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Opportunities for Novel Surgical Techniques

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Reconstruction of Large Eyelid Defects Using Tarsoconjunctival Flaps

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Opportunities for Novel Surgical Techniques

Kajsa Tenland, MD

DOCTORAL DISSERTATION

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Large lower eyelid defects resulting from tumor removal are frequently reconstructed using a tarsoconjunctival flap from the upper eyelid together with an overlying free skin graft. One disadvantage of this technique is that the tarsoconjunctival flap occludes the eye during the revascularization of the graft, which is particularly troublesome for patients with poor vision in the other eye. Alternative single-stage methods for reconstructing large lower eyelid defects have not been widely used in clinical practice, since it is generally believed that an avascular graft is dependent on a vascularized flap for survival. However, previous studies have raised the question of whether the flap contributes to perfusion in the graft, and if a single-stage surgical procedure using free full-thickness composite grafts could be a surgical option.

Microvascular perfusion and oxygenation were studied in patients and a porcine model undergoing reconstructive surgery of large lower eyelid defects, using laser speckle contrast imaging (LSCI), laser Doppler velocimetry (LDV), and a Clark electrode. Perfusion was monitored in tarsoconjunctival flaps in patients during surgery, and the results showed that perfusion decreased gradually along the length of the flap, and that there was almost no blood flow at the distal end of the flap. Perfusion was then monitored in free skin grafts overlying tarsoconjunctival flaps in patients. The results showed that, despite the minimal perfusion of the flaps, the free grafts overlying the flaps reperfused within the first 3-8 weeks postoperatively. These findings support the hypothesis that the grafts do not appear to be dependent on a vascularized pedicle for survival. The perfusion of free full-thickness composite grafts used to reconstruct eyelid skin was monitored in patients during and after surgery, showing that all grafts were reperfused within the first 8 weeks postoperatively. This paves the way for a single-step procedure in which occlusion of the eye during the revascularization period is not needed. The impact of cantholysis, often necessary during reconstruction to mobilize tissue and reduce stretching of the tissue, on blood perfusion was studied in a porcine model. Canthotomy and a wedge resection were performed in pigs, and blood perfusion and oxygenation were monitored perioperatively. Canthotomy resulted in a decrease in blood perfusion of the remaining eyelid, and this may affect healing, especially if the remaining eyelid needs to provide perfusion to an avascular graft.

In conclusion, the avascular grafts do not seem to be dependent on a vascularized flap. A single-stage graft using a free eyelid composite graft may be used as an alternative. A free composite graft would be of considerable advantage to patients, since the occlusion of vision post-surgery could be avoided, and the number of surgical procedures reduced.

Key words: perfusion, eyelid, tarsoconjunctival flap, composite graft, laser speckle contrast imaging

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MADE IN SWEDEN

To Edith and August

There is much to be done,
but each step is a nibble at the base
of the mount of knowledge.
– Wendell L Hughes

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Abstract

Large lower eyelid defects resulting from tumor removal are frequently reconstructed using a tarsoconjunctival flap from the upper eyelid together with an overlying free skin graft. One disadvantage of this technique is that the tarsoconjunctival flap occludes the eye during the revascularization of the graft, which is particularly troublesome for patients with poor vision in the other eye. Alternative single-stage methods for reconstructing large lower eyelid defects have not been widely used in clinical practice, since it is generally believed that an avascular graft is dependent on a vascularized flap for survival. However, previous studies have raised the question of whether the flap contributes to perfusion in the graft, and if a single-stage surgical procedure using free full-thickness composite grafts could be a surgical option.

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The perfusion of free full-thickness composite grafts used to reconstruct eyelid skin was monitored in patients during and after surgery, showing that all grafts were reperfused within the first 8 weeks postoperatively. This paves the way for a single-step procedure in which occlusion of the eye during the revascularization period is not needed.

The impact of cantholysis, often necessary during reconstruction to mobilize tissue and reduce stretching of the tissue, on blood perfusion was studied in a porcine model. Canthotomy and a wedge resection were performed in pigs, and blood perfusion and oxygenation were monitored perioperatively. Canthotomy resulted in a decrease in blood perfusion of the remaining eyelid, and this may affect healing, especially if the remaining eyelid needs to provide perfusion to an avascular graft.

In conclusion, the avascular grafts do not seem to be dependent on a vascularized flap. A single-stage graft using a free eyelid composite graft may be used as an alternative. A free composite graft would be of considerable advantage to patients, since the occlusion of vision post-surgery could be avoided, and the number of surgical procedures reduced.

Populärvetenskaplig sammanfattning

Ögonlockshuden är utsatt för mer solexponering än stora delar av hudkostymen, och drabbas därför oftare av hudcancer. Samtidigt är ögonlockshuden och övrig vävnad i ögonlocken mycket viktiga för att skydda ögonen mot uttorkning, skav och sår samt för att hålla tårfilmen jämn. Att operera bort tumörer runt ögonen kan därför vara utmanande. När en tumör skärs bort uppkommer ett hål i ögonlocken, en vävnadsdefekt som måste slutas. Det är av yttersta vikt att rekonstruera (återskapa) ögonlocket till sitt ursprungliga läge och funktion för att förhindra skador på ögat. Patienten måste kunna stänga ögonlocken ordentligt och blinka för att smörja den känsliga ögonytan. Om inte ögonlocket fungerar som det ska så torkar ögat snabbt ut vilket leder till smärtsamma sår på hornhinnan och kan få katastrofala följder för ögat och synen. Framför allt större tumörer, som omfattar mer än hälften av ögonlockets längd, är problematiska då de lämnar stora vävnadsdefekter.

Traditionellt har man använt sig av operationstekniker som baseras på kirurgisk erfarenhet och tradition. Idag har vi tillgång till modern teknik för monitorering av blodflöde och syresättning i vävnad, och därmed kan vi utvärdera och optimera dessa operationsmetoder. Vid rekonstruktiv kirurgi, det vill säga där man genom en operation försöker återskapa vävnaden som den såg ut innan den skadades, lånar man ofta hud och vävnad från en annan plats på kroppen för att täcka skadan i huden. För att den lånade vävnaden skall överleva och läka på det nya stället är det viktigt att blodförsörjningen fungerar.

En vanlig operationsmetod för större vävnadsdefekter i nedre ögonlocket är att låna hud från hudöverskott från övre ögonlocket eller exempelvis patientens underarm. När vävnaden som lånas skärs bort i sin helhet och inte har någon egen blodförsörjning kallas det ett fritt transplantat. En vedertagen regel inom ögonlockskirurgin är att ett fritt hudtransplantat måste läggas på en blodförsörjd bädd för syresättning och näringstillförsel. Den bakre delen av ögonlocket återskapas därför genom att slemhinna och en del av ögonlocksplattan lånas från övre ögonlocket. För blodförsörjningens skull lämnas en vävnadsbrygga av slemhinna mellan övre och nedre ögonlocket, vilket innebär att ögonlocken är ihopsydda under läkningstiden och patienten kan därmed inte öppna ögat. Vävnadsbryggan delas sedan på operation när nya blodkärl har vuxit in i hudtransplantatet, vilket beräknas ta cirka tre veckor.

Nackdelar med denna metod är att ögonlocket måste vara ihopsytt i ett antal veckor, samt att en ny operation krävs för att dela vävnadsbryggan. Att ha ögat stängt under lång tid kan innebära en stor påverkan på patientens livskvalitet. Ofta är det äldre och sjuka personer som drabbas av större tumörer på ögonlocket, och de har inte sällan dålig syn på andra ögat. Det är i dessa fall väldigt begränsande att få ögat med god syn ihopsytt. Även de som ser bra på båda ögonen förlorar sitt djupseende vilket kan leda till fallolyckor, och de får enligt svensk lag inte lov att köra bil. Det är dessutom nödvändigt att genomgå två operationer.

Tidigare studier utförda av vår forskargrupp har visat att det vid operation av grisar faktiskt saknades blodförsörjning i den yttersta änden av vävnadsbryggan, som enligt teorin ovan skall försörja det fria hudtransplantatet med blod. Detta väcker frågan om det är nödvändigt att kombinera det fria hudtransplantatet med en vävnadsbrygga om denna ändå inte har fullständig blodförsörjning, eller om man kan göra hela operationen i ett steg med ett fritt fulltjockleks-ögonlockstransplantat. Man skulle därmed slippa både att sy ihop ögat och att utföra en andra operation. Inga tidigare studier har gjorts för att undersöka detta på människor.

I den här avhandlingen studerades blodflödet vid rekonstruktiva ögonlocksoperationer med vävnadsbryggor eller fria transplantat på patienter. Vi har använt modern visualiseringsteknologi, Laser Speckle Contrast Imaging (LSCI) och Laser Doppler Velocimetry (LDV), som mäter blodflöde med laser. Vi har även studerat hur ingreppet kantolys påverkar blodflödet i ögonlocken. Kantolys används ofta vid rekonstruktiv kirurgi i ögonlocken och innebär att fästet till ett ligament i ögonlocket delas, för att kunna sträcka vävnaden ytterligare och täcka vävnadsdefekter.

I den första studien mätte vi blodflödet i vävnadsbryggor, så kallade tarsokonjunktivala lambåer, på patienter under operationen. Resultatet visar att flödet minskar gradvis längs bryggan, och i den yttersta änden finns det nästan inget blodflöde alls. Bryggan, vars syfte skulle vara att försörja transplantatet med blod, verkar inte bidra med något blodflöde.

I den andra studien mätte vi blodflödet i de fria hudtransplantat som syddes fast ovanpå vävnadsbryggorna, under och efter operationen. Resultaten visade att trots avsaknad av blodcirkulation i bryggorna så överlevde transplantaten. Blodflödet återkom inom 3-6 veckor efter operationen och alla transplantat läkte fint.

I den tredje studien mätte vi blodflödet i fria fulltjockleks-ögonlockstransplantat. Dessa användes för att rekonstruera vävnadsdefekter i ögonlock utan att samtidigt använda en blodförsörjd vävnadsbrygga. Mätningar under och efter operation visade att alla transplantat återfick blodflöde inom de första 8 veckorna efter operation.

I den fjärde studien utfördes kantolys på grisar. Blodflöde samt vävnadens syresättning mättes under operationen. Ingreppet medförde att blodflödet minskade i ögonlocket. Ett minskat blodflöde skulle kunna påverka läkningen, speciellt om det återstående ögonlocket behöver försörja ett fritt transplantat utan egen blodförsörjning.

Sammanfattningsvis verkar de fria transplantaten inte vara beroende av en blodförsörjd vävnadsbrygga för överlevnad. Våra resultat visar att ögonlock tål helt andra nivåer av syre- och näringsbrist än vad som tidigare varit känt. Ögonlocken verkar därmed vara mer tillåtande för kirurgi med fria transplantat än andra delar av kroppen. Vi tror att detta beror dels på den goda blodcirkulationen i ögonområdet, men även på att ögonlocken formligen badar i tårvätska som är rik på både syre och näring.

I vissa fall skulle en alternativ operationsmetod med fria fulltjockleks-transplantat vara till fördel för patienterna. Att slippa ha ögat ihopsytt efter operationen skulle öka många patienters livskvalitet, och det är fördelaktigt både för patienter och för sjukvården att minska antalet operationer som behövs göras. Fria fulltjockleks-transplantat utan vävnadsbrygga är en metod som vi har börjat använda med framgång. Vi är bland de första att använda denna nya operationsmetod i klinisk praktik, och den har visat sig vara väldigt framgångsrik.

Vår forskning bidrar till kunskap om hur kirurgiska ingrepp påverkar blodcirkulationen och syresättningen i ögonlocken, en kunskap som tidigare varit i princip obefintlig. Vår forskargrupp studerar nu blodcirkulationen vid andra kirurgiska ingrepp i ögonlocksregionen. Vi hoppas kunna utveckla nya kirurgiska metoder såväl som att optimera de redan befintliga och därigenom förbättra operationsresultatet och minska lidandet för patienterna.

Papers included in this thesis

This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals. The papers are reproduced with the permission of the respective publisher.

I. **Tenland K**, Memarzadeh K, Berggren J, Nguyen CD, Dahlstrand U, Hult J, Engelsberg K, Lindstedt S, Sheikh R, Malmsjö M. Perfusion Monitoring Shows Minimal Blood Flow from the Flap Pedicle to the Tarsoconjunctival Flap. Ophthalmic Plast Reconstr Surg. 2019 Jul/Aug;35(4):346-349.

II. Berggren J, **Tenland K**, Ansson CD, Dahlstrand U, Sheikh R, Hult J, Engelsberg K, Lindstedt S, Malmsjö M. Revascularization of Free Skin Grafts Overlying Modified Hughes Tarsoconjunctival Flaps Monitored Using Laser-based Techniques. Ophthalmic Plast Reconstr Surg. 2019 Jul/Aug;35(4):378-382.

