Tampere University

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# Free Flap Reconstruction and the Role of Postoperative Monitoring in Head and Neck Surgery

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ACADEMIC DISSERTATION
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of Tampere University,
for public discussion in the Jarmo Visakorpi auditorium
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Tampere University, Faculty of Medicine and Life Sciences
Tampere University Hospital, Department of Otorhinolaryngology
Finland

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*To my family*

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# ABSTRACT


Free microvascular flaps are a routine part of modern head and neck reconstructive surgery. The circulation of the flap depends on one artery and 1 to 2 veins, and it is extremely vulnerable to vascular compromises, such as thrombosis, hypotension, or vasoconstriction. The operated patients are kept sedated in the intensive care unit until the postoperative morning. Traditionally, sedation is achieved with propofol, which may have unfavorable effects on peripheral circulation. During sedation, the hemodynamic parameters of the patients and the flaps are being pharmacologically controlled by, e.g., norepinephrine, dobutamine, or dopamine, whose effects on denervated flap circulation is unclear.

Dexmedetomidine causes more sleep-like sedation, and its effect on patient hemodynamics are more favorable than propofol. Moreover, fewer inotropes and vasopressors are needed. During dexmedetomidine sedation, the patient is calm and arousable. In previous studies, dexmedetomidine has been shown to cause vasoconstriction in denervated tissue, such as microvascular flaps.

The first three postoperative days are considered to be most critical for flap survival because vascular compromise may rapidly lead to flap ischemia and re-operations. Therefore, intensive monitoring of the flap during this period is recommended. Many monitoring methods have been previously described, but clinical follow-up by an experienced surgeon has been considered to be the gold standard.

In the present study, tissue oxygen monitoring using the Licox monitoring system and microdialysis have been used for free flap postoperative follow-up. According to the findings of the present study, both are reliable methods for the monitoring of free flap oxygenation and metabolites (lactate, pyruvate, glucose, and glycerol) and are feasible for postoperative flap follow-up. Glycerol measured by microdialysis is a sign of cell destruction in the flap.

According to the findings of present study, vasopressors and inotropes (norepinephrine and dopamine) have no negative effects on flap metabolites and circulation. Moreover, dexmedetomidine was found to be as good as propofol

regarding flap circulation and metabolites. These results mean that the postoperative sedation protocol can be changed in a better and safer way.

# TIIVISTELMÄ


Mikrovaskulaariset siirteet ovat nykyaikaisen hoitokäytännön mukaan merkittävä osa pään ja kaulan alueen syöpien hoitoa. Niiden avulla rekonstruoidaan poistettu kudosalue. Kielekkeiden pahin ongelmana on hapensaannin haavoittuvuus, koska kielekkeen verenkierron hoitaa vain yksi valtimo- ja 1-2 laskimosuonta, näin ollen se on hyvin herkkä pienillekin virtaushäiriöille. Syöpäleikatut potilaat pidetään sedatoituina anestesiateho-osastolla leikkauksen päättymisen jälkeen seuraavaan aamuun. Sedaatiossa käytetään rutiininomaisesti propofolia, joka laskee potilaan verenpainetta ja sen vaikutus perifeeriseen verenkiertoon saattaa olla epäedullinen. Sedaation aikana potilaiden verenpainetta ja samalla kielekkeiden verenvirtausta säädellään lääkkeillä (esim. Noradrenaliini, dobutamiini ja dopamiini), joiden vaikutus hermottamattoman mikrovaskulaarikielekkeen verenkiertoon on epäselvä.

Propofolia optimaalisempi lääke postoperatiivisen sedaation saavuttamiseksi olisi dexmedetomidiini, jonka aiheuttama sedaatio on enemmän normaalin unen kaltainen. Sen aikana potilas on rauhallinen, mutta heräteltävissä. Näin ollen se vaikuttaisi optimaaliselta postoperatiiviseen sedaatioon. Lääke on myös vasoaktiivisesti edullisempi, eikä aiheuta niin voimakasta tarvetta verenkiertoa tukeville lääkkeille. Teoriassa dexmedetomidiinin käyttö voisi aiheuttaa ongelmia hermottamattomissa kielekkeissä, kuten mikrovaskulaarisiirteissä.

