000 SEK

Endoklinikens forskningsstiftelse, Hamburg 400,000 SEK

Regionala Forskningsfonden 200,000 SEK

Pelvic fracture research

Principal investigator: Sune Larsson

Surgical treatment of pelvic fractures has for many years been a niche area for the department of orthopedics at Uppsala University Hospital with more than 30 hospitals referring their patients to our unit. Since January 2003 all pelvic fracture patients are followed according to a strict protocol that includes questionnaires at specific time points after surgery as well as radiographic evaluations. Even with international standards we have now reached a substantial number of patients that are followed prospectively, given the type of injury and the thorough follow-up. Two new instruments intended to be used as a self-assessment tool for patients following acetabular or pelvic injuries have been constructed and are at present in the validation phase. One problem when assessing quality of life (QoL) in patients following a trauma is the lack of information about the pretraumatic QoL in these patients. Such an assessment has to be done in a retrospective fashion where patients following a trauma try to describe their pretraumatic QoL. For a number of reasons this might be difficult e.g. the reference levels might change due to the trauma, not to mention the obvious difficulties when assessing a life situation in the past. In a specific project we have been working with comparison when patients make their pretraumatic assessment of QoL at different time points after the injury in order to find out if there are differences and if it is possible to define a recommendation on when such assessments should be done. In an additional project we will use qualitative methods to find out what differences in QoL that can be translated into differences that are of clinical relevance, i.e. of relevance for the patients.

Members of the group during 2014

Sune Larsson, Professor

Tomas Borg, MD, PhD

Björn Hernefalk, PhD student

Dissertations 2014

Yasmin Hailer. Legg-Calvé-Perthes Disease – Is it just the hip? Epidemiological, Clinical and Psychosocial Studies with special focus on Etiology

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9 Oto-, rhino- laryngology and Head & Neck Surgery

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Experimental inner ear research. Pharmacokinetics, toxicity and otoprotection

Mechanisms of damage in exogenous inner ear disorders (ototoxic drugs, acoustic overstimulation) have been analyzed with special emphasis on pharmacokinetics, metabolomics, reactive oxygen species and otoprotection.

Cisplatin and oxaliplatin are two anticancer platinum-containing drugs that differ in ototoxicity during clinical use. Cisplatin induces hearing loss at high doses while oxaliplatin therapy is not ototoxic. Recent findings suggest that redox-related effects involving cellular proteins constitute a major mechanism of action for cisplatin toxicity not being related to DNA damage. Bypass of the blood-labyrinth barrier by using cultured organs of Corti, shows comparable levels of outer hair loss induced by either cisplatin or oxaliplatin, as well as inhibition of thioredoxin reductase, demonstrating that the two drugs are similarly ototoxic if cochlea is directly exposed. However, these results could not be confirmed *in vivo*.

Little is known about drug transport to and within the inner ear, but it is clear that the accessibility from blood is limited by the blood-perilymph barrier and the intrastrial fluid-blood barrier. Recent studies indicate that organic cation transporters may play an important part in the influx of cisplatin to cochlear target cells. We have identified the transport protein OCT2 in the supporting cells of the organ of Corti and in the type I spiral ganglion cells. These findings suggest that OCT2 is not primarily involved in cisplatin uptake from the systemic circulation. Experimental magnetic resonance imaging is an excellent research tool to study inner ear pharmacokinetics *in vivo*. We have in an experimental model characterized the kinetics of four different paramagnetic contrast agents in the inner ear compartments after intravenous injection. There is an extremely low transport of all four agents to the middle compartment of the cochlea (scala media). However, by reducing the endocochlear potential the permeability increases and the uptake to scala media is similar to that of the other fluid-filled compartments.

Reactive oxygen species play an important role for development of noise-induced hearing loss. Hydrogen gas has antioxidant effects and is easily administered for possible otoprotection. Inspired by the idea that hydrogen might affect noise-induced hearing loss impulse noise was given simultaneously with inhalation of hydrogen gas. Unfortunately no protective effect could be observed.

There is robust evidence that cisplatin-induced hearing loss can be prevented in experimental models, while the results in humans have so far been poor. One likely reason to the futile results in humans is that a systematically administered otoprotective drug does not reach the target cells localized in the deep compartment of the inner ear in sufficient amounts unless a very high dose is used. Local treatment of the inner ear by intratympanic injection of a semi-solid gel has earlier been demonstrated by our group. It is shown that the uptake of thiosulfate to the inner ear can be improved by direct administration to the ear instead of given intravenously. Moreover, systemic administration of a nucleophile might be risky since these species are prone to react with cisplatin and thereby reduce the antineoplastic effects. We have using an experimental model investigated the blood metabolome after cisplatin treatment with or without systemic otoprotection using thiosulfate. It was found that there is a correlation between increase in reduced glutathione in serum and electrophysiological hearing thresholds.

An important factor for local administration of drugs to the middle ear aimed for inner ear treatment is the adherence of the vehicle to the round window membrane. Experimental high resolution magnetic imaging is employed in different animal models for studying distribution and eliminations of vehicles in the middle ear and contrast agents in the inner ear. During 2015 we will test a most interesting and promising vehicle with unique mucoadhesive properties.

Pharmacokinetics and pharmacodynamics of drugs cannot be studied in human beings. Studies are performed in experimental models to further define drug transport inside the cochlea. We have demonstrated an early high concentration of cisplatin in the base of the cochlea and a delayed elimination

of cisplatin from scala tympani perilymph compared to blood. These two findings might correlate to cisplatin-induced loss of outer hair cells in the base of the cochlea.

Prevention of ototoxicity by administration of an exogenous antioxidant in conjunction with cisplatin treatment has been successful in experimental studies. One of our goals is to prevent cisplatin ototoxicity in cancer patients by local administration of an otoprotectant. We are going to evaluate a novel pharmacological method in a randomized placebo-controlled multicentre clinical trial where a thiosulfate-containing gel is injected into the middle ear of patients undergoing cisplatin-based chemotherapy.

Proteomics of the human perilymph

Proteomic studies of the human perilymph are scarce. The goal of this project is to improve the understanding of the causes of inner ear disorders. An approach is to investigate the protein composition of the perilymph and the rough concentrations of these proteins using modern mass spectrometry-based techniques. Perilymph samples are aspirated during translabyrinthine and cochlear implant surgery for proteomic analysis at Professor Jonas Bergquist's laboratory, Department of Chemistry, Uppsala University.

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Head and neck cancer

Head and neck tumor targeting

Cancer cells differ from normal cells, for example by different protein expressions on the cell surface. In targeted radionuclide therapy, we take advantage of these differences, by using e.g. antibodies, antibody derivatives, or peptides to target these structures, and by arming these “missiles” with radionuclides. By delivering the radioactivity directly to the tumor cells, small metastases and disseminated tumor cells can be found and killed. By using radionuclides as warheads, multidrug resistance can be avoided, and the need to target every single tumor cell is reduced. There is great potential for targeted radionuclide therapy in the treatment of head and neck cancer. In this disease there is a vast need for a systemic treatment that is effective in locating or treating metastases at distant sites and minimal residual disease at the local and regional levels. Furthermore, head and neck cancer is intrinsically radiosensitive, and is therefore especially suitable for radiotherapy.

In the Head and Neck Tumor Targeting Group, we are studying several steps in the targeting process. Different protein structures, targeting molecules and radionuclides are assessed, and the different properties of the constructed radioconjugates are evaluated. By creating and evaluating novel tumor seeking radioconjugates, we hope to provide more sensitive and specific methods for identifying and treating head and neck cancer, and hopefully help improve long-term survival rates for this patient group in the future.

Nutrition and head and neck cancer

There is a great need to increase knowledge of nutrition in tumor disease. Long-term malnutrition is one major sequel after treatment of head and neck cancer, possibly related to muscle loss, cachexia and psychological and emotional distress. Greater weight loss during radiotherapy (RT) has been associated with postsurgical infections and wound healing problems. Weight loss has also been found to be related to increased mortality in H&N cancer patients, but the issue is controversial and debated. Two different cohorts have been studied. Patients continue to lose weight long-term after termination of therapy with a nadir at about six months. It seems that the nutritional status before treatment is of greatest importance. We have in a secondary study in patients with oropharyngeal cancer found that a high body mass index (BMI) gives significantly better 5-year survival than a low BMI.

More knowledge is needed to increase the understanding of persistent swallowing dysfunction long-term after treatment. A finding is that swallowing dysfunction is an important factor for nutritional status in head and neck cancer survivors. We found that almost 50% of surviving patients had silent aspiration.

We are going to start a Swedish multicentre study in collaboration between the university hospitals in Uppsala, Örebro and Umeå, which creates a well-defined cohort of patients with head and neck cancer. With this study we expect to highlight correlations between inflammatory response induced by treatment, changes in body weight composition and survival.

Effects of radiotherapy

Despite improvements in treatment of head and neck cancer during the last decades, survival rates have not significantly increased. About 70% of the patients undergo radiotherapy. There is therefore a need to better understand how the tumor and adjacent tissue react to radiotherapy. Expression of different biomarkers is studied in a consecutive cohort of patients with tongue cancer. To gain insight in the mechanisms behind oral mucositis we developed an animal model where the mucosa spontaneously heals with two weeks.

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Persistent adenovirus infections in oropharynx

The most common problems affecting the tonsils are recurrent infections, chronic tonsillitis and hyperplasia. About 13,000 tonsillectomies are performed yearly in Sweden. This project aims to delineate the contribution of adenovirus in chronic tonsillitis and hyperplasia, and to develop novel therapeutic applications to reduce reactivation of adenovirus infections. The work is carried out in collaboration between the ENT clinic (Göran Laurell, Karl Sandström, Adnan Lidian) and Department of Medical Biochemistry and Microbiology, Uppsala university (Göran Akusjärvi, Tanel Punga, Catharina Svensson, Farzaneh Assadian).