III. **Tenland K**, Berggren J, Engelsberg K, Bohman E, Dahlstrand U, Castelo N, Lindstedt S, Sheikh R, Malmsjö M. Successful Free Bilamellar Eyelid Grafts for the Repair of Upper and Lower Eyelid Defects in Patients and Laser Speckle Contrast Imaging of Revascularization. Ophthalmic Plast Reconstr Surg. 2021 Mar/Apr 01;37(2):168-172.

IV. Berggren JV, **Tenland K**, Memarzadeh K, Sheikh R, Hult J, Lindstedt S, Malmsjö M. The Effect of Canthotomy on Blood Perfusion During the Repair of Lower Eyelid Defects. Ophthalmic Plast Reconstr Surg. 2020 Mar/Apr;36(2):135-138.

Abbreviations

LDV	Laser Doppler Velocimetry
LSCI	Laser Speckle Contrast Imaging
PU	Perfusion Units

Introduction

Reconstructive surgery is used to rebuild and repair defects in the body caused, for example, by disease, trauma, or congenital malformations. It is very important to achieve functionally and esthetically satisfactory results to restore normal function and prevent further damage, and to improve the patient's quality of life. The face, including the area around the eyes, is often more exposed to sunlight than other parts of the body, and the risk of developing skin cancer in this area is therefore higher. The eyelids play an important role in protecting the delicate eye and its functions, and reconstructing all the components of the eyelid is therefore important, but challenging for the surgeon.

Adequate blood perfusion in a tissue is crucial for healing after reconstructive surgery, not least when using advanced surgical techniques such as flaps and grafts. Blood perfusion is defined as the amount of blood flowing through a volume of tissue during a given time.

It was not until the introduction of laser-based techniques in the end of the 1990s, that it became possible to measure microvascular blood perfusion during and after reconstructive surgery in an objective and non-invasive way. Modern techniques now make it possible to monitor blood perfusion during and after surgery in a safe, efficient way, while having no negative effects on the patient. This allows us to evaluate and optimize surgical methods and to question old truths based mainly on empirical knowledge.

This thesis describes blood perfusion measurements during reconstructive eyelid surgery using the Hughes modified tarsoconjunctival flap and an alternative surgical method using a free composite graft.

Eyelid anatomy

The complex anatomy of the eyelids protects the eye from the outside world and keeps the sensitive cornea lubricated. This is accomplished by mechanical protection when closing the eyelid, tear film distribution across the ocular surface when blinking, tear drainage, and glands that secrete substances responsible for lubricating the ocular surface.

The upper and lower eyelids consist of two anatomical lamellae; the anterior and the posterior lamellae, as shown in Figure 1. The anterior lamella includes skin and the orbicularis oculi muscle, while the posterior lamella includes the tarsal plate and conjunctiva. The two lamellae are separated by a mucocutaneous junction called the gray line, which can be seen in the eyelid margin, and is often used by surgeons as an anatomic landmark, indicating the position of the pretarsal orbicularis muscle (1).

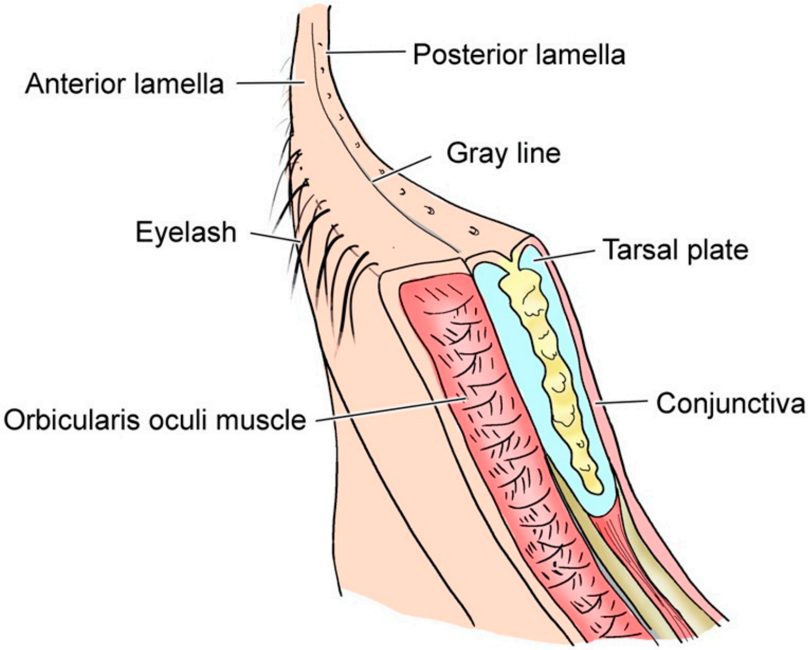

Figure 1. Anatomy of the human lower eyelid. The anterior lamella consists of skin and the orbicularis oculi muscle, and the posterior lamella of the tarsal plate and conjunctiva. The gray line separating the two lamellae is visible in the eyelid margin. (Illustration by Jenny Hult)

The skin forms an external barrier and is composed of two primary layers, the epidermis and the dermis. In the eyelid, the epidermis is about 0.05 mm thick, and the dermis is about 0.6 mm thick (2). The tarsal plate is a 1 mm thick layer of dense fibrous connective tissue that provides stability to the eyelids. The upper tarsal plate measures 10-12 mm vertically, and the lower measures 3.5-5 mm vertically, narrowing medially and laterally, and is connected to the orbital rim by the lateral and medial canthal ligaments (Figure 2). The upper and lower eyelid retractor muscles have attachments to the tarsal plate. The conjunctiva is a thin mucous membrane lining the inside of the eyelid (1).

The upper and lower eyelids are connected at the lateral and medial canthi. The medial canthus is separated from the globe by the caruncle, plica semilunaris, and the tear lake. The lateral canthus is in contact with the eye bulb. The lateral and medial canthal ligaments attach the upper and lower tarsal plates to the orbital bone structures (Figure 2). Both canthal tendons have an anterior and a posterior limb. The lateral canthal tendon attaches the upper and lower tarsal plates to the zygomatic bone at Whitnall's tubercle on the orbital rim, while the medial canthal tendon attaches the tarsal plates to the anterior and posterior lacrimal crests (3).

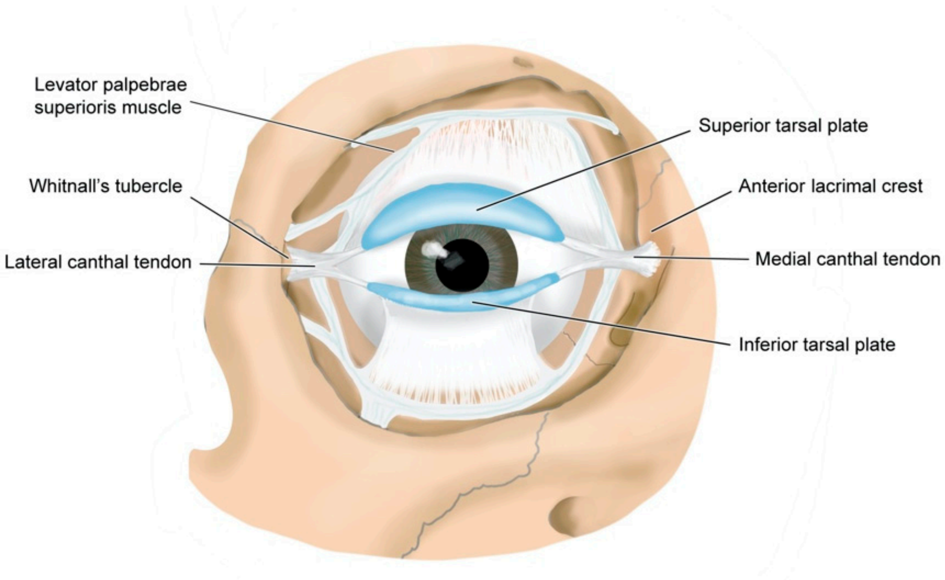

Figure 2. Anatomy of the lateral and medial canthal ligaments in a right eye. The lateral and medial canthi connect the upper and lower eyelids. The lateral canthal tendon attaches the superior and inferior tarsal plates to Whitnall's tubercle, while the medial canthal tendon attaches the tarsal plates to the anterior and posterior lacrimal crests. (Illustration by Jenny Hult)

Circulation and microcirculation of the eyelids

The eyelids have a complex vascular network containing branches from both the internal and the external carotid artery. The internal carotid artery supplies the eyelids through the ophthalmic artery, while the external carotid artery branches into the infraorbital, facial, and superficial arteries supplying the eyelids with blood. These branches form anastomoses in arcades, i.e. the marginal and the peripheral arcades in the upper eyelid and the lower palpebral arcade in the lower eyelid, as shown in Figure 3. These anastomoses result in a complex vascular network allowing blood flow to take alternative routes if necessary, to ensure tissue survival. This unique and extended vascular structure makes the eyelids a very forgiving area for reconstructive surgery.

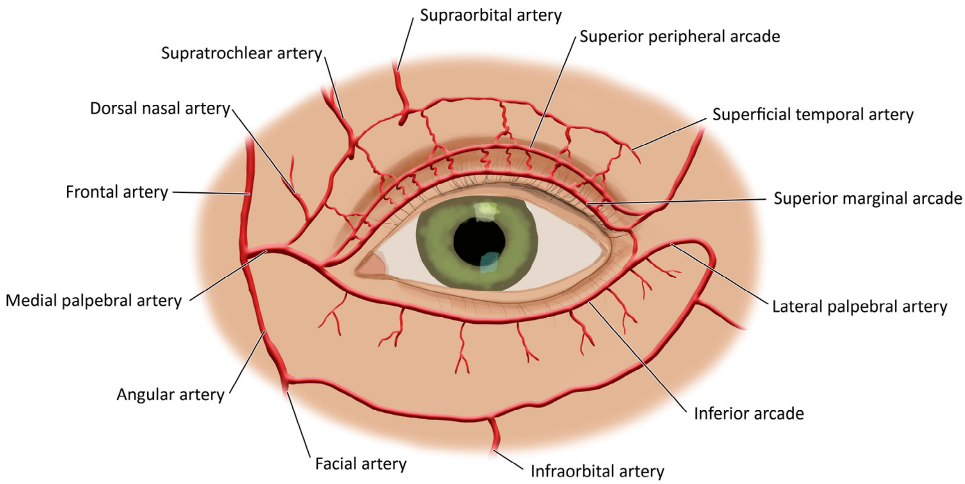

Figure 3. Vascular anatomy of the eyelids in a left eye, showing the arcades. (Illustration by Jenny Hult)

The microcirculation consists of capillaries, arterioles, and venules. Skin microvessels, like other microvessels, perform three important constitutive functions: regulation of the fluidity of the blood, as a barrier that separates and controls the transfer of molecules and cells between the circulating blood and the extravascular tissue, and regulation of local blood flow, which is crucial for the thermoregulation of the skin. The small vessels respond to nervous signals and local tissue chemical signals, and small changes in the diameter of the arterioles will lead to considerable changes in the blood flow to the tissue (4).Thermoregulatory control of the blood flow in human skin is vital for the maintenance of normal body temperature and the baroreflex control of blood pressure. Skin blood flow also increases in response to local heat due to sensorineural and nitric oxide-mediated dilation. Local cooling of the skin can reduce skin blood flow to minimal levels (5).

The microcirculation is divided into two plexuses, the superficial vascular plexus and the deep vascular plexus, which are both situated in the dermis of the skin. Capillary loops extend from the superficial plexus into the dermal papillae to supply blood to, and remove waste from, the overlying epidermis. The deep vascular plexus is located at the border between the dermis and the subcutaneous fat. Larger vessels connect the two plexuses (6).

Plastic and reconstructive surgery

Plastic and reconstructive surgery is a broad field that includes surgical repair of congenital deformities, post-surgical reconstruction, and correction of post-traumatic defects. Restoring function and appearance to the tissue after illness, trauma, or surgery demands surgical procedures tailored to the individual patient. Large tissue defects that cannot be repaired by direct closure of the remaining tissue must be reconstructed using flaps or grafts.

Flaps and grafts

A flap is a piece of tissue partly detached from the donor site and stretched and/or rotated to cover the defect, while a graft is free transplanted piece of tissue from a donor site to a recipient site. As a flap is still attached to the donor site its blood supply is still intact (Figure 4A). A free graft is completely detached from the donor site and is therefore avascular, i.e., lacking a blood supply, and is therefore dependent on the recipient site for nutrients and blood supply (Figure 4B) (7).