Kielekkeiden kuntoa on seurattava hyvin tarkkaan leikkauksen jälkeiset 3 vuorokautta, koska verenkierron heikkeneminen johtaa hyvin nopeasti kielekkeen tuhoutumiseen ja uusintaleikkauksiin. Seurantaa on perinteisesti suoritettu kliinisesti ja se vaatii kokeneen lääkärin arviointeja. Kielekkeiden kuntoa seuraamaan on kirjallisuudessa esitetty monia metodeja, tässä tutkimuksessa on käytössä Licox-kudoshappimonitori ja mikrodialyysimonitorointi. Tutkimushavaintojen perusteella ne ovat luotettavia keinoja arvioida kielekkeen solutason hapettumista ja aineenvaihduntatuotteita (laktaatti, pyruvaatti, glukoosi, glyseroli) ja näin ollen käyttökelpoisia kudossiirteiden seurantaan. Glyseroli on siirteessä solutasolta mitattuna merkki kudostuhosta.

Tutkimuksen perusteella voidaan sanoa, että kielekkeiden aineenvaihduntaan ja verenkiertoon ei saada negatiivisia vaikutuksia vasopressoreilla ja inotroopeilla

(noradrenaliini ja dopamiini). Myös dexmedetomidiini on yhtä hyvä siirteiden verenkierrolle ja aineenvaiduntatuotteille kuin propofoli. Tutkimuksen perusteella voidaan muuttaa nykyistä postoperatiivisen sedaation hoitokäytäntöä parempaan ja turvallisempaan suuntaan.

# CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| DEX | Dexmedetomidine |
| EudraCT | European Clinical Trials Database |
| ICU | Intensive care unit |
| Licox® | Tissue oxygen monitor used in the study |
| L/G ratio | Lactate to glucose ratio |
| L/P ratio | Lactate to pyruvate ratio |
| MAP | Mean arterial pressure |
| MD | Microdialysis |
| NE | Norepinephrine |
| PET | Positron emission tomography |
| $P_{ti}O_2$ | Tissue oxygen tension |
| RFA | Radial forearm flap |
| NIRS | Near-infrared spectroscopy |
| RASS | Richmond agitation sedation score |
| ALT | Anterolateral thigh flap |
| FN | False Negative |
| FP | False Positive |

# ORIGINAL PUBLICATIONS

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II. Sympathetic innervation does not contribute to glycerol release in ischemic flaps, Raittinen LP, Berg L, Nunes S, Ahonen H, Parviainen I, Laranne J, Tenhunen JJ., Scand J Clin Lab Invest. 2012 Sep;72(5):420-6

III. The Effect of Norepinephrine and Dopamine on Radial Forearm Flap Partial Tissue Oxygen Pressure and Microdialysate Metabolite Measurements: A Randomized Controlled Trial, Raittinen L, Kääriäinen MT, Lopez JF, Pukander J, Laranne J, Plast Reconstr Surg. 2016 Jun;137(6):1016e-23e

IV. The effect of dexmedetomidine on microvascular flap perfusion as depicted by tissue oxygen tension and microdialysis after reconstruction in head and neck cancer surgery, Lassi Raittinen MD, Minna Kaariainen MD, PhD, Jenny Lopez MD, Ville Jalkanen MD, PhD, Anne Kuitunen MD, PhD, Jussi Laranne MD, PhD, (Submitted)

# 1 INTRODUCTION

In Finland, about 2.5% of all new malignant diagnoses are head and neck cancers, with over 800 new cases reported in 2016 (Suomen syöpärekisteri, 2018). Most of these malignancies are oral, pharyngeal, or laryngeal cancers. The treatment options vary from surgery to chemoradiation or a combination of the two. Patients with more advanced stage cancer often require major surgery that frequently leads to major tissue defects. The complex anatomy and functions of the head and neck region, such as speech and swallowing preservation, lead to the need for reconstructive surgery. Earlier, when these reconstructive procedures were not in everyday use, the patients were considered inoperable or similar surgeries were performed that involved closing wounds with straight sutures. As a result, patients could be left disabled for the rest of their lives, with a significantly lowered quality of life. This problem led surgeons to develop better reconstructive surgical techniques. Among these, pedicled local flaps, such as the deltopectoral, pectoralis major, and latissimus dorsi together with maxillofacial prostheses, were some of the first approaches aimed at improving patient outcomes. These approaches were, however, often bulky and led to significant deformities in the head and neck region.

