Plastic and reconstructive surgery

Leader
Kim Alexander Tønseth, MD, PhD (OUH/UiO)

Scientific staff
Hans Erik Høgevold, MD, PhD (OUH)
Christian Korvald, MD, PhD (OUH)
Thomas Moe Berg, MD, PhD (OUH)
Tor Utheim, MD, PhD (OUH)
Charles Filip, MD, PhD-student (OUH)
Tyge Tindholdt, MD, PhD-student (OUH)
Torjus Wester, MD, PhD-student (OUH)
Haris Mesic, MD (OUH)
Michael Schneider, MD (OUH)
Therese Halvorsen Bjark, MD (OUH)
Christian Sneistrup, MD (Sykehuset Telemark)
Alexander Vigen, MD, PhD (Sykehuset Telemark)
Cathrine Wold Knudsen, MD, PhD (Bærum Sykehus)

Introduction
Plastic and reconstructive surgery is performed to restore normal anatomy and function in patients with congenital and acquired disorders, and in patients with tissue defects after trauma or cancer surgery. During the last decades research in plastic and reconstructive surgery has led to development of a large number of treatment options for patients with different kinds of disorders and defects. These methods are often based on experimental research which has been refined through clinical procedures. The main outcome is improved quality of life and patient satisfaction based on restoration of anomalies and dysfunction.

Research areas
Free tissue transfer is a relatively new technique which has revolutionized the field of reconstructive surgery over the past three decades. During the 1970s, reconstructive surgeons started to use the microscope to perform anastomosis of small vessels (±1mm). Tissue, based on these small vessels, could be transposed from a distant part of the body (donor site) to the location where reconstruction was needed and the vessels anastomosed to a recipient artery and vein. In 1989 a new area of free flap surgery was initiated with the introduction of flaps based on perforator vessels. This technique improved reconstruction by reducing donor site morbidity and by allowing new alternative flap designs. There is a constant need for optimising the reconstruction techniques to give the best possible result with minimal disadvantages at the donor site. Another new area in almost all surgical fields is the introduction of regenerative medicine. With this method new cells and tissue structures can be cultured to reconstruct various kinds of defects. Our research group has focused on the following areas:

1. Microcirculation, wound healing and microsurgery
   a. Microcirculation in random flaps on rats and the effect of prostaglandin E1
   In order to investigate the distribution of blood and microcirculation in random flaps we have designed a rat model that enables us to perform multiple measurements with laser Doppler perfusion imaging (LDPI)*. A random flap is raised with width-length proportions of 1:5. The flap is monitored

![Figure 1.](A) Preoperative measurement with LDPI of a random flap on the dorsum of the rat. PGE1 is planned given iv. in the tail. (B) A LDPI scan after raising the random flap based cranially. Perfusion is measured in the five zones.
in 5 equally sized squares on which a LDPI measurement is performed every hour for 6 hours (fig 1). The circulation is evaluated for every square with regards to the blood distribution within the flap.

Several studies suggest a positive effect of prostaglandin E1 (PGE1) on the circulation of flaps. In the same rat model as described above we compare the circulation of random flaps with i.v. infusion of PGE1 alternative saline and perform LDPI measurement. The circulation is evaluated and comparison between the control and intervention groups is performed and verified statistically.

b. Microcirculation and wound healing
To resemble a clinical situation, we are using animals with skin structure and function similar to the human skin. Pig skin has many similarities to human skin, including histological appearance and wound healing ability. We are using Norwegian pigs (Norsk landsvin) with weight between 25 and 30 kg in our studies. Microcirculation and histological measurements are performed to evaluate the effect of different reconstructive procedures or other interventions on wound healing. To investigate microcirculation and wound healing in an isolated setting, we use rat models as described below.

c. Experimental perforator flaps and other rat models
Dissection of the perforator flaps preserves the muscle and minimizes the donor site morbidity. Nevertheless, the method may have undesirable effects on the muscle because of damage of its innervation, blood supply or by direct injury when dissecting the perforator. We are performing studies to evaluate the surgically technique to reduce this damage to a minimum using Wistar rats where two symmetrical abdominal lipocutaneous flaps are raised around the midline (fig 2). One side is used for intervention which is compared to the other side. After dissection, the flaps are fixed to the original position by a continuous suture. Microcirculation, flap viability, wound strength and histological changes are measured preoperatively and during the first week after the operation.