Studies on peripheral facial palsy

Each year 3,000 subjects in Sweden are struck by a peripheral facial palsy. Of these palsies, 75% are of unknown origin, so-called Bell's palsy. During 2001 to 2007, the Uppsala ENT-clinic monitored the world's largest controlled Bell's palsy study (the Scandinavian Bell's palsy study) which was performed in Sweden and Finland. A beneficial effect on time to recovery and a better outcome was present in patients treated with prednisolone whereas no convincing effect was found with anti-viral valaciclovir. The study was published in *Lancet Neurology* in 2008. Subsequent analyses documented the influence of time to treatment start with prednisolone, a relation between early deterioration and outcome and also a risk curve for the recovery in Bell's palsy.

Synkinesis in Bell's palsy

Facial synkinesis is troublesome sequel after facial palsy and causes facial asymmetry, functional limitations and pain which can adversely affect quality of life. The development of synkinesis in Bell's palsy is still not clear and to what degree the different facial muscles are affected. Mapping of clinical and subclinical co-contractions in synkinesis patients may further cast light of the underlying pathology and help to increase the efficiency of the treatment with botulinum toxin. In this study, the development of synkinesis in a cohort of 150 Bell's palsy patients is analyzed according to the prevalence by gender, age and location in the face. Performed in collaboration with Andres Rodriguez, MD, PhD and David Jenson, MD, Dept. of Plastic Surgery.

Quality-of-life in Bell's palsy

The measurement methods for the severity of Bell's palsy are today physician-ranked scales. The House-Brackmann and the Sunnybrook grading scales describe the severity of facial palsy but do not address the perception of the patient's outcome, neither or the impact of quality-of-life. We recently validated two patient-reported questionnaires in Swedish regarding quality-of-life outcomes in peripheral facial palsy patients. These two instruments, the Facial Disability Index (FDI) and the Facial Clinimetric Evaluation scale (FaCE), have been used in facial palsy studies but never evaluated in consecutive follow-up studies. The two quality-of-life measures are compared with the physician's facial rankings in an estimate of 100 consecutive patients with Bell's palsy. In collaboration with Elin Marsk, MD, PhD and Professor Malou Hultcrantz, Dept. of Otolaryngology, Karolinska University Hospital.

Long-term follow-up of Bell's palsy

There are no studies on the long-term effect of corticosteroids and/or anti-viral treatment with valaciclovir in Bell's palsy. In our previous (the world's largest) controlled Bell's study, altogether 1,953 patients were examined of which 829 were included. Patients who were included and excluded in this study and examined at the University clinics in Helsinki, Stockholm, Uppsala and Lund during 2001 to 2007 will be re-examined 10 to 15 years after the onset of palsy. Difference in long-term outcome related to gender and effect of treatment will be examined. Pregnant women and patients with diabetes mellitus are reported to have a higher risk for Bell's palsy, and also a poorer outcome compared with other Bell's palsy patients. The long-term results for these patient groups have not previously been studied. It will also be examined if Bell's palsy patients have a higher incidence of other diseases, including hypertension and/or other neurologic disease. In collaboration with Elin Marsk, MD, PhD and Professor Malou Hultcrantz, Dept. of Otolaryngology, Karolinska University Hospital; Mervi Kanerva, MD, PhD, Dept. of Otolaryngology, Helsinki University Central Hospital; Anna Stjernquist-Desatnik, MD, PhD and Sara Axelsson, MD, PhD, Dept. of Otolaryngology, Skåne University Hospital, Lund.

PET-MR in Bell's palsy – etiologic perspective

The etiology of Bell's palsy remains unknown. The most prevailing theory is that the nerve injury is caused by a viral inflammatory edema. In a previous pilot positron emission tomography (PET) study in 1994 we found one Bell's palsy patient with possible radionuclide uptake in the brain stem. PET in combination with high-Tesla MR (PET-MR) allows the visualization of regions with edema and increased metabolism. In this study 8-10 patients with a severe Bell's palsy will be examined with PET-MR within 7 days of onset of palsy in order to give further etiologic information on the pathogenesis of the disease. In collaboration with Professor Håkan Ahlström and Anna Grabowska, MD, Dept. of Radiology.

Facial reanimation and brain plasticity – a neurophysiological and functional-MR study

One of the benefits of nerve transfers is to provide a source of axons very close to the target muscle and also provide direct nerve anastomosis. There are no studies analyzing the most common donor nerves used in nerve transfers (V, XII, XI) to determine which of these transfers that has the best potential for cortical plasticity. This knowledge may establish postoperative strategies for physiotherapy to improve cortical plasticity and smile relearning. Healthy volunteers undergo electrophysiological tests and functional magnetic resonance (fMR). Determination of functional co-activity between the facial nerve and the XII, XI, and V nerve muscles are determined by electromyograms. fMR will determine the cortical areas for smiling (VII), biting (V), tongue movement (XII) and elevation of shoulders (XI) to elucidate cross activation of cortical areas during different activities (smile-moving tongue, smile-biting) to analyze ways to improve postoperative training and brain plasticity. In collaboration with Andres Rodriguez, MD, PhD, David Jansson, MD, Dept. of Plastic Surgery, Johan Wikström, MD, PhD, Dept. of Radiology and Professor Roland Flink, Dept. of Neurophysiology.

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Uppsala University Hospital (ALF)

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Acta Otolaryngologica Foundation

Upper Respiratory Airways

Respiratory symptoms during exercise are common and might limit adolescents' ability to take part in physical activity. To estimate the prevalence and consequences of exercise-induced dyspnea (EID) of adolescents, a questionnaire was sent to all 12–13 year old adolescents in Uppsala (n=3838). Fourteen percent (n=330) reported EID, i.e. had had an attack of shortness of breath following activity in the last 12 months. Sixty-one percent (n=202) of the participants with EID did not have a diagnosis of asthma. This study was published in Respiratory Medicine.

To investigate the prevalence of exercise-induced laryngeal obstruction (EILO) and exercise-induced bronchoconstriction (EIB) we tested a selected group of these children, both EIA-tests and videolaryngoscopy during exercise (CLE-test) to study the number of both EIB and EILO in this cohort. The estimated prevalence of EILO was 5.7% and of EIB 19.2%. No gender differences were found. EILO is equally common among girls and boys and can coexist with EIB. The study was published in Thorax.

In the clinic we have performed CLE-tests on more than 300 patients referred to us because of EID. Many of the patients are treated with asthma medication without effect and the CLE-test discloses a laryngeal obstruction in 40-50% of them. In a follow-up survey we asked 84 consecutively CLE-tested patients to participate and 72 % responded. Among the surgically treated patients the reduction of EID was significantly better than for the conservatively treated patients. This study will soon be submitted.

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Agencies that support the group/Funding

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Ear research – Clinical and Experimental investigations

Principal investigator: Helge Rask-Andersen

The research can be separated into several areas:

“Nanotechnology based implantable and interfaceable devices”. Call: FP7-NMP-2011-two-stage.

1. ”Human stem cell applications for the treatment of hearing loss”. Call: FP7-HEALTH-2013-INNOVATION-1.
2. “Otostem” EU project Stem cell-based inner ear therapy to cure deafness.
3. Studies of the human inner ear, round window anatomy related to EAS, Mb Meniere, cell biology of tympanic membrane and regeneration (collaboration with the University of Tuebingen, Oslo and Innsbruck).
4. Hearing Implants - audiological and surgical aspects. Hearing preservation surgery (EAS; electro-acoustic stimulation) middle ear implants (MEI) and auditory brain stem implants (ABI).
5. Quality control in otosurgery in Uppsala.

EU Project - OTOSTEM

The EU project OTOSTEM has been running since September 2013. The project aims to develop stem cell-based therapy for inner ear diseases. It includes several European research centers including the US centers at Harvard and Stanford Universities. It will last for four years. Dr. Hao Li has been employed and is the main research person leading this project with the principal investigator. Our main task is to isolate and expand adult human inner ear progenitors. Consortium has devised guidance protocols for mouse and human embryonic and reprogrammed stem cells toward inner ear cell types that make use of principles of early germ layer formation and otic induction. Purification techniques for human otic progenitors from ES/iPS cell sources and in addition from native human otic tissues from foetal and adult stages will serve the dual purpose to enable the development of novel bioassays for drug screens, as well as generating cells with decreased tumorigenicity for cell transplantation studies in *in vivo* animal models. It is a collaborative study, with groups having considerable experience in ES/iPS cell work, inner ear stem cell biology and in translational research. Through surgical materials we have isolated and extracted stem cell-like progenitors from the vestibular organ and successfully differentiated these cells into neurons. In addition, we have also purified epithelium cells in the inner ear and characterized them through immunohistochemistry using various molecular markers such as *Lgr5*, *Sox2* and *Nestin*. Hopefully stem cell based inner ear therapy will be available in the future. First however the role of stem cells in the human inner ear and regeneration must be established.

EU Project - NANOCI

The EU project named NanoCI or full title “Nanotechnology based implantable and interfaceable devices” is continuing. The aim of the project is to develop the first interfaceable cochlear implant capable of giving deaf patients higher resolution hearing by chemically stimulating the nerve cells of the spiral ganglion into sprouting new axons. These axons are then guided by neurotrophic factors and a neurotrophic gel to the functionalized surface of the cochlear implant to attach on the electrode surface. Our task is to evaluate candidate guidance molecules and new gels provided to us by the consortium. As a model we will use primary cultured human auditory neurons, as well as human neural progenitor cells capable of neural differentiation. Dr Fredrik Edin and Wei Liu are main responsible for this project. Fredrik Edin has developed a technique to expand and study human embryonic stem cells using time lapse video recordings. The study is published this year in *Acta Otolaryngologica*. They have also developed techniques to study nerve guidance in a chamber. Also they managed to expand human vestibular neurons in a gel. This study is under publication. Gels must be used to expand neurons in the cochlea. WE are working with several types of gels such as Puramatrix and Matrigel which are hydrogels and laminin-based gels. During 2013 we for the first time we developed a protocol to culture human vestibular nerve in a 3D matrix. These results were replicated in guinea pig spiral ganglion and human neural progenitor cells using the same protocol in the same matrix. We have continued with pilot experiments in 2D gradient chambers and also using 3D gradient chambers with explants and gels. Attempted sphere cultures from human vestibular tissue but are yet to prove stem cell activity. We have also investigated the trophic effects of inner ear derived supporting cells on neural progenitor cell development. Several papers have been published (see publication list).

