Chairman’s annual address/comments

Another year has gone by, and it is time to reflect upon our accomplishments and extend our gratitude to all those who have been involved in research, education and administration.

During 2009 yet another investigation of the research quality has been made, now by the Swedish Research Council and the Academy of Finland in a joint effort. This time nations and universities instead of departments were compared and the results have therefore to be addressed by our faculty. As a clinical research department we do welcome discussions and new plans for a more fruitful outcome of our work. One local factor for a flourishing future is the persons available in the department. During 2009 we had the pleasure to welcome professors Anders Larsson and Gunnar Westin and clinical readers Camilla Fröjd and Björn Wikehult to the department, the latter two as teachers in the programs for specialist nurse education. These enrolments have been made to renew not only research but also give us the opportunity to have renewal of the examination rights for specialist nurses. As a consequence of Anders Larsson’s arrival and a planned reallocation of premises for experimental clinical research, new plans for large animal research have had to be made. Thus, the faculty has decided that the department during 2010 will have to take over administration of animal laboratories from the Department of Medical Sciences. Hopefully these reinforcements in our research weaponry will serve us well in the future.

During 2009 we managed to finish the old medical study program. The new program has already been in force since 2008 in our department and that meant that we had to train double as many students, i.e. approximately 150 students instead of 75 students per semester previously. This would not have been possible without an enormous amount of extra work by our teachers, and our medical colleagues both in Uppsala and at affiliated hospitals in the Uppsala region. I want to thank our colleagues for their extraordinary endurance during this period. This period of double courses is now finished and we have only some 80 medical students per semester. As mentioned above, during the autumn of 2009 the faculty has applied to the National Agency for Higher Education for the right to train and conduct examinations of specialist nurses. The decision will hopefully come in the spring
of next year. In any case, this Department will continue to promote high quality education as well as clinical science, with the clinical content aimed at contributing to the development of diagnosing and treatment, although not necessarily in the very short perspective. The term quality with regard to research is interpreted as publications with a high impact factor, with the clear knowledge that the issue of scientific quality is often determined by the eyes of the observer.

Last but not least I want to thank everyone in the department, including all teachers, researchers, the medical and nursing professions, administrators and laboratory workers, for their excellent work during this past year.

Uppsala, January 31th, 2010

Lars Wiklund
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Organization

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Anaesthesiology, Intensive care medicine and Pain treatment

Injury epidemiology

Principal investigator: Rolf Gedeborg

Injuries are the most important cause of death in the young and middle aged and a common reason for ICU admission. Injury epidemiology was introduced as a new line of research for the Department of Surgical Sciences in 2006 and 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. An important international collaboration 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. A study on the association between population density and mortality after traffic crashes has been finalized. We continue to develop the ICD-10 injury severity score in collaboration with scientists at the National Center for Health Statistics at the Centers for Disease Control, Hyattsville, USA. A joint publication on the importance of prehospital injury deaths is underway and the collaborative effort continues with the aim of defining valid indicators of injury incidence and improving injury severity models.

In collaboration with Forensic Medicine we develop prediction models for the outcome after violent crime. We are also working on models for case mix adjustment concerning comorbidity for older patients with hip fractures.
We have also during the year participated in the development of a course in epidemiological methods given at the doctoral level. As a part of the Uppsala Clinical Research Center we also offer consultations in epidemiological methods and study design.

**Funding**
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**Prognosis and quality of life after hypothermia treatment in cardiac arrest patients**

**Principal Investigator: Sten Rubertsson**

Background: Hypothermia treatment to 32-34 ° C during 24 hrs after cardiac arrest has been shown to improve survival and neurologic outcome. Fifty percent of the admitted patients treated by hypothermia are now surviving. 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-100β (astroglial protein) och NSE (neuron specific enolase).

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. To what extent do they have memory loss, anxiety and discomfort? Their situation will also have an impact on the relatives. So far there is no studies performed in surviving patients after cardiac arrest treated with hypothermia.
Questions: 1. The aim is to follow-up patients during the first 6 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. 2. What is the survival and outcome in patients after cardiac arrest and hypothermia treatment in Scandinavia?

Methods and results: 1. Markers of brain injury are sampled directly after the patient is admitted to hospital and followed up to 108 hrs after cardiac arrest. MRI of the brain is done 5 days after the cardiac arrest and EEG will be monitored up to 48 hrs after cardiac arrest. Follow-up of the patients will be performed at discharge from the hospital and 1 and 6 months after the cardiac arrest. Next of kin will be be interviewed first when the patient is discharged from hospital and at 6 months after the injury. 2. In collaboration with mainly researchers from Lund University, we started a Scandinavian registry of patient’s treated with hypothermia after cardiac arrest. In total more than 1100 patients have been registered and independent of first documented ECG rhythm at cardiac arrest the survival is 50 %. The prognosis is better after ventricle fibrillation, however, 25 % of the patients treated with hypothermia after asystole are surviving with good outcome.

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Regional Clinical Research Council, The Laerdal Foundation for Acute medicine

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The Hypothermia Network
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 a 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 h 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 trial, 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 min including 8 min CPR, and a follow-up period of at least 3 h. 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. The failing pharmacological agent mentioned above seems not to have the antiapoptotic mechanism that are observed in some other suggested neuroprotective agents. It also seems that block of nitric oxide elicited mechanisms seems essential for successful neuroprotection after long cardiac arrests.

**Funding**
The Laerdal Foundation for Acute Medicine

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**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 Ulf Landegren (the PLA method) and prof Jonas Bergquist (mass spect). It is run 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 accumulates in painful areas in patients suffering from chronic WAD, and following wrist distortions. 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).

Quantitative sensory testing (subjective temperature and mechanical thresholds and stimulus response functions) has traditionally been used to classify neuropathic pain patients and has been hypothesized to deliver mechanistic information. However, according to our concept only objective readouts will lead to discovery of molecular targets involved in the generation of neuropathic pain. Therefore, we combined standard quantitative sensory testing and clinical investigations with objective measurements. Controlled electrical stimulation evokes retrograde action potentials in the thin skin nerve fibers, which release vasodilatory neuropeptides and thus induce an erythema in their innervation territory (axon reflex erythema). The axon reflex erythema is a function of mechano-insensitive nociceptors (“silent nociceptors”) which also are involved in the generation of central sensitization which in turn is a hallmark of neuropathic pain.

Microneurography was used to record from single C-nociceptors in chronic pain patients. We assessed traditional characteristics of these nociceptors such as sensitization of their sensory endings and spontaneous activity. Moreover, we assessed modulation of axonal excitability of single fibers (activity dependent hyper/hypoexcitability) by standardized electrical stimulation protocols. Axonal excitability has lately become of major interest for pain research as mutations of an axonal voltage gated sodium channel (NaV 1.7) have been linked to chronic pain (familiar erythromelalgia) and most interestingly to inability to sense pain.

Skin biopsies and specific staining using immunocytochemistry were used to characterize structure of skin nerve fibers and possible changes of sensory and axonal markers. Our results underline the validity of our approach combining subjective quantitative sensory testing with a skin biopsy. We conclude, that cold allodynia in the patients is not linked to clinically relevant pain. Thus, further specification of cold allodynia separating out the clinically relevant patients and thus, define the relevant therapeutic targets, is crucial. Analysis of relevant ion cannnals in the biopsy material is ongoing.
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 persistant pain + 100 without pain who all have been investigated clinically. The results show that persistent postoperative pain in mainly of neuropathic character. The project is done in collaboration with professor Fred Nyberg.

Peripheral nerve lesions- effects on the central nerve system
We have found that a peripheral nerve lesions (L4) in a rat model causes a leakage in the spinal cord- blood barrier, and activates transsynaptic astrocytes. In addition cell death in the dorsal horn is seen. We believe that these changes are contributing to the development of chronic pain after nerve lesions.

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 after chronic opioid exposure. In addition a clinic pharmacokinetic analysis of methadone in pain patients is ongoing.

Effect of anaesthetic drugs on the developing brain
A collaboration with Doc Anders Fredriksson, in a PhD project for Emma Pontén.

Funding
Regional clinical research council, Astrazeneca R&D, University of Heidelberg, Uppsala Berzelii Center

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Björn Hägglöf, researcher, ASTRAZENECA
Anders Fredriksson PhD psychiatry
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Mechanical chest compressions during cardiac arrest

Principal investigator: Sten Rubertsson

Background: Every year 300 000 to 400 000 people suffer from sudden cardiac arrest outside of the hospital in Europe. Only 5 - 7 % of these patients survive and is discharged from hospital. In the latest international guidelines for CPR, published in 2005, 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 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 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 and will continue to 2012. 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. Within this study, non surviving patients in Uppsala, Gävle and Västerås will undergo autopsy.

**Funding**

Jolife AB

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Steering com for the LINC trial

**Intranasal cooling**

**Principal investigator: Sten Rubertsson, professor**

**Background:** Hypothermia after global ischemia in cardiac arrest patients can be induced with both invasive and noninvasive methods with varying efficiency. Since there is a risk for side effects and complications with systemic hypothermia, selective cooling of the brain might be an alternative in treatment of focal ischemic brain injury after trauma or stroke. We have together with researchers from Lund University developed a new method to selectively cool the brain in pigs with intranasal introduced balloon catheters. These balloon catheters are introduced into the nasopharynx and cold saline solution is circulated in a closed circuit with a pump and heater exchanger.

**Questions:** Is it possible with this method during normal circulation to selectively cool the brain? Will this method alone or together with infusion of cold saline i.v effectively cool the brain or body after cardiac arrest? Is it possible to use MR spectroscopy to measure the brain cooling? Will this intranasal cooling be clinically feasible in patients after cardiac arrest, stroke or traumatic brain injury?

**Methods and results:** Two studies have been published using intranasal cooling in pigs with normal circulation and after cardiac arrest. In the first study we were able to fast and selectively cool the brain in pigs with normal circulation and maintain brain-body gradients for 6 hours. In the second study we could show that intranasal
cooling alone or in combination with infusion with cold saline is effective in cooling and maintaining both body and brain temperature.

In a third experimental study we found a good correlation between cerebral temperature estimated by MRI spectroscopy and direct temperature measurement of the brain.

Pilot trials on volunteers showed that we can use an MRI technique to measure the temperature gradients in brain non-invasively. A study in volunteers will determine if the method can be used in awake people, as for example after focal brain ischemia, without any discomfort. This technique will now undergo testing in pilot studies of patients after cardiac arrest.

Funding
Quickcool AB

Members of the group in 2009
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Jan Weis, engineer, Assoc. Prof., Dept. of Radiology
Håkan Ahlström, Professor, Dept. of Radiology

Cardiopulmonary resuscitation (CPR) 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. Continued studies, among other things including sexual hormones, are under way.

Funding
The Laerdal foundation for Acute Medicine, ALF

Members of the group in 2009
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Gas embolisation in laparoscopic liver surgery

Principal investigator: Sten Rubertsson

Background: Laparoscopic surgery has in general been known because of several advantages for the patient compared to open surgery such as less pain, shorter hospital stay and shorter periods of sick leave. The technique has developed from initial use for an increasing number of surgical procedures in the abdomen and pelvic region. To improve the view and the availability for the surgeon CO₂ is inflated into the abdomen in the beginning of the procedure. A rare but feared
complication due to this inflated gas is the risk for venous CO₂–embolisation where even fatal cases have been reported in liver surgery. There are reasons to suspect that CO₂–embolisation could be the reason due to the liver structure with many large low pressure veins that could remain open after the incision into the hepatic parenchyma. Different methods to detect embolisation have been used, such as measurements of en-tidal CO₂, mean pulmonary arterial pressure, the use of transesofageal echocardiography or auscultation.

**Questions:** Can different interventions of the anaesthesiologist or surgeon have an impact of the risk for embolisation? How can we detect gas embolisation with the monitoring techniques used today? Will the surgical technique influence bleeding and gas embolisation during laparoscopic liver resection?

**Methods and results:** Experimental studies are performed in anesthetized pigs instrumented with catheters for measurements of hemodynamic and respiratory parameters, on-line arterial blood gas analysis and blood sampling. To detect venous embolisation, transesofageal echocardiography will be used to visualize the rights side of the heart. Two studies have already been performed where a certain amount of CO₂ has been injected into the blood circulation to detect and follow changes in hemodynamic and respiratory variables during the following four hours. We have developed a method to quantify the degree of embolisation with transesofageal echocardiography. We have also shown that early detection of gas embolisation can be done with on-line measurements of arterial blood gases.

**Funding**
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Kristin Eiriksson, PhD student
Lung function in anesthesia and intensive care

Principal investigator: Anders Larsson

Anders Larsson was appointed professor at Uppsala University in May 2009, after has had the same position at the Universities of Copenhagen and Aarhus in Denmark for ten years. The research described below is newly started projects or have been done in previous and ongoing collaboration with coworkers in Uppsala.