To continue improvements in both a clinical and scientific setting research using animal models is important. The groin flap based on the superficial inferior epigastric artery (SIEA) is well described. We have established a new model where the SIEA flap is transposed to the back of the rat with good conditions for flap monitoring, without danger of flap autocannibalisation. This model is used when performing studies on microcirculation and histological changes where we want to compare different interventions on the flap or the animal over a longer period of time.

d. Changes in microcirculation of the skin during sepsis and cardiogenic shock
Sepsis and cardiogenic shock are diseases with high mortality. New equipment for monitoring central hemodynamics has not improved survival as expected. In 1922 Freedlander studied skin microcirculation with a microscope in patients with sepsis and found decreased capillary density and increased heterogeneity of capillary density. New studies with advanced microscopes on patients with sepsis and cardiogenic shock show microcirculatory alterations in tongue mucosa in the way Freedlander described. In addition, alterations in erythrocyte flow velocity appear without changes in central hemodynamics. These characteristic changes may be valuable in diagnosing sepsis at an earlier phase, and may also have a potential in treatment guiding. Still microcirculatory monitoring is not used as a routine in any clinical field to examine patients with sepsis or cardiogenic shock.

Our hypothesis is that systemic diseases will induce microcirculatory changes everywhere in the organism. We also believe that we will see changes with our microscope before we see them in central hemodynamics and blood tests. In our last study we have induced fecal sepsis in eight pigs (Norwegian Landrace pigs, 27-33 kg) and three controls. Pigs are used of the same reason as described in 1b. In the model they have been measured regularly (every 90 minutes) from before sepsis induction to immediately before death by four different non-invasive techniques in four areas of interest (two skin sites, eye and tongue). The techniques are Laser Doppler techniques (LDPM, LDPI),spectroscope (for microvascular tissue oxygenation) and an "in vivo" microscope. The analysis of microcirculatory data are done by two blinded observers and microcirculatory data will be compared to central hemodynamics and blood chemistry and immunology. We have previously done clinical studies with microscope and LDPM on patients on extra-corporeal membrane oxygenation (ECMO) for cardiogenic shock.
e. Microcirculation and reinnervation in human perforator flaps.

The deep inferior epigastric artery perforator (DIEAP) flap from the abdomen is one of the most suitable perforator flaps used for breast reconstruction (fig 3). This procedure has had a significant impact on the field of plastic and reconstructive surgery, because of the high number of women requiring breast reconstruction after cancer surgery. Based on the experimental research and clinical experience, our group is performing investigations to optimize the reconstruction technique and to minimize the donor morbidity.

Until now little attention has been paid to reinnervation of the flap. We have investigated the spontaneous reinnervation of the DIEAP flap after breast reconstruction and at the donor site at the abdomen (fig. 3). Pressure thresholds have been analysed on the skin using Semmes-Weinstein monofilaments. Histological studies to evaluate the reinnervation in skin are planned both for the perforator flaps and for the donor site.

Through better understanding of flap anatomy, physiology and better surgical technique the complication rate has decreased and the cosmetic outcome has improved. However, partial flap necrosis is still a recurrent complication that can affect the final cosmetic result and the patient satisfaction. In most cases this can be avoided by discarding parts with unreliable capillary refilling after transferring the flap to the recipient site. We are performing quantitative evaluation of the perfusion zones and skin areas with LDPI* in order to get a more exact picture of the microcirculatory differences in the DIEAP flap (fig 4) and other skin flaps.

Laser induced fluorescence of (ICG) is a new sensitive method for evaluation of tissue perfusion. In another project ICG videoangiography is used to evaluate tissue perfusion of the DIEAP flap during conventional abdominoplasty. The perforators are isolated to investigate their effect on the microcirculation of the flap.

These studies will have major clinical impact on all surgical procedures involving flap surgery in order to improve surgical outcome of the reconstructed part and to reduce the donormorbidity.