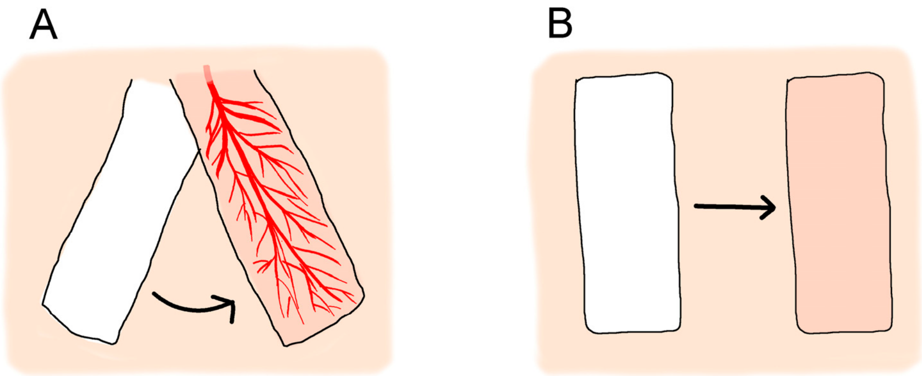

Figure 4. Flaps and grafts. A flap (A) is still attached to the donor site, and therefore has its own blood supply. A free graft (B) is completely detached from the donor site, and is thus dependent on the recipient site for nutrients and blood supply. (Illustration by Jenny Hult)

Flaps can be classified according to their blood supply and their primary movement. Random patterned skin flaps lack a specific vessel for blood supply, while axial flaps have a specific named blood vessel. Advancement flaps are stretched and moved forward to close a defect, and rotational flaps are rotated (8).

Grafts are classified by origin and thickness. An autograft is a graft transferred from a donor site to a recipient site in the same individual. All grafts described in this thesis were autografts. An allograft is a graft transplant between different individuals of the same species (e.g., human to human), whereas a xenograft is a transplant between individuals of different species (e.g., animal to human). A transplant between genetically matched genotypes, for example identical twins, is called an isograft.

The thickness of the graft of choice depends on the extent of the tissue defect. A full-thickness skin graft contains all layers, i.e. epidermis and the entire dermis. A split-thickness skin graft contains the epidermis and part of the dermis. These can be classified as thin, medium, or thick, depending on how much dermis is included in the graft. A split-thickness graft can be used to cover shallow skin defects, large skin defects, or skin defects with a limited vascular supply. However, the cosmetic outcome is often poor with split-thickness grafts, and they are therefore usually avoided in the facial area. A composite graft consists of at least two different types of tissue, for example, skin and cartilage. This type of graft is believed to be at greater risk of failure if blood perfusion is compromised (9). Table 1 shows an overview of graft types with different constituents as discussed above.

Table 1. Graft types.

Graft type	Graft constituents	Nutritional requirement
Full-thickness skin graft	Epidermis + dermis	High
Split-thickness skin graft	Epidermis + partial dermis	Low
Composite graft	More than one tissue type, e.g. skin + cartilage	High

Reconstructive surgery of the eyelid

The goals of reconstruction in oculoplastic surgery are to obtain functional and esthetically pleasing results. Skin tumors, such as basal cell carcinomas, are common in areas exposed to the sun, such as the eyelids. The unique anatomy of the eyelids presents a reconstructive challenge in maintaining function and stability without distortion of the surrounding tissues or the original eyelid contour and symmetry. In full thickness eyelid defects, both the anterior and posterior lamellae need to be reconstructed.

The reconstructive method chosen varies for each individual patient, and depends, among other factors, on the size of the tissue defect. Other important factors are the laxity of the eyelid, the patient's general health status, risk factors for healing such as smoking, and vision in the other eye. Younger patients usually have more tension in their skin, while age-related skin laxity in older patients often allows direct closure of larger defects (10).

Small tissue defects involving less than 20-30% of the length of the eyelid can often be repaired by direct closure of the wound edges. This method shows excellent postoperative outcome, and is often chosen when possible (11). When reconstructing large defects the surgeon may still be able to close the eyelid directly by releasing the tension in the eyelid. Methods of releasing the tension, such as lateral cantholysis and the Tenzel flap, are described in more detail below. Larger defects involving 50% of the length of the eyelid or more, require more advanced reconstructive surgery, using flaps or grafts.

Reconstructive methods for large eyelid defects

When reconstructing tissue defects in the eyelid, it is crucial to restore both the anterior and posterior lamellae in order to maintain adequate eyelid function and thus protection of the underlying eye. The anterior lamella must be replaced with skin and sometimes muscle lamina, and the posterior lamella must be replaced with a firm fibrous framework for replacement of the tarsal plate, and a smooth mucous lining. This can be done using eyelid grafts and flaps that contain the same tissues as those missing in the defect (skin, orbicularis oculi muscle, tarsal plate, and conjunctiva), or by using tissue from other anatomical locations in the face or body, such as skin from the inside of the arm, oral mucosa or ear cartilage.

It is generally believed that when repairing a large tissue defect involving more than half the width of the eyelid, if using a free graft for replacement of one lamella, the other lamella must be reconstructed as a flap with its own blood supply. The flap is believed to be necessary to provide an adequate blood supply to the reconstructed tissues during healing(12). The combination of a vascularized flap and a non-vascularized graft is thus the most common method in the reconstruction of large eyelid defects. Numerous reports have described this surgical principle, using different techniques, as will be described below.

Two-step reconstructive methods

Traditionally, a two-step reconstructive method is used to reconstruct full-thickness eyelid defects larger than 50% of the width of the lower eyelid, especially when the tissue defect is located centrally on the eyelid. Either the anterior or the posterior lamella is vascularized.

The Cutler-Beard flap involves the use of a full-thickness skin-muscle-conjunctiva flap from the lower eyelid to repair large upper eyelid defects. The flap must be combined with a tarsus substitute, such as tarsus from the contralateral eyelid or free auricular cartilage, for reconstruction of the upper tarsus. This technique requires a second surgery for flap division, and vision in the eye is occluded during healing (13). The Mustardé lower lid switch flap is a full-thickness flap from the lower eyelid which is switched to the upper lid. Compared with the Cutler-Beard flap, this technique provides greater eyelid stability and allows reconstruction of the lash margin. The pedicle is divided after 4 weeks and, as in the Cutler-Beard technique, a second surgery is required and the eye is occluded (12).

In tarsoconjunctival flaps containing tarsus and conjunctiva, a vascularized posterior lamella flap is combined with a free graft for the anterior lamella. This is usually a two-step procedure, with the exception of small defects where a local tarsoconjunctival sliding flap or tarsoconjunctival advancement flap can be used, and isolated defects involving the lateral canthus area of the lower eyelid suitable for a Hewes tarsoconjunctival flap. The Hewes tarsoconjunctival flap is transposed from the lateral part of the upper eyelid to the lower eyelid, with a vascularized pedicle remaining in the lateral canthus (14).

The modified Hughes tarsoconjunctival flap is one of the most frequently used techniques for the reconstruction of the posterior lamella to correct large full-thickness eyelid defects that cannot be closed with a one-stage procedure. As illustrated in Figure 5, a vascularized tarsoconjunctival flap from the upper eyelid is used to reconstruct the posterior lamella of the lower eyelid, and the flap is combined with an overlying free skin or skin-muscle graft for the anterior lamella. The tarsoconjunctival flap is believed to supply blood to the posterior lamella and thereby support the overlying free graft. It is divided when the vascularization of the reconstructed tissue is deemed to be adequate, usually after 3-4 weeks. The procedure was first described by the American oculoplastic surgeon Wendell L Hughes in 1937, and thereafter modified several times by Hughes and other oculoplastic surgeons (15-18).

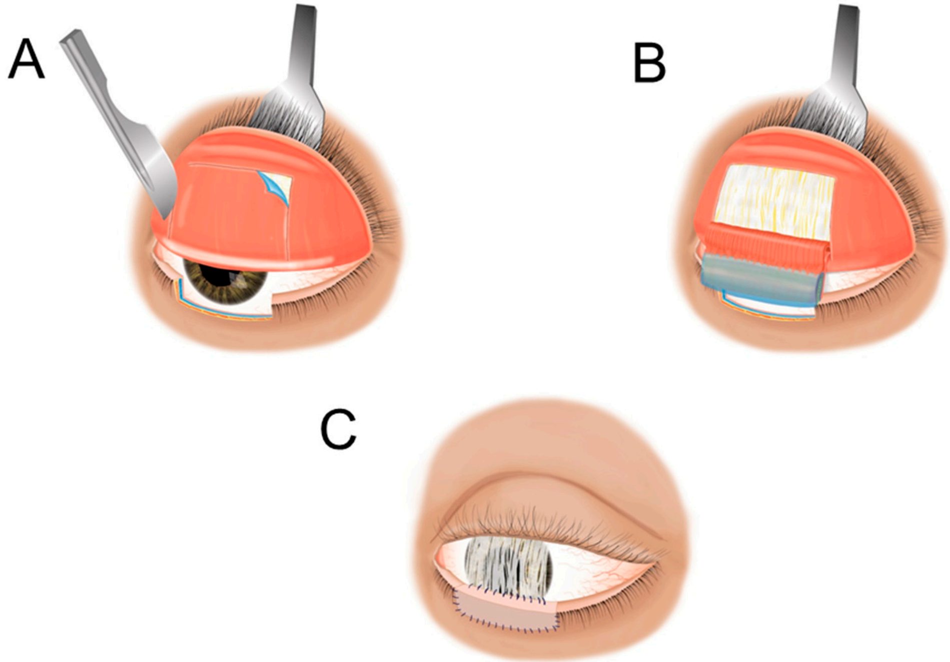

Figure 5. The modified Hughes tarsoconjunctival flap for reconstruction of the posterior lamella to correct large full-thickness eyelid defects. A vascularized tarsoconjunctival flap from the upper eyelid (A) is used to reconstruct the posterior lamella of the lower eyelid (B). This is combined with an overlying free skin or skin-muscle graft for the anterior lamella (C). (Illustration by Jenny Hult)

A major disadvantage of all the two-step methods described above is that the patient's eye is surgically closed for 3-4 weeks. This is particularly troublesome for patients who have poor vision in the other eye, and since skin tumors in the eyelid area are more common in the elderly population, poor vision on one or both eyes is not uncommon in this group of patients. Having one eye closed for several weeks is also problematic for patients with good vision in the other eye, since closing one eye leads to loss of stereo vision, which may result in increased risk of falling. Furthermore, driving a car with one eye covered is forbidden by law in Sweden. Another disadvantage of these procedures is that a second surgery is required to divide the flap. This means further discomfort for the patient, and extra costs to society and the healthcare service.

Single-step reconstructive methods

The obvious advantages of single-step reconstruction methods are that a second surgery is avoided and the patient´s eye is not occluded. A simple and efficient choice for the repair of defects involving 50-70% of the upper or lower eyelid when the laxity of the tissue allows is the Tenzel semicircular flap (19). A semicircular flap is raised from the lateral canthus, combined with cantholysis for tension release, and the flap is advanced medially to close the defect by direct closure. The McGregor flap is an alternative option, where a lateral periorbital Z-plasty is performed to advance tissue medially to close the eyelid defect (8).

Various single-step reconstructive methods have been suggested in the case of large eyelid defects where Tenzel or McGregor flaps are not an option. Methods in which the anterior lamella is vascularized using medially or laterally based myocutaneous flaps or frontal or forehead axial flaps have been described (20-22). Tarsus and tarsoconjunctival grafts, auricular cartilage grafts, and hard-palate mucoperiosteal grafts have been used as posterior lamellar substitutes (20, 23, 24), and other options such as dermis fat grafts, venous grafts, and pericranial grafts have also been described (25-27).

Single-step eyelid reconstruction using a vascularized component for posterior lamellar reconstruction and a free graft for anterior reconstruction has also been described, for example, using a tarsus advancement flap from the remaining tarsal plate after tumor removal from the eyelid margin (28). Sandwich techniques, in which a three-layer structure is fabricated to restore the eyelid, often involve an orbicularis or frontalis muscle flap combined with a skin graft and a graft for the posterior lamella (29, 30). Part of the anterior lamella is vascularized using this technique. Other single-step methods have been described, such as the combination of advancement flaps to repair both the posterior and anterior lamellae. However, this requires a sufficient amount of upper eyelid skin and tarsal plate (31).

In all these single-stage methods, the combination of a vascularized and an avascular component is used for reconstruction. The clinical outcome has been presented, but blood perfusion has not been monitored during and/or after the procedures. However, single-stage procedures for the repair of large or deep eyelid defects are challenging, and a Hughes flap is still one of the most commonly used procedures.

The need of a vascularized component

The Hughes tarsoconjunctival procedure and other two-step surgical methods were developed long before modern laser-based techniques were available for the measurement of microvascular perfusion. New technology makes it possible to monitor perfusion and to refine and optimize surgical procedures. To the best of the author's knowledge, no studies have yet been performed to investigate blood perfusion in tarsoconjunctival flaps to evaluate the possibility of single-stage grafting of a free full-thickness eyelid.