Inflammation induced by mechanical ventilation

About 10,000 patients are treated with mechanical ventilation in the Swedish intensive care units for acute respiratory failure, a condition with a mortality of about 40%. Although mechanical ventilation saves lives, it has inherent side effects by inducing mechanical trauma 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 inflammation and it has been shown by just reducing the tidal volumes (and thus reducing the trauma to the lungs), absolute mortality is reduced by 10 absolute percent. We have further improved the technique to reduce ventilator induced lung trauma and has an ongoing project where we study inflammation with positron emission tomography (PET) and by immunohistology in a porcine model of respiratory failure using two different ventilator modes; the conventional and the experimental new protective mode.

Funding:

VR (Swedish research council), HLF (Swedish heart-lung foundation), ESR (European Respiratory Society), University of Sao Paolo and ALF

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M Amato, MD, professor, Sao Paolo University, Brazil
The evolution of lung function during treatment with extracorporeal membrane oxygenation (ECMO) for acute respiratory failure

ECMO treatment is an essential modality when advanced ventilator treatment fails to provide adequate oxygenation or carbon dioxide removal in patients with acute respiratory failure (ARF). This treatment is demanding and is therefore centralised in Sweden to the ECMO centre 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 that these patients are more severely ill. However, the evolution of lung function during the ECMO treatment has not been studied. This is important since the optimal handling of the lungs during ECMO is not known, and it possible that a change of the management of the lungs would further improve the results. We are planning a prospective study with lung mechanical investigations, imaging (Electric Impedance Tomography (EIT), CT and PET) as well as lung inflammatory markers (TNF, IL1, IL6, IL8, IL10) (obtained by bronchoalveolar lavage) on the patients treated at the Karolinska ECMO centre. In addition, we plan to study the patients’ psychosocial and physical recovery after discharge from the hospital.

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Lung function in anesthetized children

In a classical paper from 1964 Bergmann reported that lung volume decreased after induction of anesthesia. Thereafter lung function in anesthetized adult patients has extensively been studied. However, very few studies in anesthetized in children have been performed, probably due to lack of adequate methodology, and therefore lung function in children has mainly been deducted from adults. Now when we have access to EIT, a non-invasive equipment, which with new modification can measure on-line both perfusion and ventilation of the lungs, we have the opportunity to do non-invasive measurements in children. A study of children undergoing anesthesia is planned to be started at the Astrid Lindgren hospital this spring.

Funding
ALF (Karolinska hospital)
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Lung recruitment in neurosurgical patients
Lung recruitment, i.e., opening of closed lung regions by application of a high airway pressure, is an important part in protective lung ventilation. There are indications that protective lung ventilation reduces mortality in intensive care patients. However, lung recruitment maneuvers may indirectly increase the intracranial pressure which may theoretically in patients with reduced intracranial compliance compromise the cerebral circulation. An animal study has been performed and a clinical study with measurements of intracranial metabolism with microdialysis, cerebral oxygen tension as well intracranial pressure during a standardized lung recruitment maneuver is planned. The hypothesis is that the cerebral changes are short-acting without harm and that this type of maneuvers may also be performed in this patient category under careful observation.

Funding
ALF

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A Larsson, MD, PhD, professor
P Kostic, MD, PhD student

Lung function measurements using optoelectronic plethysmography during anesthesia
Optoelectronic plethysmography, where the dimensions thorax and abdomen are determined by cameras in the roof of the OR by a “GPS”-system, is a non-invasive method to exactly measure 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 high frequency ventilation.

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

Optimal preoxygenation procedures at endotracheal intubation

Endotracheal intubation is a safe procedure in elective anesthesia. In contrast, in critically ill patients intubation is associated with serious complications in more than 20 percent, mostly due to hypoxemia. We have performed a porcine study where we found that hypoxemia could be prevented, even in severe respiratory distress by apneic oxygenation using pharyngeal administration of oxygen. We suggest that this method should be considered to be a routine at intubation in critically ill patients and plan further studies to improve this technique.

Members of the group during 2009
A Larsson, professor
G Hedenstierna, professor
J Engström

Pulmonary ventilation

Principal investigator: Michael Lichtwarck-Aschoff

Using heart beats to analyze lung mechanics without interrupting ongoing ventilation. Heart beats transfer mechanical energy not only to the circulation but equally to the lung, and the result of this transfer can be seen as “cardiogenic oscillations” (COS) in the pressure and flow signal at the airway opening. Our basic assumption is that the shape of the COS contains information about the mechanical properties of the lung through which the energy is transmitted from the heart to the airways. We changed the mechanical properties of the lung by applying different levels of end-expiratory pressure and ventilating lungs with or without
partial lung collapse. The data are at present analyzed together with our bio-
engineering collaborators at Freiburg University and we are developing algorithms
for automated analysis of very big databases acquired at different ventilator
settings together with a mathematical model to fit spontaneous breathing, too.

Using the flow signal to assess the mass of the lung. The inertance and, hence,
the inertive pressure component depends on the mass of the lung. We changed the
mass of the lung by either inducing lung edema or by increasing the blood volume
of the intrathoracic vessels, and we found a very tight association between the
increase in lung mass and inertance. The aim is to develop a method that, together
with our earlier work on tube obstruction, would help to non-invasively
discriminate between pulmonary and cardiac “asthma”.

Collaborators
Josef Guttmann, professor in bio-engineering and his group at Freiburg University
and Bela Suki, professor in bio-engineering at Boston University.

Funding
ALF

Members of the group during 2009
Michael Lichtwarck-Aschoff, Assoc professor
Rafael Kawati, MD, PhD
László Vimlati, PhD student

Dissertation
Adriana Miclescu

Publications
2007

and hemolytic uremic syndrome after allogeneic stem-cell transplantation.

considerations and buffer therapy. Cardiac Arrest. : The science and
practice of resuscitation medicine. Second edition: Cambridge University


2008


2009


Clinical Cancer Epidemiology

Principal investigator: Lars Holmberg, professor

Cancer of the prostate

The research group has studied different aspects of the metabolic syndrome in relation to prostate cancer. These studies have included the metabolic syndrome and its components as risk factors for acquiring a prostate cancer, as influencing the natural history of prostate cancer once it is established and also regarding interactions with different treatments for prostate cancer, especially hormonal treatment for advanced cancer. The results have led on to studies of cardiovascular and thromboembolic side-effects of different treatment modalities for prostate cancer. The prostate cancer analyses have been based on collaborations with investigators in the AMORIS study (a large cohort study for studying cardiovascular disease) and the research database PCBase Sweden, which is based on the National Prostate Cancer Register.

The research group has also begun studies of decision making in treatments for early prostate cancer based on clinical data from the Scandinavian Prostate Cancer Group Study no. 4, a randomised trial comparing watchful waiting and radical prostatectomy. Furthermore, together with biostatisticians and mathematicians at King’s College London, the group has started to develop novel methods to study competing risks, an important methodological aspect in studies of cancers that tend to occur later in life, such as prostate cancer.

Cancer survival

The research group has been involved in studies comparing cancer survival in England, Norway and Sweden. During 2009 studies of breast and lung cancer survival were undertaken and plans were made for studies of prostate, ovarian and colorectal cancer. This work has been prompted by a wish to have a deeper understanding of the lower survival probabilities generally seen in England in order to see if practice in England can be improved. The work has involved a network of researchers at the Swedish, Norwegian and English Cancer Registration Units and is funded by the Department of Health in UK.
Recurrence after breast-conserving surgery

The research group has continued its activities in studies of risk of local recurrence after breast-conserving surgery, the impact of local recurrence on prognosis and studies of the impact of bilateral breast cancer on prognosis. These studies have been based, during 2009, on Guy’s Hospital Clinical Breast Cancer Database at King’s College London, but hypotheses have been formulated that are going to be tested based on the Regional Oncological Centre in Uppsala/Örebro region and its large and well-validated breast cancer database. During 2009, a follow-up of the Swedish ductal cancer in situ study of breast conservation surgery was done and the study group has led an analysis of mammographic pattern as a risk factor for a later local recurrence or new ipsilateral breast cancer. Together with researchers at the Department of Surgery, Karolinska Institute, a large study project on prognosis and biology for breast cancer in younger women has started and produced its first report.

Pulmonary cancer

In a collaboration with a multidisciplinary and multiprofessional team in Uppsala, the Uppsala Lung Cancer Study Group, the research group has worked on analyses of prognostic markers in lung cancer and also a characterisation of long-term survival (more than five years) of lung cancer patients.

Malignant melanoma

A dataset on biomarkers in early malignant melanoma as predictors for death from the disease has been analysed and interpreted towards the end of 2009. This work will lead on further to new prognostic markers in malignant melanoma, and a collaborative effort together with King’s College London is planned.

Funding

Swedish Cancer Society 2009 SEK 750 000
AstraZeneca 2009 SEK 507 400
NIH 2009 (subcontractor) SEK 300 000
(Holmberg’s grant at King’s College London from Cancer Research UK, £300,000 per year)

Members of the group during 2009

Research projects have been based on activities at the Regional Oncological Centre in the Uppsala/Örebro region, a broad collaboration with King’s College London, and on joint projects with the Biostatistics Unit at the Memorial Sloan Kettering
Cancer Center, New York, and investigators at Dana Faber Cancer Institute, Harvard Medical School, Boston. The group leader, Professor Lars Holmberg, has worked 20% for Uppsala University during 2009 and 80% for Division of Cancer Studies, Medical School, King’s College London.

Publications

Publications during the last 3 years


Colorectal surgery

Principal investigator: Lars Påhlman

The research in colorectal surgery has been focused mainly on colorectal cancer, functional disorders, proctology and peritoneal carcinomatosis.

Colorectal cancer

Uppsala has a long tradition in research of colorectal cancer. We have been involved in and organised several multi-institutional trials in adjuvant treatment in colorectal cancer. Many of those trials have been published in well-known journals and there is still a lot of research ongoing among those patients included in the trials. We are looking for late adverse effects to adjuvant treatment (both radiotherapy and chemotherapy) in patients treated for colorectal cancer. We are also involved in several trials finding out the best way of giving adjuvant treatment in rectal cancer as well as how to combine radiotherapy and chemotherapy in rectal cancer treatment as well as how to use chemotherapy in treatment of patients with colonic cancer. Furthermore we are involved in several trials regarding the palliative care of patients with colorectal cancer.

Another branch in our colorectal cancer research is to find predictive tests and prognostic variables in patients treated for colorectal cancer. We have a strong link to the human protein research project, (HPR project) at Uppsala University and are heavily involved in finding good prognostic markers.

In the Uppsala-Örebro health-care region there is a quality control register for colorectal cancer surgery. Based upon these data and also the national quality control register for rectal cancer we have used this registration for several epidemiological studies showing the need of good pathology, good surgery and also good patient care. Also those registers are valuable to evaluate volumes in the treatment of cancer.

Another important topic is screening for colorectal cancer. Although the most evidence based screening tool is faecal occult blood testing, this has not been accepted as standard of care in Sweden. Therefore we are investigating other screening modalities like evaluating examination of DNA or tumour markers in the stools or to implement as a randomised trial exploring screening with colonoscopy.
We have also been involved in several important trials regarding surgical technique in colorectal cancer treatment. This includes a trial of preoperative bowel prep in colorectal cancer, a randomised trial regarding the use of covering stomas in rectal cancer surgery and also the use of different staplers.

**Functional disorders**

We have a long tradition in research in both incontinence and constipation. Several PhD students have finished their theses in this field and we have an ongoing project looking at patients with severe constipation as well as those with incontinence. We have adopted a modern technique like stimulating gracily plasty and a PhD student is working on this project. Another tool is sacral nerve stimulation, which also is included in a PhD-research program.

**Proctology**

Our main interest has been the treatment of patients with fistulas but also patients with haemorrhoids. Large randomised trials have been run regarding the surgical techniques in haemorrhoid surgery and fistula treatment. There are ongoing trials to try to explain and understand how a fistula in anus appears and how this should be treated.