Regeneration and localization of stem cells in the tympanic membrane

We are analyzing the regenerative capacity of the human cochlea. Progenitor/stem cells are further analyzed in the human auditory nerve. Human cochleae are dissected and nerve tissue isolated and cultured in expansion media with growth factors. Proliferation and cell division is induced and recorded using time-lapse video technique. The laboratory was the first to report the isolation of mitogen-responding neural progenitors from surgical specimens. Processing of this collected tissue has hitherto resulted in new information about human cochlear structure, *in situ* protein expression as well as novel discoveries regarding the presence of auditory nerve progenitor cells and self-renewal of cells in adults. Our local

infrastructure is built on a well-developed cooperation between surgeons and the research unit. An example of a primary auditory nerve culture done with neuroblast formation and cell division has been shown.

A project was initiated 2012 on cell, stromal activation and cell repair in the human tympanic membrane. The study is performed by Dr Nadine Schart-Moren at the ENT department in Uppsala in collaboration with Professor Magnus von Unge in Oslo. Effects of induced superficial trauma on cell activation of collected human tympanic membranes are analyzed immunohistochemically.

Human inner ear studies - Immunohistochemistry

There is evidence of a unique expression of connexin 30 (Cx30) protein in human auditory nerve analyzed with confocal microscopy. Together with Cx30, distribution of Cx26, Cx36 and Cx43 in normal human cochlea were studied further. Localization of K (kir) 4.1 and AQP4 were compared in rat and human cochlea (Eckhard et al. 2012). A book chapter about human cochlear anatomy and their relevance for cochlear implantation has been published in *Anatomical Record*. GDNF family ligand (GFLs) Neurturin and the receptors of GFLs, i.e., c-ret and GFRalpha 1 and 2 were also found in human spiral neurons for the first time. Pejvakin, a protein associated with signal transduction in auditory nerve, was found for the first time in human cochlear nerve. The results were published in *Cochlear Implant International* (Liu et al. 2013). We continue to collect human surgical specimens to analyze proliferation markers, such as Ki67 and PCNA (proliferating cell nuclear antigen); basilar membrane components, such as collagen, laminin, fibronectin; adult stem cell marker, such as Lgr 5; voltage-gated ion channels, such as KCNQ, Nav1.6 and 1.2, as well as calcium channels.

Effects of lathanoprost in Menieres disease and studies of inner ear water homeostasis

World patent of lathanoprost use in Meniere's disease has been reached. A multicenter phase IIB study is under way. A study of the aquaporins 4 and 5 in the human and mouse ear has been published in *Neuroscience*. The results suggest there is an existing water shunt within the endolymphatic compartment that could play a role for fluid homeostasis and thereby also be significant for the generation of endolymphatic hydrops.

Research and Clinical use of Middle Ear Implants

A study of the clinical use and effectiveness of middle ear implants (Vibrant Soundbridge) was performed. This is prepared together with several ENT Clinics in the Northern countries. 20 patients have been operated and the implant has been applied both on the middle ear ossicles and the round window. Experiences are excellent and first results using round window application is finished and was published 2013. Title of this paper is ("*Hearing Restoration using Active Middle Ear Implant with Round Window Application in Chronic Ear Surgery*"). "*Round window vibroplasty in chronic ear surgery – Comparison with conventional hearing rehabilitation*".

Ear surgery - Quality control - Cholesteatoma surgery in Uppsala

We have published results following on cholesteatoma surgery. A thesis was finished and presented June 12 2013 by Lennart Edfeldt on "*Middle Ear Cholesteatoma – surgical treatment, follow-up and hearing rehabilitation*". One paper in *Int J Pediatr Otorhinolaryngology*. "*Surgical treatment of paediatric cholesteatoma: long-term follow up in comparison with adults*" and another in *Acta Otolaryngologica*. "*Surgical Treatment of Adult Cholesteatoma. Long-time follow-up using total reconstruction procedure (TRP) without staging*". The studies are based on results obtained from our registry with unique long time follow-up. Third study involves the analyses of residual cholesteatoma using MRI and is "*Echo-Planar and*

Non-Echo-Planar Diffusion-Weighted magnetic resonance imaging in long-term follow-up after adult cholesteatoma surgery using one-step obliteration technique. The study was published in 2013.

ABI Brain stem implant

Further studies on the experiences and results of ABI surgery in Uppsala from 1993 to this date are made. It will be published in 2014. These studies are important for better understanding of the effectiveness of this procedure in children with congenital inner ear malformations and those with ossified cochlea following meningitis. One such child has been operated recently.

New inner ear disease can be surgically treated – Inner ear canal dehiscence

This is a rather new disease discovered by US researcher Loyd Minor. More and more patients are discovered with symptoms indicating a dehiscence on a semicircular canal. Dr Niklas Danckwardt-Lillieström has specialized himself on this disorder and has now a wide experience. His results will be published during 2014.

Cochlear implantation using hearing preservation EAS-technique

Results and experiences with hearing preservation CI surgery have been analyzed by Dr Elsa Erixon. She presented her thesis in June 5th 2014. Additional papers have been published or are under publication. A patient surveillance and quality of life study has been performed.

We have started a new EU project on stem cell derivation from the human inner ear.

Anatomy of the human round window

Human temporal bone studies have elucidated the anatomy of the human round window and the impact of cochleostomy on the inner structures of the cochlea. These studies have been performed by Dr Francesca Atturo from Rome Italy and have generated two publications. *Guest researcher from China studied the vascular bone channels of the human inner ear. Her study is already accepted for publication in the European journal of Otolaryngology 2014. The results are relevant for hearing preservation surgery and cochlear implantation.*

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Dissertations 2014

Elsa Erixon. Hearing Preservation CI Surgery and Hybrid Hearing: From Anatomical Aspects to Patient Satisfaction

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10 Burn Care and Plastic Surgery

There are two major developed research areas, the Uppsala Burn Research Program and the Epithelium-Connective Tissue Interface Programme. Those are dealt with below. In addition to those, expanding research projects have been initialized on patients with craniofacial malformations and also on microsurgical issues.

The programs are primarily patient-based and success is heavily related to an adequate number of patients and consequently the size of the scientifically active staff.

Uppsala University Hospital and Uppsala University has been appointed national centers for care of severely burned individuals and for certain advanced cases of craniofacial surgery. This has guaranteed a solid basis for research to thrive.

Network structure

In order to optimize collaborative work the national network SwedBurn has been initiated with an initiative from our research group (<http://www.swedburn.se>). The purpose is to stimulate burn related projects requiring intellectual and functional resources from different departments and universities.

The Uppsala Burn Research Program

Principal investigators: Fredrik Huss, Bengt Gerdin

A burn injury is a good model for understanding the response to a severe trauma, viewed from as well as short as a long perspective. The disastrous experience of being afflicted with an extensive burn injury affects all main integrating systems in the body (i.e. nervous, endocrine and immune). The acute phase is characterized by a relatively intense and rapidly developing physiologic inflammatory response, not only in the immediate vicinity of injured tissue, but also a generalized syndrome of systemic inflammation, which in general is proportional to the magnitude of injury. In the most severe cases it can lead to circulatory shock, organ dysfunction, and death.

A central perspective is that injured individuals exhibit widely differing premorbid characteristics, with respect to their ability to respond to the inciting event, to withstand infection and to repair tissue, to withstand stress, and also with respect to their somatic and psychiatric history, personality and socioeconomic background. They also differ with respect to type and perception of care, and in their adaptation or outcome. A subgroup will end up with irreversible damages to the skin, permanent psychological impairment, and drastic changes in body image from scarring and loss of limb function.

It is quite obvious that burn care is heavily multifactorial and multiprofessional, spanning from simple wound care to advanced tissue engineering/tissue culture, from intensive care to psycho-social support.

The Burn Research Program is an umbrella for clinical research on burns and outcome after burns and is divided into modules containing the main parts of the treatment processes for burns.

Acute burn care, including burn surgery and tissue engineering

A number of projects targeting main properties of the patient's immediate response to the trauma are running; some of these are newly commenced.

Newly started projects are e.g. an assessment of the pattern of expression of matrix metalloproteinases and their inhibitors, as well as steroid receptors and the sensitivity of those in patients with severe burns.

Another such project is a study of objective parameters correlating to the patients' description of pain-experiences. In separate studies effects of various treatment modules, e.g. surgical techniques, resuscitation models, antibiotics used, etc., in burn surgery are assessed. This includes a number of approaches to

improve healing, and the result of healing using different surgical techniques and various components tailored by tissue engineering.

Long term central nervous system consequences related to outcome

A project that has been running for more than a decade is related to the effect of trauma on the central nervous function, above expressed as psychiatric symptoms after having recovered. This is a long standing project based on the concept that the exposure and response to traumatic stress interacts with psychiatric history, personality traits and coping strategies and that this interaction is a main determinant for the adaptation process. Little attention has previously been directed to the question of which neurobiological responses are related to such resilience to psychological stress in general and to specific forms of psychopathology.