Free microvascular flaps, which are composed of combinations of vascularized areas of skin, muscle, or bone, were the next step in the development of reconstructive procedures. The flaps are harvested from the patient's donor site and then transferred to the same patient as a spare part to reconstruct the tissue defect. The flap artery and vein and sometimes nerve are sutured micro-surgically end-to-end with defect area vessels to produce flap circulation. The development of free flap reconstruction began in the 1950's but became the gold standard for treatment in the head and neck region in the 1990's (Steel & Cope, 2015). At Tampere University Hospital, free microvascular flaps have been used since the 1990's.

During surgery, the flap is harvested after or simultaneously with tumor removal. Then, the recipient vessels are prepared, the surgical defect is closed with the flap, and the graft vessels are sutured to the recipient vessels using the microvascular technique. This requires an expert team of microsurgeons that includes head and neck, plastic and maxillofacial surgeons. In the reconstruction of ablative defects in the head and neck area, a wide variety of free flaps have been used. (Disa, Hu, & Hidalgo, 1997; Hidalgo, Disa, Cordeiro, & Hu, 1998) At Tampere University hospital and in this study, the majority of head and neck cancer reconstructions are performed using a radial forearm flap (RFA)(Soutar, Scheker, Tanner, & McGregor, 1983) or a fibula flap (Hidalgo, 1989). These grafts are quite simple to harvest and they adapt well to covering surgical defects.

Flap circulation is extremely sensitive to vascular compromises, such as thrombosis or vasoconstriction, which can, if not noticed early enough, lead to ischemia and even flap loss. This occurs because flap tissue cannot tolerate ischemia for more than 4 to 12 hours without necrosis and can, in the worst case, result in flap loss. (May, Chait, O'Brien, & Hurley, 1978) In such cases, immediate re-operation to save the flap is required. As a result, surgeons have searched for more reliable monitoring methods to be able to detect ischemia early enough, and this has also influenced postoperative care in many ways.

During the postoperative period, the fear of ischemia and flap loss is of significant importance. In many hospitals, the postoperative period starts with sedation and follow-up in the Intensive care unit (ICU). (Arshad et al., 2014; Marsh, Elliott, Anand, & Brennan, 2009) During this time, sedative medication, such as propofol, midazolam, or lorazepam, is administered to keep the patient stable and to prevent flap complications. To be able to ensure good perfusion to the flap and vital organs, the anesthesiologist faces a clinical dilemma as to whether to use vasopressors or fluids. (Sigurdsson & Thomson, 1995) Moreover, surgeons are concerned about using vasopressors so as to avoid the possible vasoconstriction of a flap artery. However, the recent literature seems to question this approach. (Hand et al., 2015; Harris, Goldstein, Hofer, & Gilbert, 2012)

Traditionally, propofol has been used for postoperative sedation even though it is known to lower blood pressure and can cause difficulties in ensuring good perfusion pressure for the graft. Dexmedetomidine (DEX) is a rather new postoperative sedative used in the ICU, which could be more favorable in ensuring the perfusion pressure of the flap. On the other hand, DEX has been shown in one study to cause vasoconstriction in denervated tissues such as free flaps. (Talke, Lobo, & Brown, 2003)

The purpose of the present study is to more carefully investigate tissue oxygen monitoring and microdialysis in free microvascular flap monitoring. Furthermore, comparisons between the effects of vasoactive and sedative medications were performed to evaluate the postoperative recovery of patients in the ICU.