**Peritoneal carcinomatosis**

The treatment of patients with peritoneal carcinomatosis is a real challenge. We started the program for pseudomyxomas many years ago but have changed our attitude the last seven years with a more aggressive surgical approach combined with heated intraperitoneal chemotherapy (HIPEC). Since the program started more than 500 patients have been treated. A huge group of surgeons are involved in evaluating the results. We are running a randomised trial comparing systemic chemotherapy vs peritonectomy and intraperitoneal chemotherapy treatment in patients with carcinomatosis due to colonic cancer. Patients with pseudomyxomas, mesoteliomas and gastric cancer are involved in phase II and III trials evaluating optimised technique or use of chemotherapy as well as surgery. We are also investigating the pharmacokinteics of intraperitoneal drugs, tumour drug resistnace, molecular biology of carcinomatosis, patients quality of life, cost of treatment, patient empowerment, enviromental aspects. We have a close collaboration with other research groups in Uppsala to evaluate the side effects of this major surgery combined with heated chemotherapy in terms of tromboembolic complications but also how to use chemotherapy in an optimised way.
**Funding**

Swedish Cancer Society
(Lars Påhlman and Bengt Glimelius SEK 2 000 000
Swedish Cancer Society (L Påhlman) “ 100 000
Central ALF (L Påhlman) “ 500 000
Central ALF (H Mahteme) “ 500 000

**Dissertations**

2007-05-05 Ulla Maria Gustafsson
2009-10-23 Johan Hansson

**Members of the group during 2009**

Lars Påhlman, Professor
Wilhelm Graf, Associate Professor
Urban Karlbom, Associate Professor
Haile Mahteme, MD, Associate Professor
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Joakim Folkesson, MD, PhD
Peter Åkerud, MD, PhD
Ulrik Wallin, MD
Håkan Andréasson, MD
Hanna Bågenholm, MD
Johan Danielsson, MD
Åsa Collin, MD
Caroline Hesselager, MD
Bo Hultman, MD
Sara Näslund-Andreasson, RN
Ebbi Arakelian, RN
Peter Cashin, MD
Kurt van der Speeten, MD

**Publications**

2007


2008


2009


Forensic medicine

Principal investigator: Ingemar Thiblin, professor

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

A new Ph.D. project by Ph.D. student Lena Lundholm was started in March 2009. This project aims at investigating the role of AAS as a proximal trigger for violent behaviour. So far one article has been submitted for publication. This study describes 924 AAS users arrested for crime. Two other custody based studies were started during 2009 and are currently running. In one of those we use a case cross-over design, which allows for interpretation of causality.

The pathology of anabolic androgenic steroids

This Ph.D. project by Ph.D.- student Hamid Mobini-Far is based on autopsies and animal experiments. 100 deceased male users of AAS are described with respect to organ pathology and cause and manner of death. Some of these findings are further studied by means of animal experiments. One organ of interest, the uterus, has been studied solely in animals. So far this project has generated one publication (uterus pathology). At least two publications on autopsy findings will be submitted during 2010. These studies concern cardiac and testicular pathology.

Injury epidemiology

The epidemiology of injuries is of great interest for forensic medicine. We have found that the available models for survival estimates is not suitable for forensic issues. Therefore, we are developing new models based on large empirical materials from hospitals and the Swedish National Board of Forensic Medicine. We have explored the potential of Baysian regression in survival estimates during 2009 and continue to do so. Baysian regression is regarded as a coming tool in the forensic sciences. A special issue is a possible brutalization of violence in society. We have made observations on homicide victims suggesting a brutalization and started to investigate this phenomenon in surviving victims of assault during 2009.
Injury simulation
Occasionally it is quite hard to determine if an injury is the result of assault or accident. One example is skull fractures in infants. Since, there is no way of conducting controlled studies on such issues, there is need for alternative strategies. We have tried a computerized simulation model called finite element analyses model (FEM). FEM is an established tool in the construction industry, e.g. aviation industry. It shows how materials deform when the limit for the material’s strength is exceeded. We found that FEM works well on biological materials and started valuating the method on cases where the circumstances surrounding the injury event are known. We believe that this method will become a standard procedure in advanced injury analysis within 10 years.

Sudden death in alcoholics
The most common cause of death in alcoholics is said to be alcohol cardiomyopathy. However, this disease is not well defined. We have made observations indicating that a combination of certain mutations and massive alcohol exposure may lead to certain structural cardiac changes that predispose for sudden death. We have during 2009 investigating these observations further by means of morphometry and molecular biology.

Members of the group in 2009
Ingemar Thiblin, professor
Håkan Sandler, MD, PhD
Greta Ågren, Ass. Professor
Anne-Christine Lindström, biomedical technician
Lena Lundholm, PhD student
Hamid Mobini-Far, PhD student
Collaborations:
Rolf Gedeborg, Associate prof. UCR, Uppsala university
Svein Kleiven, Assoc professor, Dep for neuroics, KTH Royal Institute of Technology
Marie Allen, Associate prof. Inst of pathology and genetics, Uppsala university.

Education
We have held lectures at the medical students program, the pharmacists program, the masters program in forensic sciences and the police school.
Publications

2007


2008


Hand surgery

Principal investigator: Monica Wiig

Development of novel drug to prevent adhesion formations

The main objective of our research is to develop a novel drug for the prevention of post-surgical adhesion formation to benefit the patients and the society. To do that we need to understand the mechanism of how adhesions develop and parallel work with the development of new drugs to prevent adhesion formation. 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.

The inflammatory response following flexor tendon repair surgery results in the formation of peritendinous adhesions between the tendon and tendon sheath or adjacent tissues. Adhesions restrict the gliding function of the tendon and limit the range of motion of the injured digit. The formation of adhesions has long been...
recognized as a particular problem for zone I and II flexor tendon injuries and inhibition of adhesion formation is considered to improve outcome with respect to range of motion.

The process of tendon healing is complex and involves both extrinsic and intrinsic mechanisms. The balance between intrinsic and extrinsic healing components may determine the ultimate tendon strength and extent of adhesion formation and is therefore of interest to characterize further.

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 studied 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. We have demonstrated the anti-adhesion effect of PXL01 in experimental models, and the peptide has been shown to be safe in a recently conducted Phase I study. 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.

The work plan is to use the animal model that we have developed and used 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.

**Funding**

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**Members of the group during 2009**

Monica Wiig  
Maria Berglund  
David Hart  
Sara Edsfeldt  
Majvor Davidsson  
Ylva Petterson  
Ylva Gollbo Foucard  
Elisabeth Källman  
Eva Nordin
Publications

2007-2009


Nursing

The professional encounter in a hospital setting

Background

Patient-centred care is an important issue in health care. Patient-centred care is about patient participation and respect for patient’s values and expressed needs; it requires good communication skill and a professional relation in the encounter with the patient.

Patients or relatives have the possibility to report their dissatisfaction with professional encounters in health care to the Patients’ Advisory Committee. The complaints are valuable sources of insight and information for the health care organisation advancing quality improvement in the patient encounter.

In the context of surgical care, often with a high tempo, technical procedures and many patient turnovers, it is a challenge for the nurse to quickly establish a trustful relationship in the patient encounter. To implement patient-centred care the nurse need to recognize each patient’s unique knowledge and needs in different situations. The way in which the nurse acts in the patient encounter is affected by how she/he understands it and will influence how the patient experiences the encounter.
**Aims**

1. To describe patients’ and relatives’ complaints to the local Patients’ Advisory Committee about their encounters and communication in health care.

2. With a phenomenographic approach identify and describe different ways surgical nurses understand the professional encounter with the patient and the relatives in a surgical care setting.

**Results**

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

The professional encounter with the patient and the family was understood in four qualitatively different ways by the nurses. The understandings represent a hierarchy of increasing complexity and comprehensiveness. In the most restricted understanding, nurses focus only on the work task whereas in the others nurses demonstrated an increasing degree of patient centeredness.

**Members of the group during 2009**

Eva Jangland MSc, PhD student  
Lena Gunningberg, Ass professor  
Maria Carlsson, Ass professor  
Ewa Lundgren, Ass professor  
Jan Larsson, MD, PhD

**Publications**

Oral & Maxillofacial Surgery

Principal investigator: Jan-Michaël Hirsch

Tobacco, virus and malignant cell transformation

Oral squamous cell carcinoma (OSCC) is a major health problem world-wide. Incidence rates of this disease are highest in developing countries. However, the incidence of OSCC is also increasing in developed countries, e.g. Southern and Eastern Europe, Scandinavia, and among African-Americans.

In addition to tobacco and alcohol, several viruses have been reported to play a role in tumour induction by influencing the cell and cell growth regulations. Both epidemiological and molecular data suggest that certain types of human papillomaviruses (HPVs), as well as some members of the Herpesviridae family, such as Epstein-Barr virus (EBV) and human herpes simplex virus (HSV) may have an oncogenic capability.

We explore viral infections in oral tissue and gene expression profiles in head and neck squamous cell carcinomas, and oral lesions.

Not only smoked tobacco but also smokeless tobacco (ST i.e. snuff) is a risk factor for OSCC and can therefore be responsible for high frequencies of tumours in certain countries. Little is known about the molecular mechanisms deciding on malignancy therefore analyzing the exhaustive gene expression profiling is essential. Our present results demonstrate that the expression profile of the genes that we have identified could be a useful diagnostic marker and also a valuable prognostic tool, and also provide important information concerning the molecular mechanisms underlying the development of OSCC. Understanding the molecular mechanisms involved in the initiation and progression to malignancy can improve the prognosis and contribute to the elaboration of new forms of treatment.

In India, the prevalence of OSCC and oral sub-mucous fibrosis (OSMF) is high and the diseases are partly attributed to high consumption of betel quid containing tobacco. We investigate the prevalence of human papilloma viruses (HPV), herpes simplex virus (HSV) and Epstein-Barr virus (EBV) DNA in patients with OSMF and OSCC using betel quid with tobacco. HPV positive samples were analyzed separately for the high-risk types 16 and 18. The most interesting finding was the high prevalence of HPV in OSMF which warrant further studies.
We investigated the prevalence of HPV, HSV, and EBV DNA in brush biopsies and normal biopsies obtained from users of sudanese snuff, toombak and non users with clinically healthy oral mucosa, and oral cancer biopsies from toombak users and non-toombak users. HSV, HPV, and EBV infections are common and may influence oral health and cancer development. It is not obvious that cancer risk is increased in toombak users. These observations warrant further studies involving toombak-associated oral lesions, to uncover the possible mechanisms of these viruses in the development neoplastic disease in association with non-smoked tobacco.

**Members of the group during 2009**

Jan-Michaél Hirsch, Professor
Miranda Jalouli, MS,
Per-Anders Larsson, MD, PhD, Associate Professor, Dept of Surgery, Helsingborg Hospital, Helsingborg, Sweden
Mats Wallström, DDS, PhD student, Dept.Oral and maxillofacial Surgery, Göteborg University
Salah Ibrahim, DDS, PhD, Associate Professor, Biochemistry and Molecular biology, Bergen University, Norway

**Innovative technologies for cranio-maxillofacial surgery**

Despite the evidence that the outcome of reconstructive surgery can be improved significantly through detailed planning and through the use of customized grafts and implants, today’s surgery is generally done in an ad hoc fashion relying mostly on the surgeon’s knowledge and experience. The research group is part of an development of an integrated haptics-based visualization platform for planning and guiding reconstructive surgery with a new generation of customized biomaterials facilitaiting incorporation in bone and surrounding tissue to achieve restoration to an original condition. We will verify and validate the new technology and the outcome of our operations in extensive pre-clinical and clinical trials. The final result will be a design for a functional cranio-maxillofacial surgery planning system that is commercially viable. The utility of this system will by no means be limited to cranio-maxillofacial surgery. The project team is highly multidisciplinary and it includes several industrial partners; it will also work closely with the innovation organizations within the universities.
We are working on a system for planning surgery for cranio-maxillofacial complex abnormalities, which allows virtual movement of facial bone segments in a virtual model derived from an individual patient’s CT data. The methods rely on planning techniques, similar to solving a 3D puzzle. The user grasps and moves bone fragments to the proper position creating a plan for surgery.
The resulting plan can be transferred to a physical guide, to a surgical navigator or a robot to be used in the operating room.

The simulation of soft tissues is a viable tool for predicting surgical outcomes and for surgical training. Simulated procedures involving the manipulation of soft tissues are of particular relevance to craniofacial reconstruction for trauma injury or congenital deformities such as cleft lip and palate. A patient-specific simulation environment with substantial predictive power, in which procedures can be practiced and postoperative results examined would be of immeasurable value for training as well as for research and development. Computational models that will facilitate the planning of such operations and produce reliable predictions of the surgical outcome mandate the use of high-resolution, biomechanical correct models of bone and soft tissue, along with highly accurate modelling of the constitutive properties of muscle, skin, collagen, and connective tissue. Following the preclinical verification in the laboratory, a clinical evaluation will test the system.

