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Department of Surgical Sciences

Annual report 2013



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Chairman's annual address

The year 2013 was a good year with numerous achievements in the areas of teaching and research by the teachers and staff of the Department of Surgical Sciences. 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. In addition, an impressive number of scientific papers were produced: an annual production of 403 peer-review articles and 18 PhD dissertations in 2013 undoubtedly makes us one of the most productive departments at Uppsala University. Top rankings have been bestowed on several of our research groups in international evaluations: Anaesthesia and Intensive Care, Endocrine Surgery, Colorectal Surgery, Vascular Surgery, Orthopaedics, Epidemiology, Otho-Rhino-Laryngology and Urology

Throughout 2013, 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, anaesthesiology, surgical care and ambulance care. Further, our academic nursing staff are becoming an increasingly integrated component within the department's research activity. Through the important contributions of nursing PhD students to the research groups and the work of senior nurse researchers, we are now in the position of being able to develop nursing research that builds on the current research within our department. Combining the medical research perspective with nursing research is likely to generate an extended knowledge on the health and care of patients. 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 and part of semester 7 and 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. These achievements would not have been possible without the highly efficient and proficient

administrative staff handling grants, salaries and invoices with care and efficacy while at the same time facilitating all aspects of teaching and research to flow smoothly.

We feel fortunate to work within a very successful university in a well-organised institution in good economic standing. My vision for the department is that it should provide a platform for the researchers and teachers that drastically reduces their administrative duties. 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 favourable and stimulating (creative) working conditions.

I want to thank everyone at the department, including all teachers, researchers, administrators, students and laboratory personnel for their dedication and excellent work in 2013.

Olle Nilsson
Professor and Chairman

Organization

Chair

Olle Nilsson

Deputy chair

Sten Rubertsson

Department board

Permanent members of the board:

Agneta Roneus

Anders Larsson

Camilla Fröjd

Emma Pontén

Gustaf Tegler

Martin Björck

Olle Nilsson

Sten Rubertsson

Professor emeriti

Bo Johan Norlén

David Bergqvist

Henry Johansson

Lars Wiklund

Martin Holmdahl

Sven Olerud

Tom Saldén

Tor Hierton

Ulf Haglund

Department administrators

Agneta Gustafson, project administration

Anne Jennische, project administration

Birgitta Haglund, project administration

Elin Eriksson, project administration

Elisabeth Bergqvist, graduate study administration

Isabel Eriksson, undergraduate study administration

Karin Johansson, human resources management

Katja Andersson, project administration

Malin Gadeborg, project administration

Mona Björklund, registration of scientific articles

Siv Andersson, financial administration

Siv Utterberg, financial management

Åsa Eriksson, project administration

Computing

Bernth-Erik Eriksson

Technicians

Agneta Roneus

Babette Willinger

Birgitta Bondeson

Birgitta Linder

Breiffni Leavy

Brittmarie Andersson

Carina Fredriksson

Charlotte Ersson

Katarina Bruun

Kerstin Ahlgren

Linda Lyttkens

Maimun Abdi Poljarevic

Maria Swälas

Marie Essermark

Marja Boström

Nilla Westöö

Olivia Grip

Peter Lillhager

Rebecka Hallbeck

Sofia Lindell

Åsa Forsberg

Anaesthesiology, Intensive care medicine and Pain treatment

Cardiac arrest-neuroprotection

Principal treatment in cardiac arrest patients

Hypothermia treat investigator: Sten Rubertsson

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 (neuronspecific 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.

Members of the group during 2012

Sten Rubertsson, Professor

Lucian Covaciu, MD, PhD

Erik Lindgren MD, PhD student

Ing-Marie Larsson, RN, PhD student

Eva C Wallin, RN, PhD student

Marja Leena Kristofferzon, RN, PhD, senior registrar, Gävle University

Marie Sellert-Rydberg, RN, Falu Hospital

Agencies that support the work/Funding

Institutional Grants, Uppsala University

Uppsala University Hospital (ALF)

The Laerdal Foundation for Acute Medicine

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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 2500 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 will be analyzed during spring 2013 and results will be presented during the second half of 2013. Within this study, non surviving patients in Uppsala, Gävle and Västerås will undergo autopsy. A total of more than 200 patients have been included.

Members of the group during 2012

Sten Rubertson, Professor

Jakob Johansson, MD, PhD

David Smekal, MD, PhD student

Erik Lindgren, MD, PhD student

In collaboration with:

Steering com for the LINC trial

Agencies that support the work/Funding

Institutional Grants, Uppsala University

Uppsala University Hospital (ALF)

Physio Control/Jolife AB

Cardiopulmonary resuscitation after experimental hypovolaemic cardiac arrest

Principal investigator: Lars Wiklund

Background: Trauma is the main cause of death in citizens of the whole west hemisphere between the ages 1 and 38 years. It is estimated that by year 2020 deaths from injury are predicted to increase up to 8.4 million world-wide and uncontrolled haemorrhage will be responsible for 30% of these deaths. Despite improvements in resuscitation techniques and surgical management of trauma victims, survival rates remain extremely low in trauma patients who exsanguinate to cardiac arrest and have not improved significantly during the last decades. Thus, resuscitation from hemorrhagic shock and subsequent cardiac arrest is a major clinical challenge in the care of patients after motor vehicle accidents, gunshot or stab wounds, and combat. Nevertheless, even after successful restoration of spontaneous circulation (ROSC) following cardiac arrest, the morbidity and mortality depend mainly on the recovery of neurological function. However, the immediate challenge in emergency and operating rooms also when handling these in many instances young patients is to achieve restoration of spontaneous circulation that is the ultimate aim and demand in order to achieve preservation of neurological function.

This is because the general experience in such situations is that even after very short circulatory arrests it is often almost impossible to achieve ROSC, in contrast to normovolaemic cardiac arrests of considerably longer duration. This has been confirmed also experimentally, and in addition, we have also observed that intrathoracic cardiac massage is a prerequisite for success. Different blood volume substitutes have been tried and hypertonic saline with dextran has so far been superior to autologous blood and Ringer's acetate. Block of nitric oxide action has not improved the results, in contrast to normovolaemic cardiac arrests of longer duration. Hypovolaemic cardiac arrests of somewhat longer duration can be successfully treated when and if an antiarrhythmic agent (amiodarone) is administered during open thoracic CPR. Lately gender differences in circulatory and cerebral adaptation to ischaemia have been investigated in immature piglets where there are no differences in sexual hormone concentration in plasma. We have found that female piglets have a better capacity to adapt both circulatory and cerebral parameters to serious ischaemia. Methylene blue, probably by its inhibitory action on the nitric oxide-guanylyl cyclase pathway, improves circulatory and cerebral adaptation to ischaemia only in male piglets. However, not quite up to the still better level in female piglets. Our findings do indicate that female animals already before having sexual hormones have a better innate protection against ischaemia than their male counterparts.

Members of the group during 2012

Lars Wiklund, Professor

Ingemar Thiblin, Professor in Forensic Medicine

Sten Rubertsson, Professor

Hari Shanker Sharma, PhD, Associate Professor

Ala Nozari, MD, PhD, Harvard Medical School

Egidijus Semenas, MD, PhD

Agencies that support the work/Funding

The Laerdal Foundation for Acute Medicine

Neuroprotective mechanisms elucidated by molecular biological methods

Principal investigator: Lars Wiklund

Background: During the last decades outcome after myocardial infarction has improved tremendously. The same cannot be stated about cardiac arrest. In spite of intense research and training of medical staff only about 5% of the patients brought in to the emergency rooms after witnessed cardiac arrest survive, and out of those surviving many have neurological deficits. However, not many of the patients survive in neurological vegetative states, the main problem being that those being hurt by an ischaemic cerebral injury die within weeks. When the National Institute of Health some years ago came out with a statement on this problem, it was obvious that no better outcome than in the 1960's could be expected now unless substantial progress in the field of ischaemic neurological protection could be achieved. After this statement was made public, however, a significant improvement has been published when 2 different groups independently have found that therapeutic hypothermia in the range 34-32 °C during 24 hours after resuscitation from a cardiac arrest improved survival and neurological outcome. This has changed the chances to find also pharmacological agents that could have the same or even better effects in this situation. In addition it is possible to make valid comparisons between effects of hypothermia and suggested pharmacological agents for screening purposes. A few hundred of such pharmacological compounds have already been tested in different experimental models, and at least one agent has been brought a stage 2 controlled clinical trials, where it unfortunately failed. This knowledge makes it possible both to make comparisons with a successful method as well as with a failing one. All these facts, also including new evidence of why artificial circulation during cardiopulmonary resuscitation (CPR) more or less always is insufficient *and* that there is no single receptor or molecular mechanism that, when used, elicits efficient neuroprotective mechanisms, has resulted in a knowledge background that seems to indicate that it seems highly probable that efficient neuroprotection after ischaemia and reperfusion is indeed possible.

Action taken: Since a decade we have had an experimental well-functioning model of cardiac arrest in piglets. Gradually the arrest period has been possible to increase. Presently we use a cardiac arrest of 21-23 min including 8 min CPR, and a follow-up period of at least three hours. After this the animal is sacrificed and the heart and the brain are harvested within a minute. The molecular biology of especially the brain is studied by microarrays, quantitative PCR and protein staining methods.

Considerable evidence has so far been collected implying that different neuroprotective mechanisms and pharmacological agents exhibit both similarities and differences as regards effects in gene activation and proteomics. It seems that block of nitric oxide elicited mechanisms seem essential for successful neuroprotection after long cardiac arrests. During 2011-2012 we have published two major articles on cerebral structural and gene activation changes after cardiac arrest and CPR as well as combined effects of methylene blue and induced mild hypothermia. In addition we have found that tight management of glucose blood concentrations does not have a major influence on cerebral injury after cardiac arrest and CPR.

Members of the group during 2012

Lars Wiklund, Professor

Cecile Martijn, PhD, post-doc

Hari Shanker Sharma, PhD, Associate Professor

Samar Basu, PhD

Fredrik Lennmyr, MD, PhD

Adriana Miculescu, MD, PhD

Egidijus Semenas, MD, PhD

Maria Molnar, MD, PhD student

Agencies that support the work/Funding

The Laerdal Foundation for Acute Medicine

Uppsala University Hospital (ALF)

Injury 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. Injury epidemiology is an integrated part of the Epidemiological & Statistical Group (EpiStat) at Uppsala Clinical Research Center. 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, Plastic surgery, Vascular surgery and Forensic Medicine. International collaboration in several projects has also been established with the International Collaborative Effort on Injury Statistics (ICE).

During the year, the focus has been to develop methods for injury epidemiology and its practical application. The ability to identify and study prehospital injury deaths and consequences of prehospital management remains a focus. We continue to develop the ICD-10 injury severity score in collaboration with ICE researchers in seven other countries. A joint publication with researchers from Centers for Disease Control (CDC) on the importance of prehospital injury deaths was finalised and the collaborative effort continues with the aim of defining valid indicators of injury incidence and improving injury severity models. A particular focus of our efforts is also on the ability to develop reliable estimates of comorbidity in injured patients and also applied to myocardial infarction. We also continue to work with Bayesian models to improve injury severity estimation. In collaboration with Forensic Medicine we have developed prediction models for the outcome after violent crime. A regional study of effects of prehospital trauma life support training (PHTLS) has been published and analysis and reporting of a follow-up using a semi-individual study design and hierarchical Bayesian modelling have been finalised.

As a part of the Uppsala Clinical Research Center we have also offered consultations on epidemiological methods and study design.

Members of the group during 2012

Rolf Gedeberg, Associate Professor

Jakob Johansson, MD, PhD

Hans Blomberg, MD, PhD student

Karin Andersson; MD, PhD student

In collaboration with:

Karl Michaëlsson, Professor

Ingemar Thiblin, Professor

Liisa Byberg, PhD, Associate Professor

Håkan Melhus, Professor

Margaret Warner, Injury Epidemiologist. NCHS, CDC, USA

James Harrison, Professor, Research Centre for Injury Studies, Flinders University South Australia

Agencies that support the work/Funding

Institutional Grant, Uppsala University

Uppsala University Hospital (ALF)

Lung function in anaesthesia 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 anaesthesia 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 Paulo, University of Helsinki and Jules Verne University, Amiens, France..