# 2 REVIEW OF THE LITERATURE

## 2.1 Microvascular free flaps

Microvascular free flaps were introduced to head and neck reconstructions more than 50 years ago (Daniel & Williams, 1973; Hidalgo, 1989; Soutar et al., 1983; Steel & Cope, 2015) and they have been in routine use for 20 to 30 years (Spiegel & Polat, 2007). Due to the complex anatomy and functions of the head and neck region, reconstructions are extremely important. Without them, radical surgery would lead to major postoperative problems lowering quality of life and resulting in long-lasting rehabilitation processes. During the last 30 years, more than 20 donor sites for free flaps in the head and neck region have been introduced, although an individual surgeon normally uses only a few of them. (Hidalgo et al., 1998; Steel & Cope, 2015) The most commonly used free flaps in head and neck surgery are septo- or fasciocutaneous containing skin, underlying subcutaneous tissue and fascia like the RFA, and anterolateral thigh (ALT). Sometimes these fasciocutaneous flaps may have external part of muscle or even bone based on vascular perforators. The flaps may also be muscular like latissimus dorsi, and rectus abdominis. Osteocutaneous composite flaps may also have perforator parts of muscle like fibula, scapula and crista iliaca. (de Bree et al., 2008; Hurvitz, Kobayashi, & Evans, 2006).

### 2.1.1 Radial forearm flap

The RFA is a septocutaneous flap based on the radial artery and cephalic vein and their perforators. It has been used for head and neck reconstruction since the 1980's with excellent results. (Urken, Weinberg, Vickery, & Biller, 1990) The skin flap is raised together with superficial fat, the radial artery, its concomitant veins, and the superficial cephalic vein. The flap is usually thin and has a rich vasculature, making it reliable in reconstructive use, and it is therefore the flap of choice in the oral cavity (Moscoso & Urken, 1994). The anastomoses are easy to perform because its pedicle is relatively long and the vessels are reasonably large in diameter (Medard de Chardon et al., 2009). The limitations of the flap are its relatively small size and, in some cases, donor site morbidity (Wong & Wei, 2010b). Lateral antebrachial cutaneous nerves can be raised together with the RFA and sutured in the side of the lingual nerve. This technique allowed 10 out of 17 patients to have sensory function in their tongue after reconstructive surgery. (Kuriakose, Loree, Spies, Meyers, & Hicks, 2001)

### 2.1.2 Fibula flap

Fibula flap is an osteoseptocutaneuous graft based on peroneal artery and its concomitant vein. It is extremely suitable for mandibular reconstruction but can also be used for maxillary reconstruction. The pedicle is sufficiently long to reach the neck vessels and a muscular part is also available if a bulkier flap is needed. Fibula graft has an intact bony cortex which makes it good for multiple osteotomies and dental implantation. (Y. M. Chang et al., 1998; Wong & Wei, 2010b) Sometimes the height difference of original mandible and fibular graft is too big for sufficient dental rehabilitation, in these cases a double-barrel fibular graft can be used (Horiuchi et al., 1995). Recently a computer-aided 3-dimensional operation planning has been used to shorten the ischemia time smoothening the reconstruction procedure (Kaariainen et al., 2016). Arteriosclerosis in the vessels of the leg is a contra-indication for fibular flap, therefore the vessels of the leg need to be examined before operation (Young, Trabulsy, & Anthony, 1994).

### 2.1.3 Anterolateral thigh flap

The ALT is either a cutaneous, fasciocutaneous, or myocutaneous flap based on the lateral circumflex femoral artery, its two veins, and musculocutaneous perforator vessels. Large skin islands with subcutaneous tissue and the vastus lateralis muscle provide enough tissue to reconstruct remarkable tissue defects. Furthermore, its pedicle is long enough for anastomosis to the neck vessels. The ALT flap may also have multiple skin islands but still has only minor donor site morbidity. In head and neck reconstruction, this flap may sometimes be even too bulky. (Wong & Wei, 2010a) The only true contraindication of this flap is the absence of skin perforators, which is extremely rare (Wong, Wei, Fu, Chen, & Lin, 2009).