**Members of the group during 2009**

Jan-Michaël Hirsch, Professor
Ingrid Carlbom, Guest Professor, Centre for Image Analysis (CBA), Uppsala University
Ewert Bengtsson, Professor and Director of Centre for Image Analysis (CBA), Uppsala University.
Gunnar Jansson, Senior lecturer, Associate Professor in Psychology
Stefan Johansson, Adjunct Professor at the Ångström Laboratory, Chief Technology Officer of PiezoMotor AB
Martin Ericsson, research engineer
Håkan Lanshammar, Professor Automatic Control and Systems Analysis. Head of the Dept of Information Technology
Lars Mattsson, Professor and Head of the Industrial Metrology and Optics Group at KTH
Jonny Gustafsson, Holovision AB
Per Dérand, DDS, research fellow
Kjartan Halvorsen, PhD, research assistant

**Patient specific implant**

The design and manufacturing of biocompatible implants, grafts and medical devices have been hampered by inadequate tools for patient-specific tailoring.
However, a new technology, referred to as Free Form Fabrication (FFF), enables the rapid manufacturing of objects with almost any shape and internal porosity adapted to the conditions of the patient host site. In the FFF process parts are manufactured, “printed”, layer by layer from a virtual 3D model. We have employed the electron beam melting (EBM) method invented by Arcam AB, Mölndal. EBM–processed material properties will be available as the result of the work by Mid Sweden University. So far patient specific implants for reconstructive surgery have been clinically tested. The next part of this the project is to find the optimal design and processing parameters for bone regeneration in preclinical tests prior to clinical validation.

**Members of the group during 2009**

Jan-Michaël Hirsch, Professor  
Andreas Thor, MD, DDS, PhD  
Lars-Erik Rännar, Assistant Professor, Mid Sweden University, Dept. of Engineering and Sustainable Development (THU) Mid University Sweden in Östersund.  
Mikael Bäckström, Associate Professor, Dept of Technology and Sustainable Development (THU) Mid University Sweden in Östersund.  
Peter Thomsen, Professor, MD, PhD, Dept of Biomaterials Institute for Clinical Sciences, Sahlgrenska Academy at University of Gothenburg  
Håkan Engquist, Professor, M.Sc. Material Physics, Uppsala University Ph. D. in Materials Science, Uppsala Materials Science, Uppsala University  
Per Dérand, Consultant, researcher, Dept of Surgical Sciences, Oral & Maxillofacial Surgery, Medical Faculty Uppsala, University

**Reconstruction with bone and biomaterials**

Loss of teeth and jaw bone due i.e. trauma and pathology may result in oral invalidism. Our group focuses on the development of regenerating bone before the installation of dental implants, enabling patients to have a functional chewing ability and a satisfactory social life. We work on minimizing morbidity for patients during these procedures using the interaction of the healing wound and the involved biomaterials to enhance these therapies (using thrombogenic properties of titanium).
The impact of this research is rising as the phenomenon of osseointegration is not solved and as the dental implant therapy is made possible for more demanding patient groups and situations. Parallel with clinical studies at our department we try to further develop the collaboration with the department of Clinical Immunology where basic research questions can be solved. This will further develop the materials used in our therapy on patients to their direct advantage.

Members of the group during 2009
Andreas Thor, Assistant Professor, MD, DDS, PhD
Jaan Hong, Researcher, PhD Dept of Oncology, Radiology and Clinical Immunology
Bo Nilsson, Professor, MD, PhD Dept of Oncology, Radiology and Clinical Immunology
Jens Sörensen Researcher, MD, PhD, Dept of Medical Sciences, Clinical physiology
Lars Rasmusson, Professor, MD, DDS, Dept of Oral & Maxillofacial Surgery, University of Göteborg

Facial fractures
Due to the complex anatomy and function of the face a wide range of maxillofacial injuries appear and affect facial aesthetics, vision, hearing, olfactory sense, food intake or speech. As part of the project we have classified, entered fractures in to our computer base system and evaluation of functional outcome, quality of life and health economy associated with different maxillofacial fractures are on its way. An important component in surgery planning is to be able to accurately measure the extent of certain anatomical structures. Of particular interest in CMF surgery are the shape and volume of the orbits (eye sockets) comparing the left and right sides. These properties can be measured in CT images of the skull, but this requires the orbits to be extracted from the rest of the image, a process called segmentation. Today, segmentation is usually performed by manual tracing of the orbit in a large number of slices of the CT image which is very time consuming, and sensitive to operator errors. Alternative semi-automatic systems for segmenting the orbit in CT images have been developed and are now evaluated. Specifically we use these methods to evaluate outcome of different surgical approaches and material for reconstruction in orbital reconstructions.
Members of the group during 2009
Petter Gavelin, DDS, Consultant, PhD student
Elias Messo, DDS, Consultant, Oral & Maxillofacial Surgery, Uppsala University
Daniel Nowinski, MD, PhD, Assistant Professor, Dept of Surgical Sciences, Plastic Surgery, Uppsala University
Anders Hedlund, Consultant, Dept of Surgical Sciences, Plastic Surgery, Uppsala University
Gerd Holmström, senior lecturer, MD, PhD of Neurosciences, Ophthalmology, Uppsala University
Per Enblad, Professor, MD, PhD, Dept of Neurosciences, Neurosurgery, Uppsala University
Ingela Nystöm, Senior lecturer Dept of Information Technology, Division of Scientific Computing, Centre for Image Analysis, Uppsala University
Filip Malmberg, PhD, Researcher, Dept of Information Technology, Division of Scientific Computing, Centre for Image Analysis, Uppsala University
Anne Söderlund, Professor, School of Health, Care and Social Welfare Mälardalens University Sweden
Carlos H. Buitrago-Tellez, Professor, MD, Inst. of Radiology, Zofingen Hospital, Zofingen, Switzerland
Basel University, Medical faculty, Reconstructive Surgery, Dept. of Cranio-Maxillofacial Surgery,
University Hospital of BaseHigh Tech Research Center, Basel Switzerland
Hans-Florian Zeilhofer, Professor, MD, DDS, HC
Christoph S Leiggener, MD, DDS
Philip Jürgens, MD, DDS
Zdzislaw Krol, PhD, Head, Computational Medicine Group, High Tech Research Center Basel, Switzerland

Cleft lip and palate
Outcome of the combined orthodontic and surgical treatment in cleft lip and palate children is studied. This part elucidates the importance of initial cleft size on occlusion, jaw growth and speech in children with cleft lip and palate or isolated cleft palate. This will help in determine the treatment prognosis and define an individualised treatment plan. The study is a retrospective and longitudinal study of all children born between 1990 and 1999.
Funding

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Members of the group during 2009

- Erika Reiser, PhD student, Dept of Surgical Sciences, Oral & maxillofacial Surgery, Uppsala University
- Anna Andlin Sobocki DDS, PhD, Assistant Professor, Stockholm Public Dental Health Service
- Valdemar Skoog, MD, PhD, Senior lecturer, Dept of Surgical Sciences, Plastic Surgery, Uppsala University
- Bengt Gerdin MD, PhD, Professor, Dept of Surgical Sciences, Plastic Surgery, Uppsala University

Publications

2007


2008


Orthopedics

Medical Epidemiology

Principal investigator: Karl Karl Michaëlsson

The epidemiology research group is based at the Uppsala Clinical Research Center (UCR, www.ucr.uu.se). This facilitates fruitful interaction with the biostatisticians and data managers at UCR. We also collaborate with external epidemiological, nutritional, genetic, cardiovascular, injury, osteoporosis and bone density expertise. Our main research topics are osteoporotic fractures but we are involved in other areas of epidemiological research such as injuries, outcome in intensive care, cardiovascular diseases, nutrition and the impact of physical activity on disease and mortality. We also administrate a multidisciplinary network of epidemiologists at Uppsala University (www.ucr.uu.se/epinet) as well as a national network on osteoporosis (www.ucr.uu.se/osteoporosnet) funded by the Swedish Research Council. We use different internationally unique cohort designs with the main overall aim to study the etiology and prevention of osteoporotic fractures.

Funding
The Swedish Research Council 2334 kSEK in 2009
The Swedish Council for Working Life and Social Research 1000 kSEK
ALF

Members of the group during 2009
Head Karl Michaëlsson, senior research position financed by the Swedish Research Council
Liisa Byberg, PhD, researcher
Eva Warenşjö Lemming, PhD, researcher
Carina Fredriksson, research nurse
Breiffni Leavy, research physiotherapist

PhD students
Greta Snellman (Vitamin D and osteoporosis)
Bengt Östman (Ischemia and reperfusion in skeletal muscle); Dissertation December 2009
Helena Hallström (Coffee and tea consumption and osteoporosis)
Helene Wagner (Genetic and environmental influences on osteoporosis and fractures)
Bioimplant Research Group

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. We are planning for studies with adjuvant pharmacological therapy to enhance implant stability.

Funding
CFP Project 274 KSEK
Rotalikn-project 124 kSEK
Gait analysis 158 kSEK
ALF 250 kSEK

Members of the group during 2009
Professor Hans Mallmin
Professor Olle Nilsson
Associate professor Jan Milbrink
Associate professor Nils Hailer
Associate professor Per Mattsson

PhD students
Gregor Sisask (dissertation 04/2009)
Stergios Lazarinis
Biomaterials

Principal investigator: Sune Larsson

By the use of preclinical as well as clinical models we are involved in the development and evaluation of new biomaterials aimed to be used as bone substitutes. One main goal is to develop materials that can be used to heal large bone defects after trauma, so called critical size defects, while a second goal is to optimise compounds that will stimulate bone healing in patients with compromised healing capacity. These goals seem to require different types of bone substitutes. A considerable and crucial part of the development of new materials is done in collaboration with the departments of polymer chemistry and material science at Uppsala University. At present the development of a new polymer based carrier for bone morphogenetic protein (BMP), a growth factor well known to stimulate bone formation, have shown very promising results. With this new carrier the biological efficacy of the BMP molecule seems much higher than with previously used carriers, which means that the BMP dosage can be lowered dramatically while still, the same bone forming capacity will be achieved. A second research line is to optimise calciumphosphate compounds with respect to injectability, mechanical properties, carrier ability and resorption characteristics when used as bone substitutes for filling of bone defects.

PhD students
Dr Anders Westermark
Gry Hulsart

Pelvic fracture research

Principal investigator: Sune Larsson

Surgical treatment of pelvic fractures has for many years been a nich 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 included in a large prospective observational study with the major aims to assess outcome from the patients perspective using quality of life instruments along with conventional radiographic and clinical results. All patients are followed according to a strict protocol that includes filling out questionnaires at specific time points after surgery as well as radiographic evaluations. The study is done in collaboration with specialists in psychiatry and sexology. So far more than 400 patients have been included in the study. Even with international standards this is a substantial number of patients, given the type of injury and the thorough follow-up.
This is the first prospective study where patients with severe pelvic fractures have been followed and outcome is given from the patient’s perspective. The first results have been well received by the orthopedic community following presentations at international meetings and the first publications have been accepted. The intention is to continue inclusion of forthcoming patients in order to increase the number and the follow up even further.

Members of the group during 2009
Professor Sune Larsson
Assoc prof Kenneth Jonsson
PhD students
Dr Tomas Borg
Dr Peter Ström

Spine surgery

Principal investigator: Claes Olerud

There are four main research objectives for the Spine Surgery Unit:

Results of different surgical methods in lumbar spinal stenosis. This is a multi-center RCT, the Spinal Surgery Unit of Uppsala is the coordinating center. The effects of fusion in lumbar spinal stenosis are studied. The follow-up includes generic and condition-specific outcome measures as well as radiological studies.

Prognostic factors in lumbar surgery. This is a cooperation with the Pain Research Unit. Specific genetic changes and several humoral factors as signal substances and inflammatory substances are analyzed before surgery and 6-12 months after surgery. Increased spontaneous activity and sensitivity of the pain system is recorded.

Cervical spine research. The effects of fusion on the inflammatory tissue in the craniocervical junction are investigated with MRI, CT and PET-CT in a prospective study. Ligamentous injuries of the craniocervical junction in chronic WAD-syndroms are investigated with specific MRI techniques in another study. Patients with detected injuries are treated with fusion surgery in a prospective study.
Studies on the Swedish Spine Register (SSR). The SSR is a unique database. The results of surgery for lumbar spinal stenosis and the results of fusion surgery are analyzed. This is a cooperation with the Epidemiology Group.

Members of the group during 2009
Professor Claes Olerud
Associate professor Bengt Sandén
Associate professor Gunnar Ordeberg
Associate professor Anders Bjurholm
Dr Peter Försthr
Dr Johan Robbinson

SpineLab

Principal investigator: Nils Hailer

Spinal cord injury is a hitherto 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. In the chronic phase, microglial cells and astrocytes take part in the formation of glial scar tissue and prevent axonal regeneration.

We have previously shown that several immunomodulatory substances, among them mycophenolate mofetil, interleukin (IL)-1 receptor antagonist (IL-1ra), IL-4 and IL-10 potently suppress microglial activation and proliferation and promote neuronal survival. A valid and reliable in vitro-model that allows us to analyse important aspects of both the acute and chronic phases after spinal cord injury has been established, and axonal sprouting of cortical neurons occurs in such preparations.