It is not known whether there is sufficient vasculature in the conjunctiva to nourish a thick piece of tarsus at the end of the flap. As mentioned above, a non-vascularized graft is traditionally believed to be dependent on a vascularized flap for survival when repairing a defect involving more than 50% of the lower eyelid. However, the results of previous studies have called this truth based on empirical knowledge into question.

Several studies have indicated that the flap pedicle in Hughes tarsoconjunctival flaps could be divided earlier than previously believed, which would support the hypothesis that blood perfusion in the flap does not affect graft survival. Premature flap dehiscence after 1-14 days has been reported in numerous patients, both as a result of accidental trauma and in clinical studies, all of which resulted in good functional and cosmetic outcomes (32-34). Furthermore, surgical methods that theoretically might compromise flap perfusion have been described, such as the use of two tubed conjunctival flaps or a "buttonhole" in the flap (35, 36). The postoperative results were reported to be good despite these flap designs. In 2005, Boboridis et al. speculated that a vascularized pedicle may not be necessary for tarsal flaps less than 13 mm in length. This suggestion was based on four patients who underwent reconstructive surgery using a combination of a free mucosal graft for the posterior lamella and a free skin graft for the anterior lamella. All grafts were viable and healed with no signs of ischemia (37).

This raises the question of whether perfusion from the flap is essential for the survival of the graft. To further investigate the necessity of blood perfusion by the tarsoconjunctival flap, a study was conducted by our research group in which blood perfusion was measured in tarsoconjunctival flaps in a porcine model using laser Doppler velocimetry (LDV) and oxygen tension (38). This showed virtually no blood perfusion or oxygenation of the tissue at the time when the flap was sutured into place. Furthermore, the possibility of surgical vasospasm as a cause of the hypoperfusion was ruled out by injecting the vasodilator verapamil, which did not alter the hypoperfusion, and the hypoperfusion remained unchanged 12 hours post-surgery. In spite of this, all the flaps were viable, and there was no sign of necrosis upon histologic examination. The results of this study show that there is indeed reason to question the contribution of perfusion from the flap to the free skin graft.

Lateral cantholysis

During reconstructive surgery on the eyelids, the closure of the wound is often limited by a lack of tissue laxity, and the surgeon is required to release tension in the tissue. This mobilizes eyelid tissue and minimizes the tension in the wound, which can allow for direct closure of a large defect, or the reconstruction of a large defect using a smaller graft.

Lateral cantholysis is one method of tension release, which is sometimes performed when repairing full-thickness lower eyelid defects. Lateral cantholysis involves surgically releasing the lateral canthal tendon from the orbital rim by cutting the superior or inferior part of the tendon or, if necessary, both, which mobilizes tissue medially in the lower eyelid (Figure 6).

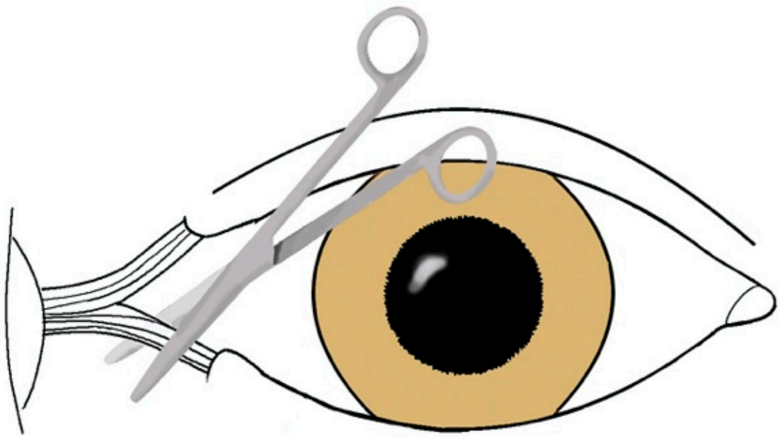

Figure 6. Lateral cantholysis, where the lateral canthal tendon is surgically released from the orbital rim. This is a surgical procedure used to release tension in the tissue during reconstructive surgery in the eyelids. (Illustration by Jenny Hult)

Lateral cantholysis may result in severing of the lateral palpebral artery (Figure 3), which crosses the lateral canthal tendon. When a tumor in the lower eyelid is resected, the medial palpebral artery is usually severed, and this may affect tissue perfusion and healing, especially if the remaining tissue needs to support a free graft. Performing a canthotomy, with a risk of severing an additional artery, may further compromise perfusion of the tissue.

The question of whether tension release is necessary in the forgiving area of the eyelids has arisen. In addition to severing the arteries and possibly reducing the blood supply, canthotomy also harms the canthal ligament which serves to stabilize the eyelids. This might lead to ectropion. Studies on direct closure or reconstruction without tension release have shown promising results, as the eye bulb seems to function as an expander for the eyelid tissue (39). After a few weeks, eyelids with high tension after surgery will expand, leading to excellent results. This brings the need for cantholysis into question.

If cantholysis is not sufficient for mobilization of the tissue, a Tenzel semicircular advancement flap can be used. This method was originally described in 1975 by RR Tenzel, and combines the flap with a lateral cantholysis. A myocutaneous flap is dissected at the lateral canthus and advanced medially to cover the eyelid defect, and the conjunctiva in the lateral fornix is dissected and advanced to the tissue (40).

Perfusion monitoring

Measurement techniques

Although conventional methods of estimating blood flow clinically, such as assessment of temperature, color, and capillary refill, are fast and easily accessible, they are highly observer dependent and not very accurate (41). Several techniques for estimating blood flow more objectively have been described over the years, including the use of fluorescein or indocyanine green in angiography, pH monitoring, clearance of radioactive isotopes or pharmacological agents, spectroscopic methods and microdialysis (42). Unfortunately, many of these methods have drawbacks, for example, they are invasive, time-consuming, unreliable, or only provide information from a very small area. Table 2 presents a summary of commonly used methods.

Table 2. Methods of estimating blood flow (43-47)

Method	Advantages	Disadvantages
Clinical examination	Accessible, non-invasive, low cost	Subjective, inaccurate, not reliable
Thermography	Accessible, low cost, repeatable	Needs stable conditions, does not measure perfusion
Fluorescein angiography	Accessible, low cost	Invasive, not repeatable within 24 h, risk of allergic reaction.
Indocyanine green angiography	Accessible, low cost, lower allergy risk than fluorescein	Invasive, risk of allergic reaction
Blue dyes	Low cost, easy to use	Invasive, risk of allergic reaction, not suitable for postoperative follow-up
pH monitoring	Repeatable, suitable during surgery	Invasive, not suitable for postoperative follow-up
Radioactive isotope clearance	Reliable, low recirculation	Invasive, exposure to radioactivity, radioactive waste
H2 clearance	Repeatable, reliable, quantitative measurements	Invasive, small volume of tissue examined, technically challenging
Microdialysis	Reliable, easy to use	Invasive, delay in delivering results
Diffuse reflectance spectroscopy (DRS)	Non-invasive	Superficial, motion artifacts
Near-infrared spectroscopy (NIRS)	Non-invasive, deep measurements, high resolution, quantitative measures	Low spatial resolution in heterogeneously perfused tissues
Pulse oximetry	Low cost, easy to use, fast, can be non-invasive	Accuracy compromised, invasive if catheter is used, arterial blood only
Tissue oxygenation (Clark electrode)	Sensitive and reliable	Invasive, time lag, small area measured
Laser Doppler velocimetry (LDV)	Repeatable, can be non-invasive, high accuracy	Motion artifacts, arbitrary units, small area measured, invasive if catheter used
Laser Doppler perfusion imaging (LDPI)	Repeatable, can be non-invasive, high accuracy, larger sampling area than LDV	Motion artifacts, arbitrary units, data acquisition is long
Laser speckle contrast imaging (LSCI)	Non-invasive, fast, large area, good spatial resolution, repeatable, not dependent on user experience	Motion artifacts, arbitrary units, superficial measurements, stable conditions needed
Magnetic resonance angiography	High resolution	Limited availability, invasive if contrast agent needed

Laser-based techniques

Laser-based techniques provide opportunities for fast and non-invasive perfusion monitoring during and after surgery. Laser-based techniques were used for perfusion monitoring in all the studies presented in this thesis.

Laser Doppler velocimetry

Laser Doppler velocimetry (LDV) is a method based on backscattering of a beam of laser light undergoing changes in wavelength as a result of Doppler shift. Doppler shift is the change in frequency of a wave in relation to an observer who is moving relative to the wave source(48). A familiar example of this is when a vehicle with a siren and high speed, such as an ambulance, is first approaching and thereafter moving away from an observer. The siren will sound differently when moving towards and away from the observer because of the Doppler shift of the soundwaves (Figure 7).

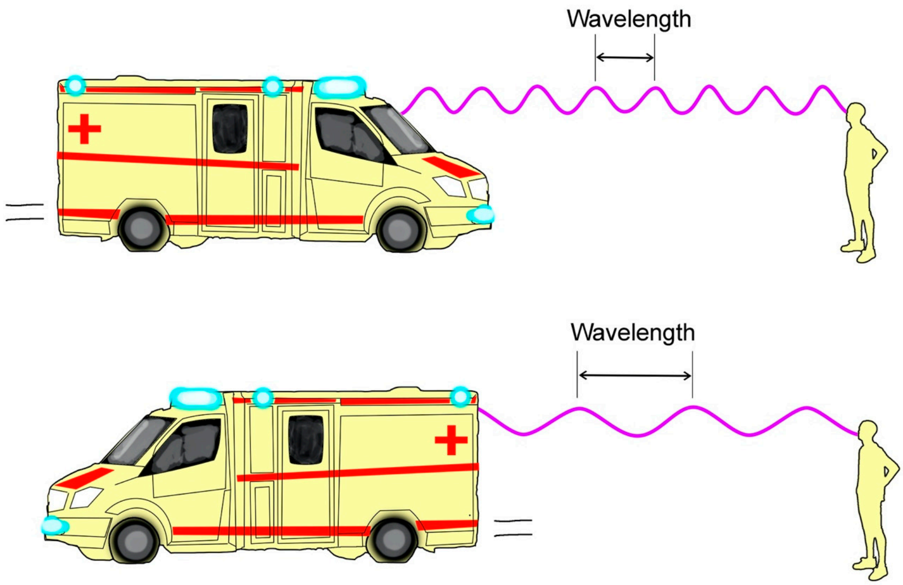

Figure 7. The Doppler shift illustrated by a moving ambulance with a siren first approaching and thereafter moving away from an observer. The frequency of the soundwaves changes when the vehicle is moving towards or away from the observer, making the siren sound differently. (Illustration by Jenny Hult)

In LDV, coherent laser light in the infrared or near infrared part of the spectrum illuminates the skin, penetrating the surface. Photons impinging on moving red blood cells will undergo a Doppler shift and be reflected with a slightly different wavelength, whereas photons impinging on static structures will be reflected unchanged (Figure 8) (48). LDV is a portable and fast technique, suitable for bedside monitoring of blood perfusion. However, contact with the tissue is required, using either skin surface probes, as in Study II, or filament probes that are inserted into the tissue, as in Studies I and IV.

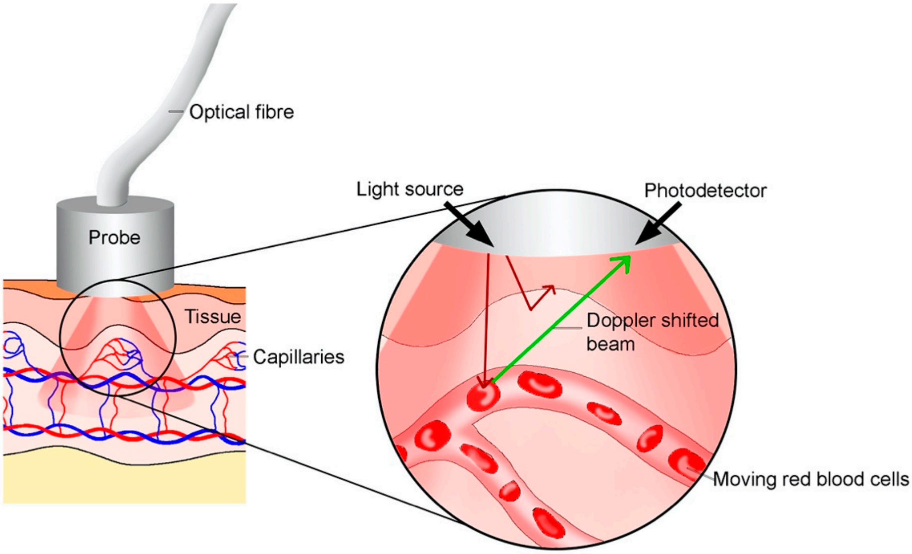

Figure 8. Principle of LDV. Coherent laser light illuminates the skin, penetrating the surface. Photons impinging on moving red blood cells will undergo a Doppler shift and be reflected with a slightly different wavelength, whereas photons impinging on static structures will be reflected unchanged. (Illustration by Jenny Hult)

LDV provides information on perfusion in a 1 mm^3 volume surrounding the tip of the probe, although the measurement depth and volume may differ depending on the laser wavelength and the concentration of red blood cells in the tissue (49). The small sampling volume may be a drawback if blood supply to the tissue is heterogeneous and the measurements are carried out in a small area not representative of the tissue. Since the area of interest in the periorbital region measured in these studies is so small, this should not be a problem, but it could affect the reproducibility of the results. Laser Doppler perfusion imaging is a technique similar to LDV, developed to overcome the problem of the small sampling area. However, the acquisition time is long and it is not widely used in the clinical setting or in medical studies (50).