Inflammation induced by mechanical ventilation

About 3000 patients are treated with mechanical ventilation in the Swedish intensive care units due to ARF, a condition with mortality of about 30-40 per cent. 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 10 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 lungs 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.

Lung recruitment in neurosurgical patients with ARF

Lung recruitment is an important part in protective lung ventilation. However in neurosurgical, mechanically ventilated patients, lung recruitment maneuvers may, through increasing airway pressure indirectly increase the intracranial pressure, which in theory may compromise the cerebral circulation. An experimental study has been performed and a clinical study with measurements of intracranial metabolism with microdialysis, cerebral oxygen tension and intracranial pressure during a standardized lung recruitment maneuver is ongoing. The hypothesis is that the cerebral changes are short-acting without harm and that this kind of maneuvers may also be performed in this patient category under careful observation.

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 centralised 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 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 anaesthesia

In obese patients undergoing anaesthesia 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.

Members of the group during 2013

A Larsson, MD, PhD, Professor

Fredrik Lennmyr, MD, PhD, Associate Professor

Filip Freden, MD, PhD

Fernando Suarez Sipmann,, MD , guest reseacher

Joao Baptista Borges, MD, PhD

Peter Frykholm, MD, PhD

Rafael Kawati, MD, PhD

Laszlo Vimlati, MD, PhD

Jamie Retamol Montes, PhD student

Mariangela Pellegrini, PhD student

Robert Sütterlin, MD, PhD student

Peter Kostic, MD, PhD student

Henrik Reinius, MD, PhD student

Staffan Höstman, MD, PhD student

Joakim Engström, RN, PhD student

Göran Hedenstierna Professor, Dept. of Medical Sciences, Uppsala University

Bernard Holzgraphe, MD, Karolinska Hospital, PhD student

Michael Lichtwarck-Aschoff, Ass Professor, University of Freiburg, Germany

In collaboration with:

A Pedotti, PhD, Politecnico di Milano, Milan, Italy

A Aliverti, PhD, Politecnico di Milano, Milan, Italy

M Quaranta, PhD, Politecnico di Milano, Milan, Italy

E Zennin, Politecnico di Milano, Milan, Italy

M Amato, MD, PhD, Univerity of Sao Paolo, Brazil

M Senturk, Professor, University of Istanbul, Turkey'

G. Perchiazzi, University of Bari, Italy

L Porra , University of Helsinki, Finland

S Bayat, Jules Verne University, Amiens , France

Agencies that support the work/Funding

Swedish Research Council (VR)

Swedish Heart and Lung Foundation (HLF)

University of Sao Paolo

Uppsala University Hospital (ALF)

Institutional Grants, Uppsala University

Pain research group

Principal investigator: Torsten Gordh

Biological markers relevant to pain pathophysiology

A cooperation with Uppsala Berzelii center. The aim is to collect blood samples and tissue from very well characterized groups of pain patients, and to analyze relevant biomarkers. We have in this project access to extremely sensitive analytic methods, in cooperation with Prof Masood kamali (the PLA method) and dr med sci Magnus Wetterhall (mass spec). It is run as a PhD student project by Anne-Li Lind.

Visualisation 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 PETscan” is ongoing, in order to pin point to what cellular structure the relevant marker is binding to.

This is a PhD project for dr Mikko Aarnio.

Neuropathic pain

In this project, mechanisms of neuropathic pain are explored by a combination of clinical routine methods and a range of newly developed techniques to objectively test neuronal function. Three basic approaches are combined:

- patient evaluation including quantitative sensory testing and newly developed objective tests for C-fiber function
- Microneurography allowing for single fiber recordings to assess specific *functional* changes in sensory and axonal membrane properties.

Skin biopsies to assess *structural* changes of axons and endings including modulated channel expression (results being provided by collaboration with Frank Rice, Albany, USA)

Persistent postoperative pain

In this project, a genetic analysis of patients who have developed chronic pain after inguinal hernia 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 100 with persistent pain + 100 without pain who all have been investigated clinically. The results show that

persistant postoperative pain in mainly of neuropathic character. The project is done in collaboration with Professor Fred Nyberg.

Strong opioids for long term treatment of pain

We are undertaking a study on long term effects, side effects and effects on quality of life, opioid receptor polymorphism as related to effect, and nerve cell culture receptor studies efter chronic opioid exposure. In addition a clinic pharmacokinetic analysis of methadone in pain patients is ongoing.

Effect of anaesthetic drugs on the developing brain

Collaboration with Doc Anders Fredriksson, in a PhD project for Emma Pontén. PhD exam was successfully obtained in 2012.

Members of the group during 2012:

Torsten Gordh, Professor Pain Research, anaesthesiology

Maija-Lisa Kalliomäki, MD, PhD, post-doc

Annica Rhodin, MD, PhD

Emma Pontén, MD, PhD

Mikko Aarnio, MD, PhD student

Anne-Li Lind, PhD student

In collaboration with:

Roland Schmidt, MD, PhD, clinical neurophysiology

Martin Schmelz, Professor, University of Heidelberg

Rolf Karlsten, MD, PhD, ASTRAZENECA

Björn Hägglöf, resercher, ASTRAZENECA.

Anders Fredriksson PhD, psychiatry

Fred Nyberg, Professor, Uppsala University

Agencies that support the work/Funding

Regional Clinical Research Council

Astrazeneca R&D

University of Heidelberg

Vinnova and Vetenskapsrådet via Uppsala Berzelii Center

Uppsala University Hospital (ALF)

Institutional Grants, Uppsala University

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, characterised 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. 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.

Does tigecycline exert antiinflammatory effects?

Tigecycline is a novel antibiotic, the first in the glycylycylcline class, to be used in critically ill humans. It is not dependent of renal function. 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. The aim of this study is to evaluate whether tigecycline might have such effects and, if so, whether tigecycline might have beneficial effects on the pathophysiological responses in the endotoxemic pig, a “sterile” model of septic shock associated with an extensive inflammatory reaction.

Steroids and sepsis

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.

Renal function during 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.

Proteomics

Vasodilation and leakage through the capillary bed is a part of the septic response. This causes a considerable need for fluids and vasopressor support. We are aiming to study biopsies and investigate the degree of endotoxin mediated vascular changes /capillary leak from the mucosa in experimental septic shock. Possibly, some of the molecules passing through the vascular bed can be analyzed. We have been taken biopsies from the mucosa at baseline, before administrating endotoxin infusion and after 6 h of endotoxemic challenge. The biopsies were washed in physiological saline, then immediately frozen in liquid nitrogen, cut in the cryostat and mounted onto specific glass for the mass spectrometry. Next step is to make a histological examination in order to identify the interesting areas for detailed examination. We have in pre-tests detected protein expression of approximately 20 kDa. One interesting observation is that the expression of thymosin may be increased.

Blood sampling 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 prioritised. 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 analysed within a cartridge that is never in contact with the device itself. Utilising an experimental model, we have compared intraosseous bone marrow aspirates analysed 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 analyser, 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 6 h 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 CV:s 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 CV:s. This work was published 2012 in Resuscitation. We have also presented a report in: Scand J Lab Clin Invest (e-publication ahead of print), 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.

In summary, analysis of intraosseous samples with a handheld, cartridge-based system is convenient and should bypass the proposed problem with bone marrow contents damaging conventional laboratory equipment. There is a reasonable agreement between intraosseous

and arterial blood for electrolytes and haemoglobin, consistent with previous results. pH and lactate clearly covariate between intraosseous and arterial blood but pH is lower and lactate higher in the intraosseous compartment. There also seems to be a better agreement for bicarbonate than for Base Excess. There is generally a good agreement between intraosseous samples from different sites.

Members of the group during 2012:

Mats Eriksson, MD, PhD, Associate Professor

Anders Larsson, Professor, Dept. of Medical Sciences, Uppsala University

Miklos Lipcsey, MD, PhD

Gunnar Strandberg, MD, PhD student

In collaboration with:

Mats Gustafsson Professor, Dept. of Medical Sciences, Uppsala University

Agencies that support the work/Funding

The Laerdal Foundation for Acute Medicine

Model of living bacteria

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 anaesthetised 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.

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 anaesthetised endotoxemic pigs. Huma studies in sepsis patients are planned later this year.

Members of the group during 2012

Mats Eriksson, MD, PhD, Associate Professor

Miklos Lipcsey, MD, PhD

Ewa Söderberg, MD, PhD student

Magnus von Seth, MD, PhD student

In collaboration with:

Anders Larsson, Professor, Dept. of Medical Science, Uppsala University

Jan Sjölin, Professor, Dept. of Medical Sciences, Uppsala University

Per Andreen, Professor, Dept. of Pharmaceutical Biosciences, Uppsala University

Ricardo Feinstein, Laborator, Swedish University of Agricultural Sciences, Uppsala

Mats Sjöquist, Professor, Swedish University of Agricultural Sciences, Uppsala

Markus Castegren, MD, PhD, Eskilstuna County Hospital, Eskilstuna

Agencies that support the work/Funding

Institutional Grant, Uppsala University

Uppsala University Hospital (ALF)

WyethAB

Metabolism and nutrition

Principal investigator: Torbjörn Karlsson

Nutrition and body composition in traumatic head injured patients

Background: The scientific background and evidence for nutritional efforts after severe head trauma is weak, but observational studies show that many of these patients (68% in our material) suffer malnutrition according to specific criteria during the course of treatment. We have observed that this affects the rehabilitation of this group of patients.

We aim to explore the course of energy balance the first months after head injury and to develop a clinical method to measure and predict energy expenditure after traumatic brain injury-

We have used daily indirect calorimetry and the doubly labeled water technique to assess energy expenditure in a group of TBI patients. We are using repeated CT scans to study the effects on muscle and fat catabolism and preliminary results show different effects on peripheral fat and intraabdominal fat deposits, while muscular catabolism seem to be more general.

Metabolic and hormonal effects of Subarachnoid hemorrhage

SAH can give rise to an intracerebral metabolic crisis and we have observed that changes in the blood glucose by insulin injection (aiming at a tight glucose control) might give rise to a

potentially to low intracerebral glucose concentration. We have also observed an increased level of non-transmitter amino acids 3-4 days after the onset of SAH, with a difference between non-awake patients with less affected consciousness. Possibly as a result of the intracerebral repair process.

Questions: What is the EE in the acute phase after SAH and how does it change over time? Is there a relation between EE and the severity of SAH as measured with Fisher, WFNS and the development of delayed ischemic neurologic deficits? Is there a relation between EE and the brain's metabolism as measured with intracerebral microdialysis? Is there a relation between the EE, the endocrinological reactions and systemic complications? Is there a relation between the EE and the cerebral blood flow as measured with Xe-enhanced CT?

We are using clinical data, hormonal analyses, intracerebral microdialysis and general hemodynamic monitoring completed with indirect calorimetry and radiology to answer the above questions. Preliminary results from an ongoing study (n 83 SAH patients) show increased p-NT-proBNP after SAH; probably both from the heart and the brain, and, the results indicate that p-NT-proBNP could be used as a marker of more severe SAH disease.

Members in the group 2012:

Torbjörn Karlsson, MD, PhD

Elisabeth Ronne-Engström, MD, PhD

Jörgen Borg, Professor Karolinska Institutet

Karolina Krakau, RN, PhD

Maria Zetterling, MD, PhD

Christoffer Nyberg, MD, PhD student

In collaboration with:

Anders Magnusson, Professor Radiology Uppsala

Lars Ellegård, MD, PhD Gothenburg

Agencies that support the work/Funding

Institutional Grants, Uppsala University

Uppsala University Hospital (ALF)

Fresenius Kabi

GE Healthcare

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Endocrine Surgery

Principal investigators: Per Hellman, Gunnar Westin, Peter Stålberg, Göran Åkerström

Genetics and treatment of endocrine tumors

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

Endocrine tumours are of special interest in tumour biology because of a common extended disease course, and often presence of only few specific genetic changes, which can be related to variable tumour biology. For many endocrine tumours histopathology can often not distinguish tumours 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 tumour genes and other prognostic markers of importance for the development and progression of endocrine tumours, reveal gene changes with new technology, and investigate new possibilities of treatment against tumour progression.