We now characterize the potential of mycophenolate mofetil, IL-1ra, IL-4, IL-10 and others substances to promote axonal sprouting in various in vitro- and in vivo-models. The experiments are undertaken in close collaboration with the group of professors Håkan Aldskogius and Elena Kozlova-Aldskogius, Department of Neuroscience, Uppsala University.

Members of the group during 2009
Associate professor Nils Hailer
Dr Nikos Schizas
Osteoporosis

Principal investigator: Hans Mallmin

Background: For a very long time the Osteoporosis Unit and the Orthopedic Clinic have worked in close collaboration, primarily involving Professor Östen Ljunggren and Associate Professor Hans Mallmin. This collaboration comprises a great number of national and international projects, and the Osteoporosis Unit is a major international center of excellence regarding both scientific and clinical activities involving metabolic skeletal disorders.

Selection of ongoing projects:

Mr OS. An intercontinental study (four centers in the U.S. — 6,000 men, one center in Hong Kong — 2,000 men), with Sweden as the third base, is studying risk factors for male osteoporosis in a 5-year perspective to be concluded in 2008. In Sweden, participants are Uppsala (Östen Ljunggren and Hans Mallmin), Malmö, and Göteborg with 1,000 men (ages 65-85) each. Incidence of fractures, bone density, and body consistency are key parameters. Five articles have thus far been presented by the Swedish cohort.

Mr Peak. In a follow-up study to Mr OS, Östen Ljunggren and Hans Mallmin, in collaboration with Professor Magnus Karlsson, Orthopedic Clinic, MAS University Hospital, Malmö, plan to recruit 1,000 men, aged 18-30 years, with related parents in Malmö and Uppsala, respectively. The aim is to document the level of maximum bone density (attained between the ages of 18 and 30) in men in Sweden and to study the effects on maximum bone density of heredity, biochemistry, and lifestyle.

Randomized controlled studies with one-year follow-up with one iv infusion of bisphosphonate in 60 patients >70 years old with low-energy provoked cervical hip fracture operated on with uncemented total hip prosthesis. Results from UAS clinic show good fixation of uncemented prostheses in arthrosis patients. Annual intravenous infusion with bisphosphonate has shown strong increases in bone density and strong reduction in fractures in a major intercontinental RCT. Primarily, the stability of the implant fixation is studied using Roentgen stereogrammetric analysis, RSA. Secondarily, the relationship between implant fixation, and bone quantity, measured with dual energy X-ray absorptiometry, DXA, patient satisfaction measured by clinical evaluation scales like SF36, etc. (prospective doctoral candidate Olof Wolf)

Randomized controlled study with five-year follow-up regarding the effects on implant fixation and bone density around uncemented hip prostheses of immediate versus delayed post-operative loading. 46 men and women<65 years and body
weight <100 kg with x-ray-verified unilateral coxarthrosis. Regular monitoring of implant fixation with RSA, bone density and body consistency with DXA, clinical x-ray, and clinical score (prospective doctoral candidate Olof Wolf). Two-year data presented.

Together with several other clinics, such as the surgical clinic, kidney medicine, children’s clinic, etc., Hans Mallmin is taking part as a bone density resource. Examples: studies at surgical clinic—Emil Hagström, whether patients with hyperparathyroidism evince effects on bone desity, (best 2006 dissertation at Faculty of Medicine, Uppsala University), Eva Lundgren and Helene Siilin, hyperparathyroidism surrounding and following menopause, Hella Hultin and Per Hellman significance of calcium and glucose regulation in development of osteoporosis through studies of obesity surgery; children’s clinic—Swedish multicenter study of injection treatment with GH for stunted growth; kidney medicine clinic—Ulf Nisbeth, effect of kidney transplant on bone density and propensity for fracture, etc.

Knee prostheses are fixed almost exclusively with bone cement. Uncontrolled studies have shown good results with uncemented fixation. We have launched a random controlled study with two-year follow-up comparing uncemented and cemented knee arthroplastic surgery with 45 patients. Fixation of implants is evaluated with the help of RSA (prospective doctoral candidate Jonatan Berglund).

The Uppsala Osteoporosis Research Unit, UORO, is building a quality control center for bone densitometry. This will enable the UORO to be a quality assurance center multicenter research and pharmaceutical studies.

Publications

2007


2008


8. Hailer NP. Immunosuppression after traumatic or ischemic CNS damage: it is neuroprotective and illuminates the role of microglial cells. Progress in Neurobiology 84 (3): 211-33, 2008.


2009


Otolaryngology and Head & Neck Surgery

Principal investigator: Matti Anniko, professor

Radical scavengers and otoprotectants preventing damage to hearing and balance

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. Main 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 systemic and local treatment of infectious diseases and also topically applied into the middle ear for treatment of Meniere’s disease. The TRPVs change also with age.

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 edavarone as otoprotectants.

**Funding**

Japanese Medical Research Council and Akademiska sjukhuset (Uppsala university hospital) SEK 150,000

**Members of the group during 2009**

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Barbara Canlon, professor; Karolinska institutet, Stockholm
Masaya Takumida, Department of Otolaryngology and Head & Neck Surgery, Hiroshima University, Japan

**Radioimmunotherapy and radioimmunoimaging of squamous cell carcinoma in the head and neck**

**Principal investigator: Matti Anniko, professor**

Radioimmunotherapy (RIT) has been shown to be a practicable way to treat head and neck squamous cell carcinoma (SCC). A specific antibody recognizes the characteristic structure of tumour cells when loaded with cytotoxic agents. RIT kills not only tumour cells with attached radionuclides but also adjacent tumour cells due to the “cross fire effect”. To be efficacious, RIT depends on suitable monoclonal antibody, on the properties of the chosen radionuclides, and on a
suitable labelling method for attaching radionuclide to antibody. Antibody-based radionuclide targeting can provide more sensitive and specific methods for identifying and treating head and neck cancer, and improve long-term survival rates for this patient group in the future.

Differences in antigen expression between tumours and normal tissue provide a means for application of antibody-based targeting techniques. By targeting a structure that is abundant on tumour cells but not on normal cells, radioactivity can be delivered selectively. RIT seems to be a future adjuvant therapy or treatment of residual disease in head and neck SCC. Biodistribution studies on the monoclonal antibody U36 have shown considerable differences between tumour uptake versus normal tissues (CD44v6, EGFR and HER2). Besides quantification of receptors we have, in co-operation with Royal Polytechnical University, Stockholm, analysed the binding of affibodies to HER2-overexpressed SCC cells. A micro-imaging technology has been developed using the coupling of the monoclonal antibody U36 with $^{111}$In and $^{177}$Lu.

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**Members of the group during 2009**
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Anna-Karin Haylock, Kristina Lundberg, Heewa Kareem
Marika Nestor, Jörgen Carlsson (professor) and Hans Lundquist (professor) – at the Rudbeck Laboratory, Uppsala university.

**Collaboration**
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Guus van Dongen, professor, Department of Otolaryngology and Head & Neck Surgery, University of Amsterdam, Netherlands

**Genetic analysis of Meniere´s disease**
A family with five males displayed progressive low- and mid-frequency hearing impairment from the first or second decade of life. Female carriers were affected by high-frequency hearing impairment from the 4th decade. Constitutional DNA
has been analyzed from individuals with neurofibromatosis 2 (NF2) showing deletions in more than 20% of the samples. A screening of the total genome is under way.

Members of the group during 2009
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Carina Frykholm
Hans Christian Larsen.

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. Due to small patient groups the results of these studies are often not reliable. A cause for Bell’s palsy that has been suggested is the reactivation of viruses from the herpes group. This has led to studies with corticosteroids and antiviral treatment but with diverging results.

In 2001 the Scandinavian Bell’s Palsy Study (SBPS), organized from the Department of Otolaryngology and Head & Neck Surgery, Uppsala University hospital, started to include patients in a double-blind randomized multicentre study. The aim was to include at least 800 patients in four different treatment arms comparing prednisolone, valacyclovir, the combination of the two active drugs and placebo. The last inclusion was in 2006 and last follow-up performed in September 2007.

The main report, including 829 patients, was published in the November issue of Lancet Neurology, 2008. The results show a beneficial effect on time to recovery and a better outcome for patients treated with prednisolone whereas no beneficial effect was found with valacyclovir. Further analyses are in progress.

Funding
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Members of the group during 2009
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Thomas Berg
Upper Respiratory Airways

Principal investigator: Mats Holmström

Form and function of the upper airways in adults treated for unilateral cleft lip and palate

Nasal form and function is of concern to cleft palate patients. The aim of the study was to analyze the form and function of the nasal airways and quality of life in adults operated for unilateral cleft lip and palate (UCLP). All UCLP-patients born 1960-1987, treated at the Cleft lip and palate (CLP)-center, Uppsala University Hospital, Sweden, were invited to participate. Seventy-six percent (n=83) of the patients participated at an average of 32 years after primary surgery. The patients had been treated according to the same protocol except for palate closure, which was performed in one stage until 1977 and two stages thereafter. An age-matched control group underwent the same examinations.

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Snoring and sleep apnea in women – Risk factors, signs and consequences

Obstructive sleep apnea syndrome (OSAS) is characterized by snoring, apneas and excessive daytime sleepiness (EDS). Obesity is a risk factor for snoring and sleep apnea, but data on other factors in relation to obesity are ambiguous. Symptoms of sleep apnea in women have not been fully elucidated. OSAS is an important risk factor for cardiovascular disease (CVD). A common feature in patients with CVD and sleep apnea is an increase in systemic inflammation.
In 2000, 7,051 women ≥ 20 years from the general population answered a questionnaire on snoring and sleep disturbances. Habitual snoring was found in 8% of the total population, and influenced by age, obesity and smoking. The highest prevalence (14%) was found in women 50-59 years. In lean women, alcohol dependence was associated with snoring, while physical inactivity was a risk factor for snoring in obese women. Furthermore, 230 snoring women and 170 women regardless of snoring status were investigated with polysomnography, blood sampling and anthropometric measurements. Of these, 132 participants underwent an ocular and endoscopic examination of their upper airways. Several findings in the upper airways characterised normal-weight women with an apnea-hypopnea index (AHI) ≥ 10. In women with BMI of > 25, no pharyngeal characteristics predicted sleep apnea. When adjusting for age, obesity, smoking, AHI and sleep parameters, several aspects of daytime sleepiness correlated to snoring independently of AHI. No symptoms correlated to AHI independently of snoring. Strong correlations were found between obesity and inflammatory markers. AHI and nocturnal hypoxia correlated to all markers except MPO. When adjusting for age, obesity and smoking, only IL-6 and TNF-α were independently associated with nocturnal hypoxia. No independent relationship was found between systemic inflammation and AHI. In conclusion, age and obesity influence the prevalence of snoring and sleep apnea in women from the general population. Other risk factors differ according to body habitus. Daytime symptoms appear to be independently related to the snoring per se, while systemic inflammation is mainly attributed to obesity.

**Members of the group during 2009**
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**Publications**

2007


2008


2009


V. Disputationer 2009

Berg T. Medical treatment and grading of Bell’s palsy.

Tideström-Löfstrand B. Sleep disordered breathing and orofacial morphology in relation to adenotonsillar surgery. Development from 4-12 years in a community based cohort.

Svensson M. Snoring and sleep apnea in women.
Otology

Principal investigator: Helge Rask-Andersen, professor

Otosurgery – Meniere’s disease, Cochlear Implant and NanoEar

Implantation of the deaf

Our unit analyses the treatment of various implants in connection with deafness. This includes middle ear implants such as Vibrant-Medel implants. These are used either as ossicular implantation or round window application. Uppsala leads the Swedish multi-centre study at present. In addition, Uppsala has started hearing preservation techniques and cochlear implantation; so-called EAS technique. The results so far on eleven patients are very good. In all cases has hearing been preserved. The approach is through the round window membrane which allow for a better non-traumatic technique than the conventional cochleostoma technique. Our results are being processed and are under publication. The Oto/Neurosurgical team consists of three neurosurgeons and four otosurgeons. The group has performed more than 1000 skull base procedures since 1988. Our results are followed-up through a computer-based program assuring quality. The results have been presented at several international meetings in Barcelona (2008) and at national meetings (RS). The team has implanted 20 NF2 patients with ABI. They recently published results from ABI surgery in adults and is hosting the first international symposium on ABI treatment in Uppsala in June 2010. At the congress new indications of CI/ABI in children with inner ear malformations and ossified cochlea was discussed. First child was operated with ABI in Scandinavia here at Uppsala January 2009. CI surgery in children is undergoing rapid changes. Children with CI will probably be re-implanted up to two to three times during their lifetime. A non-traumatic surgery technique must therefore be performed in all patients. Miniaturization of devices enables a change of the surgical approach from cochleostomy to round window insertion. Round window technique is more a-traumatic and preserves residual inner ear function. The unit possesses a temporal bone bank that is used in education and advanced studies of the human inner ear related to surgery. The bank consists of 325 inner ear molds and 85 micro-dissections displaying anatomical landmarks including the facial nerve. The bank is used for training of several international surgeons and for scientific purposes.
Clinical studies in Meniere´s disease and surgical quality control

Follow-up studies and life quality data have been analysed after otosurgical procedures in otosclerosis and atresia. Computer-based analyses are made also after skull base surgery, cholesteatoma and cochlear implant surgery.