All patients referred to the National Burn Center of Uppsala since 2000 are asked to participate in an extensive prospective and longitudinal investigation involving premorbid characteristics with respect to sociodemographic and psychosocial characteristics, and previous somatic and psychiatric history. The prospective investigations also include a detailed assessment of the physical stress during the ICU period and during recovery, and genotyping. After injury they are assessed up to one year. The assessment of the stress response involves an analysis of how it is affected by the extent of trauma, treatment and care, and how it is affected by factors mentioned above. Relations with genes that are associated with outcome and various aspects of the stress response are investigated. Neurophysiologic and neuroimaging techniques will be utilized to characterize neurobiological alterations which are putatively related to adaptation.

Since burn injury provides an excellent model for severe trauma with an increased risk for somatic and psychosocial sequel, the results can be generalized and facilitates treatment strategies that can improve outcome also after other severe physical trauma with an increased risk for late morbidity.

Epidemiology and prevention

The complete epidemiology and sociodemography of fire-related injuries and deaths in Sweden is investigated in collaboration with *inter alios* the Swedish civil contingencies agency. One aim is to identify risk-groups and preventive measures lowering number of accidents and people injured, to launch preventive measures and follow up on effects.

Members of the programme during 2014

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The Epithelium-Connective Tissue Interface Programme

Principal investigators: Daniel Nowinski and Bengt Gerdin

This project has its origin in the clinical observation that hypertrophic scarring after burn injury occurs where an open skin wound is imperfectly covered with keratinocytes. Earlier studies by this group have shown that keratinocytes have a direct paracrine effect on connective tissue cell with a decreased expression of profibrotic genes. The project now continues with the aim to further elucidate different mechanisms in the paracrine intercellular communication between the epithelial layer of the skin, the keratinocytes, and fibroblasts that regulate various events during the activation of the supportive loose connective tissue during tissue repair and wound healing. This work includes the development, use and exploitation of sophisticated organotypic co-culture models with broad applications in investigations of cutaneous biology. The focus is placed on the regulation of extracellular matrix (ECM) synthesis and turnover. The effect of normal and malignant keratinocytes on the synthesis of structural ECM-molecules, fibrosis regulating factors and ECM-degrading enzymes by fibroblasts will be analyzed. The role of different keratinocyte-derived signaling molecules in the regulation of the above factors will be investigated. The mechanisms studied will be compared in normal dermal fibroblasts and fibroblasts from fibrotic lesions. In particular, the role of interleukin-1 α , which previously has been defined as an inhibitor of the profibrotic response in fibroblasts, is further investigated. In one part of the project which is carried through at Brigham and Women's hospital in Boston, the role of connective tissue growth factor (CCN2) in the epithelial response to wounding is studied. Results have shown that there are distinct differences in gene expression between benign and malignant keratinocytes that may have consequences for the interaction with the underlying connective tissue.

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Dissertations 2014

Malin Hakelius. Interactions between Malignant Keratinocytes and Fibroblasts: Studies in Head and Neck Squamous Cell Carcinoma

Elizabeth Kiwanuka. CCN2 – Keratinocyte Interactions *In Vitro* and *In Vivo*

Agencies that support the work/Funding

Evaluation of an internet-based self-help programme for parents of children with burns: a randomized controlled trial, Swedish Research Council

Psychiatric outcome after longstanding severe somatic stress; a nationwide study in severe burns on mechanisms, post burn PTSD and a cognitive behavioral intervention program. Swedish Research Council

Personskador till följd av bränder (Injuries to man due to injuries); MSB (Swedish Civil Contingencies Agency)

Reconstructive Microsurgery Research Programme

Principal investigators: Andres Rodriguez and Maria Rydevik Mani

Within the area of reconstructive microsurgery several research projects are carried out.

Clinical Applied Anatomical Studies in Face transplantation and Facial Paralysis

This project is carried out in collaboration with the Department of Plastic Surgery of the University of Texas Southwestern Medical Center. Anatomical studies are performed to study the technical feasibility of the application of new techniques in the field of face transplantation and facial paralysis.

Virtual Planning in Microvascular Head and Neck Reconstruction

In collaboration with Maxillofacial Surgery and the Center of Image Analysis at Uppsala University a study is carried out to study the application of a new virtual planning system (UHASP) in microvascular reconstruction of the mandible using free vascularized fibula flap.

Clinical Studies in Facial Paralysis

In collaboration with the department of ENT and Electrophysiology, a study of the implications of different cranial nerves (V, XII, XI) in relation to the Facial Nerve (VII) is carried out by performing electrophysiological studies and Functional MRI to elucidate the cortical interconnections of this nerve and to analyze ways to increase the cortical plasticity after nerve transfers in facial paralysis.

Cancer Recurrence after Breast Reconstruction

Collaboration between department of general surgery (breast surgery) and department of oncology, Uppsala and Malmö, with the aim to evaluate potential risk of breast cancer recurrence after breast reconstruction. The project includes retrospective analysis of patients who was mastectomized in 1992-2009 and reconstructed between 2000 and 2009 as well as a prospective study arm.

Lymphoedema – risk of and treatment of lymphoedema

Evaluation of the risk of lymphoedema of the arm after microsurgery reconstruction of the breast and cephalic vein usage. Retrospective analysis of a cohort of already reconstructed patients as well as prospective study of patient operated 2014–2016. The project also includes evaluation of microsurgical treatment of lymphoedema by lymphnode transfer at the time of free flap reconstruction of the breast. The evaluation includes clinical measurements, displacement test, photographs and questionnaires.

Quality of Life, Patient satisfaction and Optimizing resources in Breast reconstruction

Collaboration with Breast Cancer Surgery, Patient Reported and Clinical Outcomes Research Group in Bristol, United Kingdom. Development of the Swedish version of the questionnaire EORTC BRR-24. International collaboration between more than 15 countries for a common instrument to use for breast reconstruction. This project further includes studies of patients already reconstructed and comparison of different methods as well as a prospective study. Parameters evaluated are QoL, patient satisfaction, resource management and socioeconomic impact.

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Agencies and Grants that support the work/Funding

Thúreus Stipendium 2014 for the project “Incorporation of Fibula Flaps into a Virtual Cranio-Maxillofacial Planning System”

Nystrom Amerika stipendium 2014-2016 for the research collaboration with University of Texas Southwestern Medical Center for anatomical studies in Face Transplantation.

FOU-Medel (Landstinget I Uppsala Län) 2014 for the research project “Hjärnbarkens omformbarhet vid plastikkirurgiska rekonstruktioner av leendet: En funtionell MR- och neurofysiologisk studie. Bergholm och Erikssons stiftelse: Breastcancer recurrence after post mastectomy reconstruction

Uppsala University Hospital (ALF)

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11 Thoracic Surgery

Principal investigator: Elisabeth Ståhle

Project 1. Studies on hemostasis in cardiac patients

In collaboration with Professor Agneta Siegbahn and Christina Christersson studies on coagulation and hemostasis in cardiac patients with focus on aortic valve disease.

Biomarkers and risk factors associated with bleeding in aortic valve surgery

Symptomatic narrowing of the aortic heart valve, aortic valve stenosis, is preferably treated with surgical valve replacement. This generally requires an open-heart surgical procedure using a heart lung machine. Bleeding is a common associated problem, and up to 7 % of patients need a subsequent acute operation to stop bleeding. Early identification of patients at risk of bleeding complications through blood tests would be of benefit, as specific procoagulative medical treatment and transfusions can be planned and carried out early. Excessive bleeding after surgery is associated with an increased risk of adverse outcome, including death. Valve surgery has been shown to have more bleeding complications when compared to coronary bypass surgery, the other most common type of cardiac surgery. Patients are treated with different anticoagulant and anti-platelet drugs before, during and after surgery, which can contribute to increased risk for bleeding.

During 2013 a project focusing on bleeding after heart valve surgery was initiated. The main purpose of the study is to investigate causes of abnormal bleeding after valvular heart surgery. Patients undergoing aortic valvular surgery are to be compared to patients undergoing coronary artery bypass, in order to try to identify biomarkers and risk factors that could explain and foresee an increased risk of bleeding in the valve surgery group.

In this study, biomarkers present in blood, patient related risk factors and effects of prior medical treatment are analyzed. These markers are known to describe the condition of the bloods hemostatic components: proteins, platelets and the cells lining the inside of blood vessels. Levels of von Willebrand factor, micro-RNA and cell fragments reflect the degree of platelet activation, which in turn could correlate to excessive bleeding or inadequate thrombus formation. Platelet protein content is examined in masspectromy in order to identify markers for platelet activation.

Until February 2015, 160 patients have been included and blood samples from before, during and after surgery have been stored. Ten patients platelet protein content has been examined so far and data is being analyzed.

To further evaluate perioperative changes in the coagulation system in this study, a tromboelastography analyze is performed before and directly after surgery. The test measures time until blood clotting begins and the firmness of the produced clot. Results indirectly show that fibrinogen levels are decreased during surgery. However, the results do not correlate to later postoperative bleeding and a preoperative analysis with tromboelastography does not seem to help in foreseeing abnormal postoperative bleeding.

Following valve surgery, patients are prescribed warfarin to prevent thrombosis and stroke. The dose requirement varies more than ten times between patients, and over treatment can lead to life threatening bleedings. Therefore the anticoagulative effect, measured as INR, is monitored with blood tests. Genetic variances in the vitamin K cycle protein VKORC1 have been identified as the main determinant of warfarin sensitivity. This project aims to investigate if these genetic variances effects bleeding complications and concentrations of coagulation factors and other biomarkers after cardiac surgery. A second goal is to develop an algorithm for safer and easier warfarin dosage after cardiac surgery. Our results show that even though treatment is guided by daily INR measurements, sensitive patients still receive to high doses and non-sensitive to low doses of warfarin. Interestingly, preliminary data also shows that patients with the warfarin sensitive genetic variant of VKORC1 have a higher INR after surgery even before the warfarin treatment has been initiated.