Parathyroid

In parathyroid tumours 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 tumour growth in SCID mice, supporting our identification of a new important receptor for Wnt-mediated tumourigenesis. The same mutation has been revealed and found to influence tumour 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 tumour 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 tumour DNA methylome has revealed several epigenetically deregulated genes of putative importance to benign and malignant parathyroid tumourigenesis. The HIC1 tumour 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 tumours regardless of the hyperparathyroid disease state.

Carcinoids

Small intestinal neuroendocrine tumours (SI-NETs; midgut carcinoids) have been studied with molecular methods. We have as the first group revealed presence of a suspect tumour suppressor gene for SI-NETs on chromosome 18q. Chromosome 18q was also shown to be involved in familial tumours in collaboration with Professor E Tiensuu-Janson. A candidate tumour suppressor gene at 18q, Elongin, has been thoroughly studied. Expression array has identified different clusters of tumours, and further methylation as well as single nucleotide polymorphism arrays have continued the search for molecular deficits in these tumours. Presently, novel mutations in candidate genes are being analysed. Also, the large local cohort

in Uppsala, but also nationally, are identified clinically and tumour 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 tumours. In an ongoing study, we have by exome sequencing identified a gene involved in the development of insulinoma; and further studies in other tumours 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 tumours to cover the majority of the tumours. 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 tumour 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 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 so called PIVUS cohort). The implication of vitamin D deficiency is specially studied. In this context, also associations of aldosterone, PTH and cardiovascular factors are investigated.

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

Members of the group during 2013

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 2013

Katarina Edfeldt, Genetics in small intestinal neuroendocrine tumours

John Eriksson, Epidemiological studies of small intestinal neuroendocrine tumours

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

Elham Barazeghi, epigenetic derangements in parathyroid tumours

Maria Annerbo, hypocalcemia in Graves disease

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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.

Esophageal- and Gastric Surgery

The research in Esophageal- and Gastric Surgery is focused on two main areas; bariatric surgery, and esophageal- and gastric cancer.

Bariatric surgery

In bariatric surgery, we have three main areas of research; 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.

At present, we are conducting studies in preoperative reduction of liver fat, different anastomotic techniques, appetite-regulation in operated patients and controls as well as calcium homeostasis and vitamin-D levels.

In collaboration with Örebro, we are finishing a 10-year follow-up of 880 GBP-operated patients, focusing on long term weight results, vitamin-D status, nutritional status, and quality of life. Results show good weight results in generally satisfied patients.

The effects of bariatric surgery on colorectal- and anal sphincter function is evaluated in a PhD project using manometry and validated questionnaires.

Much of our work is performed in collaboration with other units in the hospital or at the University, such as the Dept of Endocrinology, the Metabolic unit at the University Hospital, and MRI, Institution of Radiology, Oncology, and Radiation Sciences.

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 working on detailed loco-regional evaluation of oesophageal cancer with 3T MRI and endoscopic ultrasound.

In esophageal resections, the gastric tube is evaluated with continuous pH_i-measurements in an attempt to identify early ischemia.

Patient outcome is studied on a national level in collaboration with the national quality register, NREV.

Members of the Esophageal- and Gastric Surgery group

The research group is headed by Magnus Sundbom, MD, PhD, associate professor of surgery. Further participants are: Jakob Hedberg, MD, PhD, David Edholm, MD, PhD, Zakaria Abdulla, MD, Eduardo Sima, MD, Gustav Linder, MD, and Martin Skogar, MD.

Publications (last 3 years)

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External Funding

Bergholms fond, 300 000 SEK, M Sundbom

Bergholms fond, 100 000 SEK, J Hedberg

Liver surgery

Introduction

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 oxaliplatin based 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

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, (awaiting ethical approval).

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 12 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. One 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

This research group is headed by Ulf Haglund, MD, PhD, professor em of surgery and Agneta Norén, MD, PhD, Frans Duraj, MD, and Jozef Urdzik, MD.
New member 2014 MD Petter Fruhling

Ongoing collaboration with Prof Per Artursson dep of pharmacy BMC, assoc prof Åke dep of oncology, Berglund, assoc prof Tomas Bjerner, dep of radiology

Publications (last 3 years)

Early identification of clinically relevant drug interactions with the human bile salt export pump (BSEP/ABCB11).

Pedersen JM¹, Matsson P, Bergström CA, Hoogstraate J, Norén A, LeCluyse EL, Artursson P. *Toxicol Sci.* 2013 Dec;136(2):328-43.

Magnetic resonance imaging flowmetry demonstrates portal vein dilatation subsequent to oxaliplatin therapy in patients with colorectal liver metastasis.

Urdzik J, Bjerner T, Wanders A, Duraj F, Haglund U, Norén A. *HPB (Oxford).* 2013 Apr;15(4):265-72.

The value of pre-operative magnetic resonance spectroscopy in the assessment of steatohepatitis in patients with colorectal liver metastasis.

Urdzik J, Bjerner T, Wanders A, Weis J, Duraj F, Haglund U, Norén A. *J Hepatol.* 2012 Mar;56(3):640-6. Epub 2011 Oct 23.

Insights Imaging. 2012 Aug;3(4):387-93. Epub 2012 May 3.
Stereology: a novel technique for rapid assessment of liver volume.
Torkzad MR, Norén A, Kullberg J.

External Foundings

Erikssons fond (A Norén)
Further MRI studies on liver and SI
100 000 kr october 2013

Lions fond (assoc prof Åke Berglund)
Further studies of proteomics and Oxaliplatin with BMC

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 randomised 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.

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 2013

This research group is headed by Britt-Marie Karlson, MD, PhD and includes Ann Langerth, MD, Stefan Linder MD, PhD, Christopher Månsson MD and Bahman Darkahi MD.

Britt-Marie Karlson is on the board of National Registry of Pancreatic Cancer.

Agencies that support the work/Funding

The research is funded by "*ALF-medel*".

Publications last 3 years

Safety and preliminary efficacy of ultrasound-guided percutaneous irreversible electroporation for treatment of localized pancreatic cancer. Månsson et al. *Anticancer Res* 2014 Jan;34(1):289-93

Effectiveness of antibiotic prophylaxis in cholecystectomy: a prospective populations-based study of 1171 cholecystectomies. Darkahi et al. *Scand J Gastroenterology* 2012 Oct;47(10):1242-6

Un unusual presentation of a solid pseudopapillary pancreatic tumor. Månsson, Karlson. *E-pub* 2012

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-tRNA synthetase, 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 analysed concerning various outcomes. One project aims at evaluating the histopathological specimens, and we have observed that neoplastic cells are absent in 15%. Closer characterization of this subgroup is under way. We are also studying the morbidity after surgery and HIPEC, its effect on outcome and predictors of morbidity. We have together with the other Swedish centers formed a network and a national registry as well as national multicenter studies are planned.

Functional bowel disorders and proctology

In depth analyses of bowel motility has since long been a focus of the group. We have analysed 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 5 (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 stabilised hyaluronic acid against placebo has been followed up after 3 years and the effect was essentially unchanged. We have also analysed 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 is about to start.

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 12 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 as an etiological factor. This project is performed together with The Pediatric gastroenterologists. We participate in the research network: Swedish organisation for inflammatory bowel disease.

Members of the group 2013-2014

Wilhelm Graf, professor, director

Helgi Birgisson, ass professor

Urban Karlbom, ass professor

Lars Pählman professor emeritus

Joakim Folkesson, MD, Ph D

Helene Silliin, MD, Ph D

Filip Sköldberg, MD, Ph D

Peter Cashin, MD, Ph D

Helgi Johansson, MD, Ph D

Åsa Collin, MD

Lana Ghanipour, MD

Malin Enblad, MD

Johan Danielsson, MD

Jan Lehman, MD

Saraj Abolghasem MD

Torbjörn Zackari MD

Publications 2011-2014

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Dissertations 2013

Håkan Andreasson. Pseudomyxoma peritonei. Aspects of natural history, learning curve, treatment outcome and prognostic factors. 2013-05-25.

Bo Hultman. Clinical and Experimental Studies in Peritoneal Metastases from Gastric Cancer. 2013-05-18.

Experimental Surgery

Principal investigators: Peyman Björklund and Per Hellman

The group of Experimental Surgery has 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 tumour 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 tumour. Viable tumour cells are then subjected to screening for druggable targets.

Adrenal tumours; genetics, epigenetics and new therapeutic strategies

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

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

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

Complicated Graves disease

Even though Graves 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 tumours, aiming at improved diagnostic imaging procedure.

Examinations

Lee Starker MD, PhD defended his doctoral thesis entitled " New Insights in Genetic and Epigenetic Mechanisms Involved in Parathyroid Tumorigenesis" in October 2013.

Members of the group during 2013

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

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

Maria Annerbo, MD, PhD student (Calcium Metabolism in Graves disease)

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

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

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

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Selander Foundation

Lions Cancerfond

Uppsala University Medical Faculty Starting Grant

Scientific Reports

Forskningsområde 1: Clinical cancer epidemiology

Forskargrupp 1: Clinical cancer epidemiology

Forskargrupperledare: 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, Italy. Researchers at the Dana-Farber Cancer Institute at Harvard Medical School, Boston, USA, collaborates 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 a 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 2013 (last year)

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 candidate, MD, 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.

Publications 2011-2013

1. Van Hemelrijck M, Garmo H, Holmberg L, Walldius G, Jungner I, Hammar N, Lambe M. Prostate cancer risk in the Swedish AMORIS study: The interplay among triglycerides, total cholesterol, and glucose. *Cancer* 2011; 117(10):2086-95.
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Agencies that support the work/Funding

Cancerfonden 2010-2012: 900.000 – 1.000.000 kr/år.

Cancer Research UK, Cancer Research UK, £300.000

Forensic medicine

Principal investigator Ingemar Thiblin

The research at the Division of Forensic Medicine essentially follows two lines; consequences of abuse of anabolic androgenic steroids (AAS) and injury epidemiology/injury interpretation.

The connection between use of anabolic androgenic steroids (AAS) and substance abuse and criminality

The relationship between the use of AAS, premature death, and violent crime has been investigated for many years. In 2008, two dissertations were presented: one concerned the link between the use of AAS and the abuse of illegal drugs and the other concerned the link between the use of AAS and criminality. In 2013 a dissertation on the acute influence of alcohol illegal drugs, benzodiazepines and AAS on violence or suicide was presented. Currently, there are two on-going projects. 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 2002–2009. 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

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 focussed 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 Dept of Forensic Psychiatry, Stockholm.

Sudden cardiac death

Deaths that are sudden and unexpected and affect younger persons are generally subjected to forensic medicine investigations. In a significant number of such cases, the forensic pathologist cannot identify any cause of death. All organs appear to be healthy and there are no toxins in the body. Most such deaths are probably connected to genetic defects/mutations affecting the cardiac conduction system or the functionality of the cardiac myocytes. A series of such mutations affecting different mechanisms is described. We focus on mutations affecting the proteins that structurally and functionally connect the cardiac myocytes. According to our hypothesis, the importance of this form of mutation for sudden cardiac death is underestimated. The project is conducted in cooperation with researchers at the Department of Genetics and Pathology, Uppsala University.

Members of the group during 2013

Ingemar Thiblin, professor

Håkan Sandler, MD, PhD

Greta Ågren, Ass. Professor

Lena Lundholm, PhD student

Hamid Mobini-Far, PhD student

Fredrik Tamsen, PhD student

Collaborations:

Rolf Gedeberg, Ass professor UCR, Uppsala University

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

Marie Allen, Ass. Prof. Inst. Of pathology and genetics, Uppsala university.