NanoEar: Nanoparticle based inner ear therapy

Uptake, toxicity and localisation of different nanoparticles (NPs) in spiral ganglion cells in vitro have been studied and documented within the EU-project. Findings have also resulted in a manuscript under review for publication. Both nerve cells and glia cells (adult guinea pig, pig and human) incorporated NPs in their cytoplasm with varying uptake (J Nanoneuroscience 2009). Several experiments on nanotargeting the TrkB molecule on auditory nerves have been performed. We have used various targeting molecules and results have been obtained of more selective up-take of NP in neurons compared to glia cells. The results are under publication.

Molecular studies of the human ear

Distribution and significance of connexins in the human cochlea. (Cx26,30,31,32,36,43) have been analysed. These results have been published in Hearing Research journal during the year. Expression of electric synapses in the human auditory nerve has also been analysed (“gap junction” proteins). These highly interesting results are under publication. Expression of prestin in human cochlea have also been analysed and the data published. Studies of NF2 gene are on-going. In vitro analyses of NF2 cells and Nanoparticle mediated gene transfer of merlin and receptor mediated pharmacotherapy are under way. (NanoEar project). Aquaporin studies of the human inner ear have been studied and published. We have published papers about the human organ of Corti, containing fine structure morphology and immunochemistry. Freshly obtained human tissue has been analysed with high resolution SEM. So-called extra inner hair cells are possible indicators of regeneration in the human. Gene analyses are performed with expression of hair cell markers (Math-1/Atoh1 and Myosin VIIA).
Studies on regeneration
Progenitor capacity in the inner ear has been studied and ganglion cells have been analysed using electron microscopy, immunocytochemistry, time lapse video microscopy etc. Stem cells/Neurospheres were isolated from the spiral ganglion and differentiated into inner ear specific nerve cells. Transplantation studies of spiral ganglion progenitor cells from GFP-transgenic mice into the rat inner ear, in vitro and in vivo, were performed in collaboration with Karolinska hospital. Experimental studies of in vitro cultured auditory nerve cells have been made such as the effects of axotomy, guidance molecules, growth factors, and electric stimulation.

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ALF

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Publications


Review articles, book chapters, books


Patents
Patent EP 1351693
Plastic Surgery and Burn Care

**Principal investigator: Bengt Gerdin**

The research conducted within the plastic surgery research group is currently almost entirely related to various aspects of burn injury.

In order to ascertain a multiprofessional approach The Uppsala Burn Research Programme was established ten years ago and has been fully operative since 2000. It is based on a collaborative effort involving the Departments of Neuroscience, psychiatry and of Surgery, Plastic Surgery at Uppsala University and the National Burn Unit at Akademiska sjukhuset. Within the frame of the project two main research lines are ongoing

**Consequences of burn injury**

An excellent model for severe trauma is the catastrophic experience of being afflicted with an extensive burn injury. It affects all main integrating systems in the body (i.e. nervous, endocrine and immune). Injured individuals exhibit widely differing premorbid characteristics, with respect to their ability to repair tissue, to withstand stress, and with respect to their 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. This project is 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 10, 70.

All patients referred to the National Burn Unit 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. Reinnervation of the deep injuries will be studied utilizing clinical neurophysiologic techniques and observations made will be related to perceived pain and itch during the adaptation process.

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 facilitate treatment strategies that can improve outcome also after other severe physical trauma with an increased risk for late morbidity.

**Members of the group during 2009**
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Silvester von Bülow, MD
Caisa Öster, RN, Department of Neuroscience, Psychiatry

**Keratinocyte - connective tissue interactions in tissue remodelling, repair and tumor growth**
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 his 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. 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.

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**Members of the group during 2009**

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**Publications**

2007


2008


2009


Surgical endocrinology

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

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, DNA-based whole genome CGH microarrays, and concomitant studies of proteomics. 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 aberrations.

Parathyroid tumours/hyperparathyroidism

We have in previous studies identified a genetic risk factor for development of parathyroid tumours, and revealed the genetic background of a special form of hereditary parathyroid disease. We have shown expression of 25-hydroxyvitamin D3 1α-hydroxylase, and thereby revealed local activation of vitamin D in parathyroid cells. Results have supported the hypothesis that non-1α-hydroxylated vitamin D analogues could be locally activated in parathyroid tumour cells, with potential use for treatment of hyperparathyroidism (HPT) with minimal risk for hypercalcemia. Such vitamin D analogue precursors had the effect to suppress PTH mRNA and PTH secretion, increase expression of 24-hydroxylase, and inhibit proliferation of parathyroid tumour cells from patients with primary and secondary HPT. We have recently established the first human parathyroid tumour cell line.

Aberrant Wnt regulation has been revealed as the cause of many forms of tumours. We have found activated Wnt/β-catenin signalling, with accumulation of stabilized non-phosphorylated β-catenin, occurring frequently in parathyroid tumours from patients with primary and secondary HPT. The β-catenin accumulation is caused by stabilizing mutation in β-catenin or by an aberrantly spliced internally truncated Wnt receptor LRP5 (LRP5Δ). Since the deleted part of LRP5Δ is required for inhibition of β-catenin by the Wnt antagonist DKK1, this may contribute to overall signalling of the truncated LRP5 receptor.

The truncated LRP5 receptor was required for parathyroid tumour growth in a SCID mouse model, and represents a potential target for therapeutic intervention,
and we now try to develop monoclonal antibodies for diagnostic and therapeutic use. Dysregulated Wnt signalling with the same LRP5 deletion together with β-catenin accumulation has been demonstrated in breast carcinoma specimens of variable differentiation and is now further explored. We have also in collaboration identified NALP5 as the antigen causing autoimmune hypoparathyroidism in polyendocrine insufficiency (APS1). Further studies aim to investigate function and possible use of this antigen for tumour treatment. Future research will further explore parathyroid tumour genetics and new means of treatment.

Clinical studies of HPT will also explore relation to vitamin D deficiency to try to establish adequate prophylaxis against parathyroid disease. Population studies evaluate risk for cardiovascular disease and risk factors (vitamin D status, dyslipidemia, insulin sensitivity, and vascular endothelial cell abnormalities) for development of vascular disease and metabolic syndrome in patients with hyperparathyroidism. Calcium-regulatory disturbances are investigated in obese patients (BMI>35) by calcium and insulin clamping experiments and related to vitamin D status of individual patients. Minimally invasive operative procedures for primary HPT have been evaluated in a randomized study.

**Adrenal tumours**
- **Pheochromocytoma**

RNA expression array has revealed gene and protein expression as marker for malignant pheochromocytoma. DNA-based CGH microarrays has been applied in a unique series of benign and malignant pheochromocytoma, collected in collaboration between groups in Uppsala, Stockholm, and Halle, Germany. An increased patient series is presently investigated with whole genome microarray-CGH. Tumour-specific aberrations have been identified and investigated with high-resolution arrays for specific chromosomal areas. Malignant tumours have more frequent deletions and amplifications, and further studies aim to reveal relations between genetic changes and prognosis. Epigenetic control of tumour genes is a major contributor to neoplastic transformation, and a parallel study is undertaken in collaboration (C Wadelius, Uppsala) to map epigenetic alterations in the same tumours using ChIP coupled with microarray analysis (ChIP on chip), and analyzing histone H3K4me3 and H3K27me3, associated with activation or repression of transcription. The process of induction of apoptosis is studied in detail in primary cultures and cell lines derived from pheochromocytomas.
- **Adrenocortical tumours**

New molecular techniques, expression array, whole genome sequencing, illumine methylation array, and tissue microarray are used to study adrenocortical tumours causing Cushings disease and hyperaldosteronism (in collaboration with Dept of Surgery, Yale University, USA). Continued studies have evaluated the role for metomidate-PET for visualization of adrenal tumours, and efforts are made to develop a new marker for aldosteron-producing tumours with PET-technique. A long-term follow-up study of patients with primary hyperaldosteronism has been done, and a screening study of patients with hypertension is planned.

**Pancreatic endocrine tumours (PETs)**

Allelic loss on chromosomes 11q13 and 3p25 was related to malignant behaviour in sporadic PETs. Allelic loss at 18q21 was found in a subset of sporadic and MEN1-associated tumours, and mutation analysis of Smad4 excluded a tumor suppressor function. In tumours with allelic loss on chromosome 3p25, mutation analysis of WNT7A and HDAC11 excluded function as tumour suppressor genes. Menin, encoded by the MEN1 gene, was reported to regulate expression of the cyclin-dependent kinase inhibitors CDKN2C/p18, CDKN1B/p27, and CDKN2B/p15 in a mouse pancreatic islet tumour model. Our investigations could not relate mRNA expression of these genes to MEN1 gene mutations in human PETs, and recently we could exclude a possible tumour suppressor role for CDKN2C/p18 and CDKN1B/p27 in sporadic PETs. Cyclin-dependent kinase 4 (CDK4) and the protooncogene MYC were found overexpressed regardless of MEN1 gene mutational status. The CDK4 gene was neither amplified nor mutated. Targeting of CDK4 may represent an alternative to conventional chemotherapy in PETs.

**Carcinoids**

Genetic studies of carcinoid tumour specimens have revealed deletions and presence of a putative tumour suppressor gene on chromosome 18q, which is investigated with mRNA expression array, whole genome sequencing, illumine methylation array, and tissue microarray (in collaboration with Dept of Surgery, Yale University, USA). Moreover, the Wnt and Notch signalling pathways are investigated in carcinoids, and studies are made to concomitantly evaluate mRNA and protein expression in carcinoids.
Epidemiological studies of carcinoid patients, use the Swedish Cancer Registry, Cause of Death registry, and Disease-specific registers, to investigate cause of death and relation to other intestinal tumours or diseases (Mb Crohn). A nested-case control analysis is used to evaluate survival data. The outcome of Radiofrequency ablation of liver metastases from endocrine tumours has been reported.

**MEN1**
Mechanisms behind tumourgenesis in familial MEN1 tumours are investigated with RNA and proteome-based approaches, and with a MEN1 knock-out model, in collaboration with NIH, Bethesda, USA.

**Funding**

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<th>Source</th>
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</tbody>
</table>

**Members of the group during 2009**

Göran Åkerström, professor  
Gunnar Westin, professor  
Per Hellman, professor  
Peter Stålberg, ass professor  
Peyman Björklund, PhD, researcher  
Ola Hessman, PhD, doctor

**Research students**

Johanna Sandgren, Jessica Svedlund, Hella Hultin, Helene Siilin, Tommy Ahlström, Katarina Edfeldt, John Eriksson, Olov Norlén, Alberto Delgado, Maria Annerbo

**Dissertations 2009**

Joakim Hennings  
Tijana Krajsnik
Publications

2007


2008


2009


Thoracic surgery

Principal investigator: Elisabeth Ståhle, professor

Morbidity and mortality after cardiac surgery; focusing on postoperative atrial fibrillation and stroke

The most common complication of open cardiac surgery is atrial fibrillation. Approximately one third of all patients are inflicted and the incidence is increasing with age.

In the recently published SYNTAX study CABG was compared with PCI in patients with coronary three vessel disease or main branch stenosis. The result of the study showed a significantly greater incidence of cardiovascular incidents in the PCI group leading to the conclusion that CABG should be a first alternative for this patient group. Incidence of stroke, however, was significantly greater in the CABG group (2.2%) compared with the PCI group (0.6%) in spite of the fact in both groups had comparable risk factors for stroke. The reason for this greater risk for stroke after cardiac surgery might be due to postoperative atrial fibrillation and less efficient antithrombotic medication in the CABG group. Atrial fibrillation is known to be an independent risk factor for ischaemic stroke increasing the risk 4-5 times. However, the association between atrial fibrillation and stroke has not been investigated.

The study will be based upon the quality data base obtainable in the Thoracic surgery clinic since 1970 for CABG, and for other operations since 1980. Information available includes data from the postoperative period such as
incidence of arrhythmias and neurological complications. By combining data from the National Board of Health’s registers on institutional care and causes of death we determine if and how risk factors, surgical procedure courses and postoperative complications are associated with mortality and morbidity. Our first aim is to verify the findings of the SYNTAX study. Moreover, a possible correlation between presence of postoperative atrial fibrillation as a consequence of cardiac surgery and risk for stroke will be studied.