The increase in perfusion in response to heating is thought to be related to the metabolic and thermoregulatory function of the skin, and can be used to determine the viability of tissue and the degree of microcirculatory impairment (51). This technique is called local thermal hyperemia. In Study II, LDV measurements were made in combination with heating of the tissue to obtain information on the vascular reactivity. Thermostatic laser Doppler probes allowing for precise heating at the measurement site were used with the laser Doppler unit. In healthy subjects, local thermal hyperemia is characterized by an initial peak within the first five minutes, a subsequent dip, and thereafter a plateau (52). Heating to 42-43°C is usually sufficient to induce maximal vasodilation, and is well tolerated by patients (53).

In summary, LDV is a well-proven method suitable for bedside monitoring of blood perfusion. However, it suffers from the drawbacks of being invasive and only measuring a limited area. In Studies I, II and IV, LDV was used together with other measurement techniques (Laser Speckle Contrast Imaging (LSCI) in Studies I & II, and tissue oxygen tension monitoring in Study IV) to verify the LDV measurements.

Laser speckle contrast imaging

Laser speckle contrast imaging (LSCI) was introduced in biomedical applications in the 1980s, when it was used to measure retinal blood flow (54). It has since been used to image burn wounds, cerebral blood flow and skin microvasculature, among others (55). This non-invasive technique visualizes motion in a larger tissue area than LDV, up to 24x24 cm. As in LDV, the measurement depth is dependent on the laser wavelength and tissue characteristics such as the concentration of red blood cells, but is approximately 700 μm (56). The skin penetration depth is however more superficial (300 μm) than that with LDV (1 mm) (52).

LSCI is based on the interference pattern, so-called speckle pattern, that is formed at the detector when a biological tissue is illuminated with coherent light. This is due to irregularities in the surface. Dark and bright areas in the pattern are formed by random interference of the light backscattered from the illuminated area, which is recorded by a photodetector. Movement of particles, in this case red blood cells, causes fluctuations in this speckle pattern, resulting in blurring of the speckle image (Figure 9). This is the same mechanism of the blurring in a photograph when photographing a moving object. The degree of blurring can be quantified by calculating the contrast, where fast moving particles will cause more blurring and thus lower contrast, while static particles will cause less blurring and higher contrast (55).

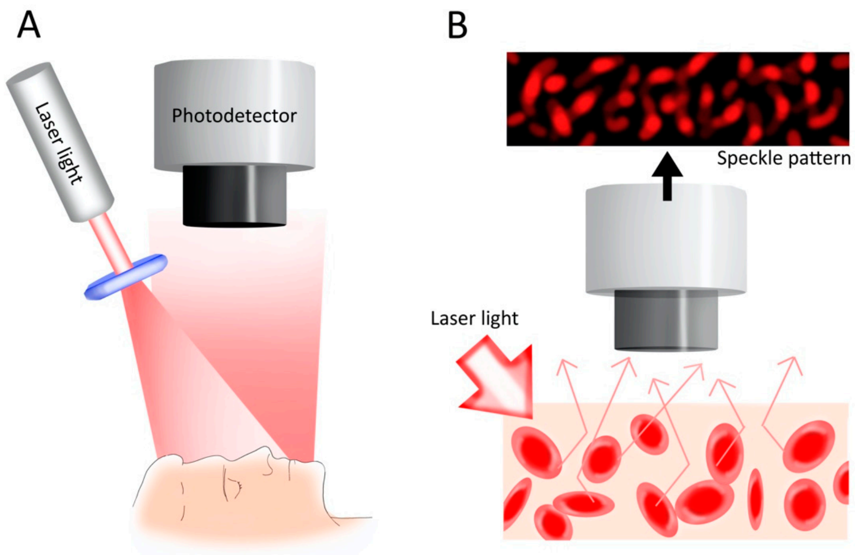

Figure 9. Laser speckle contrast imaging. (A) The laser light illuminates the skin and interference will produce a speckle pattern which is recorded in the photodetector. (B) Moving red blood cells will cause fluctuations in the speckle pattern. (Illustration by Jenny Hult)

The changes in the speckle pattern are recorded with a spatial resolution of up to 100 µm/pixel and analyzed by the system, resulting in an instantaneous image of the motion of red blood cells, which is interpreted as perfusion (Figure 10). The perfusion is given in arbitrary perfusion units (PU). This makes direct comparison between different patients, or even measurements from the same patient at different times difficult. The perfusion is thus often expressed as a percentage of that in a representative reference area to allow comparisons.

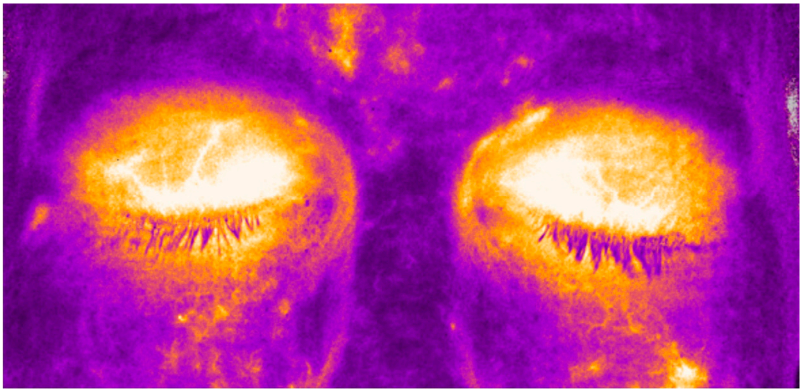

Figure 10. LSCI image of the periorbital area of a patient. The dark purple areas represent regions with low blood perfusion, and the light yellow areas regions with high perfusion (Illustration by author).

LSCI is a fast, non-invasive method for measuring blood perfusion, thus making it very suitable for clinical measurements on patients. The LSCI equipment is fairly small and portable, making it easy to move it into the operating room for peroperative measurements (Figure 11).

Figure 11. LSCI equipment (PeriCam) used for perfusion monitoring during surgery. (Photograph by Stellan Molander)

However, the technique is highly sensitive to motion artifacts. Movement of the patient, such as heartbeats, breathing, coughing, and trembling, will result in artifacts that may be difficult to distinguish from the signal derived from the microcirculation. This can be minimized by urging the patient to lie still, but breathing and blinking affect the measurements in the periorbital region. Furthermore, the measured perfusion signal is never zero, but always has a residual value (57). This phenomenon is called the "biological zero" and is thought to be generated by Brownian motion of macromolecules in the interstitium (58, 59). Biological zero should be taken into consideration when using both LDV and LSCI.

The problems associated with motion artifacts and the biological zero can be partly solved by recording the signal backscattered from an adjacent opaque surface, or by measuring an unaffected region of the tissue, and calculating the results as a percent change.

Tissue oxygen tension monitoring

Tissue oxygenation measurements are made to predict tissue viability during reconstructive surgery as the information provided is considered to be a sensitive and reliable measure of tissue perfusion (60). Oxygenation can be measured by surface probes, as in the case of a pulse oximeter, or using implantable probes, such as the Clark electrode, as was used in Study IV. The pulse oximeter is based on the clinical implementation of a spectroscopic technique in which tissue is exposed to light of a certain wavelength, and the light that is reflected back from the tissue is measured. Since hemoglobin absorbs different wavelengths when oxygenated and deoxygenated, tissue oxygenation can be determined by calculating the light absorbed by the tissue, and thus not reflected back.

The Clark electrode was invented by Leland Clark in 1954, and has been used to predict flap viability by monitoring flap oxygenation (60, 61). The electrode is enclosed in a semipermeable membrane, and the tissue oxygen diffuses into the electrode chamber. An electric current is produced which corresponds to the degree of tissue oxygenation. A disadvantage of this technique is that only point measurements can be made around the electrode, making it unsuitable for studying tissue with heterogeneous oxygenation.

Thesis at a glance

The studies described in this thesis are summarized below.

Study	Aim	Type of surgery	Subject	Method
I	To study peroperative perfusion in Hughes tarsoconjunctival flaps	Tarsoconjunctival flap	Human eyelid	Blood perfusion monitored using LSCI and LDV
II	To study the reperfusion of free skin grafts overlying Hughes tarsoconjunctival flaps	Free skin graft overlying tarsoconjunctival flap	Human eyelid	Blood perfusion monitored using LSCI and LDV
III	To study the reperfusion of free bilamellar grafts	Free bilamellar graft (composite graft)	Human eyelid	Blood perfusion monitored using LSCI
IV	To study the effect on perfusion when performing cantholysis	Cantholysis and wedge resection	Pig eyelid	Blood perfusion monitored using LDV and tissue oxygen tension monitored using a Clark electrode

Aims

General aim

The general aim of this work was to investigate blood perfusion and oxygenation during and after reconstructive surgery of large eyelid defects, using perfusion monitoring techniques and tissue oxygen tension measurements on human eyelids and in a porcine model.

Specific aims were:

- to study the blood perfusion during reconstruction of lower eyelid defects following tumor excision using the modified Hughes tarsoconjunctival flap procedure with overlying free skin grafts (Studies I & II),
- to study a novel, simplified reconstructive technique for large eyelid defects using composite grafts (Study III), and
- to study the impact on blood perfusion of using cantholysis to release tension in the tissue during eyelid reconstruction after tumor removal (Study IV).

Methods

Ethics

Studies I-III included patients referred to the Department of Ophthalmology at Skåne University Hospital. Study III also included patients admitted to the St. Erik Eye Hospital in Stockholm, Sweden. The protocols for these studies were approved by the Ethics Committee at Lund University, Sweden. All patients participating in Studies I-III gave their fully informed written consent to participate in the studies, and were informed that participation was voluntary. Patients who were incapable of providing consent or who were physically or mentally unable to cooperate during the surgical procedure under local anesthesia, were excluded from the studies.

Study IV included eight pigs. The Ethics Committee for Animal Research at Lund University, Sweden, approved the experimental protocol for this study. The animals were treated in accordance with the European Convention on Animal Care. The animals were also subject to other experiments, not affecting the present study. The pigs received continuous infusion of anesthetics, and were euthanized after the completion of all experiments.

Hughes tarsoconjunctival flap

Studies I & II included patients who underwent the modified Hughes tarsoconjunctival flap procedure after skin tumor removal from the lower eyelid. Study I included 13 patients and Study II, 9 patients. Surgery was performed under local anesthesia using lidocaine without adrenaline, to avoid hypoperfusion due to vasoconstriction. After the tarsoconjunctival flap had been dissected (Figure 12A), LDV and LSCI measurements were carried out on the flap, first on the dissected tarsoconjunctival flap (Figure 12B), thereafter on the flap after the dissection of Müller's muscle (Figure 12D), and finally after gentle occlusion of the perfusion (Figure 12F).