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

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Hand surgery

Principal investigator: Monica Wiig

A) Flexor tendon surgery. 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 remodelling, inflammatory response and fibrosis. We have also looked at changes in mRNA expression of neuropeptides and factors involved in angiogenesis.

Recently, 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.

We have used the animal model that we have developed and utilized in earlier studies. The rabbit model is highly relevant for the human situation, regarding the anatomy, biochemistry and molecular biology of the tendons, tendon sheath etc.

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

We have performed a prospective, randomised, 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. Efficacy was assessed by measurements of total active motion of the injured finger, tip-to-crease distance, rate of tenolysis and grip strength, and safety parameters were followed, for up to 12 months post-surgery. The study ended in 2013, we are now in the process of analysing data and evaluate the results.

The plan is to continue the work with mechanism of action studies for the test substance by extracting and measuring mRNA for different inflammatory cytokines and genes participating in the fibrinolytic process in the tendon and tendon sheath at different time points after surgery.

B) 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.

During 2013 we started a clinical study involving 140 patients referred to the Department of Hand surgery, Uppsala University Hospital, with the trigger finger diagnosis. The study will analyze risk factors for the development of trigger finger and address outcome after surgery. Biomaterials will be collected and used to study the mechanisms behind the disease.

Members of the group during 2013

Monica Wiig ,MD,PhD, ass. Prof.

Sara Edsfeldt, MD, PhD student

Björn Holm, MD, PhD student

David Hart, Prof.

Majvor Davidsson,

Ylva Petterson,

Ylva Gollbo Foucard

Elisabeth Källman

Eva Nordin

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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 in 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 2013

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 research group during 2013

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 centre 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 research group

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 research group during 2013

Björn Wikehult, RN, PhD

Linda Yngvedotter, RN, MSc Burn Center Uppsala University Hospital

Bengt Gerdin, MD, Professor

Surgical care

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

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.

Investigator

Eva Jangland, RN, PhD

Collaborations 2013

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 realise patient-centred 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 research group during 2013

Eva Jangland, RN, PhD

Lena Gunningberg, RN, ass Professor

Maria Carlsson, RN, ass 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 Randomised Control Study.

Members of the group during 2013

Anna-Karin Gunnarsson, RN, PhD student

Lena Gunningberg, RN, ass Professor

Kenneth B Jonsson, MD, ass Professor

Sune Larsson, MD, Professor

Torbjörn Åkerfeldt, MD, PhD student

Operating room care

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

Aims to analyse 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 research group during 2013

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

Anaesthesia 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 organisation within an operating department understand and experience operating room efficiency.
- Explore how organised surgical team members (Peritoneal Carcinomatosis team) and their leaders understand operating room efficiency.

Members of the group during 2013

Erebouni Arakelian, RN, MSc, PhD student

Haile Mahtheme, MD, ass Professor

Lena Gunningberg, RN, ass 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.

To search for new diagnostic and prognostic markers.

Members of the research group during 2012

Katarina Edfeldt, RN, MSc PhD student

Per Hellman, MD, Professor Supervisor

Peter Ståhlberg, MD, ass Professor Supervisor

Gunnar Westin, Professor Supervisor

Publications 2011 – 2013

1. Andersson C, Wassberg C, Johansson S, Ahlström H, Wikehult B. 18F-Fluorid-PET-CT : Patient expectations and experiences. Annual Congress of the European-Association-of-Nuclear-Medicine (EANM); OCT 19-23, 2013; Lyon, FRANCE. European Journal of Nuclear Medicine and Molecular Imaging. 2013;40(Suppl. 2):S510-S510.
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hyperthermic intraperitoneal chemotherapy treatment : a retrospective study. *World Journal of Surgical Oncology*. 2012;10:258-.

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9. Jangland E, Carlsson M, Lundgren E, Gunningberg L. The impact of an intervention to improve patient participation in a surgical care unit : a quasi-experimental study. *International Journal of Nursing Studies*. 2012;49(5):528-538.
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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, Lars Sand and Jan Hirsch

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, 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. Furthermore we are involved in establishing a hands-on digital workflow for planning of maxillofacial surgery where computerized tomography of the face are combined by scanning technologies of the teeth and jaws. Alloplastic reconstruction of the temporo-mandibular joint is another area where we focus and aim to report the Swedish experience and report follow-up results.

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 2013

Jan-Michaél Hirsch, DDS, PhD, Professor emeritus

Jamshid Jalouli, PhD, BSc, MSc

Lars Sand, DDS, MD, PhD, Associate Professor

Andreas Thor, DDS, PhD, Associate Professor

Mats Wallström, PhD, DDS

Doctoral-students

Anders-Petter Carlsson, DDS

Petter Gavelin, DDS

Miranda Jalouli, RN, BSc

Björn Lindell, DDS

Johanna Nilsson, DDS

Jani Talvilahti, DDS

Amela Trbakovic, DDS

Bent Williger, DDS, MD

Research Fellows

Lena Blomstrand, DDS

Maria Erkapers, DDS

Christoph Riben, DDS

Collaboration

Ewert Bengtsson, Ingrid Carlbom, Ingela Nyström, Centre for Image Analysis Uppsala University

Peter Thomsen, BIOMATCELL, Gothenburg University

Lars-Erik Rännar, Mikael Bäckström, Mid Sweden University

Jaan Hong, Department of Immunology, Genetics and Pathology, Uppsala University

Håkan Engquist, Uppsala University Ångström Laboratory Dept. of Engineering Sciences

Gunnar Antoni, Jens Sörensen; Pet-centre Uppsala University

Daniel Nowinski; Dept. of Surgical Sciences, Plastic surgery

Bengt Magnusson, Bengt Hasséus; Oral Medicine and Pathology, Sahlgrenska Academy, Gothenburg University

Hans-Florian Zeilhofer, Dep. of Cranio-Maxillofacial Surgery, University Hospital Basel, Switzerland

Salah Ibrahim, Faculty of Medicine and Odontology Dept. of Biomedicine, University of Bergen, Norway, Avd för Biomedicin University Bergen Norge, University of Khartoum, The Toombak Research Centre and Oral Cancer Campaign, Sudan

Lars Rasmusson, Lars Sennerby, Göran Kjeller, Dept. of Oral & Maxillofacial Surgery, Sahlgrenska Academy, Göteborg University

Jöns Hilborn, Thomas Engstrand, Uppsala University, Ångström Lab Dept. of Materials Chemistry, Polymer Chemistry

Lena Larsson, Oral Medicine and Pathology, Sahlgrenska Academy, Gothenburg University
Patricia Hedenqvist, Marianne Jensen Waern, Swedish University of Agricultural Sciences,
Uppsala

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Uppsala University Hospital (ALF)

Folktandvården, Uppsala

Several Foundations Sweden

TUA region Västra Götaland

Thuréus Foundation

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11. Klobas L. Stabilization appliance therapy has an equally extensive alleviating effect on jaw pain and frontal headache in patients with myogenous temporomandibular disorders (TMD), with or without chronic whiplash-associated disorders (WAD) grades 2 and 3. . 2013;
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13. Riben C, Thor A. The Maxillary Sinus Membrane Elevation Procedure : Augmentation of Bone around Dental Implants without Grafts - A Review of a Surgical Technique. *International journal of dentistry*. 2012;2012:105483-.
14. Hillbertz N S, Hirsch J, Jalouli J, Jalouli M M, Sand L. Viral and molecular aspects of oral cancer. *Anticancer Research*. 2012;32(10):4201-4212.
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Orthopedics

Medical epidemiology

Principal investigator: Karl Michaëlsson

The epidemiology research group is based at the UppsalaClinicalResearchCenter (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/>

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Swedish Research Council 2012-2015, VR 2011-2427, Påverkan av genetik och livsstil för osteoporos och osteoporosfrakturer, 4900 kSEK

ALF During the present year 2013, 1700 kSEK

The Swedish Council for Health, Working Life and Welfare 3000 kSEK 2012-2014

Members of the group during 2013

Head Karl Michaëlsson, professor

Liisa Byberg, PhD, associate professor

Carina Fredriksson, research nurse

Breiffni Leavy, research physiotherapist

Eva Warensjö-Lemming, PhD

PhD students during 2013

Breiffni Leavy (principal adviser Liisa Byberg)

Björn Knutsson(principal adviserat present Karl Michaëlsson)

Helena Hallström (dissertation 2013; principal adviser Karl Michaëlsson)

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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 couple of 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 getting the same amount of bone being formed. During the last year 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. Recently we did the first head on head study where our hydrogel was compared with the two commercially available carriers for BMP when used in a critical femoral defect in one of the preclinical models we are using. At present evaluation has yet to be completed.

A second research line is to optimise 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 have been done. By the use of our new micro-CT equipment formation of bone tissue and the in vivo behaviour 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 2013

Sune Larsson, professor

Richard Marsell, MD, PhD

PhD students

Anders Westermark

Gry Hulsart Billström

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7. Larsson Sune. Periarticular fractures around the hip and knee – Fix or replace? *J Orthop Trauma*. 2011 Jun;25 Suppl 2:S90-4.
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10. Wolf Olle, Mattsson Per, Milbrink Jan, Larsson Sune, Mallmin Hans. The effects of different weight-bearing regimes on press-fit cup stability: a randomized study with five years of follow-up using radiostereometry. *Int Orthop*. 2012 Apr;36(4):735-40.

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21. Hulsart-Billström Gry, Xia Wei, Pankotai Eszter, Weszl Miklós, Carlsson Elin, Forster-Horváth Csaba, Larsson Sune, Engqvist Håkan, Lacza Zsombor. Osteogenic potential of Sr-doped calcium phosphate hollow spheres in vitro and in vivo. *J Biomed Mater Res A*. 2013 Aug;101(8):2322-31.

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Spinal surgery

Principal investigator: Professor 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. An other project deals with Odontoid fractures in the elderly with a clinical multi-centre 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-centre RCT with the Spinal Surgery Research Group as the coordinating centre. 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 behaviour of spinal fixation in the anchylosed 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 2013

Professor Claes Olerud

Associate professor Anders Bjurholm

Associate Professor Håkan Jonsson

Associate Professor Yohan Robinson

Dr. Bengt Sandén

PhD students:

Dr. Peter Försth, Stockholm Spine Center

Dr. Thomas Karlsson

Dr. Björn Knutsson, Sundsvall

Dr. Anna MacDowall

Dr Anna-Lena Robinson

Dr. Martin Skeppholm, Stockholm Spine Center

Caroline Sköld, MD, resident, PhD student

Christian Carrwik, MD, resident, PhD-student

Jan Triebel, MD, MBA, resident, PhD-student

The Spine study group is financially supported by

Socialstyrelsen, Riksförbundet för trafik- och polioskadade, ALF, Cervical Spine Research Society - European Section, Depuy Spine Johnson & Johnson, Svensk Ryggkirurgisk Förening, European Spine Society.

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1. Bodon G, Glasz T, Olerud C. Anatomical changes in occipitalization: is there an increased risk during the standard posterior approach? *Eur Spine J.* 2013 May;22Suppl 3:S512-6. doi: 10.1007/s00586-013-2768-7. Epub 2013 Apr 11. PubMed PMID: 23575658; PubMed Central PMCID: PMC3641254.
2. Gulle E, Skärvinge C, Runberg K, Robinson Y, Olerud C. Pharmacological strategies to reduce pruritus during postoperative epidural analgesia after lumbar fusion surgery - a prospective randomized trial in 150 patients. *Patient Saf Surg.* 2011 May 14;5(1):10. doi: 10.1186/1754-9493-5-10. PubMed PMID:21569600; PubMed Central PMCID: PMC3118101.
3. Knutsson B, Michaëlsson K, Sandén B. Obesity is associated with inferior results after surgery for lumbar spinal stenosis: a study of 2633 patients from the Swedish spine register. *Spine (Phila Pa 1976).* 2013 Mar 1;38(5):435-41. doi:10.1097/BRS.0b013e318270b243. PubMed PMID: 22941097.
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Epub 2013 Jan 31. PubMed PMID: 23368746; PubMed Central PMCID: PMC3584606.