**GUCH – a new and important patient group**

The incidence of congenital cardiac malformations is approximately 500 per 100 000 living infants in most countries. Children born before the 1980’s had a very poor prognosis while current survival in individuals born in the 1990’s and onwards is 80-85%. As the majority of these patients seldom are cured by surgery alone many of them are dependent upon life long cardiac follow-up. In addition they might need new surgery as e.g. exchange of valves and/or vascular grafts that are too narrow or have degenerated or been calcified. These patients also need surveillance and counselling regarding prophylaxis against endocarditis, regarding physical activities, insurance, employments and pregnancy. No Swedish study has so far addressed the need of care in this patient group. The availability of the National Board of Health’s registers on congenital malformations, institutional care and causes of death give us the opportunity to estimate the number of grown-ups born with congenital cardiac malformations and their survival, need for institutional care and causes of death.

**Hemostais and bleeding in cardiac surgery focusing on patients with unstable angina and reinforced antithrombotic medication**

Patients with unstable coronary vessel disease have proved to exhibit increased coagulation activity and are therefore treated with low molecular heparin and thrombocyte aggregation inhibitors. In certain advanced coronary vessel conditions or if PCI has not proved to have desired effects, an acute surgical revascularisation is made by performing a coronary bypass. Thirty per cent of those subject to an acute CABG results in more or less pronounced bleeding problems by negative influence on thrombocyte function and coagulation. Previous anticoagulation treatment in unstable coronary vessel disease promotes this bleeding tendency during this kind of surgery. In comparison with elective operations the acute operations seem to necessitate more blood transfusions and more reoperations. We also know that not all patients treated with thrombocyte inhibitors bleed
excessively. We are intending to identify risk factors and coagulation tests or combinations thereof which can predict patients at risk for increased perioperative bleeding and how to treat those patients. Using our database and similar databases from our neighbouring clinics a propensity score matched case-control study is made aiming at identifying risk factors including pharmaceuticals and their significance for this problem. This study will also address the costs associated with pharmaceutical treatment of those conditions especially regarding possible gains in using expensive coagulation factors.

Cerebral perfusion and protection during surgery of thoracic aorta

During surgery on the thoracic aorta a temporary circulatory arrest is needed. Due to this there is a great risk of cerebral complications with ensuing mortality and morbidity. A method using antegrade perfusion to the brain is under development based upon the heart-lung machine perfusing the vasculature of the brain. This is currently studied experimentally.

Surgery in cardiac failure with a focus on heart pumps and assist devices

Cardiac failure is a growing problem and in our country 20 000 persons are inflicted annually. The majority of these patients can be treated by medications and as outpatients, but some 2000 out of these demand hospital care once or at several occasions which might be economically burdensome for hospital budgets. Some will be judged for their suitability for a cardiac transplant but only a minority will be really considered. Furthermore 20% of the patients awaiting cardiac transplant die before their new heart is in function. Some may even deteriorate to such a degree during the waiting time that they do not qualify for transplantation as other organs such as liver and kidneys are hurt meanwhile by the gradually decline of heart function. Treatment with a mechanical assist device may be offered to the patient as assist of the left ventricle only (LVAD) or for both ventricles, so-called BIVAD. Unfortunately results with BIVAD are relatively poor with a mortality of 40%. Results after LVAD treatment are considerably better if the patient does not have a marginal right ventricular function. A significant clinical problem at LVAD treatment is right cardiac failure owing to momentarily increased work load for the right ventricle during surgical insertion of a LVAD. It has previously been shown in a canine study that shunting between the cava superior and pulmonary artery during LVAD treatment has given possibilities to greater flow. This method has been used in patients with right cardiac failure in connection with cardiac surgery. In order to elucidate this problem an experimental model is developed for the
question at issue is if right cardiac failure during LVAD treatment can be reduced by use of a Glenn shunt between superior vena cava and the pulmonary artery or a total cavo-pulmonary connection.

Development of an animal experimental model of pulmonary hypertension

Pulmonary hypertension implies increased blood pressure in the pulmonary vessels and inflicts a large and heterogeneous group (1 out of 1000 newborn, and associated with e.g. congenital cardiac malformations and chronic obstructive lung disease). The increased blood pressure gradually leads to right cardiac failure and death. Pulmonary hypertension and right cardiac failure are one of very few absolute contraindications to cardiac surgery. In common to all forms of pulmonary hypertension is that pulmonary vessels contract and vascular walls are thickened. Efficient pharmaceuticals against these developments are unfortunately lacking. The animal selected for the model is the mouse also because this species can generate transgenic offspring. Anaesthesia is induced in a small chamber with isoflurane. The animal is intubated and mechanically ventilated. By way of a left sided parasternal minithoracotomy and under ultrasound guidance a 2F needle is introduced through the left ventricular wall and the septum. Then a microablation catheter (1.4 F) is introduced and a hole is burnt in the septum after having retracted the needle from the heart. The hole in the left ventricular wall is sutured and the thoracotomy is closed. The experiment is then carried out for a varying time, up to 8 weeks, when the animal is sacrificed. The extent of right and left ventricular hypertrophy is estimated by weighing and the dry weight of each ventricle is calculated. The lungs are isolated for morphometric and immunohistochemical analyses.

Studies of nitrogen oxide (NO) and inflammation during extracorporal circulation (ECC)

ECC is a necessary part of cardiac surgery, dialysis and extracorporeal membrane oxygenation (ECMO). The use of ECMO is associated with negative side effects leading to functional disturbances in the organs of the body. One of the more serious is infection. NO is a parcrinous gas regulating the microcirculation both in normal and pathological conditions. In the inflammatory process NO has proved itself as possessing both pro- and anti-inflammatory properties and is considered important in the activation of blood during ECC.

We intend to study the role of NO in the infectious process and evaluate if NO donors as nitroglycerine increase the risk of peri- and postoperative infections.
**Funding:**
ALF

**Publications**

2007


2009


Transplantation surgery

**Principal investigator: Gunnar Tufveson, professor**

**Transplantation of islets of Langerhans**

Transplantation of islets of Langerhans is performed as a project with clinical application on patients at the hospital. A pilot study of 55 patients is nearly complete. A very important finding is that transplanted islets release tissue factor. By this activation of natural immunity, all the prerequisites for a "danger signal" is at hand which in turn may activate the adaptive immune defense. By the use of PET-scan we can demonstrate that 80 percent of the islets are destroyed within two hours. Finally, a randomized study is on the way where one arm is treated with low molecular dextran to prevent this activation of coagulation. NIH is a direct sponsor in this study and the first patient was included just before Christmas.
Antibody mediated rejection

Antibody mediated rejection is less common but often very difficult to treat. In its extreme forms the patient has anti-HLA-antibodies already prior to transplantation which makes it impossible to find a crossmatch-negative donor. Naturally preformed antibodies as with AB0-incompatibility was earlier regarded as an almost unsurpassable obstacle for transplantation. The same type of immediate rejection as with AB0-incompatibility is seen in transplantation of organs from other species, as for example pig to primate. These preformed xeno antibodies are often anti-carbohydrate antibodies. AB0-incompatible transplantations performed in Huddinge, Uppsala and Freiburg have shown that it is feasible to overcome this antibody barrier. We are now intending to continue our research to test new immunosuppressive regimens in xeno- and allo-transplant models. We are also continuing our work with depletion of B-lymphocytes with Rituximab, perhaps a key success drug in preventing AB0-incompatible rejection.

Living donor

Our work follows the line to show that transplantation is good for the recipient, safe for the donor and can be formed in an ethically sound way, both regarding society as well as donor and recipient. We have shown that hand assisted laparoscopic nephrectomy is safe for both donor and recipient. The next challenge is to establish tolerance between donor and recipient, a tolerance protocol is underway to be tested in a clinical setting. The basic idea is that autologous regulatory T-cells fairly specific for a certain donor will be identified and expanded in vitro and then given back to the recipient of the organ. Prior to the organ transplantation the robustness will be tested with skin transplantation. In case of acceptance the organ transplantation will be carried out.

Malignancy after transplantation

It is well known that after transplantation many patients develop malignancies as compared with the general population. We have gotten the impression that these patients get fairly bad clinical care mainly due to suboptimal renal function and due to the fact that the patient is taking immunosuppressive drugs. To alter this and optimize treatment we have in a clinical study form gathered a multi-disciplinary task force/team consisting of oncologists, nephrologists, transplantation surgeons and dermatologists. So far, almost 20 patients have been included in the study to get tailor made future immunosuppression and oncologic treatment. Tumour
progress/regress, renal function and immunological activity will be followed for
three years.

**Funding**

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<td>Swedish research council</td>
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**Members of the group during 2009**

- Gunnar Tufveson, professor
- Lars Bäckman, associate professor
- Jonas Wadström, associate professor
- Tomas Lorant, assistant professor
- Bengt von Zur-Mühlen, assistant professor
- Alireza Biglarnia, Shinji Yamamoto and Vivan Hellström, MDs

Cooperation with other researchers within the University and Hospital is a cornerstone in our research structure.

**Publications**

2007


2008


2009


Upper abdominal surgery

Principal investigator: Ulf Haglund, professor

In bariatric surgery, changes in regulatory gastrointestinal hormones and physiology as well as ways for optimising the outcome for patients are continuously studied. During the last year, vasoreactivity and magnesium status have been demonstrated to be improved after bariatric surgery as well as proinsulin and insulin dynamics. By applying positive end-expiratory pressure atelectasis can be prevented during surgery in general anaesthesia as studied by repeated CT-scans. The value of preoperative low calorie diet (LCD) has been studied by magnetic resonance imaging and evaluated in peroperative scoring. Intrahepatic liver fat was reduced by 40% and this facilitated the operation when comparing with non-LCD patients. Studies of gastric emptying after duodenal switch by scintigraphy and acidity in the gastric pouch by a novel measuring technique (wireless pH-metry) have been performed by Jakob Hedberg, in completing his thesis. Body composition is being compared between non-operated patients with BMI 30-35 and patients reaching the identical BMI after bariatric surgery. A completed comparison of 117 superobese patients (BMI>50) 4 years after surgery has shown an increased weight loss for duodenal switch (median 66 kg) compared to gastric bypass (median 49 kg). No major increase in side effects was seen. Results have discussed in media and will be presented in our Scandinavian workshop in March. Several of the above mentioned studies have been presented at scientific meetings, national and abroad.

In gastro-esophageal surgery, nation-wide results of antireflux surgery has been studied and found to be sufficient, however, not optimal. The study has been awarded best scientific presentation in the upper abdominal section of the annual national meeting in surgery. Studies on esophageal- and gastric cancer are ongoing; the multinational Critics trial, safety and cost-effectiveness in treatment of disseminated gastric cancer by intraabdominal cytostatic therapy.

In hepatic surgery studies aimed at defining the possible risk following liver resection induced by pre-operative chemotherapy has been studied. We have studied the clinical outcome in our own clinical patient material of approximately 300 resected patients during the last 10 years, of whom about half have been given pre-operative chemotherapy. We have found two late deaths (after release from hospital but within 90 days from surgery) due to liver insufficiency in the group given pre-operative chemotherapy. In an ongoing project using pre-operative 3 T MR we have studied 20 patients with pre-operative chemotherapy and 7 without the day before surgery with special techniques to reveal and grade steatosis and steatohepatitis. The results is coupled to the histopathological evaluation, to
changes in blood chemistry and to the clinical outcome. The data is under analysis and we believe we will be able to publish by the end of this year. A special analysis of patients undergoing chemoembolisation for hepatocellular carcinoma has been performed and the results have been summarized in a manuscript submitted for publication.

In collaboration with prof. Per Artursson, department of pharmacy, we have started studies aimed at developing a model using cultured human liver cells, obtained from waste liver tissue after resection for tumors. Some of this tissue has been used to study expression of proteins in liver cells. The cultured cells will in the first hand be used to study membrane transport function, the influence of preoperative chemotherapy as well as the influence of cytostatic drugs on this function.

The biliary-pancreatic group has focused on surgery for gall stones and particularly studied the reliability of intra-operative cholangiography in order to detect stones in the common bile duct. The gastrointestinal Quality of Life Index in Swedish has been validated for assessing the impact of gallstone surgery on health-related quality of life. In addition the use of per-cutaneously inserted bile duct stents in patients with malignant obstruction has been studied as regards primary patency and the risk for fractures. The group has also been involved in clinical multicenter studies on hernia surgery. Together with assoc. professors Fredrik Rorsman and Per Sangfelt, Department of Medical Sciences, studies in primary sclerosing cholangitis is ongoing and a consecutive patient material with this disease is accumulated with endoscopic cholangiographic data.

Magnus Sundbom is chairman of the hospital Center for Obesity Research. He is also on the board of the National Registry of Esophageal and Gastric Cancer (NREV) and the Scandinavian Obesity Surgery Registry (SORReg).