In a retrospective study of patients who underwent aortic valve replacement at our clinic between 2000 and 2012, clinical risk factors for bleeding including preoperative anti-platelet medical treatment are examined. Effects on short and long term survival and complications due to bleeding are also investigated.

The results show that reexploration due to bleeding is three times more common after valve surgery than after coronary artery bypass surgery. Patient related risk factors for bleeding are high age, male sex and symptoms of left ventricular heart failure. The use of the antitrombocytic drug clopidogrel prior to the operation causes a statistically significant three-fold increased risk of reexploration due to bleeding. Surgical bleedings are equally prevalent as non-surgical bleedings with general coagulopathic oozing. Postoperative complications are significantly more common in reexplored patients and early mortality is three times higher than in patients not reexplored. These risks are however only present during the first 30 days, as long term follow up during a mean of five years shows no further negative effect on survival for patients reexplored due to bleeding.

Members of the group during 2014

Elisabeth Ståhle

Ulrica Alström

Axel Dimberg

Project 2. Management of right heart failure during LVAD-therapy and ECMO

Right heart failure

The group has created an experimental model in animal to study right heart failure and potential methods of treatment. Focus has been to define heart failure in this model since a clear definition for this state is lacking in the literature. The second part has strived to treat right heart failure with a surgical method that bypasses the right ventricle part of the circulating blood volume. This new method aims to treat patients which suffer right heart failure during left ventricular assist device (LVAD).

The method used for volume exclusion is a cavo-pulmonary shunt, i.e. connection between the superior vena cava and the pulmonary trunk. This shunt enables all venous return from the upper body (i.e. 30% of cardiac output) to passively flow to the pulmonary circulation without passing the right ventricle. The concept of cavo-pulmonary shunting has been used for long to palliate congenital heart defects; however, it has never been used as a treatment for right heart failure.

The effect of a cavo-pulmonary shunt was evaluated in an experimental setting of right heart failure induced by isolated right coronary ligation, and defined by a right atrial pressure of >20 mmHg. The shunt treatment resulted in decreased right atrial pressure as well as increased mean arterial pressure and mixed venous oxygenation.

The effect of a cavo-pulmonary shunt was also evaluated during experimental right heart failure induced by pulmonary banding. In this setting, the ability of the shunt to reduce right atrial pressure was confirmed. Further, the genetic expression during acute right heart failure was studied using microarray; this revealed a profound impact on the genetic expression involving almost half the genome.

Since a cavo-pulmonary shunt is dependent on a normal pulmonary resistance, patients with elevated pulmonary resistance are excluded from this therapy. Therefore, the concept of a cavo-aortic shunt, which can be used in cases of elevated pulmonary resistance, was also evaluated. Experimental right heart failure was induced by coronary ligation and LVAD-treatment was initiated. A cannula from the right atrium was connected to the LVAD-system, 30% of the cardiac output was then shunted directly from the right atrium to the aorta. Treatment with the cavo-aortal shunt resulted in decreased right atrial pressure and increased mean arterial pressure. Since the cavo-aortal shunt delivers desaturated blood to the aorta, the arterial

oxygen saturation was decreased. However, the oxygen delivery to the tissues was unaffected since the cardiac output was increased simultaneously by the shunting.

In summary, the work regarding partial volume exclusion of the right ventricle as treatment for right heart failure is completed during 2014 and will be summarized in Per Vikholm thesis during the first part of 2015.

ECMO

During 2014, an experimental model for extracorporeal membrane oxygenation (ECMO) has been created in animal. ECMO is more frequently used to support either the heart in heart failure, the lungs in respiratory failure or both in combination if this is needed. There is increasing use of ECMO-support during myocardial infarction in younger patients in clinical practice. This method is still uncommon and the accumulated experience in this group of patients is small. There is a need for systematic examination of certain methods used in association with ECMO treatment that has become standard clinical practice but has never really been evaluated.

One example of such a method frequently used in clinical practice is unloading of the left ventricle to reduce the size of the myocardial infarction and to improve the chance of recovery of the failing left ventricle.

A model was therefore created in which a myocardial infarction was established in pigs. The animal was thereafter put on ECMO-support and a randomization was completed into three groups. The first with no left ventricular unloading; the second with moderate left ventricular unloading; and finally the third with complete unloading. The hemodynamics was analyzed. Moreover the hearts were stained and carefully examined with regard to size of infarction and reperfusion area. These analyses were undertaken in collaboration with the department of Pathology (Professor Erik Larsson). In addition, the myocardium in undergoing analyses of Tissue Micro Array (TMA) to establish the morphologic expression of the myocardium in this model.

Members of the group during 2014

Laila Hellgren

Petter Schiller, MD

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Project 3. Arrhythmia surgery

The Cox-Maze III operation in Sweden – Registry-based and clinical long-term follow-up in 536 patients

This is a multicenter collaborative study between cardiac arrhythmia surgeons and cardiologists in Uppsala, Stockholm and Gothenburg. The study has been granted support by the Swedish Heart-Lungfoundation. The Cox-Maze III operation was introduced in Sweden in 1992 and performed in four different centers. It is an open heart procedure for treatment of medically refractory and highly symptomatic atrial fibrillation, in which multiple incisions are made in both atria to block re-entrant circuits causing atrial fibrillation. Initially it was used in patients with lone atrial fibrillation but has subsequently been performed in conjunction with other heart surgery. From 1992-2009, 536 patients in Sweden underwent this procedure. Early results were good with up to 90% of patients free of atrial fibrillation. However, long-term results have not been evaluated in Sweden. This is an effort to determine patient outcomes through Registry-based studies of mortality and in-hospital care as well as individual patient surveys of quality of life, actual rhythm and on-going medication.

Part 1: "Early and Long-Term Mortality in 536 Patients After the Cox-Maze III Procedure: A National Registry-Based Study" Albåge A et al. *Ann Thorac Surg.* 2013;95(5):1626-32.

This recently published study showed low early and long-term cardiovascular mortality and no stroke-related mortality after the Cox-Maze III procedure.

Part 2: Long-term follow-up of quality of life, actual rhythm, cardiac symptoms and on-going medication. In this study, surveys and recent ECG-recordings have been collected from 339 patients in three centers. Results show 82% of patients in SR, nodal or atrial pacing rhythm. QoL in patients with successful rhythm equaled the general population. This data has been presented at SATS in Gothenburg 2014. Two manuscripts are in the submission process.

Part 3: Registry-based evaluation of in-hospital care of patients having undergone the Cox-Maze III procedure in Sweden, to analyze stroke/TIA morbidity long-term postoperatively. This study is in collaboration with associate Professor Ulrik Satirpy, Stockholm. Data-analysis phase.

National research group

The research group is collaborating closely with arrhythmia surgeons from all cardiac surgical units in the country, in an organization called **SRAK** (Svenska Referensgruppen för Arytmkirurgi). This national workgroup is quite unique in cardiac surgery in Sweden and its purpose is to address and unify clinical issues and research projects in the field of arrhythmia surgery. The group has recently produced guidelines in this field:

1. "A Swedish consensus on the surgical treatment of concomitant atrial fibrillation". *THE SWEDISH ARRHYTHMIA SURGERY GROUP. Scand Cardiovasc J.* 2012 Aug;46(4):212-8.
2. Kirurgisk behandling av förmaksflimmer i samband med hjärtkirurgi. Konsensusrapport från Sveriges arytmiansvariga hjärtkirurger. *Läkartidningen* 2012 Feb 1-7;109(5):214-7.

In addition, there are several on-going collaborative projects including the start-up of a national registry for atrial fibrillation surgery, which will be included in the National Registry for Percutaneous ablation.

Another ongoing project is forming a consensus statement regarding anticoagulant treatment in connection with postoperative atrial fibrillation.

Local follow-up of patients undergoing surgical treatment of atrial fibrillation at the Dept of Cardiothoracic Surgery, University Hospital, Uppsala

The Cox-Maze III procedure has been further developed and at present most of the surgical incision in the atria of the original procedure have been replaced by cryoablation. This allows for a faster and safer procedure and this therapy of atrial fibrillation can be offered to older and sicker patients. There is a completed local long-term follow-up study of patients who were operated between 2009 and 2012 for **structural heart disease (valves or CABG) and concomitant cryo-Maze procedure**. Follow-up of quality of life, rhythm and medication has been performed in 50 patients and the study is in data analysis phase. Cardiac rhythm has been evaluated by telephone-conveyed "thumb-ECG" recordings in each patient. This has been presented by medical student Kristina Dalin in January 2015. This study is continuing including patients prospectively.

In another collaborative project between Uppsala and Karolinska, we are doing long-term follow-up of patients who have undergone **open heart closure of atrial septal defect and concomitant surgical ablation of atrial fibrillation** between 2000 and 2012. This study is in the start-up phase and end points are quality of life, rhythm and present medication. In an era of increased use of catheter-based therapies for ASD, we hope to show consistent and good results with open surgical treatment in the ASD-patients who also have atrial fibrillation.

Minimal invasive surgical ablation

This is a collaborative project between cardiac arrhythmia surgeons and cardiologists in Uppsala. It is a total thoracoscopic bilateral procedure for treatment of medically refractory and highly symptomatic atrial fibrillation, in which multiple epicardial ablation lines are made on the left atrium to block re-entrant circuits causing atrial fibrillation. From 2008 to 2013, 100 patients in Uppsala underwent this procedure. Early results were good with up to 90% of patients free of atrial fibrillation. Long-term results are in data analysis phase.

Miscellaneous

Research group members have participated actively as lecturers in various Symposia at Svenskt Kardiovaskulärt Årsmöte, in 2008, 2013 and 2014 in the field of surgical treatment of atrial fibrillation. We have also participated actively as lecturers at Svensk Thoraxkirurgiskt Årsmöte, in 2011, 2012 and 2014 in the field of surgical treatment of atrial fibrillation.