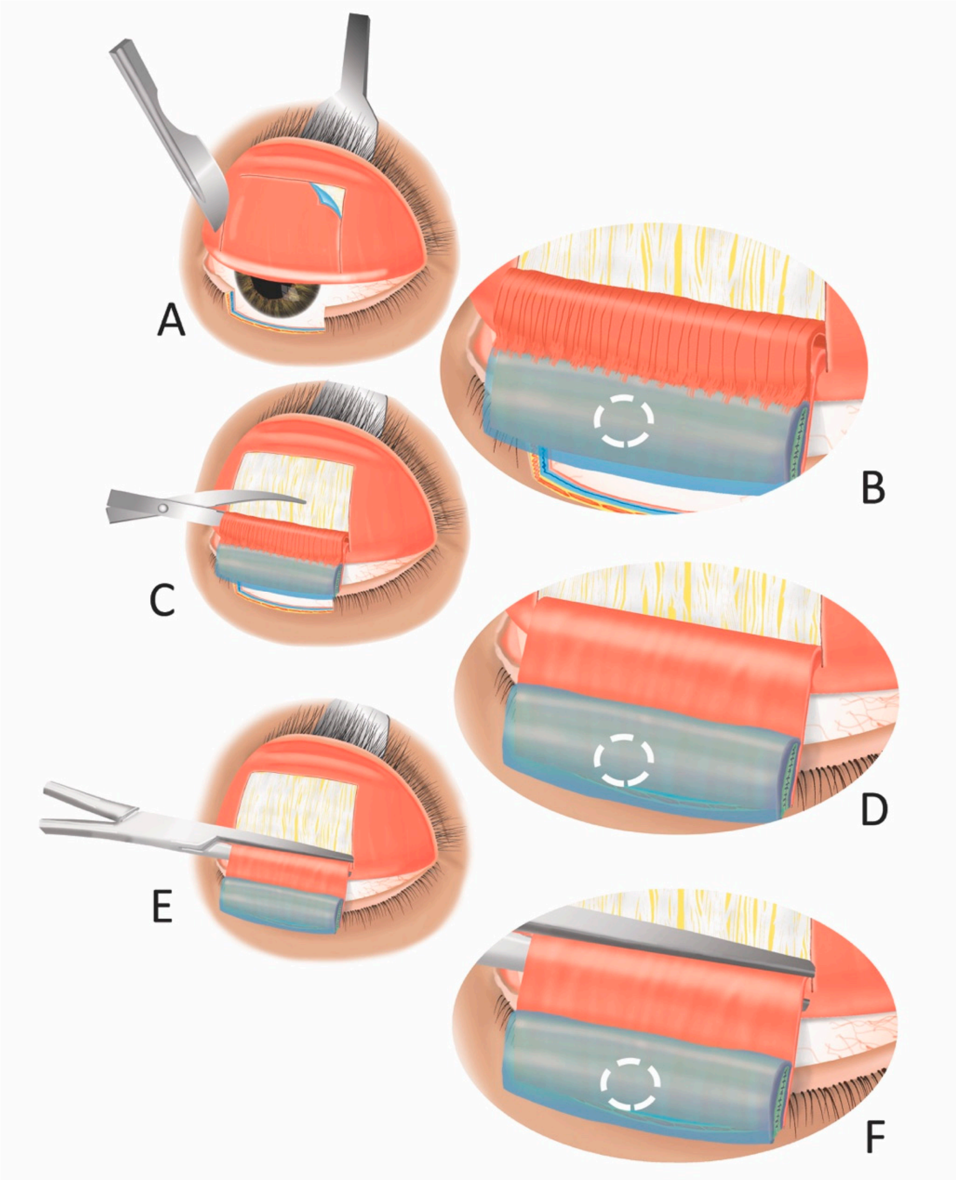

Figure 12. Surgical procedure of the tarsoconjunctival flap and LSCI and LDV measurements during surgery (Study I). The tarsoconjunctival flap was first dissected (A), and measurements on the tarsoconjunctival flap were performed (B). Thereafter remaining strains of Müllers muscle were dissected (C) and measurements were performed (D) and finally gentle occlusion of the perfusion was applied (E) and measurements were performed (F). (Illustration by Jenny Hult)

After the perfusion measurements, the tarsoconjunctival flap was sutured to the lower eyelid defect to reconstruct the posterior lamella. Thereafter, the anterior lamella was reconstructed using a free skin transplant from the upper eyelid or the arm. The skin grafts measured approximately 15x25 mm and were used to cover defects measuring approximately 10x20 mm. The perfusion of the free skin grafts overlying the tarsoconjunctival flaps was measured during surgery using LSCI, and 1, 3, 8, and 16 weeks postoperatively, using LSCI and LDV with thermostatic probes (Figure 13).

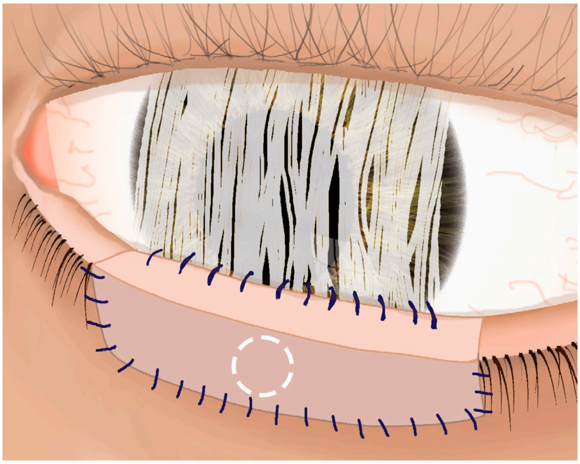

Figure 13. LSCI and LDV measurements on the free skin grafts overlying the tarsoconjunctival flaps (Study II). The perfusion was measured during surgery, and 1, 3, 8, and 16 weeks postoperatively. (Illustration by Jenny Hult)

Composite graft

Study III included 10 patients who underwent reconstructive surgery after tumor removal from the upper or lower eyelid using bilamellar composite grafts harvested from the opposing or ipsilateral eyelid. Composite grafting is a one-step procedure, not requiring a second surgery or the eyelids being sutured together, occluding the eye for several weeks. The composite grafts consisted of skin, muscle, tarsal plate, and conjunctiva. Bilamellar means that the same graft was used to reconstruct both the anterior and the posterior lamellae at the same time. This technique is a full-thickness skin-mucocutaneous-tarsoconjunctival graft without a pedicle. The size of the defects ranged from 12 to 23 mm, and the length of the grafts ranged from 9 to 19 mm. Perfusion was measured using LSCI during surgery, and 1, 2, 4, and 8 weeks postoperatively (Figure 14).

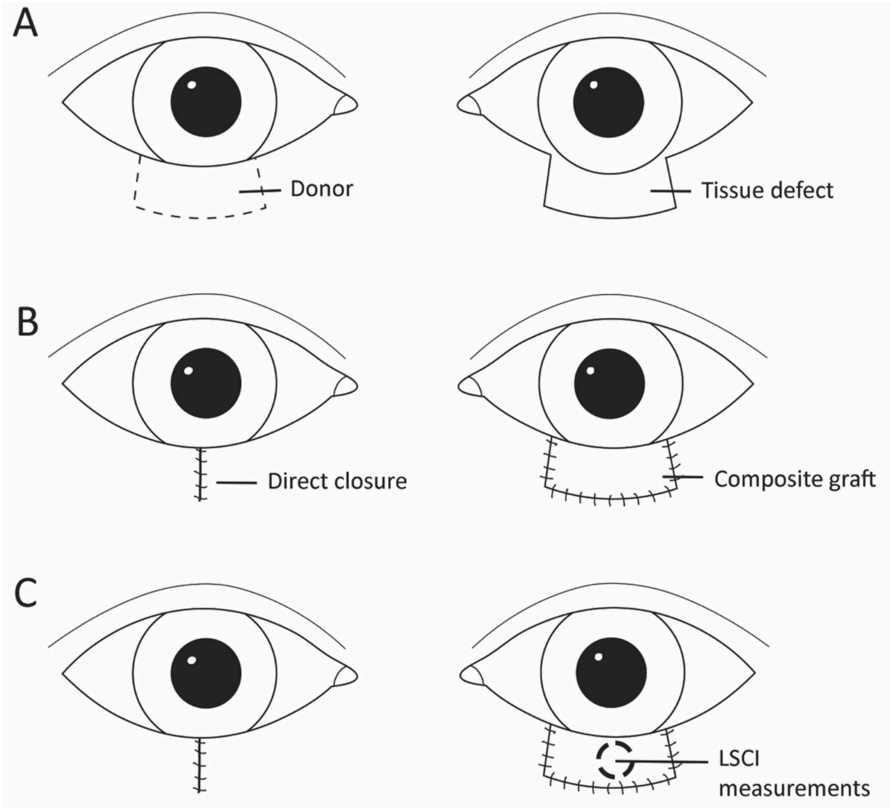

Figure 14. Surgical procedure of the composite grafts and LSCI measurements (Study III). The grafts were harvested from the opposing or ipsilateral eyelid (A) and sutured into the tissue defect (B). The perfusion was measured during surgery, and 1, 2, 4, and 8 weeks postoperatively (C). (Illustration by Jenny Hult)

Cantholysis

The impact of cantholysis combined with a wedge resection of the lower eyelid on blood perfusion was investigated in Study IV. A porcine model was used in this study. Eight pigs with a body weight of 70 kg, were put under general anesthesia and orally intubated. The ventilation settings were identical for all animals.

Surgical procedure

A wedge resection was made in the lower eyelid margin to create a lower eyelid defect, simulating a defect due to tumor removal. Lateral canthotomy and cantholysis were then performed. The initial wedge resection was made 4 mm long, and was gradually lengthened to resemble a large eyelid defect. Perfusion and oxygen tension were measured each time the length of the defect was increased, using LDV and a Clark electrode (Figure 15). Measurements were also carried out after an injection of the vasodilating agent verapamil (0.2 ml, 2.5 mg/ml), and 12 hours after surgery, to investigate the possible effects of surgical vasospasm on perfusion and oxygen tension.

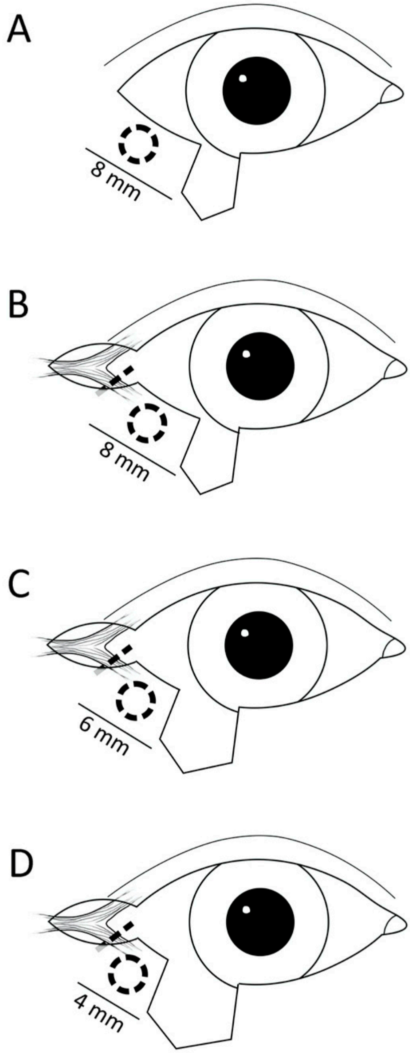

Figure 15. Surgical procedure of wedge resection and cantholysis and LDV and tissue oxygen measurements (Study IV). A wedge resection was made in the lower eyelid margin to create a lower eyelid defect (A). Lateral cantholysis was then performed (B). The initial wedge resection was 4 mm long and was gradually lengthened (C-D), and perfusion and oxygen tension were measured using LDV and a Clark electrode. (Illustration by Jenny Hult)

Perfusion measurements

Laser Doppler velocimetry

LDV was used in Studies I, II, and IV. In Studies I and IV, a filament probe (MT A500-0, straight microtip with a slanted microtip; Perimed AB, Stockholm, Sweden) was inserted into the tissue using a 22G Venflon infusion cannula. The filament probe was attached to a master probe (Probe 418), which was then connected to a PF5010 laser Doppler unit (Perimed). In Study II, LDV measurements were made in combination with tissue heating to obtain information on the vascular reactivity, and in this study a thermostatic laser Doppler probe (PF457, Perimed) was used with the laser Doppler unit.

Laser speckle contrast imaging

In Studies I-III blood perfusion was monitored using a PeriCam PSI NR system (Perimed AB, Järfälla, Sweden) calibrated in accordance with the manufacturer's instructions. The PeriCam PSI system consists of an invisible near-infrared laser (785 nm) for perfusion measurements, a visible red laser (650 nm) for positioning of the image, a CCD camera, and processing software.

Safety aspects

LSCI and LDV use class 1 lasers with low tissue penetration and energy output. The manufacturer states that the LSCI equipment is safe to use without eye protection, however, a corneal shield (Ellman International Inc., Oceanside, NY) was used in the human studies to protect the patient's eye from laser irradiation.

Tissue oxygenation measurements

In Study IV, tissue oxygen tension was measured with a LICOX CC1.SB system (Integra Neuroscience, Saint Priest, France), using a Clark electrode. The electrode was inserted into the eyelid between the wedge resection and the canthotomy, using a 22G Venflon infusion cannula. The tissue oxygenation tension was measured during surgery, after the injection of verapamil, and 12 hours after surgery, similar to the LDV measurements.

Calculations and statistics

GraphPad Prism (GraphPad Software, San Diego, California, USA) was used for statistical calculations. Since the sample size was small in all four studies, and the distribution of data was unknown, non-parametric tests were used to compare groups: i.e., the Mann–Whitney test for single comparisons (Study I), Friedman's test with Dunn's post-hoc test (Studies I-III), and the Kruskal–Wallis test with Dunn's post-hoc test (Study IV). Detailed descriptions of perfusion and tissue oxygenation monitoring, and the statistical analysis can be found in the respective papers.