### 2.1.4 Rectus abdominis flap

The rectus abdominis is a musculocutaneous flap based on the deep inferior epigastric artery and vein. It has been widely used in breast reconstruction and has a large skin island possibility together with the rectus abdominis muscle. Its donor site morbidity is minimal, and it is reasonably easy to harvest. The flap has been used in orbital and skull base reconstruction and also in the neck, face, mouth, and pharynx. The pedicle length of the flap is about 7 cm. The length can, however, vary, depending on the entrance of the vessels into the muscle, although the pedicle can be lengthened by cutting the muscle fibers around it but still it may cause some problems in the head and neck area. (Kroll & Baldwin, 1994; Urken, Turk, Weinberg, Vickery, & Biller, 1991)

## 2.2 Complications in free flap surgery

According to Sigurdsson and Thompson, free flaps differ from normal tissue in several aspects, such as having already suffered from ischemia during transfer, being denervated, and being without lymphatic drainage leading to a risk of edema. Also, during the first 6 to 12 postoperative hours, the blood flow to the flaps decreases to half of the pre-transfer values before slowly returning to normal, yet the arteries still respond to physical and pharmacological stimuli. (Daniel & Kerrigan, 1979; Sigurdsson & Thomson, 1995) Different types of flaps have been shown to have significant differences in their blood flow. Mucke et al. studied the perfusion of four different types of free flaps with laser doppler flowmetry and found that after the first postoperative day the perfusion of septocutaneous flaps, such as the RFA, was much better when compared with muscular like fibula or ALT flaps. (Mucke et al., 2014)

Because only one artery and normally only one or two veins are responsible for the circulation of the flap, vascular complications may jeopardize the survival of the whole flap. Suh et al. studied 400 consecutive head and neck free flaps and reported that perioperative complications occurred in 36% of the cases. Reconstructive complications such as infection, salivary fistula, partial or total flap necrosis, donor site problems occurred in 19% and the rest were medical complications, such as pulmonary, cardiac, and infective problems. Of these reconstructive complications, only 0.8% led to total flap necrosis and flap loss. Partial flap necrosis occurred in 3%. (Suh et al., 2004) In a study by Winterton et.al., the vascular reasons leading to re-operation were 18.7% arterial and 27.1% venous occlusions. Hematoma occurred in 43.5% of the cases reported. (Winterton et al., 2010)

Although the survival rate of the free flap is generally between 95% and 98% (Disa et al., 1997; Hidalgo et al., 1998; Spiegel & Polat, 2007), every failure is still devastating for the individual and results in the need for re-operations and a lengthened hospital stay. The failure of free flaps may occur on multiple levels, such as harvest, complex inset of the flap, non-ideal pedicle geometry, prolonged ischemia time, and inadequate postoperative care. (Luu & Farwell, 2009) In addition, previous irradiation and previously failed microvascular operation have been reported to predispose to flap failure. (Arshad et al., 2014; Mucke et al., 2016) Free flaps can tolerate ischemia from 4 to 8 and up to 12 hours. Therefore, it is during this time period that revision should be performed to save the flap. (Carroll & Esclamado, 2000; Esclamado & Carroll, 1999; May et al., 1978)

More than 80% of vascular occlusions take place in 1 to 4 postoperative days. Bui et al. studied 1193 free flaps, 883 of which were in the head and neck. Of these, 71 patients were re-operated, and the mean time from primary operation to re-exploration was 2.5 days. In breast reconstructions, the majority were re-operated on the first postoperative day. However, in head and neck reconstructions only 32% were re-operated on the first postoperative day, and one was operated as late as day 7. Their main finding was that salvaged flaps were re-operated sooner after detection than failed flaps (4 vs 9 hours). (Bui et al., 2007) Similar findings were also reported in a study by Brown et al. who found that vascular occlusions later than two days from the primary operation led to flap loss more often than in days 1 and 2 (Brown et al., 2003). Kadota et. al. reported that 54% of the thrombosis after day 5 was caused by wound infection (Kadota, Sakuraba, Kimata, Yano, & Hayashi, 2009). Winterton et al. studied 2567 free flaps and also stated that re-operation should take place immediately if any doubt of imminent flap failure occurs (Winterton et al., 2010).

## 2.3 Monitoring of microvascular flap

To notice vascular compromises early enough is the most important reason for free flap monitoring. To achieve this goal, most surgeons use clinical monitoring techniques, such as observation of flap color and turgor as well as pinprick testing (Hirigoyen, Urken, & Weinberg, 1995; Jallali, Ridha, & Butler, 2005; Spiegel & Polat, 2007). These methods should be repeated every 1 to 4 hours and require repeated control visits for the first postoperative days.