We are also co-authors in an upcoming Swedish textbook of cardiac arrhythmias.

Members of the group during 2014

Lena Jidéus (Group Leader)

Anders Albåge

Vitas Zemgulis

Project 4. Heart surgery; indications, complications and long-term outcome

Atrial fibrillation after heart surgery – prediction and outcomes

The most common complication after cardiac surgery is atrial fibrillation (AF). Approximately a third of all patients have an episode of AF after coronary artery bypass grafting (CABG), so called postoperative atrial fibrillation (POAF). This arrhythmia has associated with a negative outcome after surgery, but the causes behind this are not fully understood.

This project aimed at identifying predictors and early complications associated with POAF after CABG, as well as its associations with early and late mortality and cause of death. Further, we wanted to follow the heart rhythm of patients with and without POAF to see to what extent recurrent or new AF occurred after discharge.

The first two studies included approximately 7,000 patients, with data collected from the clinic's database and the Swedish cause of death registry.

The first study revealed several predictors of POAF, including increasing age, decreased kidney function, male gender, symptoms of heart failure, smoking, history of myocardial infarction, and absence of hyperlipidemia. There was also an association between POAF and early complications after surgery, such as heart failure and infection, and stroke.

In a second study there was an association between POAF and late cardiac death, and death related to arrhythmia, heart failure, and cerebrovascular death. The effect remained after adjusting for age and other pre- and perioperative variables, more than eight years after surgery. The results indicate a negative prognosis associated with POAF.

A third, prospective study examined heart rhythm the first 30 days following discharge after CABG, with a mobile ECG device. Preliminary results show a high incidence of recurrent AF, despite all patients being in sinus rhythm at discharge. A surprisingly high number of patients without POAF also registered AF during

follow-up. A third of the patients with AF did not experience any symptoms related to AF. There seems to be room for a more active treatment of POAF, and a more thorough follow-up of heart rhythm after CABG.

The fourth study examines the association between POAF and morbidity, where more information is needed, especially in long-term follow-up. Focus is on diseases related to arrhythmia, cardiac ischemia, heart failure, and thromboembolic events, including stroke. We want to examine when these conditions occur, how much in-hospital treatment they require, and how they are treated. The study is still in its early stages, and a control group of patients from the general population is currently being created. By first comparing this control group to CABG patients, the additional effect of POAF can then be extracted.

In summary, the overall purpose of this project is to identify risks associated with POAF after CABG, and hopefully find ways to minimize these risks in the future.

Members of the group during 2014

Elisabeth Ståhle

Emma Thorén

Project 5. Surgery in lung cancer treatment

Aspects on lymph node metastasis in lung cancer

This project's focus is on molecular analysis of lymph nodes, lymph node metastasis and primary tumors with special reference to lymphangiogenesis. Surgical, radiological and pathological implications.

Lung cancer kills 1.2 million people in the world every year. It is one of the cancers with the worst prognosis. Only 10-20% of the patients can be subject to the only possible cure that is surgery. Thus, in the majority of cases, at the time of diagnosis, the disease has progressed too far to be able to cure, usually through metastatic spread to lymph nodes or distant organs. Among those patients subjected to surgery, the mean five year survival is around 50%, worse in those with larger tumors with signs of local lymph node spread and better in those with smaller tumors and no evidence of metastatic lymph node spread. However, the five year survival in these patients, with a totally radical removal of a small tumor and no signs of lymph node spread, is still far from 100%. This could indicate that there in some cases still could be, although with today's methods unrecognizable, a very low degree of metastatic spread present at the time of surgery. To be able to understand the basic driving mechanisms and earlier find such a spread would help to better help these patients to a longer life.

This is a joint venture between the departments of thoracic surgery, oncology, radiology and pathology, still in an early phase. The goal is to:

With the use of advanced surgical, molecular and radiological methodology, increase our understanding of lymph node metastasis in non-small cell lung cancer in order to be able to better diagnose, operate and prognosticate patients with this disease. This includes to:

- In detail, from an anatomical surgical level down to a basic molecular level, study and map the metastatic spread in lymph nodes in patients with NSCLC.
- In detail, from an anatomical surgical level down to a basic molecular level, study and map the concept of lymphangiogenesis in patients with NSCLC.
- Try to find methods for earlier and more precise detection of lymph node metastasis and lymphangiogenesis in patients with NSCLC.

Detection of Mutations in Epidermal Growth Factor Receptor and Monitoring of Therapy in Non-Small Cell Lung Cancer

The objective of this study is to identify predictive markers for EGFR inhibitors and drug resistance in blood samples from patients with non-small cell lung cancer. The overall aim is to obtain optimal staging prior to surgery.

Background

A rapid development of molecular biology has opened new possibilities for the staging and corresponding treatment of non-small cell lung cancer (NSCLC) and the receptor for epidermal growth factor receptor (EGFR) has lately been the focus of targeted therapy of NSCLC. EGFR has been shown to be commonly expressed in lung tumors and be important for the growth of lung cancer. Gefitinib (Iressa) and erlotinib (Tarceva) are small molecule tyrosine kinase inhibitors (TKIs) blocking the activity of EGFR and in clinical studies have demonstrated clinical activity in lung cancer patients resulting in tumor reduction and prolonged survival. Research groups have subsequently identified somatic mutations in the tyrosine kinase domain of EGFR associated with response to EGFR TKIs. The most common EGFR sensitizing mutations, which account for approximately 85% of all EGFR mutations in NSCLC, include deletions in exon 19 and a point mutation, L858R, in exon 21. Both gefitinib and erlotinib are now approved for treatment of advanced NSCLC patients with sensitizing EGFR mutations. Resistance development is a major clinical problem, and this is also true for EGFR targeted therapies. In 50% of patients resistant to gefitinib or erlotinib a mutation in exon 20 of the EGFR, leading to the substitution of the amino acid threonine to methionine at position 790 (T790M) in the kinase domain of the receptor has been found. Attempts are now underway to develop irreversible EGFR TKIs to overcome this resistance mechanism.

Department of Thoracic Surgery at Uppsala University Hospital has since 2002 collected consecutive blood samples (plasma, whole blood) from surgical lung cancer patients, up to date 728 lung cancer patients in all. Linked to these patients are full clinical data including tumor stage, sex, age, survival, EGFR mutation status (from 2009). This database is planned to be used as a basis for collaboration with the SciLifeLab in Uppsala in order to:

1. Using the proximity ligation assay technique (PLA) for high-performance DNA -assisted protein analyses to find sensitizing EGFR mutations in blood from lung cancer patients in order to easily identify the optimal patients for EGFR TKI treatment using only a blood test instead of tumor tissue.
2. Using the same PLA technique to monitor lung cancer patients being treated with EGFR TKIs by looking at levels of sensitizing EGFR mutations in blood and correlate that to treatment response as determined by radiological evaluation. The intention would be to replace laborious monitoring using radiological exams with easy monitoring using blood tests.
3. With the help of PLA technique detect the emergence of EGFR resistance mutations during treatment with EGFR TKIs in blood samples from lung cancer patients. This would be helpful in early detection of resistance and guiding further therapeutic decisions.
4. The same methodology as described in 1-3 above can be applied to other novel targeted therapies in lung cancer where there is a predictive biomarker for treatment response. One example already in routine clinical use is the ALK gene rearrangement in a subpopulation of NSCLC patients where the targeted agent crizotinib (Xalkori) is used to treat these patients.

Members of the group during 2014

Simon Ekman

Per Landelius

Elisabeth Ståhle

Project 6. Clinical and experimental studies of malperfusion of the Central Nervous System in conjunction with cardiovascular surgery

Cerebral perfusion during surgery of the thoracic aorta

Description of the research: Irreversible neurological injuries are a major complication to complex cardiovascular surgery. There is to date no treatment available for these patients, only therapies that aim at minimizing the consequences of established injury.

The goals of the current project are to both develop potential therapeutic strategies and also identify analytic tools to be applied in a clinical setting where ischemic injury to the central nervous system (CNS) could have occurred. The research is translational, with a clinical and an experimental arm. The clinical material consists of a well characterized cohort of patients where blood and more importantly cerebrospinal fluid samples, which is unusual, have been collected from patients that have undergone open cardiovascular surgery. The experimental part is carried out in a porcine model, implying that the results obtained likely are of more clinical relevance than those from murine models.

The aim of developing an active strategy to treat ischemic CNS injury in the clinical setting is realistic on selected patients undergoing cardiovascular surgery, as the operative strategy already today isolates and cannulates the major vessels supplying the CNS with blood. In the longer term, a similar treatment could be relevant also in situations with major cerebrovascular infarctions or following cardiac arrest, but this is more speculative. In order to be a candidate for intervention early identification of ischemic injury needs to be possible. As it is difficult to detect brain injury in the early phase following extensive surgery that could have put the brain at risk, there is a need to develop better biomarkers that can improve the diagnostics in this setting.

Members of the group during 2014

Rickard Lindblom

Stefan Thelin

Detection of markers of neurologic injury in cerebrospinal fluid and blood following complex aortic surgery

Description of the project: It is challenging to detect and quantify neurologic injury in the early post-operative setting following extensive aortic surgery, as the patient as a rule is sedated or under general anesthesia for many hours, sometimes even days due to circulatory and respiratory instability. This means that the patient is bound to the intensive care unit, making detailed radiological examinations difficult. Also, radiological examinations of the brain early following suspected ischemic injury are not always reliable with regard to sensitivity [1].