6. Robinson Y, Olerud C. Vertebroplasty and kyphoplasty--a systematic review of cement augmentation techniques for osteoporotic vertebral compression fractures compared to standard medical therapy. *Maturitas*. 2012 May;72(1):42-9. doi:10.1016/j.maturitas.2012.02.010. Epub 2012 Mar 16. Review. PubMed PMID: 22425141.
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13. Skeppholm M, Olerud C. Comparison of dysphagia between cervical artificial disc replacement and fusion: data from a randomized controlled study with two years of follow-up. *Spine (Phila Pa 1976)*. 2013 Nov 15;38(24):E1507-10. doi:10.1097/BRS.0b013e3182a516ef. PubMed PMID: 23883828.
14. Skeppholm M, Olerud C. Pain from donor site after anterior cervical fusion with bone graft: a prospective randomized study with 12 months of follow-up. *Eur Spine J*. 2013 Jan;22(1):142-7. doi: 10.1007/s00586-012-2456-z. Epub 2012 Aug 14. PubMed PMID: 22890567; PubMed Central PMCID: PMC3540321.
15. Skeppholm M, Ingebro C, Engström T, Olerud C. The Dysphagia Short Questionnaire: an instrument for evaluation of dysphagia: a validation study with 12 months' follow-up after anterior cervical spine surgery. *Spine (Phila Pa 1976)*. 2012 May 15;37(11):996-1002. doi: 10.1097/BRS.0b013e31823a7a5b. PubMed PMID: 22037524.

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17. Gargiulo P, Pétursson T, Magnússon B, Bifulco P, Cesarelli M, Izzo GM, Magnúsdóttir G, Halldórsson G, Ludvigsdóttir GK, **Triebel J**, Jónsson H. Assessment of Total Hip Arthroplasty by Means of Computed Tomography 3D Models and Fracture Risk Evaluation. *Artif Organs*. 2013 Jun;37(6):567-73 (*IF= 1.96*).
18. Magnússon B, Jónsson H, Pétursson T, Magnúsdóttir G, Halldórsson G, **Triebel J**, Gargiulo P. Gait Analysis, bone and muscle density in THA patients Basic and applied myology 2012; 22(3&4):135-140. (*IF=n.a.*)
19. Gulle E, Skärvinge C, Runberg K, **Robinson Y**, Olerud C. Pruritus during postoperative analgesia with epidural bupivacain, epinephrine and fentanyl is dramatically reduced if replaced with epidural ropivacain and peroral oxycodone in lumbar fusion surgery - A prospective randomized trial in 150 patients

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 i) that the pivotal role of inflammation after spinal cord injury has not been adequately addressed by current experimental strategies, ii) 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 suppresses 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 Håkan Aldskogius and Elena Kozlova-Aldskogius, Department of Neuroscience, Uppsala University.

Members of the group:

Nils Hailer, Associate Professor

Nikos Schizas, PhD student

Hannah Eriksson, MD student

Halgord Hassan, Bachelor of Sciences, project student

Lista över gruppens publikationer under de tre senaste åren:

1. Hailer NP, Bengtsson M, Lundberg C, Milbrink J. High Metal Ion Levels After Use of the ASR™ Device Correlate With Development of Pseudotumors and T Cell Activation. *Clinical Orthopaedics and Related Research*. 472(3):953-61. 2014.
2. *Schizas N, Rojas R, Kootala S, Andersson B, Pettersson J, Hilborn J, Hailer NP. Hyaluronic acid-based hydrogel enhances neuronal survival in spinal cord slice cultures from postnatal mice. *Journal of Biomaterial Applications*. 28(6):825-36. 2014.
3. Hailer NP, Hänni M, Widerström E, Mallmin H. Chronic obstructive pulmonary disease, younger age and impaired preoperative flexion increase the risk of stiffness after total knee arthroplasty: a retrospective case–control study. *European Orthopaedics and Traumatology*. 4:137-145. 2013.
4. Lazarinis S, Mattsson P, Milbrink J, Mallmin H, Hailer NP. A prospective cohort study on the short collum femoris-preserving (CFP) stem using RSA and DXA. Primary stability but no prevention of proximal bone loss in 27 patients followed for 2 years. *Acta Orthopaedica*. 84(1):32-9. 2013.
5. Hailer NP, Weiss RJ, Stark A, Kärrholm J. Dual-mobility cups for revision due to instability are associated with a low rate of re-revisions due to dislocation. *Acta Orthopaedica*. 83(6):566-71. 2012.
6. Weiss RJ, Kärrholm J, Hailer NP, Beckman MO, Stark A. Salvage of failed trochanteric and subtrochanteric fractures using a distally fixed, modular, uncemented hip revision stem. *Acta Orthopaedica*. 83(5):488-92. 2012.
7. Hailer NP, Weiss RJ, Stark A, Kärrholm J. The risk of revision due to dislocation after total hip arthroplasty depends on surgical approach, femoral head size, sex, and primary diagnosis. *Acta Orthopaedica*. 83(5):442-8. 2012.
8. Lazarinis S, Kärrholm J, Hailer NP. Effects of hydroxyapatite coating of cups used in hip revision arthroplasty: A Swedish Hip Arthroplasty Register study on 1,780 revisions. *Acta Orthopaedica*. 83(5):427-35. 2012.
9. Weiss RJ, Hailer NP, Stark A, Kärrholm J. Survival of uncemented acetabular monoblock cups. *Acta Orthopaedica*. 83(3):214-9. 2012.
10. Gudnason A, Milbrink J, Hailer NP. Implant survival and outcome after rotating-hinge total knee revision arthroplasty: a minimum 6-year follow-up. *Archives of Orthopaedics and Trauma Surgery*. 131(11):1601-7. 2011.

11. Lazarinis S, Kärrholm J, Hailer NP. Effects of hydroxyapatite coating on survival of an uncemented femoral stem. A Swedish Hip Arthroplasty Register study on 4,772 hips. *Acta Orthopaedica*. 82(4):399-404. 2011.

12. Hailer NP, Blaheta RA, Dahlstrand H, Stark A. Elevation of circulating HLA DR(+) CD8(+) T-cells and correlation with chromium and cobalt concentrations 6 years after metal-on-metal hip arthroplasty. *Acta Orthopaedica*. 82(1):6-12. 2011.

Forskningsanslag, anslagsgivare och storlek (belopp på 100 000 kronor och över)
- Link GmbH & Co KG, Hamburg: 400 Tkr (CFP-studien)

Disputationer det aktuella året
-2013: Stergios Lazarinis

Principal investigator: Hans Mallmin/Jan Milbrink

The Bioimplant research group evaluate new knee and hip implants through prospective and longitudinal studies, often in form of randomised, 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 a two year follow-up.

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 randomised 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 a osteoprotegrin-like action will be studied and followed for two years. Screening for inclusion has started and the first 35 patients have now been included.

Thesis:

2010 Olof Wolf. Osteoarthritis of the Hip Uncemented Total Hip Arthroplasty

2013 Stergios Lazarinis. Form and Finish of Implants in Uncemented Hip Arthroplasty: Effects of Different Shapes and Surface Treatments on Implant Stability

Peer-reviewed publications

1. Snellman G, Byberg L, Lemming EW, Melhus H, Gedeberg R, Mallmin H, Wolk A, Michaëlsson K.

Long-term dietary vitamin D intake and risk of fracture and osteoporosis: a longitudinal cohort study of Swedish middle-aged and elderly women.

J Clin Endocrinol Metab. 2013 Dec 10;jc20131738. [Epub ahead of print]

2. Karlsson MK, Ribom EL, Nilsson JA, Karlsson C, Cöster M, Vonschewelov T, Mallmin H, Ljunggren O, Ohlsson C, Mellström D, Lorentzon M, Leung PC, Lau E, Cauley JA, Barrett-Connor E, Stefanick ML, Orwoll E, Rosengren BE; for the Osteoporotic Fractures in Men (MrOs) Research Group

International and ethnic variability of falls in older men.

Scand J Public Health. 2013 Nov 20. [Epub ahead of print]

3. Hailer NP, Hänni M, Widerström E, Mallmin H

Chronic obstructive pulmonary disease, younger age and impaired preoperative flexion increase the risk of stiffness after total knee arthroplasty: a retrospective case-control study European Orthopaedics and Traumatology: Volume 4, Issue 3 (2013), Page 137-145

4. Wolf O, Mattsson P, Milbrink J, Larsson S, Mallmin H

Effects of postoperative weight-bearing on body composition and bone mineral density after uncemented total hip arthroplasty.

J Rehabil Med. 2013 May;45(5):498-503. doi: 10.2340/16501977-1140.

5. Leavy B, Åberg A.C., Mallmin H, Michaelsson K, Byberg L

When and where do hip fractures occur? A population-based study.

Osteoporosis International March 2013

6. A prospective cohort study on the short collum femoris-preserving (CFP) stem using RSA and DXA. Primary stability but no prevention of proximal bone loss in 27 patients followed for 2 years.

Lazarinis S, Mattsson P, Milbrink J, Mallmin H, Hailer NP.

Acta Orthop. 2013 Feb;84(1):32-9.

7. Analysis of bone mineralization on uncemented femoral stems by [18F]-fluoride-PET: a randomized clinical study of 16 hips in 8 patients.

Ullmark G, Nilsson O, Maripuu E, Sörensen J.

Acta Orthop. 2013 Apr;84(2):138-44

8. Ontogeny of sensory and autonomic nerves in the developing mouse skeleton.

Sisask G, Silfverswärd CJ, Bjurholm A, Nilsson O.

Auton Neurosci. 2013 Oct;177(2):237-43. doi: 10.1016/j.autneu.2013.05.005.

Epub 2013 Jun 12.

9. Rats treated with AZD2858, a GSK3 inhibitor, heal fractures rapidly without endochondral bone formation.

Sisask G, Marsell R, Sundgren-Andersson A, Larsson S, Nilsson O, Ljunggren

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Bone. 2013 May;54(1):126-32. doi: 10.1016/j.bone.2013.01.019. Epub 2013 Jan 19.

10. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial.

Eriksson BI, Dahl OE, Huo MH, Kurth AA, Hantel S, Hermansson K, Schnee JM, Friedman RJ; RE-NOVATE II Study Group.

Thromb Haemost. 2011 Apr;105(4):721-9.

30. Ontogeny of sensory and autonomic nerves in the developing mouse skeleton.

Sisask G, Silfverswärd CJ, Bjurholm A, Nilsson O.

Auton Neurosci. 2013 Jun 11.

11. Consensus document on prosthetic joint infections.

Lazarinis S, Lidgren L, Stefánsdóttir A, W-Dahl A.

Acta Orthop. 2013 Dec;84(6):507-8. doi: 10.3109/17453674.2013.867399. Epub 2013 Nov 29. No abstract available.

12. Effects of hydroxyapatite coating of cups used in hip revision arthroplasty.

Lazarinis S, Kärrholm J, Hailer NP.

Acta Orthop. 2012 Oct;83(5):427-35.

13. Inferior physical performance tests in 10,998 men in the MrOS study is associated with recurrent falls.

Karlsson MK, Ribom E, Nilsson JÅ, Ljunggren Ö, Ohlsson C, Mellström D, Lorentzon M, Mallmin H, Stefanick M, Lapidus J, Leung PC, Kwok A, Barrett-Connor E, Orwoll E, Rosengren BE.

Age Ageing. 2012 Nov;41(6):740-6.