Ib Ramussen is a member of the board of the Swedish Gallstone Surgery Register. He has been active in workshops on resistance to antibiotics and on innovation systems.

Ulf Haglund has been the R&D director of the Uppsala County. He has also been member of the expert panel in the national Inquiry on Clinical Research (professor Olle Stendahl; SOU 2009:43)

**Funding**

ALF
Members
Anders Ahlström MD
Frans Duraj MD
David Edholm MD
Anna Ehrenborg RN research nurse
Ulf Haglund, MD PhD professor
Jakob Hedberg MD
Ann Langerth MD
Britt-Marie Karlson MD PhD
Agneta Norén MD PhD
Ib Rasmussen MD PhD associate professor
Felicity Svensson MD
Rune Sandbu MD PhD
Magnus Sundbom MD PhD associate professor
Jozef Urdzik, MD

Publications

2007


2008


2009


Urology

Research in urological cancer

Principal investigator: Per-Uno Malmström

Urological cancer is increasing in number. The available diagnostic and therapeutic methods have several disadvantages. We aim to develop more specific instruments for the clinician and more effective treatments for the patients. The Unit of Experimental Urology at the Rudbeck Laboratory is equipped technically and with staff to facilitate translation of new management strategies into the clinic. In experimental diagnostics we have the following projects;

Identification of biomarkers for clinical management of bladder, renal and prostate cancer

For bladder we use a combined approach, screening for:

– Aberrations at the genomic level with array-based comparative genomic hybridization in cooperation with Assoc. prof. T. Diaz de Ståhl, Experimentell patologi at the Rudbeck Laboratory, in Uppsala.

– Changes in protein expression using antibodies, assessed by immuno–histochemistry on tissue microarrays and serum in collaboration with Prof. Fredrik Ponten from the Swedish Human Proteome Resource project group (HPR) at the Rudbeck Laboratory.

– High resolving mass spectrometry (MS) to study the urinary proteome of patients with bladder cancer with Prof. U. Pettersson, IGP.
– Genetic and epigenetic profiling in cooperation with researchers at Johns Hopkins University in Baltimore, USA.

The series of samples to be included in the study represent a large unique material collected in our biobank. It is important to remark that, candidate markers will be finally validated in an independent collection of tumor samples within the Nordic trial database (chairman Per-Uno Malmström) but also through our EU collaborative project (UROMOL). The later prospective project has the aim to find urinary markers for outcome of bladder tumors.

We have established a multi-disciplinary collaboration between our department and Pathology and Physical and Analytical Chemistry to search for novel biomarkers for prostate cancer progression. In this collaboration where proteomic analyses of prostate cancer tissues have been performed a number of potential, novel biomarkers have been identified. These novel candidates might be useful in prostate cancer diagnosis to predict prognosis for the individual men, but their possible use in the future has to be further evaluated.

In renal cancer 362 patients with serum samples collected between 1983 and 1998 have been analyzed regarding clinical follow up and a search for biomarkers have been initiated with researchers at KTH Stockholm.

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. The present project is preclinical but the developed substances are made available for clinical tests when relevant. One clinical trial with AFFIBODY® in cooperation with industry is planned to start in the near future.

In collaboration with the Department of Clinical Immunology projects have been initiated to develop tumor vaccines. In bladder a model for immunostimulating gene therapy has been initiated and we have identified a promising vector, CD40L for clinical trials. A phase 1 trial has been completed and a manuscript submitted.

**In prostate cancer two projects are headed by Anna Bill-Axelson:**

**Treatment benefits, prognostic markers and quality of life.**

Method: A Scandinavian randomized study with 695 men allocated to radical prostatectomy or watchful waiting. Follow-up time is now almost 15 years. We investigate differences in prostate cancer mortality, risk of metastases and overall mortality. We further investigate different prognostic markers as prostate specific
antigen, pathological findings and subgroups of age. In a companion study we investigate differences in quality of life between men randomized to radical prostatectomy and watchful waiting in the Swedish cohort.

Prostate cancer and risk factors: Prostate Cancer Base Sweden is a nationwide merged database including all men registered in the national prostate cancer register between 1997 and 2007 and linked to a number of other registers. We study different risk factors for men diagnosed with prostate cancer such as tromboembolic events, heart diseases etc. We have investigated the risk to commit suicide and are currently investigating the risk of depression and stress reactions necessitating psychiatric care after a prostate cancer diagnosis. The database includes 5 controls per case for comparisons.

Finally there is an epidemiological study based on the National Prostate Cancer Register regarding the outcome of treatment with curative intent for men with different grades of prostate cancer (PI Gabriel Sandblom). Survival for men with well-differentiated tumours was close to that of the general population, regardless of treatment, but the outcome is dismal for men with poorly differentiated tumours, whichever treatment is applied. Nevertheless, men with poorly differentiated tumours benefited more from curative treatment than men with well-differentiated tumours did.

Funding
Swedish Cancer Foundation  SEK 500 000 + 650 000
ALF  SEK 500 000 + 400 000

Members of the group during 2009
Per-Uno Malmström, professor
Anna Bill Axelson, MD, PhD
Michael Häggman, MD, PhD
Truls Gårdmark, MD, PhD
Frej Filén, MD
Eva Johansson, MD
Sam Ladjevardi MD
Ulrika Segersten PhD
Gabriel Sandblom MD, PhD
Publications

2007


2008


2009


Vascular Surgery

Principal investigator: Martin Björck, professor

Description of research-activities (brief summary)

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 methods, to train the research-fellows in different scientific methodology.

The activity of the research group is high, illustrated by the list of publications. The most important research projects are the following:

Aneurysmal disease

This is the most important project, focusing on three principal areas: 1) Etiology/pathogenesis with multiple translational research projects that are implemented in collaboration with other research groups, one of them focusing on inflammation, another on multiple aneurysm disease. One project focuses on the relation between COPD and AAA. 2) Prevention by screening, where the role of Uppsala as pioneer in Sweden is exploited in various projects. Three of our PhD
students at neighbouring hospitals, as well as two in Uppsala, are engaged in evaluating the screening program. 3) Improvement of treatment results including methods how to prevent and treat the abdominal compartment syndrome and intestinal ischaemia, evaluating hybrid operative techniques, and characterizing cardiac complications after vascular surgery. 4) Several projects studying aortic dissection have been initiated during 2009.

This research-line has been scrutinized by the Swedish Research Council during 2009, and the grant was prolonged and increased. The Heart and Lung Fund, and the Regional research fund also support this research-line.

**Peripheral arterial occlusive disease**

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 blood-flow during carotid endarterectomy. Intestinal ischaemia is studied with both epidemiological and translational methodology, including micro-array analysis of tissue from porcine experiments. Iatrogenic vascular injuries are studied in different registries with the aim of defining preventive strategies, and in a collaboration with the orthopaedic department popliteal artery injuries after both elective orthopaedic surgery and knee trauma are studied. In a basic research project levels of PAI-1 are studied among patients with critical limb ischaemia. In collaboration with Karolinska Institute a large epidemiological study in all of Sweden is performed, studying geographical and gender differences, as well as risk factors and treatment.

**Venous disease**

Prophylaxis of venous thromboembolism has focused on the effects of selective blocking of activated Factor II and X. The relationship between venous and arterial thromboembolism is studied, as well as the epidemiology of venous ulcers. There is an ongoing multicenter RCT assessing the role of perforator surgery with SEPS to minimize the risk of recurrence of venous leg ulcers long term. Recurrence of varicose veins following intervention is analysed in a series of prospective clinical studies, assessing both short and long term recurrence.
Funding

Swedish Research Council, VR (2007-2009) 825.000
(275.000/year)
(Increased to 975.000 2010-2012)
Heart and Lung Foundation (2007-2010) 800.000
(200.000/year)
Regional Research Council Dec. 2008, for 2009 450.000
(Increased to 570.000 2010)
Local ”ALF”, 2009 1,325.000
Linné + Young researchers, AW 08-09 350.000
Post-doc, BK, 08-09 250.000
AstraZeneca support to PAI-1 study, 09-10 900.000
(A non-therapeutic, basic science study)

Senior investigators
David Bergqvist; Professor emeritus
Anders Wanhainen; Associate Professor
Mats Ögren, Adj Professor, AstraZeneca, Göteborg
Olle Nelzén, Associate Professor, Adj Lecturer, Skövde
Thomas Troëng, Associate Professor, Karlskrona

Post-doc (PhD)
Christer Liungman; Annika Boström-Ardin; Björn Kragsterman; Johnny Steuer; all Uppsala,
Hans Ravn, Eksjö and Lars Karlsson, Gävle

PhD-students
Thomas Block, Stockholm, half-time control September 2009
Anne Cervin, Trollhättan
Khatereh Djavani, Gävle, half-time control January 2009
Nakisa Esfahani, Uppsala
Åsa Eliasson, Göteborg
Domenika Högborg, Trollhättan
Kerry Filler, Gävle
Nils-Peter Gilgen, Eskilstuna
Mikael Gurtelschmid, Eskilstuna
Achilleas Karkamanis, Västerås
Kevin Mani, Uppsala, half-time control November 2008, dissertation February 2010
Håkan Rudström, Uppsala, half-time control January 2009
Sverker Svensjö, Falun
Gustaf Tegler, Uppsala
Martina Ålund, Uppsala
**External PhD-students (to whom senior members of the research group are co-tutors)**

Mats-Ola Eriksson, Radiology, Uppsala

Anders Hallin, Falun, main tutor Lars Holmberg, ROC

Olli-Pekka Leppänen, BMC, Uppsala

Hanna Ljungbäge, colorectal surgery, Uppsala

**Dissertations 2009**

Lars Karlsson; The role of Chlamyphila pneumoniae in the inflammatory response and expansion of abdominal aortic aneurysms.

(Birgitta Sigvant: Main tutor from KI, David Bergqvist was co-tutor)

**Publications**

2007


2008


2009


Graduate Teaching

**Medical teaching leading to Medical degree (Old program)**

According to the system in the education of medical students in Uppsala they stay with us for eleven semesters. Semester 8 is the semester of surgery. During that time period, 20 weeks, we have in total 80 students divided in 8 groups, indicating that there are 10 students per group. All students will rotate in order to follow general surgery in the following matters:

- Orthopaedics 4 weeks
- Anaesthesiology 2 weeks
- Urology 2 weeks
- Upper GI tract surgery 2 weeks
- Colorectal surgery 2 weeks
- Endocrine and plastic surgery 2 weeks and
- Vascular and thoracic surgery 2 weeks

Moreover, there is a trauma course over 1 week. The students will be examined regarding practical knowledge as well as theoretical knowledge.

In total we have 160 medical students/year. 80 in the spring and 80 in the autumn semester

**Responsible teacher:** Lars Påhlman

**New program**

In 2008, we for the first time at our department hosted medical students within the new program during the autumn semester. Since we at the same period had students within the previous program, we ended up with altogether 145 students. In consequence of this we have extended the collaboration with hospitals within our region. Medical students have in several of their clinical rotations been allocated to practice outside Uppsala. However this has at most of times been working excellent. The extended collaboration will also continue during the spring semester of 2009. The new program is a challenge for both teachers and students using new
pedagogical tools and way of working. We have now also new collaborators from mainly the department of medicine but also from many of the preclinical departments. Our department is also involved in several other semesters within the medical program which is a totally new situation but also an opportunity. We have had both a practical and a theoretical examination which only a few students failed to pass. In the course evaluation of the 6th semester the students are generally satisfied but we have several things to adjust which are mainly due to this being the first time this new semester was offered.

**Responsible teacher:** Sten Rubertsson
New PhDs

2007
Sahlén Göran Urologi
Lindberg Daniel Kirurgi
Low Aili Plastikkirurgi
Rapp Kesek Doris Anestesiologi och intensivvård
Gustafsson Ulla-Maria Kirurgi
De Boniface Jana Kirurgi
Ravn Hans Kirurgi
Hellström Hans-Olov Ortopedi
Frykholm Carina ÖNH
Röing Marta Maria Käkkirurgi
Arnell Kai Barnkirurgi
Stolt Björklund Peyman Kirurgi
Hägg Mary Käkkirurgi

2008
Ekberg Tomas L ÖNH
Silverswärd Carl-Johan Ortopedi
Klötz Fia Rättsmedicin
Marsell Richard Ortopedi
Vinnars Bertil Handkirurgi
Zar Niklas Kirurgi
Wikelhult Björn Plastikkirurgi

2009
Svensson Malin ÖNH
Nordmark Johanna Anestesi
Moe Berg Thomas ÖNH
Miclescu Adriana Anestesi
Eklund Arne Kirurgi
Tideström Löfstrand Britta ÖNH
Hansson Johan Kirurgi
Karlsson Lars Kirurgi
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