In other neurological diseases, such as Multiple Sclerosis or Alzheimer's disease biomarkers of disease activity have been developed in cerebrospinal fluid (CSF). However, these are diseases with chronic course, and it is therefore not evident that the markers identified [2,3], which correlate with degree of nerve injury are applicable on acute ischemic injuries. After acute traumatic brain injury, it has been demonstrated that levels of certain CSF proteins correlate with degree of survival [4], and recently it was identified that elevated levels of several proteins in CSF following aortic surgery to a certain extent correlated with the degree of neurologic injury [5]. However, it is not known if these proteins also are detectable in blood. Blood sampling is an easier and safer technique than sampling from the intradural cavity. It would therefore be of great value to in a simple, fast and reliable way detect acute ischemic neurological injury in order to rapidly undertake adequate treatment.

All patients at the Department for Cardiothoracic Surgery at Uppsala University Hospital admitted for either open or endovascular operative treatment of complex disease of the thoracic aortic that have a spinal catheter introduced are included, on condition of written consent. The criterion of getting a spinal catheter is that the planned procedure carries a significant risk of disturbing the circulation to the CNS, which could cause ischemic injury to the brain or spinal cord. CSF and blood samples are collected concomitantly during the perioperative phase, until the catheter is removed. In the current material, where 21 patients are included at this stage, there are patients without injuries, with transient CNS symptoms and also permanent CNS injury. The paired sampling, of blood and CSF simultaneously, enables a kinetic characterization of when neurological proteins are possible to detect in the blood compartment. It can also help establish the degree of potential blood-brain barrier defect caused by the surgery. Proteomic analysis of the serum and CSF will be performed during 2015, in collaboration with SciLife and Professor Ulf Landegren. Initial analysis will examine a panel of 90 proteins linked to neurological processes.

Members of the group during 2014

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Experimental studies of global cerebral ischemia and controlled reperfusion

Description of the project: Inadequate blood supply to the brain is harmful, but the exact mechanisms leading to tissue injury following ischemia are not fully understood. It is likely the combination of ischemia with the uncontrolled reperfusion that occurs once the circulation is re-established that causes the damage. It has been demonstrated in both heart [6] and lungs [7] that a controlled reperfusion following ischemia can reverse and minimize tissue injury. However, it is important how this reperfusion occurs, since a number of parameters can be manipulated, for instance velocity, pressure and temperature of the perfusate, as well as its content with regard to immunologic factors, balance of electrolytes and content of anti-oxidants or other drugs [8].

Recently, an extensive research series performed in pig demonstrated that a controlled reperfusion was able to salvage a brain exposed to a 30 minute long global, normothermic ischemia [9,10,11]. But a number of questions remain even after this pioneering work- for instance; what is the most important parameter in the controlled reperfusion? And also, after how long ischemia is it possible to prevent permanent injury from affecting the brain?

In the current project, an animal model (pig) has been developed where we by surgically identifying all vessels that supply the brain with blood are able to induce a global, reproducible cerebral ischemia. In the control group all brain vessels are occluded for 30 minutes, after which they are opened and the regular circulation resumes. This is what we term uncontrolled reperfusion. In the interventional group ischemia is induced in the same way, but after the 30 minute ischemic period a controlled reperfusion of the brain is performed during 20 minutes, using extra-corporeal circulation and heart-lung machine connected to the cerebral vessels. This is the controlled reperfusion, as we are able to modulate the pressure, flow, temperature and content of the perfusate. After the controlled reperfusion, the vessels are opened and the regular circulation again takes over. During the experiment extensive monitoring and regular taking of blood and tissue samples is performed. At the end of the experiment the brains of the animals are examined by experts in neuropathology at Uppsala University Hospital. The aim is to evaluate and develop an optimal reperfusion strategy that minimizes, or perhaps altogether hinders development of brain injury following ischemia.

Members of the group during 2014

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12 Transplantation Surgery

Principal investigator: Gunnar Tufveson

Transplantation research is based on clinical need but encompasses both clinical and experimental research.

Most of the research is done in a collaborative fashion within the University in particular with the Departments of Immunology, Genetics and Pathology (Clinical Immunology, Morphological Pathology and Clinical Oncology), Medical Sciences (Nephrology), Surgical Sciences (Anesthesiology and Radiology) and Neurosciences (Neurosurgery) are involved.

The field of transplantation research is very heterogeneous but it has a common focus of clinical need.

Although the topics can be listed as separate items these may in several aspects be interrelated either by technology or goal. Under the broad heading *transplantation immunology* we conduct clinical research on tolerance and the generation of regulatory T-cells and mesenchymal stem cells to reduce or abolish the use of immunosuppression. Also research is directed to overcome the ABO-barrier as well as anti-HLA antibody barriers. The latter is dependent on the use of complement inactivation and/or IgG-degradation.

The second topic may be assembled under the broad heading of *regenerative medicine*. The common denominator is the knowledge that organs transplanted are damaged all the way through the procedure until after reperfusion. The following damaging events have been identified: brain death, harvesting procedure, storage with ischemia and finally reperfusion injuries. It is also recognized that all these factors together generate rather non-specific damages, which may switch the organs from a neutral to a pro-inflammatory state. Further, it is recognized that especially the storage period with cold storage or machine perfusion, warm or cold, may offer an opportunity of repair by endothelial or perfusion solution modulation to improve the long-term transplant outcome. More specifically ischemia reperfusion is studied in a large animal model in renal, pancreatic and islet transplants.

Outside of the heading of regenerative medicine patient management and live donor management are important areas for both technical and psychological development. Thus, we have research and developmental programmes for clinical islet transplantation, live donor kidney donation, clinical pancreas transplantation and management of malignancies after transplantation.

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Dissertations 2014

Amir Sedigh. Management of Ischemia and Brain Death-Associated Injuries in Porcine Kidney Grafts

David Berglund. Preparatory Studies to Introduce Regulatory T Cells in Clinical Transplantation

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13 Urology

Identification of biomarkers for clinical management of patients with urinary bladder carcinoma

Principal investigator: Per-Uno Malmström

The purpose of this project is to identify a panel of biomarkers that can improve the clinical management of patients with bladder cancer. Their function would be to predict response to specific therapies and also to find new targets for therapy. To achieve this, our specific aims are to;

- Screen a large well categorized biobank consisting of frozen tissue, blood and urine for candidate markers
- Validate these candidates in an independent biobank consisting of formalin fixed tissue from five large prospective randomized trials.
- Incorporate these markers in a prospective evaluation through our international network.
- Translate use of biomarkers to the clinical management

Our lab, headed by Ulrika Segersten PhD, is located in the Rudbeck building facilitating cooperation with preclinical research groups.

External cooperation

We participate in an international study funded by EU/FP7 of gene-signature classifiers (Uromol). This is a prospective trial validating our retrospective results with molecular classifications for the clinical outcome of non-muscle invasive bladder cancer.

Members of the group during 2014

Per-Uno Malmström, Professor

Ulrika Segersten, PhD

Mårten Lindén, PhD

Tammer Hemdan, Specialist

Agencies that support the work/Funding

Cancerfonden 500,000 SEK

Prostate cancer: Epidemiology, Survival and Quality of Life

Principal investigator: Anna Bill-Axelson

SPCG-4 main study: The SPCG-4 randomized study between radical prostatectomy and watchful waiting in localized prostate cancer has been analysed every third year since the first analyses in 2002 regarding differences in risk of overall mortality, prostate cancer mortality and risk of metastases. The first and second analyses were published in NEJM 2002, 2005 and the third in JNCI 2008 and the fourth in NEJM 2011. The research group is a collaboration where the first authors Anna Bill-Axelson and Professor Lars Holmberg are from Uppsala University and the PI is from Örebro University. The fifth analysis was undertaken in 2013 and published in NEJM March 2014. We collaborate with the British study ProtecT

about PSA as a marker for intervention and with Harvard Medical School in a project of biomarkers. The monitoring is on-going and next follow-up will be in 2017.

SPCG-4 Quality of life study: The included men in SPCG-4 have twice been asked to participate in a separate quality of life study. They have been sent a questionnaire with multiple questions concerning urinary, sexually function as well as psychological and quality of life questions. Results from the first round were published in NEJM 2002 and European Urology 2006. We have now collected new data with an extended questionnaire, where the first manuscript has been published concerning hernias in European Urology 2010 and the manuscript concerning long-term symptoms and quality of life after radical prostatectomy versus watchful waiting was published in Lancet Oncology 2011 (Eva Johanssons thesis work with main supervisor Anna Bill-Axelsson). Further studies from this material are ongoing.

PcBaSe is a database, based on the National Prostate Cancer Register (including 98 percent of all prostate cancer cases) and a number of other linked registers. (Anna Bill-Axelsson is in the steering committee). PCBaSe enables us to look at uncommon but important consequences of a prostate cancer diagnosis.

During 2014 we have published a number of studies among them we have investigated the risk of androgen deprivation therapy after curative treatment published, in European Journal of Cancer with Ph.D. student Magdalena Lycken as first author. Together with Karl-Johan Lundström we have looked at the incidence of infections following prostate biopsies and different risk factors, published in the Journal of Urology. We have also investigated the risk of small bowel obstruction and abdominal pain after robotic versus open radical prostatectomy and the manuscript is submitted. Eva Johansson is studying functional outcomes in correlation to prescribed drugs for erectile dysfunction published in Journal of sexual medicine and sick leave after radical prostatectomy.

U-Care is an initiative where cancer patients with signs of depression according to HADS will be randomized between standard care or internet based cognitive therapy.

We have also started a new project with Dr Oskar Karlqvist to investigate the quality of life among men with low risk prostate cancer in active surveillance. We have sent out the questionnaire to the included patients and are collecting the data.

A new project is the linkage of Uppsala-Örebro PSA data from 2005-2015. The PSA data will be linked to a number of other databases to investigate patterns of testing for diagnosis, curative treatment and palliative treatment. We have just received the ethical approval and started to build the database.