14. Inferior physical performance test results of 10,998 men in the MrOS Study is associated with high fracture risk.

Rosengren BE, Ribom EL, Nilsson JÅ, Mallmin H, Ljunggren O, Ohlsson C, Mellström D, Lorentzon M, Stefanick M, Lapidus J, Leung PC, Kwok A, Barrett-Connor E, Orwoll E, Karlsson MK.

Age Ageing. 2012 May;41(3):339-44.

15. The effects of different weight-bearing regimes on press-fit cup stability: a randomised study with five years of follow-up using radiostereometry.

Wolf O, Mattsson P, Milbrink J, Larsson S, Mallmin H.

Int Orthop. 2012 Apr;36(4):735-40.

16. Metabolic development of necrotic bone in the femoral head following resurfacing arthroplasty. A clinical [18F]fluoride-PET study in 11 asymptomatic hips.

Ullmark G, Sundgren K, Milbrink J, Nilsson O, Sörensen J.

Acta Orthop. 2012 Feb;83(1):22-5.

17. Legg-Calvé-Perthes disease and the risk of injuries requiring hospitalization: a register study involving 2579 patients.

Hailer YD, Montgomery S, Ekblom A, Nilsson O, Bahmanyar S.

Acta Orthop. 2012 Dec;83(6):572-6.

18. Analysis of bone formation on porous and calcium phosphate-coated acetabular cups: a randomised clinical [¹⁸F]fluoride PET study.

Ullmark G, Sörensen J, Nilsson O.

Hip Int. 2012 Mar-Apr;22(2):172-8. doi: 10.5301/HIP.2012

19. GSK-3 inhibition by an orally active small molecule increases bone mass in rats.

Marsell R, Sisask G, Nilsson Y, Sundgren-Andersson AK, Andersson U, Larsson S, Nilsson O, Ljunggren O, Jonsson KB.

Bone. 2012 Mar;50(3):619-27. doi: 10.1016/j.bone.2011.11.007. Epub 2011 Nov 25.

20. Effects of hydroxyapatite coating on survival of an uncemented femoral stem. A Swedish Hip Arthroplasty Register study on 4,772 hips.

Lazarinis S, Kärrholm J, Hailer NP.

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Medlemmar i Bioimplantatgruppen

Professor Olof Nilsson

Adj Professor Hans Mallmin

Doc Jan Milbrink

Doc Nils Hailer

Med Dr Per Mattsson

Med Dr Stergios Lazarinis

Doktorand Asgeir Gudnason

Doktorand Andreas Nyström

Doktorand Aspirant Demostenis Kiritopoulos

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.

Members of the group during 2012

Sune Larsson, Professor

Tomas Borg, MD, PhD

Björn Hernefalk, PhD student

Oto-, rhino- laryngology and Head & Neck Surgery

Principal investigator: Matti Anniko/Göran Laurell

Experimental inner ear research, Pharmacokinetics, toxicity and otoprotection

Mechanisms of damage in inner ear disorders (infection, ischemia, ototoxic drugs, acoustic overstimulation) have been analyzed with special emphasis on free radicals, nitric oxide and reactive oxygen species. In one of the projects focus was to investigate if an overproduction of nitric oxide can be a final common pathway in inner ear disorders. The following techniques were used for analysis of nitric oxide: immunohistochemistry, DAF-2DA loading of cells with a detection limit of 5 nM and functional studies by auditory brainstem recordings including otoacoustic emissions and caloric testing.

Studies started at the individual hair cell level (isolated hair cells in vitro) followed by analysis at the organ level (organ culture in vitro and later functional – caloric - testing in vivo). Otoprotectants for nitric oxide were used in experimental models for acute and chronic otitis media using *Pseudomonas aeruginosa* exotoxin A as model substance in vivo. Since generation of nitric oxide and reactive oxygen species seems to be important factors causing experimental inner ear damage, treatment with radical scavengers is likely to be effective also in clinical inner ear disorders. This was favourably shown in a pilot study in patients with Ménière's disease. In another clinical study we documented the benefit of radical scavengers for elderly patients with age-related hearing loss.

The otoprotectant effect of edaravone has been documented for tobramycin-induced ototoxicity, *Pseudomonas aeruginosa* exotoxin A and in the development of experimental endolymphatic hydrops.

Expression of transient receptor potential vanilloid (TRPV) 1, 2, 3 and 4 has been demonstrated in the inner ear and also how this expression changes when the inner ear becomes exposed to gentamicin challenge – a drug used for treatment of infectious diseases and also topically applied in treatment of Meniere's disease. The TRPVs change also with age. TRPV3 seems to play a distinct role in the inner ear such as stereociliar organization, sensory cell transduction and inner ear fluid homeostasis.

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, cisplatin and oxaliplatin induced comparable levels of outer hair loss and 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.

The round window membrane (RWM) is a possible local entry route for pharmacological clinical treatment of inner ear disorders. The RWM is analysed experimentally with regard to permeability during normal and pathological conditions using brain derived neurotrophic factor (BDNF) and edaravone as otoprotectants.

Local treatment of the inner ear by intratympanic injection of a semi-solid gel has earlier been demonstrated by our group. 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.

Little is known about drug transport to and within the inner ear, but it is clear that the accessibility from the blood is limited by the blood-perilymph barrier and the intrastrial fluid-blood barrier. The endothelial cells of the stria vascularis capillaries, cochlear pericytes, and perivascular resident macrophage-type melanocytes are important components of the intrastrial fluid-blood barrier. The constitution of the blood-perilymph barrier is less well characterized. We are using experimental magnetic resonance imaging to better understand the permeability of the blood-perilymph barrier. Our experiments with three different gadolinium-containing contrast agents have demonstrated the pattern of distribution to the different scalae of the cochlea and the vestibular organs.

Pharmacokinetics and pharmacodynamics of drugs cannot be studied in human beings. Studies are performed in an experimental model 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 the 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 have 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 now planning to perform a randomized placebo-controlled clinical trial where we are going to evaluate a novel pharmacological method that has earlier shown good otoprotective effects in animals

Members of the group during 2013

Göran Laurell (project leader)

Adnan Lidian

Monika Stenkvist-Asplund

Birgitta Linder

Victoria Hellberg

Cecilia Engmér Berglin

Pernilla Videhult-Pierre

S. Allen Counter (Professor Harvard University, U.S.A.)

Masaya Takumida (Professor; Department of Otolaryngology and Head & Neck Surgery, Hiroshima University, Japan).

Collaborations

Karolinska institutet (Professor Barbara Canlon)

Linköping University (Professor Anders Fridberger)

Charité, Berlin (Dr. Agnieszka J. Szczepek)

10117 Berlin

Agencies that support the group/Funding

Japanese Medical Research Council,

Uppsala University Hospital (ALF)

Afa Insurance

Tysta Skolan

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.

Subproject 1: Characterization of suitable target antigens

We assess the amount of antigen expression in patient tumour tissue and cultured tumour cells using e.g. flow cytometry and radioimmunoassays. Current target antigens of interest in our research group are cell surface bound proteins such as CD44 and its isoforms, EGFR and HER2. CD44 is a multistructural and multifunctional cell surface molecule involved in cell proliferation, cell differentiation, cell migration, angiogenesis, as well as in signaling for cell survival. It has just recently come in focus in the field of tumour targeting, since it is one of the most common markers used for isolation of cancer stem-like cells. This makes it a highly interesting candidate for selective cancer targeting. CD44v6, an isoform of the membrane-associated glycoprotein CD44, is expressed in many types of human cancer, including head & neck squamous cell carcinoma. The difference in CD44v6-expression between healthy and malignant cells makes the CD44v6 antigen an attractive target for radionuclide tumour targeting. During 2012, we have been able to demonstrate that CD44v6 and CD44v7 expression is dramatically increased in tumor cells treated to increase the cancer stem cell

population. This indicates that these antigens may be involved in cancer stem cells, and we will pursue this field during 2013. Furthermore, we have thoroughly characterized CD44v6-targeting antibody fragments, both in culture tumor cells and in tumor bearing mice, and have found that the ^{111}In -labelled fragment AbD15179 may be very suitable for radionuclide diagnostics of head and neck cancer. During 2013, we will further characterize and optimize this molecule.

Subproject 2: Development and characterization of suitable targeting molecules

Suitable targeting molecules towards the most promising antigens for targeted diagnostics and therapy of head- and neck cancer are developed and characterized for potential in radionuclide tumour targeting in this project. Novel targeting molecules and radioconjugates, using antibodies, antibody fragments, Affibody molecules or natural ligands, are selected, radiolabelled, and characterized in cultured tumour cells. In combination with targeting vectors, different radionuclides are assessed for suitable targeting applications, e.g. ^{111}In and ^{124}I for imaging and ^{177}Lu , ^{131}I , and ^{211}At for therapy. The best conjugates are then evaluated for diagnostic or therapeutic purposes in tumour bearing mice.

Nutritional aspects

Long-term malnutrition is one of the reported sequelae 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.

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 tumour 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.

Members of the group during 2013

Department of Otolaryngology and Head and Neck Surgery

Göran Laurell (project leader)

Tomas Ekberg

Karl Sandström

Anna-Karin Haylock

Eva Lindell Jonsson

Kristina Lundberg

Ylva Tiblom-Ehrsson

Rudbeck Laboratory (Unit of Biomedical Radiation Sciences, Department of Radiology, Oncology and Radiation Science), Uppsala University

Heewa Kareem

Marika Nestor

Jörgen Carlsson (Professor)

Hans Lundquist (Professor)

Department of clinical sciences, Umeå University

Sandra Ottosson

Christos Loizou

Collaborations:

Department of Pathology, Umeå university hospital (Professor Karin Nylander). Department of social work, Umeå University (Professor Pär Salander) Department of clinical sciences (Katarina Olofsson).

Royal Institute of Technology (KTH) (Prof Sophia Hober)

Affibody AB

Department of Immunology, Genetics and Pathology, Uppsala University (Johan Botling, Kenneth Wester)

Uppsala Applied Science Lab, GE Healthcare (Irina Velikyan)

Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands (Professor Guus van Dongen)

National Institutes of Health (NIH/NCI), USA (JacekCapala)

Department of Otolaryngology and Head & Neck Surgery, University of Turku, Finland (Professor Reidar Grénman)

Agencies that support the work/Funding

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Uppsala University Medical Faculty

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Svenska Sällskapet för Medicinsk Forskning (SSFMF)

Studies on Bell's palsy (idiopathic facial nerve paralysis)

Each year 2,000 subjects in Sweden are struck by peripheral facial palsy. Of these 75% are of unknown origin, i.e. Bell's palsy. Until now no effective treatment has been established in this disease although several medical treatment studies have been performed.

In 2001 the Scandinavian Bell's Palsy Study (SBPS), organized from the Department of Otorhinolaryngology and Head & Neck Surgery, started to include patients in a double-blind randomized multicentre study. A beneficial effect on time to recovery and a better outcome occurred for patients treated with prednisolone whereas no beneficial effect was found with valacyclovir.

Further analyses documented the relation between early deterioration and outcome in Bell's palsy. The influence of time to treatment start and age in Bell's palsy and prednisolone treatment has been described.

Members of the group during 2012

Lars Jonsson

Mats Engström

Thomas Berg

Nina Bylund

Agencies that support the work/Funding

Uppsala University Hospital (ALF)

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 is accepted for publication 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. Though not as common as EIB, EILO is not uncommon in a general population and can therefore be an important differential diagnosis. EILO is equally common among girls and boys and can coexist with EIB. This manuscript will be submitted soon.

Ear research – Clinical and Experimental investigations

Principal investigator: Helge Rask-Andersen

Research can be separated into several areas:

1. “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

A new EU project started in September of 2013 called “Otostem”. This project aims to develop stem cell-based therapy for inner ear diseases. It includes several European research centres including the US centres at Harvard and Stanford Universities. It will last for four years. A post-doc has been employed who will be the main research person leading this project with the principal investigator. Our main task is to isolate and expand 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 material we will isolate and extract progenitors in cooperation with other centres. In addition, the localization of progenitors will be assessed through immunohistochemistry using various molecular markers such as Lgr5, Sox2. 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.