*Measurements of microcirculation with laser Doppler perfusion imaging (LDPI)

Measurements of microcirculation are a central part of all our animal and human experiments. It is performed with a PIM 3.0 LDPI from Perimed, Stockholm, Sweden. The LDPI generates, processes and displays colour-coded images of tissue perfusion. An optical scanner guides a low power laser beam stepwise to the tissue surface. The LDPI measures microcirculation to a depth of a few hundred micrometers. When the laser beam hit moving erythrocytes in the subepidermal plexus the light is backscattered and detected by a photodetector, this convert the light intensity to electrical signals and colour-coded images.

Microcirculation endrineng I hud ved ssytemsykodom

2. Treatment of facial palsy

a. 3-dimensional evaluation of outcome after surgical reanimation of facial palsy.

Patients with persistent facial palsy are evaluated for surgical treatment. One of the treatment options is dynamic reconstruction with cross-facial nerve grafting and subsequent gracilis muscle transfer to the face. In cooperation with the department of plastic surgery in Vienna, Austria, we are analysing the 3-dimensional outcome of these surgical procedures.
b. Medical treatment of Bell’s palsy
Bell’s palsy is an acute, idiopathic, unilateral peripheral facial palsy of unknown cause with an incidence of 30 per 100,000 inhabitants per year. Treatment of Bell’s palsy has been a matter of debate for decades, and treatment with corticosteroids and antivirals have been the most commonly described treatments. To evaluate the treatment effect of these two drugs, the Scandinavian Bell’s palsy study was performed from 2002 to 2007 at 17 different clinics in Scandinavia (Fig. 5). This randomized, double-blind, placebo-controlled, multicenter trial included 839 patients with Bell’s palsy with a 12-month follow-up. Patients were randomized to treatment with prednisolone plus placebo, valacyclovir plus placebo, prednisolone plus placebo, and placebo plus placebo. The primary endpoint and some secondary endpoints have already been published showing significantly higher recovery among prednisolone treated patients. We are still analyzing some secondary endpoints that will be published in 2012 and 2013.

3. Regenerative medicine
Regenerative medicine is of great interest in plastic surgery due to the possibility to reconstruct defects which has been difficult or impossible to handle with traditional surgery. Still, there are many aspects of the techniques which have to be improved before they can replace the methods used to day. Our group has focused on the following areas:

a. Fat transplantation
Transplantation of autologous fat has been performed for many decades. Improvements in harvesting techniques and advantages such as availability and biocompatibility have led to its widespread application. In addition, potential positive effects of regeneration on the surrounding cells has been described. We are using fat transplantation in a number of different clinically conditions. However, there are still areas where the use of fat transplantation not has been sufficient described, and where the longterm outcome of the procedure is unknown. We have investigated the use of fat transplantation to the velum and pharynx in patients with velopharyngeal insufficiency (VPI). In these patients there is an incomplete velopharyngeal closure during speech producing hypernasality. Fat transplantation can possible improve this closure and perceptual speech assessments and MRI evaluation (fig 5) is performed to investigate this effect.

b. Cultured urothelial cells
In reconstructive surgery within the genitourinary tract, autologous urothelial cells cultured in vitro could be of considerable value. To acquire urothelial cells for in vitro engineering of urothelium, bladder washings from adult patients as well as children can be performed. These samples will contain enough proliferative and colony-forming uroepithelial cells to regenerate urethral mucosa in vitro. The cultures could be expanded to confluent, stratified sheets, which can be used for reconstruction of the urethra in urogenital anomalies or in patients with other needs (transsexuals, reconstruction after trauma or cancer surgery). The laboratory work will give a large improvement in the clinical treatment of these patients.

c. Cultured epidermal cells
This project is performed in cooperation with the department of Ophthalmology (OUS), and focus on how cultured epidermal epithelial cells can be (1) successfully cultured on electrospun scaffolds, (2) optimally stored within a small temperature interval, (3) successfully stored in a tailor-made medium, and (4) reliably transported under specific conditions. These methods might ultimately be applicable in the treatment of a number of diseases as for example burns, chronic wounds, stem cell deficiency in the cornea, and more.