In a rabbit model, Prasetyono and Adianto studied cutaneous flap color changes after clamping the flap artery or vein. Surprisingly, they noticed that with a clamped artery the color change was not noticeable at all. When the vein was clamped, it took more than half an hour before any noticeable change in graft color occurred. (Prasetyono & Adianto, 2013) Muscular flaps, such as the latissimus dorsi, or muscular and bony flaps, such as the fibula, are more difficult to monitor because of the complex vascularity of muscle and bone. Postoperatively, the flap surface may have a spotted appearance making clinical observation difficult and, in the worst case, can result in delays if re-operation is needed. In a previous study, muscular flaps showed irreversible histopathological changes, such as red cell platelet thrombus, dilatation of postcapillary venules, endothelial swelling, and microhemorrhage formation, already within 6 hours of ischemia (Siemionow, Manikowski, & Gawronski, 1995).

Complications can be detected if the flap follow-up is meticulous and the flap is visible. However, in head and neck microvascular surgery, some flaps are situated deep in the hypopharynx or oropharynx and are only partly visible, if at all. These flaps are called buried flaps, and their clinical follow-up, through direct visualization or by checking the vital signs of the flap, is extremely difficult or even impossible. Disa et al. analyzed a total of 750 free flaps with a loss rate of 1.8% for visible flaps and 6.5% for buried flaps, with a 0% salvage rate for buried flaps. (Disa, Cordeiro, & Hidalgo, 1999)

Buried flaps remain a challenge in head and neck surgery because their clinical monitoring is impossible. Moreover, doppler ultrasound may be difficult to use with large carotid arteries nearby. Some monitoring methods, such as tissue temperature monitoring inside of the intraoral cavity, are good for external flaps but are not suitable for buried flaps. Some surgeons try to bypass this problem by creating an exteriorized flap or distal skin paddle to allow clinical monitoring and to provide indirect information about the “real” flap. However, the external part may have vascular complications of its own or vice versa, so interpreting the information must be done carefully. (Dodakundi et al., 2012; Hallock, 1991; Hallock, 2017; Kashimura, Nakazawa, Shimoda, & Soejima, 2013; Laporta, Longo, Sorotos, Pagnoni, & Santanelli Di Pompeo, 2015; C. T. Lin, Chen, Chen, & Tzeng, 2014; Tan et al., 2012)

Another reason for using different monitoring devices is to ease the workload of the surgeon. The number of surgeons capable of performing microsurgery among head and neck surgeons and otolaryngologists seems to have gradually increased in recent years, but still remains low in many centers. In 2007, Spiegel and Polat surveyed otolaryngologists in the United States and found that in an average medical facility performing head and neck surgery there was on average 1 to 2 surgeons able to perform microvascular surgery. In 2018, this number had increased to between 2 and 3. (Kovatch, Hanks, Stevens, & Stucken, 2018; Spiegel & Polat, 2007) Therefore, routine control visits have to be also performed by specialized nurses or resident physicians. Patel et al. surveyed the records of 1085 patients from different hospitals with different resident flap control frequencies ranging from 1 hour to as much as even 12 hours. They found no difference in flap salvage rate between institutions, regardless of the resident flap monitoring frequency. Furthermore, they stated that the number of routine resident control visits could be decreased and the workload of the surgeons made easier, however the flaps were still controlled every hour by trained nurses. (Patel et al., 2017)