Regeneration and localisation of stem cells in the tympanic membrane

We are analysing the regenerative capacity of the human cochlea. Progenitor/stem cells are further analysed 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 analysed 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 analyse 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 analysed by Dr Elsa Erixon. She will present her thesis in June 5 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 has 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 has generated two publications.

Participants in the group

Wei Liu, Ass. Professor, MD, PhD

Fredrik Edin, PhD-student

Karin Strömbäck. MD, PhD, Ass. Pofessor

Anders Kinnefors

Niklas Danckwardt-Lillieström, Ass. Professor

Professor Gunnar Nyberg, Dept. of Neurosurgery

Assistant Professor Olafur Gudjonsson, Dept. of Neurosurgery

Rudolph Glueckert, PhD, Dept. of Otolaryngology, Innsbruck University

Annelies Schrott-Fischer, PhD, Dept. of Otolaryngology, Innsbruck University

Professor Hubert Löwenheim, University of Tuebingen

Professor Fred H. Linthicum, House Ear Institute, Los Angeles, USA

Hao Li PhD

Francesca Atturo, Rome, Italy

Agencies that support the work/Funding

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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 recently 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, BengtGerdin

A burn injury is a good model for understanding the response to a severe trauma, viewed from as well a 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.

1. 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.

2 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 sequelae, 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.

3 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 2013

Bengt Gerdin, Professor

Lisa Ekselius, Professor, Dept. of Neuroscience, psychiatry

Morten Kildal, MD, PhD, Associate Professor

Mimmie Willebrand, PhD, Associate Professor, Dept. of Neuroscience, Psychiatry

Fredrik Huss, MD, PhD, Associate Professor

Björn Wikehult, RN, PhD, Senior lecturer

Caisa Öster, RN, PhD, Senior lecturer, Department of Neuroscience, Psychiatry

Andreas Lindahl, MD, PhD

Filip Fredén, MD, PhD

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 signalling 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. Preliminary 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.

Members of the programme during 2013

Daniel Nowinski, MD, PhD, Associate professor

Bengt Gerdin, Professor

Malin Hakelius, MD

Elizabeth Kiwanuka, MD
Fredrik Huss, MD, PhD, Associate Professor
Daniel Saiepour, MD, PhD
Kristofer Rubin, Professor, IMBIM
Mikael Ivarsson, PhD, Örebro University

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, PI: Mimmie Willebrand (UU), co-applicant Bengt Gerdin 2011-2013.

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, PI: Lisa Ekselius (UU), co-applicant Bengt Gerdin 2011-2013.

Personskador till följd av bränder (Injuries to man due to injuries); MSB (Swedish Civil Contingencies Agency) PI: Fredrik Huss 2011.

Uppsala University Hospital (ALF)

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Members of the group during 2013 (last year)

Elisabeth Ståhle, Professor

Stefan Thelin, MD, visiting professor

Anders Albåge, MD, associated professor

Lena Jideus, MD, PhD

Laila Hellgren, MD, PhD

Thoracic Surgery

Rickard Lindblom MD, PhD

Ulrica Alström MD, PhD

Per Vikholm MD

Petter Schiller MD

Emma Thoren MD

Axel Dimberg MD

Principal investigator: Elisabeth Ståhle

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“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.

Kirurgisk behandling av förmaksflimmer i samband med hjärtkirurgi. Konsensusrapport från Sveriges arytmiensvariga hjärtkirurger. Läkartidningen **2012** Feb 1-7;109(5):214-7.

Preventive strategies for atrial fibrillation after cardiac surgery in nordic countries. Maaros M¹, Tuomainen R, Price J, Rubens FD, Jideus RL, Halonen J, Hartikainen J, Hakala T.

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Dissertations 2013 (last year)

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Agencies that support the work/Funding

Anslagsgivare, storlek (belopp på 100 000 kronor och över)

Project 1: Studies on hemostasis in cardiac patients

Namn på medverkande: Elisabeth Ståhle, Ulrica Alström, Axel Dimberg

In collaboration with professor Agneta Siegbahn and Christina Christersson studies on coagulation and hemostasis in cardiac patients with focus on heart surgery and heart valve prosthesis.

Biomarkers and risk factors associated with bleeding in aortic valve heart surgery.

Symptomatic narrowing of the aortic heart valve, aortic valve stenosis, is preferably treated with surgical valve replacement with a prosthesis. This generally requires an extensive open-heart surgical procedure using a heart lung machine. Bleeding is a common problem associated with valvular replacement, and up to 7 % of patients need a subsequent acute operation to stop bleeding. During 2013 a project focusing on bleeding problems in relation to and after heart valve surgery was initiated. Until February 2014 forty patients have been included. The project includes prospective studies of the mechanisms for the increased trombogenesis and results of anticoagulant treatment in these patients. Clinical studies with the aim to establish the magnitude of thrombotic and hemorrhagic incidences in these patients, both in relation to surgery and afterwards. The extent to which these events affect the long-term outcome. are also studied.

Patients are treated with different anticoagulant and anti-platelet drugs before, during and after surgery, which can contribute to increased risk for bleeding. Valve surgery has been

shown to have 2-3 times more bleeding complications when compared to coronary bypass surgery, the most common type of cardiac surgery.

Predicting bleeding complications is likely to benefit patients undergoing cardiac surgery. Excessive bleeding after surgery is associated with an increased risk of adverse outcome, including death. Patients are therefore treated aggressively with transfusion of different blood components, medications and sometimes hasty surgical intervention to stop bleeding.

In this study, patient related risk factors and prior medical treatment will be analysed. Biomarkers present in patient blood analyses before and after surgery will be measured. These markers are known to describe the condition of the bloods haemostatic components: proteins, platelets and the cells lining the inside of blood vessels. Levels of von Willebrand factor, sP-Selectin and cell fragments reflect the degree of platelet activation, which in turn could correlate to excessive bleeding or inadequate thrombus formation.

The main purpose of the study is to investigate causes of abnormal bleeding after valvular heart surgery. Patients undergoing 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. Effects on short and long term survival and complications due to bleeding are also investigated.

Projekt 2: Management of right heart failure during LVAD-therapy

Namn på medverkande: Laila Hellgren, Petter Schiller, MD and Per Vikholm, MD

Severe heart failure can be treated with a left ventricular assist device (LVAD), most commonly as a bridge to a future heart transplantation. After the surgery, most patients can be discharged with the LVAD and wait for the transplantation in their home.

Varying degrees of right heart failure is common after LVAD-surgery, the reasons for this are to some extent unknown. Mild right ventricular failure is expected and can be managed through optimizing volume status and medications, severe right heart failure on the other hand is a serious condition with high mortality. The conventional way of handling severe right heart failure after LVAD-surgery is to add a pump to the right ventricle as well; resulting in a bi-ventricular assist device (BiVAD). However, there are drawbacks with a BiVAD-system. Firstly, it involves a large surgical procedure on critically ill patients. Secondly, the patients are bound to a intensive care unit waiting for heart transplantation since there are no BiVAD-systems that allows discharge.

An experimental model has been created in pigs in order to study partial volume exclusion as a potential treatment for right heart failure. 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-aortic shunt resulted in decreased right atrial pressure and increased mean arterial pressure. Since the cavo-aortic 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, partial volume exclusion as a treatment for right heart failure by the means of a cavo-pulmonary and cavo-aortic shunting has been shown feasible in an experimental setting. These therapies might be useful in a clinical situation of right heart failure during LVAD-treatment, as an alternative to a BiVAD-system.

Project 5: Arrhythmia surgery

Research group: Lena Jidéus (group leader), Anders Albåge, Vitas Zemgulis

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 4 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 and on-going medication. In this study, surveys have been sent out to over 450 individual patients in 3 centers and almost 300 recent ECG-recordings have been collected. The acquisition of data is almost complete and will be analyzed during the spring of 2014.

Part 3 : Registry-based evaluation of in-hospital care of patients having undergone the Cox-Maze III procedure in Sweden, to analyze health care consumption and morbidity long-term

postoperatively. This study is in the start-up phase and data collection will be on-going during 2014.

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 Arytmikirurgi). 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.

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 an on-going local long-term follow-up study of patients who were operated between 2009 – 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.

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 – 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 2008-2013, 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 and 2012 in the field of surgical treatment of atrial fibrillation. We are also co-authors in an upcoming Swedish textbook of cardiac arrhythmias.

Project 4 Heart surgery; indications, complications and long-term outcome Atrial fibrillation after heart surgery – prediction and outcomes

Research group: Elisabeth Ståhle, Laila Hellgren, Emma Thorén

The most common complication after cardiac surgery is atrial fibrillation (AF). Approximately one third of all patients have an episode of AF after coronary artery bypass grafting (CABG).

After coronary artery bypass grafting (CABG), approximately 30% of all patients suffer from postoperative atrial fibrillation (POAF). This arrhythmia is associated with a number of negative consequences after surgery, but the causes behind this is not fully understood.

This project sought to study predictors and early complications associated with POAF after CABG, as well as its association to early and late mortality and cause of death. Further, we sought to closer examine heart rhythm during the first postoperative month to observe if POAF led to a higher frequency of arrhythmias after hospital discharge.

Postoperative fibrillation triggered by left atrial premature beats

The pathogenesis of postoperative atrial fibrillation (POAF) after cardiac surgery remains unresolved. In the general population, repetitive electrical activity from the pulmonary veins are the main triggers of atrial fibrillation (AF). The purpose of this study is to localize the origin of POAF, and study if the mechanism for triggering POAF is the same as for AF in general. By placing temporary epicardial electrodes during by-pass, or CABG, surgery, the origin of POAF can be mapped in order to answer our question. Since POAF is connected to an increased mortality after CABG, this is an important clinical problem and more knowledge can hopefully lead to new and more efficient therapies.

The first study in the project revealed several predictors of POAF, including high age. There was also an association between POAF and early complications, such as stroke, heart failure and postoperative infection.

In a second study there was an association between POAF and late cardiac death, and death related to arrhythmia, heart failure, and cerebrovascular disease, that remained more than seven years after surgery.

A prospective study examining the occurrence of atrial fibrillation the first month after CABG surgery is presently conducted using a mobile ECG-device. The frequency of atrial fibrillation after discharge is compared between patients with and without POAF.

Further work includes examining the association between morbidity and POAF, with emphasis on diseases related to arrhythmia.

The purpose of this project is to identify the risks of POAF after CABG, and hopefully find ways to minimize these risks in the future. With an increasingly older patient population, which leads to a higher operative risk, it is important to lower that risk as much as possible. This project might contribute to that process.

Project 5 Surgery in lungcancer treatment

Research group: Simon Ekman, onk klin, Per Landelius, Elisabeth Ståhle thoraxklin

Aspects on lymph node metastasis in lung cancer

This project's focus is on molecular analysis of lymph nodes, lymph node metastasis and primary tumours 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 to far to be able to cure, usually through metastatic spread to lymph nodes or distant organs.

Among those patients subjected to surgery, the mean 5-year survival is around 50%, worse in those with larger tumours with signs of local lymph node spread and better in those with smaller tumours and no evidence of metastatic lymph node spread. However, the 5-year survival in these patients, with a totally radical removal of a small tumour 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:

- (i) 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 a 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.

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 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 an experimental and a clinical arm. 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 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 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.

Experimental studies of global cerebral ischemia and controlled reperfusion.

Name of involved researchers: Rickard Lindblom, Thomas Tovedal, Bo Norlin, Lars Hillered, Irina Alafuzoff, Stefan Thelin.

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 (1) and lungs (2) 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 reperfusate, as well as its

content with regard to immunologic factors, balance of electrolytes and content of anti-oxidants or other drugs (3).

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 (4-6). 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 reperfusate. 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.

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

Names of involved researchers: Rickard Lindblom, Anita Bertilsson, Stefan Thelin

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 (7).

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 (8, 9), 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 (10), 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 (11). 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 criteria 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 14 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.