Perfusion measured with LDV and LSCI is expressed in perfusion units (PU) which is an arbitrary unit. To be able to compare data from different series of measurements, baseline values were recorded, which were defined as 100% perfusion at a reference point and 0% perfusion when the blood flow had been occluded (Studies I and IV), or in the avascular grafts immediately after suturing them into place, when the grafts were known to be completely avascular (Studies II-III). In Study I, perfusion was measured using both LDV and LSCI. Careful consideration was given to the possible effects of motion artifacts.

Results and Discussion

Study I and II: Perfusion in tarsoconjunctival flaps and overlying free grafts

The basic principle of the modified Hughes tarsoconjunctival flap procedure is the combination of a vascularized flap and the avascular free skin graft. The tarsoconjunctival flap is believed to preserve the blood supply to the reconstructed tissue, however, findings in previous studies have brought this into question. To further investigate the need for blood perfusion from the tarsoconjunctival flap, perfusion was studied in the flaps and grafts during and after surgery. To the best of the author's knowledge, blood perfusion has not been studied previously in Hughes tarsoconjunctival flaps in patients using modern imaging techniques.

The perfusion measurements in the tarsoconjunctival flaps (Study I) showed minimal perfusion at the distal end of the flap (Figure 16). LDV measurements showed a gradual decrease in perfusion during dissection and advancement of the flap, and very low perfusion (0-6 PU) when the flap was sutured into place. LSCI measurements showed 4% perfusion at the distal end of the flap. This is in line with a previous study of perfusion in tarsoconjunctival flaps in pigs (38).

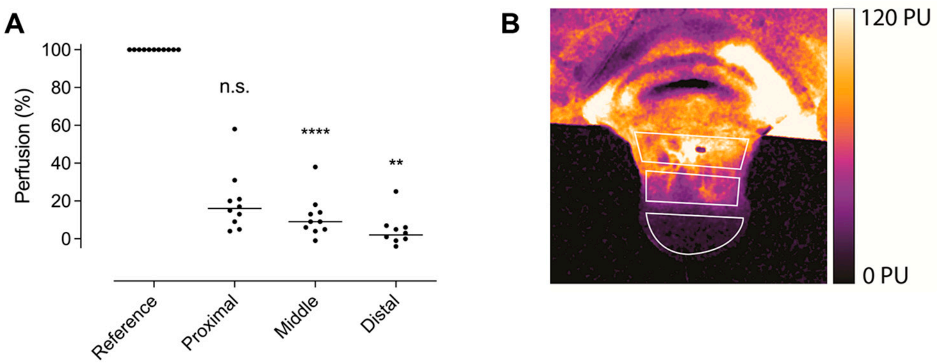

Figure 16. A. Blood perfusion in tarsoconjunctival flaps during surgery, measured with LSCI (Study I). The perfusion is shown in the proximal, middle and distal part of the tarsoconjunctival flap as a % of that at a reference point on the tarsal conjunctiva. Horizontal lines indicate the median values. B. LSCI image of the tarsoconjunctival flap. The darker the color, the lower the perfusion. Note the minimal blood perfusion at the distal end of the flap. (Photograph by author).

Despite the minimal perfusion in the flaps, all free grafts healed well (Study II). There was no sign of ischemia or tissue necrosis, and the final results after healing were functionally and cosmetically satisfactory. LSCI measurements showed that the blood perfusion increased gradually, the free grafts being fully reperfused after 8 weeks (Figures 17 and 18).

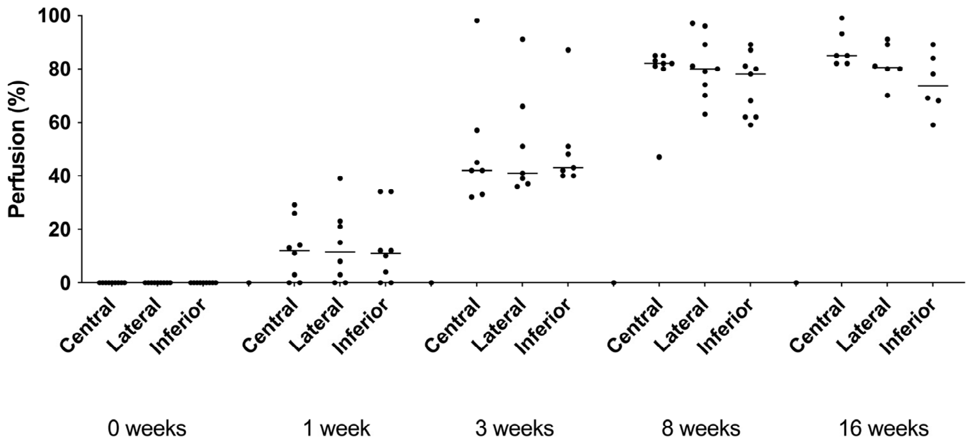

Figure 17. Perfusion in free skin grafts overlying the tarsoconjunctival flaps, during surgery (0 weeks) and 1, 3, 8, and 16 weeks after surgery, measured with LSCI (Study II). Perfusion was measured in the central, inferior and lateral part of the graft. Horizontal lines indicate the median values. The grafts were fully reperfused after 8 weeks.

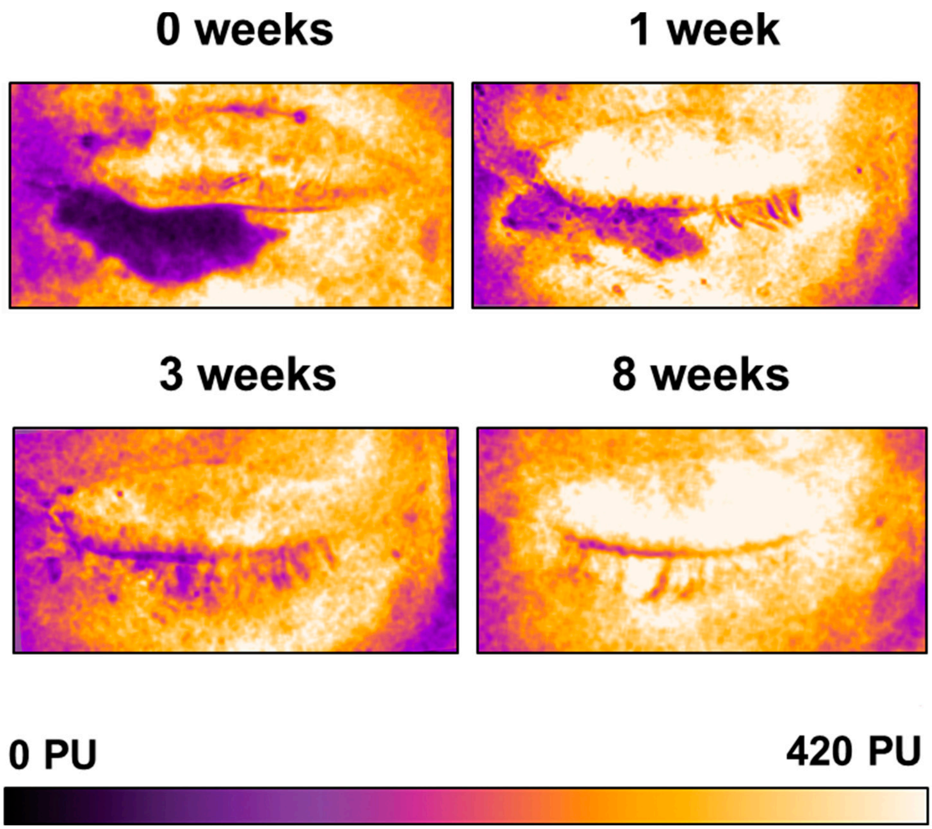

Figure 18. LSCI images of a representative example of a free skin graft overlying the tarsoconjunctival flaps, during surgery (0 weeks) and 1, 3, and 8 weeks after surgery. Dark/purple color indicate low perfusion and yellow/white color indicate high perfusion. The graft is fully reperfused after 8 weeks. (Photographs by author)

The LDV measurements showed that the heat-induced hyperemic response of the perfusion increased gradually over time, as would be expected in tissue being reperfused. However, after 16 weeks, the heat response was still less than that at a reference point outside the surgical area, suggesting that vascular reactivity had not returned to its normal value during the course of the study.

Despite the initial lack of perfusion in the tarsoconjunctival flaps, all the grafts survived and healed well. These results are in line with previous results from our group when studying the reperfusion of free skin grafts in the periorbital area in 2021, when it was found that the grafts reperfused gradually during healing, and were completely reperfused after 7 weeks (62). The good healing results could be due to the periorbital region being a well-vascularized region, and the grafts may be nourished by the rich vascular supply of the remaining eyelid. Furthermore, the grafts are constantly soaked in tear fluid, which has the same spectrum of nutrients as the blood (63).

It could be speculated that using tarsal plate from the upper eyelid might result in a loss of glands in the upper eyelid, which could in turn lead to a decrease in tear film quality. It has been shown that the Hughes tarsoconjunctival flap may affect the Meibomian glands, causing tear film dysfunction and damage to the corneal surface (64). Hawes et al. compared the outcome of a Hughes tarsoconjunctival flap with an overlying skin graft, to a free tarsoconjunctival graft combined with a mucocutaneous advancement flap. The free tarsoconjunctival graft with the advancement flap was associated with less erythema, fewer donor site problems, and fewer revisions (20). These findings support the use of free tarsoconjunctival grafts, or tarsal substitutes such as banked sclera, nasal cartilage, ear cartilage, and periosteum for posterior lamellar repair. On the other hand, the Hughes tarsoconjunctival flap procedure also causes vertical lifting of the tissue of the lower eyelid, possibly leading to better postoperative results (65).

It is important to bear in mind that the terms "reperfusion" and "revascularization" do not refer to the same thing. A different technique, such as histological examination, would be needed to study revascularization. LSCI and LDV do not provide any information on the vascular architecture, but measure only the perfusion. Both these techniques also have limitations, such as being sensitive to motion artifacts, however, the studies were designed to minimize the impact of these limitations.

Study III: Perfusion in composite grafts

The results of Studies I and II raised the question of whether the tarsoconjunctival flap is necessary for graft survival when reconstructing large eyelid defects. A single-step procedure using free full-thickness grafts, removing the need to occlude vision for several weeks, would be a preferable alternative in some cases.

Our research group has published two case reports that further support the use of full-thickness grafts without a vascular component for the repair of large eyelid defects. The first case was a large eyelid defect after trauma in a young man where the eyelid was simply sutured back in place 15 hour later. The eyelid healed well and the result was still excellent 10 years after the trauma (66). The other case was a large eyelid defect resulting from tumor surgery that was successfully reconstructed with a free full-thickness graft from the other eyelid (67).

Several reports have been published on free composite grafts for the repair of large eyelid defects, however, no systematic study could be found on the use of composite grafts where perfusion and reperfusion were monitored. The reperfusion of composite grafts used to repair large eyelid defects in patients was studied in 10 cases (Study III) where the occlusion of one eye would have been problematic for the patient, for example, due to poor vision in the other eye. The free composite graft was harvested from the other eye, ensuring the possibility to reconstruct the eyelid using a Hughes tarsoconjunctival flap if necessary due to graft failure.

All composite grafts survived and no graft failure or tissue necrosis was seen. The grafts reperfused gradually; LSCI showed 50% perfusion after 4 weeks and almost complete reperfusion (90%) after 8 weeks (Figures 19 and 20). One patient had a few surviving eyelashes, while no lashes survived in the other nine patients.

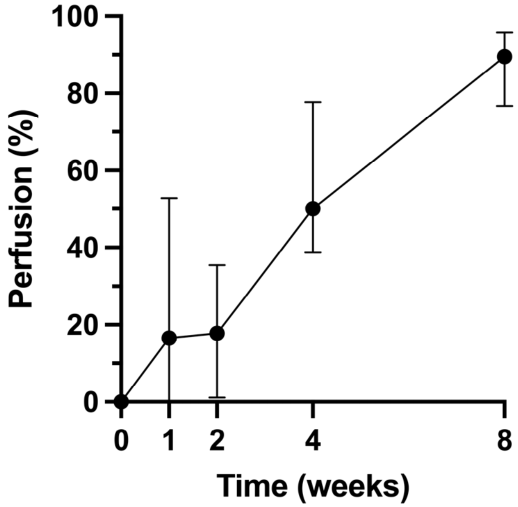

Figure 19. Perfusion in composite grafts measured with LSCI at the time of surgery, and 1, 2, 4, and 8 weeks after surgery (Study III). The grafts were fully reperfused after 8 weeks.