Prior to 1995, most of the monitoring methods used were non-invasive. (Hirigoyen et al., 1995) Since then, an optimal postoperative follow-up method for free flaps has been sought. There are many follow-up methods in everyday use, but still no gold standard follow-up method exists. An ideal monitoring method should be harmless to the patient, easy-to-use, reliable in rapidly detecting vascular compromise, and continuously cost-effective and simple and safe to use. The method should also be able to monitor muscular, bony, and cutaneous as well as buried and superficial flaps. (Furnas & Rosen, 1991) Because at present no such method exists and there is no evidence of a particular technique being superior to others, many different devices are in use. Indeed, the monitoring devices used seem to vary according to the personal preferences of surgeons and institutions. Even if the most obviously unsuitable monitoring methods are left out, there are still many feasible ones that can be used for the monitoring of free microvascular flaps. Some methods, such as tissue oxygen ($P_{ti}O_2$) monitoring and Near-infrared spectroscopy (NIRS), directly measure oxygen or oxygenized hemoglobin in the flap. Microdialysis (MD) measures the metabolites, and thus indirectly the status of circulation in the flap. Doppler ultrasound detects the speed of the blood flowing in the flap arteries and veins, which also indirectly reflects the flap oxygenation. Ultrasound can be delivered through the skin of the neck to the pedicle artery, directly to the flap, or by an implantable device around the vein or artery of the flap. (Cervenka & Bewley, 2015; Chae et al., 2015; Kaariainen, Halme, & Laranne, 2018)

The reason for using a monitoring device is the time of response compared with clinical follow-up. Some of the monitoring methods are, however, quite expensive. For example, MD adds around 500€ each time it is used, and therefore the cost-effectiveness of such methods should also be calculated. (Smit, Zeebregts, Acosta, & Werker, 2010) There have been numerous studies on the cost-effectiveness of monitoring methods. The results of these studies, however, seem to be controversial. Some authors state that routine monitoring even with rather expensive devices seems to be cost-effective. On the other hand, Subramaniam et al. calculated that to be cost-effective with only clinical monitoring the flap failure rate should be 15.8% or more, being less than 5% in most microsurgical units. (Pelletier, Tseng, Agarwal, Park, & Song, 2011; Poder & Fortier, 2013; L. Setala, Koskenvuori, Gudaviciene, Berg, & Mustonen, 2009; Subramaniam, Sharp, Jardim, & Batstone, 2016)

In conclusion, most authors agree that the monitoring of the flaps is important to be able to find vascular compromises in time to save the flap. (Brown et al., 2003; Kruse, Luebbers, Gratz, & Obwegeser, 2010) In 2009, Abdel-Galil and Mitchell reviewed the monitoring literature. They reported that clinical bedside monitoring seems to be the only universally accepted method even though they could not find good prospective randomized studies to confirm this. (Abdel-Galil & Mitchell, 2009a; Abdel-Galil & Mitchell, 2009b) The monitoring frequency and the methods are controversial because there also seems to be the pros and cons in every method. Without a universal gold standard, follow-up methods will continue to be selected based on the individual opinions of microvascular surgeons and the availability of different methods in each institution. Critical studies on free flap monitoring in the literature do not distinguish between flaps that are situated in places that are visible, such as the extremities, or hidden, for example, inside the oropharynx, pharynx and larynx. Therefore, in head and neck flap monitoring, a reliable monitoring device is desirable.

### 2.3.1 Monitoring methods

### 2.3.2 Non-invasive monitoring methods

Non-invasive monitoring methods cause no additional trauma to the flap or to the patient. Many non-invasive methods have also been described in head and neck free flap surgery. However, with the exception of clinical monitoring and Doppler ultrasound, questionnaires completed by head and neck surgeons show that only a few of them are in everyday use. (Hirigoyen et al., 1995; Jallali et al., 2005; Spiegel & Polat, 2007)

Some non-invasive monitoring methods, such as surface temperature monitoring, seem to be more experimental and have only been used clinically by a few surgeons or were used purely for research. These methods include microlightguide spectrophotometry, green light photoplethysmography, and impedance plethysmography. (Concannon, Stewart, Welsh, & Puckett, 1991; Holzle, Loeffelbein, Nolte, & Wolff, 2006; Khouri & Shaw, 1992; Wolff, Marks, Uekermann, Specht, & Frank, 1996)