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 department of Clinical Immunology, but also Pathology, Nephrology, Anaesthesiology, Neurosurgery and Radiology 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 to reduce/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 re-perfusion. The following damaging events have been identified: brain death, harvesting procedure, storage with ischemia and finally re-perfusion injuries. It is also recognised 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 recognised 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 re-perfusion 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/developmental programmes for clinical islet transplantation, live donor kidney donation, clinical pancreas transplantation and management of malignancies after transplantation.

Members of the group during 2013

David Berglund, MD

Alireza Biglarnia Associate Professor

Lars Bäckman, Associate Professor

Vivian Hellström, MD

Tomas Lorant, Associate Professor

Amir Sedigh, MD

Gunnar Tufveson, Professor

Bengt von Zur-Mühlen, MD, PhD

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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, two of these from IGP Uppsala University:

1. Histological protein profiling in collaboration with F. Ponten, Professor of pathology, site director for the Swedish Human Proteome Resource project.
2. Profiling of the urinary proteome in collaboration with senior prof. U. Pettersson

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.

We co-operate with researchers from Johns Hopkins University in profiling gene expression in formalin-fixed, paraffin-embedded (FFPE) bladder biopsies and with Rosetta Genomics analyzing microRNA expression ratio. Two PhD students work with these projects.

Concerning experimental therapy we collaborate with the Division of Biomedical Radiation Sciences to develop nucleide based tumor targeting (PI Truls Gårdmark). The aim of the research is to develop new methods for treatment of tumours, especially such tumours that have a tendency to cause metastasis. One clinical trial with AFFIBODY® in cooperation with industry has started.

Members of the group during 2013

Per-Uno Malmström

Ulrika Segersten

Mårten Lindén

Tammer Hemdan

Localized prostate cancer: Survival and Quality of Life

Supervisor: Anna Bill-Axelson, Associate Professor, Eva Johansson PhD and Magdalena Lycken PhD student and Oskar Karlqvist PhD student (not yet registered)

- 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.
- 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 Johansson's thesis work with main supervisor Anna Bill-Axelson). Further studies from this material are ongoing together with Eva Johansson.

In a subgroup including the Swedish participants, a separate longitudinal quality of life study was undertaken where they had answered the same questions multiple times during follow-up. This study was analysed and published in 2013.

- 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-Axelson is in the steering committee). PCBaSe enables us to look at uncommon but important consequences of a prostate cancer diagnosis.

During 2013 we have published a number of studies among them we have investigated the risk of suicide after a prostate cancer diagnosis, the risk of hormonal therapy after curative treatment, which is just accepted for publication, in European Journal of Cancer with 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, the manuscript is submitted and pending in Journal of Urology.

- U-Can is a research initiative with a range of different cancer diagnosis including prostate cancer where Anna Bill-Axelson is responsible for prostate cancer. U-Can prostate include the majority of men diagnosed with prostate cancer in Uppsala where tissue and blood is sampled for a bio-bank and connected to the NPCR and including additional longitudinal clinical data as well as longitudinal sampling of tissue and blood. U-Can prostate started in November 2010 and have included more than 400 patients at the end of 2013. U-Can prostate will provide excellent possibilities to investigating new tumor markers and follow-up new adjuvant therapies for biomarker researchers.

- U-Care is a connected project to U-Can and is an initiative where cancer patients with signs of depression according to HADS will be randomized between standard care or internet based cognitive therapy.
- 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 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
- 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 developed the questionnaire and will submit the ethical application. We plan to send out the questionnaires in September 2014.

Members of the group during 2013

Anna Bill-Axelsson

Eva Johansson

Magdalena Lycken

Oskar Karlqvist

Agencies that support the work/Funding

Swedish Cancer Foundation

Percy Falk foundation

Uppsala University Hospital (ALF)

EU/FP7

Publications 2011 – 2013

1. Robinson D, Garmo H, Bill-Axelsson A, Mucci L, Holmberg L, Stattin P. Use of 5 α -reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer in Swedish men : nationwide, population based case-control study. *BMJ. British Medical Journal.* 2013;346:f3406-.
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3. Hemdan T, Johansson R, Jahnson S, Hellström P, Tasdemir I, Malmström P. Five year outcome of a randomized prospective study comparing bacillus Calmette-Guerin with epirubicin and interferon α 2b in patients with T1 bladder cancer. *Journal of Urology.* 2013;

4. Bill-Axelsson A, Garmo H, Holmberg L, Johansson J, Adami H, Steineck G, et al. Long-term Distress After Radical Prostatectomy Versus Watchful Waiting in Prostate Cancer : A Longitudinal Study from the Scandinavian Prostate Cancer Group-4 Randomized Clinical Trial. *European Urology*. 2013;64(6):920-928.
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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 focuses on women with AAA, using both SNP analyses, and another is investigating epigenetical differences between normal and diseased aorta. The research group has organized an investigator driven multicentre randomised 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 of our PhD students, and one post-doc, at neighbouring hospitals 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 ischaemia, 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, Paris and Rotterdam being the most important centres, as well as the VASCUNET, a collaboration of eleven national and regional vascular registries.

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 organisation 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.

5) Intestinal ischaemia is studied with both epidemiological and translational methodology, including micro-array analysis of tissue from porcine experiments.

6) Iatrogenic vascular injuries are studied in different registries with the aim of defining preventive strategies, and in collaboration with the orthopaedic department popliteal artery injuries after both elective orthopaedic 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 ischaemia are evaluated.

Members of the group during 2011

Principal investigator

Martin Björck; Professor of Vascular Surgery

Senior investigators

Anders Wanhainen; Senior Lecturer in Surgery and Associate Professor

Kevin Mani; Associate Professor

Thomas Troëng, Associate Professor, Karlskrona

David Bergqvist; Professor emeritus

Post-doc (PhD)

Christer Liungman; Björn Kragsterman; Gustaf Tegler, Håkan Rudström, all Uppsala, Hans Ravn, Eksjö, Lars Karlsson and Khatereh Djavani, Gävle, Anders Hellberg, Västerås, Sverker Svensjö, Falun, Tomas Block and Johnny Steuer, Stockholm.

PhD-students with main supervisor from this research group

Sofia Bohlin, Uppsala

Anne Cervin, Trollhättan

Åsa Eliasson, Göteborg

Karin Bernhoff, Orthopedics, Uppsala

Domenika Högberg, Trollhättan

Mikael Gürtelschmid, Eskilstuna

Achilleas Karkamanis, Västerås

Karin Pansell-Fawcett, Eksjö

Jonas Wallinder, Sundsvall

Samuel Ersryd, Gävle

Karl Söreljus, Uppsala

Kim Gunnarsson, Gävle

Elisabet Skagius, Sundsvall

Jakob Swanberg, Radiology, Uppsala

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

Anders Hallin, Falun, main tutor Lars Holmberg, ROC

Olli-Pekka Leppänen, BMC, Uppsala

Hanna Ljungbåge, Colorectal surgery, Uppsala

Otto Stackelberg, Epidemiology, KI, Stockholm

Johanna Swärd, Radiology, Uppsala

Christina Lundberg, Radiology, Uppsala

Dissertations 2013:

Håkan Rudström. Title: Vascular iatrogenic injuries

Sverker Svensjö. Title: Screening for Abdominal Aortic Aneurysm

Gustaf Tegler. Title: Abdominal Aortic Aneurysm. Molecular Imaging Studies of Pathophysiology.

Mats-Ola Eriksson. Title: Aspects on imaging and endovascular treatment of aortic dissection and aneurysm (two vascular surgeons were co-supervisors)

External funds 2013:

Swedish Research Council (VR, projektanslag): 700.000/year 2013-15

Swedish Research Council (VR, kunskapsluckor, clinical research): 815.000/year 2013-15

Heart and Lung foundation: 200.000/year 2012-13

AstraZeneca: 150.000 (MRI studies)

Swedish Surgical Society, "Stora Forskarpriset", Anders Wanhainen, 200.000

Regional Research Fund. 500.000, 2011-13

Publications 2011 – 2013

(1-133)

1. Björck M, Wanhainen A. Pathophysiology of AAA : Heredity vs Environment. Progress in cardiovascular diseases. 2013;56(1):2-6.
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New PhDs

Surgery

Lee Starker	2013-10-03
Sverker Svensjö	2013-06-07
Gustaf Tegler	2013-05-21
Håkan Andréasson	2013-05-25
Bo Hultman	2013-05-18
Birgitta Grundmark	2013-04-25
Håkan Rudström	2013-04-12
Olov Norlén	2013-01-25

Orthopedics

Helena Hallström	2013-04-26
Stergios Lazarinis	2013-01-11

Anesthesia

David Smekal	2013-07-27
Hans Blomberg	2013-03-15

Plastic Surgery

Andreas Lindahl	2013-06-14
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Urology

Mårten Linden	2013-05-03
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Oto-, rhino- laryngology

Adnan Lidian	2013-06-13
Lennart Edfeldt	2013-06-12

Maxillofacial surgery

Luciano Kobas	2013-05-30
---------------	------------

Forensic medicine

Lena Lundholm	2013-03-15
---------------	------------

Personell

Teachers

Gunnar Westin	
Helge Rask-Andersen	prof
Ingemar Thiblin	prof
Karl Michaelsson	prof
Lars Pålman	prof
Per Hellman	prof
Sten Rubertsson	prof
Sune Larsson	prof
Lars Holmberg	prof
Göran Laurell	prof
Torsten Gordh	prof
Wilhelm Graf	prof
Anders Larsson	prof
Bengt Gerdin	prof
Elisabeth Ståhle	prof
Göran Åkerström	prof
Martin Björck	prof
Olle Nilsson	prof
Per-Uno Malmström	prof
Peter Stålberg	guest teacher
Björn Wikehult	assist prof
Camilla Fröjd	assist prof
Eva Jangland	assist prof
Anna Hauffman	junior lecturer
Birgitta Ekbohm	junior lecturer
Erebouni Arakelian	junior lecturer
Eva Kvidal	junior lecturer
Ingbrith Olausson	junior lecturer
Iris Hübinette	junior lecturer
Johan Lingsarve	junior lecturer
Maria Susanne Magnsbacka	junior lecturer
Therese Avalin	junior lecturer

Adjunct Teachers

Eugen Yu-Hui Wang
Louise Olsson
Andreas Thor
Fredrik Lenmyr
Monica Wiig
Claes Olerud
Hans Mallmin
Jonas Wadström
Stefan Thelin

Researchers and Post Doctoral Fellows

Anders Wanhainen
Cecile Martijn
Cihan Cetinkaya
Fernando Suarez Sipmann
Hari Shanker Sharma
Jamshid Jalouli
Liisa Byberg
Peyman Björklund
Rolf Gedeberg
Ulrika Segersten
Wei Liu
Ylva Tiblom Ehrsson

Research Engineers

Maimun Abdi Poljarevic
Maria Swålas
Birgitta Bondeson
Brittmarie Andersson
Peter Lillhager
Åsa Forsberg
Agneta Roneus
Charlotte Ersson
Katarina Bruun
Linda Lyttkens
Marie Essermark
Nilla Westöö
Rebecka Hallbeck
Sofia Lindell
Kerstin Ahlgren
Olivia Grip

PhD-students

Anna-Karin Gunnarsson
Anne-Li Lind
Birgitta Grundmark
Breiffni Leavy
Fredrik Edin
Gry Hulsart Billström
Joakim Crona
Joao Batista Borges
John Eriksson
Mårten Lindén
Rajani Maharjan
Tobias Åkerström

Magdalena Lycken
Between 110 and ...etc

Department administrators

Agneta Gustafson
Anne Jennische
Mona Björklund
Elin Eriksson
Malin Gadeborg
Åsa Eriksson
Siv Utterberg
Siv Andersson
Isabel Eriksson
Karin Johansson
Birgitta Haglund
Katja Andersson

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Department of Surgical Sciences

Uppsala University Hospital
SE-751 85 Uppsala
Sweden
www.surgsci.uu.se

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