A new randomized study Scandinavian Prostate Cancer Group nr 17 is in planning where the main aim is to find the trigger for curative treatment in men under active surveillance for prostate cancer. Today a large proportion of men are diagnosed with low-risk prostate cancer and followed with PSA and re-biopsies. We will investigate a high threshold for curative treatment compared to a low threshold.

Anna Bill-Axelsson is also co-supervisor to PhD student Katrin Below who is a radiologist and her projects involves prostate cancer and MRT 3 Tesla with endorectal probe. Karl-Johan Lundström is also co-supervised by Anna Bill-Axelsson.

Eva Johansson is also working with Quality of Life in two large new research projects, one is a prospective study concerning active surveillance in prostate cancer (SAMS) and the other is a randomized study between surgery and radiotherapy for locally advanced prostate cancer (SPCG-15) she have developed the questionnaires for Quality of Life. She is further involved in the LAPPRO study comparing open to robotic radical prostatectomy and functional outcomes.

Members of the group during 2014

Anna Bill-Axelsson MD, Associate Professor

Eva Johansson, MD, PhD

Magdalena Lycken, MD, PhD student

Oskar Karlqvist MD, PhD student

Hans Garmo, statistician

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Swedish Cancer Foundation

Percy Falk foundation

Prostate Cancer foundation

Uppsala University Hospital (ALF)

EU/FP7

Publications 2012-2014

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14 Vascular Surgery

Principal investigator: Martin Björck, Professor

The research group uses several different methods including prospective clinical studies, registry-based research, data-simulation (Markov-analysis), animal experiments, biochemical analyses and complex imaging techniques. The PhD projects normally include several different scientific methods. The activity of the research group is high, illustrated by the list of publications. The most important research projects focus on aneurysmal disease.

Aneurysmal disease, in particular abdominal aortic aneurysm (AAA)

1) Etiology/pathogenesis with multiple translational research projects that are implemented in collaboration with other research groups. They are focused on inflammation (studied with PET/CT and MRI imaging), relative telomere length, SNP analyses, infectious agents and possible auto-immune reactions. A population-based blood- and tissue-bank has been created, as well as a blood-bank from patients with multiple aneurysms. A multicentre genome-wide-analysis (GWA) project has been initiated. One project focus on women with AAA, using both SNP analyses, another is investigating epigenetically differences between normal and diseased aorta, yet another one studies microRNA fragments in peripheral blood. The research group has organized an investigator driven multicentre randomized controlled trial, studying if growth of AAA can be inhibited by the platelet inhibitor ticagrelor, which is sponsored by AstraZeneca.

2) Prevention by screening, where the role of Uppsala as pioneer in Sweden is exploited in various projects. Two PhD students and one post-doc are engaged in evaluating different aspects of the screening program. The prevalence of, and risk factors for, the disease in different risk groups are being studied in a multicentre collaboration. The cost-effectiveness of different screening strategies is evaluated. Methodological aspects of ultrasound measurement are studied as well as the importance of the definition of AAA. One project focuses on how to help patients with small AAA to stop smoking.

3) Improvement of treatment results including methods how to prevent and treat the abdominal compartment syndrome and intestinal ischemia, and evaluating new endovascular and hybrid operative techniques. The group is involved in several projects related to the dynamic endovascular development within vascular surgery, including treatment of diseases of the thoracic aorta, and infected aneurysms. Epidemiological studies on treatment of AAA include international comparisons.

There are multiple international collaborators: Zürich, London, Oxford, Lisbon, Paris and Rotterdam being the most important centers, as well as the VASCUNET, a collaboration of eleven national and regional vascular registries. Anders Wanhainen is co-chairing a working group revising evidence-based international Guidelines on AAA, under the auspice of the European Society of Vascular Surgery.

Peripheral arterial occlusive disease

4) Several projects focusing on carotid artery stenosis, and surgery to prevent stroke, are under evolution. One project studies population based screening of carotid artery stenosis in 65-year old men, profiting from the screening organization for AAA, another focuses on the importance of contra-lateral occlusion when operating on patients with carotid artery stenosis, and a third one analyses symptoms occurring between a qualifying symptoms and surgery. The possible association between asymptomatic carotid artery stenosis and later development of dementia is explored in a large database created by a previous international multi-center RCT.

5) Intestinal ischemia is studied with both epidemiological and translational methodology. The PI is chairing a working group developing evidence-based international Guidelines, under the auspice of the European Society of Vascular Surgery. 6) Iatrogenic vascular injuries are studied in different registries with the aim of defining preventive strategies, and in collaboration with the orthopedic department popliteal artery injuries after both elective orthopedic surgery and knee trauma are studied.

7) Lower extremity arterial occlusive disease is studied in different projects. Two PhD students focus on popliteal artery aneurysm disease. The PI is responsible for the Swedish arm of the EUCLID, investigating the effect of a new thrombocyte inhibitor among patients with peripheral arterial occlusive disease. New imaging techniques (in particular CT angiography with direct puncture of the artery) to improve treatment

of especially patients with diabetic foot ulcer are tested. New endovascular treatment modalities for lower extremity ischemia are evaluated.

Members of the group during 2014

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Senior investigators

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Kevin Mani, Associate Professor

Thomas Troëng, Associate Professor, Karlskrona

David Bergqvist, Professor Emeritus

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Kim Gunnarsson, Gävle
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External PhD students (to whom senior members of the research group are co-tutors)

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Hanna Ljungbåge, Colorectal Surgery, Uppsala
Otto Stackelberg, Epidemiology, KI, Stockholm
Johanna Swärd, Radiology, Uppsala
Christina Lundberg, Radiology, Uppsala
Magnus Jonsson, Vascular Surgery, SÖS, Stockholm
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Heart and Lung Foundation: 200,000SEK/year 2014-2015
AstraZeneca: 4,900,000 SEK, sponsored RCT on ticagrelor and AAA
Konung Gustaf V's och Drottning Victorias Frimurarestiftelse: 200,000 SEK/year 2014-2015

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New PhDs

Surgery

David Edholm	28/2 2014	Gastrointestinal Surgery
Katarina Edfeldt	11/4 2014	Endocrine Surgery
Lena Burström	29/8 2014	Emergency treatment, Västerås
Alberto Delgado Verdugo	29/8 2014	Endocrine Surgery
Arezo Ghanipour	6/9 2014	Surgery
Jozef Urdzik	22/11 2014	Gastrointestinal Surgery
Joakim Crona	5/12 2014	Endocrine Surgery

Anesthesia

Robert Sütterlin (f Leiter)	12/9 2014	Anesthesiology
Joao Borges	3/10 2014	Anesthesiology
Ing-Marie Larsson	29/8 2014	Anesthesiology

Orthopedics

Yasmin Hailer	25/4 2014	Orthopedic
Anna-Karin Gunnarsson	14/11 2014	Orthopedic

Oto-, rhino- laryngology

Elsa Erixon	5/6 2014	Ear research
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Plastic Surgery

Elizabeth Kiwanuka-Semakula	28/2 2014	Plastic Surgery
Malin Hakelius	21/5 2014	Plastic Surgery

Transplantation Surgery

David Berglund	10/5 2014	Transplantation
Amir Sedigh	31/5 2014	Transplantation

Undergraduate Teaching

A list of programs at the Department of Surgical Sciences can be seen below.

- Speech and Language Pathology Programme ([Logopedprogrammet](#)) 240 c
- Medicine Programme ([Läkarprogrammet](#)) 330 c
- Physiotherapy Programme ([Fysioterapeutprogrammet](#)) 330 c
 - Biomedicine
- Specialist Care in Nursing ([Specialistsjuksköterskeprogrammet](#))
- Emergency Medicine ([Akutsjukvård](#)) SAKU 60 c
- Ambulance Care/ Pre-hospital Emergency Care ([Ambulanssjukvård](#)) SAMB 60 c
- Specialist Nursing Programme Anaesthesia Care ([Anestesisjukvård](#)) SANE 60 c
- Specialist Nursing Programme Intensive Care ([Intensivvård](#)) SINT 60 c
- Specialist Nursing Programme Surgical Care ([Kirurgisk vård](#)) SKIR 60 c
- Specialist Nursing Programme Theatre Care ([Operationssjukvård](#)) SOPE 60 c

Centres and Facilities

Hedenstierna Laboratory

The Hedenstierna laboratory is a university core facility for large animal experimental research. The main users are researchers from the departments of anesthesiology and intensive care, infectious diseases, cardiothoracic surgery, vascular surgery, clinical physiology and the medical technical industry, as well as SLU, the Swedish university of agricultural sciences. The laboratory staff consists of four full time laboratory technicians/engineers and one director. About 250 large animal studies are performed in the laboratory each year contributing to about 40 scientific articles, mainly within the fields of respiratory physiology and infectious disease. The laboratory is recognized both nationally and internationally and attracts many foreign scientists; at present researchers from Germany, Spain, Italy, Brazil, Chile and Japan are working in the laboratory. The economic turnover is approximately 4 million SEK/year. The laboratory is financed by contributions from Uppsala University and via grants to the researchers, from the Swedish Research Council and the Swedish Heart and Lung Foundation.

CKMF

Laboratories for Experimental Research is located at the focal point of the hospital (CKMF, Centrum för klinisk medicinsk forskning). The Center accommodates research groups from Department of Surgical Sciences, Department of Medical Sciences, and Department of Neuroscience. Four research groups at our Department are presently localized at CKMF; Endocrine Surgery, Experimental Surgery, Biomaterials, and Oto-, Rhino-, Laryngology and Head & Neck Surgery.

Awards and Appointments 2014

1. Tomas Lorant Svensk kirurgisk förenings stora forskarpris 2014
2. Sten Rubertsson Fellows of the European Resuscitation Council (FERC) diploma

List of Authors

For lists of Authors, se each research group.