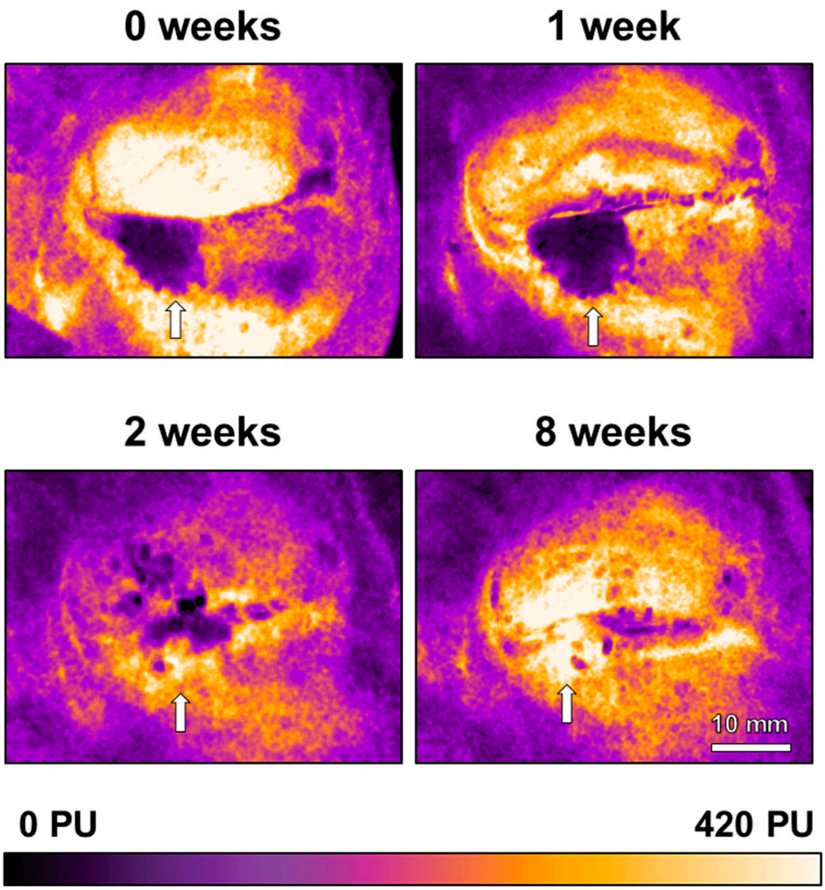

Figure 20. LSCI images of a representative example of composite graft, during surgery (0 weeks) and 1, 2 and 8 weeks after surgery. Dark/purple color indicate low perfusion and yellow/white color indicate high perfusion. The graft is fully reperfused after 8 weeks. (Photographs by author).

The use of free composite grafts is common in other specialties, for example, a free composite graft from the outer ear, without any vascularized flap, is sometimes used for the repair of nasal wing defects (68, 69). However, composite grafts have not been widely used for the repair of both the posterior and anterior lamellae in reconstructive surgery in the eye region, and the revascularization of free bilamellar eyelid grafts has not previously been studied using modern imaging techniques.

There are case reports of single-stage composite grafts in pigs (70), and single-stage lower eyelid reconstruction procedures on patients have been described in the literature (71-74). Grafts for eyelid reconstruction are usually harvested from the contralateral or opposing upper or lower eyelid, but other techniques have been described, such as a chondromucosal-auricular graft and a skin-tendon-mucosal graft (75, 76).

In 1951, Callahan reported a case of the successful use of a free composite graft to repair a defect involving more than 50% of the lower eyelid (11 mm) after coloboma surgery in a 37-year-old patient (71). Youens described a case in 1967 in which a full-thickness lid autograft was used for the successful repair of a large lower lid defect after tumor surgery in an 83-year-old patient with poor vision in the other eye (72). In 1969, Fox presented five cases of eyelid repair using autogenous free full-thickness grafts measuring 12-13 mm in length. All grafts healed successfully (73). However, there are studies reporting failures. Smith included the technique in his 1970 textbook (69), but partial graft necrosis has been reported in some patients (74, 77). The grafts in the present studies were fairly small, never more than 10 mm in length, and in most cases the tension in the eyelids was alleviated by Tenzel flaps, which might have influenced the healing results.

In 2023, McDonald et al presented a case study with a larger sample of 31 patients who underwent surgery with composite grafts (free bilamellar autografts). Mean width of recipient site was 18.8 mm, and all surgeries resulted in functionally and cosmetically good results (78). This case series is in line with our results and adds to the data on the composite graft procedure.

There are potential benefits of using a free composite graft to reconstruct both lamellae in eyelid surgery, namely avoiding both occlusion of the eye and a second surgery. It is easier to move the anterior and posterior lamellae “en bloc”, as opposed to repairing them separately, and the appearance immediately after surgery is cosmetically better. Taking the graft from the other eyelid may also improve the cosmetic result, as it provides a better match in color and texture than harvesting the graft elsewhere. However, potential disadvantages are associated with this method, such as a lack of vertical lifting during healing, as is provided by the flap pedicle in the Hughes procedure (65). When using a two-step technique, the second surgery allows the surgeon to adjust the position of the lid margin if necessary. However, only two of ten patients in Study III developed minimal ectropion, which did not require surgical correction.

The eyelashes protect the eye by catching airborne debris. A lack of eyelashes after composite graft surgery may thus lead to problems for the patients. However, both the Hughes procedure and the Cutler-Beard procedure also result in the loss of eyelashes. In a review of 51 patients who had undergone composite grafting (conjunctiva and tarsus) combined with a skin flap, Werner et al. found survival of the cilia in 14% (79). Combining a composite graft with a skin flap may increase eyelash survival somewhat, but the loss would still be substantial, and such a procedure would make little difference to the patient.

The patients in the studies presented in this thesis were reasonably healthy, however, the results might have been different in patients with impaired microcirculation. Subgroup analysis, taking the effects of smoking, cardiovascular disease, diabetes, and age into account, was not possible due to the limited number of participants in the studies. A larger study would be needed to investigate the survival and reperfusion of a free composite graft in higher-risk populations. The laxity of the eyelids usually increases with age; which affects the choice of surgical procedure and might affect the results. Therefore, subgroup analysis according to age would also be of great interest in a future study.

The Hughes tarsoconjunctival flap procedure is well proven, and many years of surgical experience have shown good results. This method, or others using a vascularized flap to reconstruct one lamella and a non-vascularized graft for the other lamella, is still the best option for eyelid reconstruction, especially very large lower eyelid defects. However, surgeons must consider which is the best approach for each patient. Alternative procedures such as laissez-faire (healing by secondary intention) and composite grafting are one-stage procedures and the visual axis will thus not be impaired during healing, which might be desirable in some cases. A composite graft will protect the eye during healing, and there is no gap in the eyelid exposing the eye as in the laissez-faire approach, which might be beneficial for patients with dry eyes or lack of Bell's phenomenon. A free composite graft may also be a suitable option for patients who would find undergoing a second surgery problematic.

Study IV: Perfusion after lateral cantholysis

When repairing large eyelid defects, tissue tension sometimes makes wound closure difficult. Tissue tension release by lateral cantholysis is common during reconstructive surgery on the eyelid. However, the procedure requires the severing of the lateral palpebral artery, which might reduce the blood supply to the reconstructed tissues. The impact on blood perfusion and tissue oxygen tension of cantholysis combined with a wedge resection of the lower eyelid, commonly performed when operating on a tumor, was therefore studied in a porcine model (Study IV).

Performing the wedge resection alone did not affect the perfusion or oxygen tension. After performing canthotomy the perfusion and oxygen tension were reduced, and decreased gradually as the wedge resection was lengthened to resemble a large eyelid defect (Figure 21). The decrease in perfusion and oxygen tension was not affected by the administration of the vasodilator verapamil, and the values were the same 12 hours post-surgery, suggesting the results were not due to surgical vasospasm.

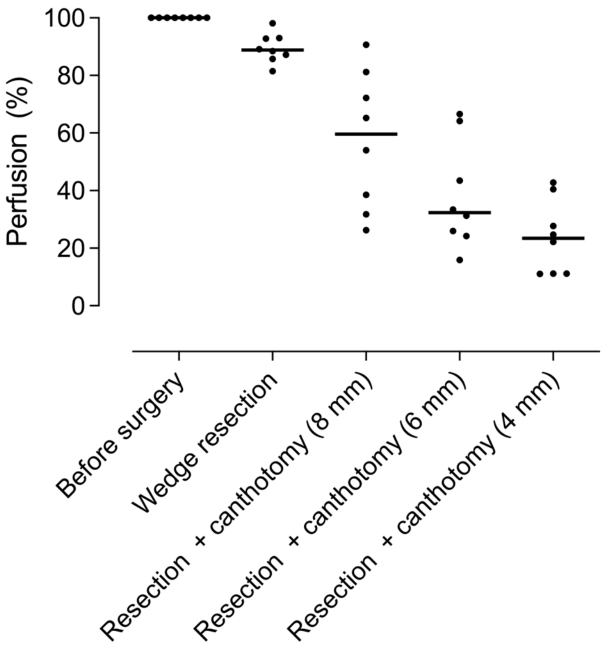

Figure 21. Perfusion in the lateral eyelid of 8 pigs after performing wedge resection and cantholysis, measured with LDV. The perfusion decreased as the wedge resection was lengthened (length of remaining eyelid in mm).

When using free grafts without a vascularized component, it is important that the vasculature in the eyelid is not compromised. The reduction in blood perfusion after performing canthotomy in combination with a wedge resection must be taken into account, especially when using avascular grafts. Perfusion was particularly affected after cantholysis when the remaining part of the eyelid was short, representing a larger eyelid defect.

The degree of perfusion required for survival of the eyelid tissue is not known; the perfusion remaining after cantholysis may be sufficient for direct closure, but not for the survival of a free graft, especially a large avascular graft. Refraining from cantholysis maintains the tension in the eyelid, leading to eyelid expansion, allowing direct closure of large defects (80). Cantholysis may also result in lateral lid margin thinning and lateral canthal rounding (39). Cantholysis is widely performed, and is a very useful surgical method in reconstructive surgery. However, the risk of reducing the perfusion of the surrounding tissue, especially in patients with compromised microcirculation, must be considered. Further studies on human subjects are needed to confirm these results.

Conclusions

The conclusions drawn from the studies presented in this thesis can be summarized as follows.

- A tarsoconjunctival flap does not contribute significantly to the perfusion of the reconstructed lower eyelid.
- A single-step surgical technique using free composite grafts to repair large eyelid defects in selected cases may reduce patient suffering and healthcare costs, while at the same time providing excellent functional and cosmetic outcomes.
- Free composite grafts may serve as a good, and even preferable, alternative to a two-step procedure such as the Hughes tarsoconjunctival flap, in some patients with large eyelid defects. Tailoring the reconstructive procedure to each patient is important.
- Cantholysis implies a risk of reducing the blood perfusion of the surrounding tissue.

Future perspectives

Knowledge on blood perfusion and oxygenation is of great importance in predicting the survival of grafts and flaps in reconstructive surgery, and there is therefore a need for more research in this field. In the work described in this thesis perfusion was mainly studied using laser-based techniques. New techniques suitable for monitoring perfusion during and after reconstructive surgery are being developed. Hyperspectral imaging (HSI) measures oxygenation non-invasively, and provides a more accurate estimate of oxygen saturation than standard methods, but has not been widely used in reconstructive surgery (46). A study has recently been conducted by our research group on the oxygenation of cutaneous flaps using this technique and preliminary results show that it is a useful tool to non-invasively map the change in oxygenation during reconstructive surgery. Photoacoustic imaging is also a promising new technique for imaging of the circulation. This employs laser light that is converted into heat in the tissue, causing thermoelastic expansion and ultrasound emission. This technique provides a spectral signal of the tissue and enables the detection of small variations in tissue composition. Photoacoustic imaging is not yet suitable for use in the periorbital region, but might be useful for reconstructive surgery in other parts of the body, for example in cases of burn injuries (47).

Clinical surgeons are constantly developing and refining surgical techniques. An alternative to surgical reconstruction of tissue defects is wound healing by secondary intention. Laissez-faire, which is French, meaning leaving things to follow their own course without interfering, was described in 1957 in the periorbital region, but has recently become more widely used due to the good clinical outcome. This approach has not been extensively studied, but has been successfully applied for healing large eyelid defects, and seems to be especially favorable in the medial canthal region and in cases of full-thickness lower lid defects (81-83). Secondary reconstruction is still possible if laissez-faire fails to give good results. In directed laissez-faire, the surgeon contracts the wound with sutures, leaving a much smaller area to heal by secondary intention and to prevent secondary ectropion and lid margin retraction. This appears to be a suitable alternative to reconstructive methods in some cases. The laissez-faire approach should be further studied to gain a better understanding of revascularization during the healing process, and how wound contraction affects the final outcome. This would allow us to predict which patients are suited for this technique.

There are still many areas in reconstructive surgery that can be further developed where systematic studies through research can be of great value. The findings presented in this thesis have helped to shed light on the possibility to develop and refine surgical procedures.

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