#### 2.3.2.1 Bedside clinical monitoring

Bedside clinical monitoring is the only method that is universally accepted as the gold standard for free flap monitoring. Clinical monitoring means flap appearance, color and turgor observation, and pinprick testing. The bedside monitoring of clinical signs is time-consuming, but for most flaps sufficient, although results may depend on the experience and subjective opinions of the person in charge. Chubb et al. studied the clinical monitoring of 1140 free flaps by nurses or junior residents whose suspicions led them to consult a senior surgeon. The flaps were assessed at half-hourly intervals for the first postoperative day, 1 hourly intervals for the second day, and gradually extending the observation intervals until they were stopped by the fifth to seventh postoperative day. Their results were a good flap salvage rate and low false-positive rate. Moreover, they stated that every new monitoring method study should be compared with the results of their study. (D. Chubb et al., 2010) In clinical monitoring, digital images can be sent to the surgeon in charge via the Internet or cell phone to speed-up the re-exploration process (Hwang & Mun, 2012; Varkey et al., 2008).

#### 2.3.2.2 Doppler Ultrasound

Surface Doppler monitoring with low–frequency continuous-wave ultrasound can be used in combination with clinical monitoring. It is simple to use, and the equipment required is cheap. The device is handheld, and the sound of arterial or venous pulsation is the main signal. The device is used by 30% to 80% of head and neck microsurgeons. (Hirigoyen et al., 1995; Jallali et al., 2005; Spiegel & Polat, 2007) In the head and neck region, however, this system has certain limitations. For example, close proximity to the carotid artery and jugular veins can sometimes make it very difficult to detect whether the Doppler sound comes from the pedicle artery (Abdel-Galil & Mitchell, 2009a). Moreover, it is also difficult to use with buried flaps. In addition, arterial pulsation can also be heard after venous occlusion, thus lengthening the decision-time for re-operation (Smit et al., 2010).

#### 2.3.2.3 Laser Doppler flowmetry

Laser Doppler flowmetry is a continuous non-invasive method for the measurement of tissue oxygen and perfusion. Laser Doppler measures red blood cell movement from the surface of the flap only to a depth of 8 mm, which makes it unsuitable for buried flaps. The advantage of the system is two numeral parameters: average velocity of blood cells and total intensity of the reflected light, which is inversely proportional to total blood contained in the tissue. (Abdel-Galil & Mitchell, 2009a; Smit et al., 2010) The trend of perfusion values is important but not the absolute value per se. Hence, according to Yuen and Feng who found this system reliable in 232 patients, the learning curve of the method is longer. (Yuen & Feng, 2000)

#### 2.3.2.4 Colour duplex sonography

Color duplex sonography is a non-invasive method to visualize the arterial and venous flow inside flap pedicle vessels. The flow can also be quantitated. However, experienced personnel are needed to interpret the findings. In a study by Rosenberg et al., a radiologist together with a microsurgeon examined the flaps, making it slightly impractical in everyday use (Rosenberg, Fornage, & Chevray, 2006). The value of color duplex sonography in searching for the perforators of free flaps has been previously shown, although in the era of CT- and MRI-angiography its role has become limited(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010)(Smit, Klein, & Werker, 2010) (Rand, Cramer, & Strandness, 1994; Smit et al., 2010) The method has also been used in the monitoring of free flaps after surgery mainly to confirm the status of the anastomoses after displacement of an implantable doppler-probe. (Few, Corral, Fine, & Dumanian, 2001; Khalid, Quraishi, Zang, Chadwick, & Stack, 2006; Rosenberg et al., 2006; Stone, Dubbins, & Morris, 2001)

#### 2.3.2.5 Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive and continuous method used for monitoring the end-organ delivery of oxygen. Near-infrared light (650-900 nm) is delivered into the tissue up to a depth of 20 mm. The absorption of the light varies according to the level of the oxygen in the hemoglobin, which can then be measured. The concentrations of hemoglobin and deoxygenated hemoglobin are calculated and the variation changes detected. (Y. Chen, Shen, Shao, Yu, & Wu, 2016; Steele, 2011) Kagaya & Miyamoto performed a meta-analysis of scientific articles dealing with aspects of NIRS and reported a success rate of 99.5% and a flap salvage rate of 91.1%. Moreover, vascular compromises could be detected with sensitivity of 99.1% and specificity of 99.9% even earlier than by the other monitoring methods analyzed. (Kagaya & Miyamoto, 2018) In the method, a probe is placed on the skin and secured with a sticking plaster. The method can also be used inside the oral cavity because of a special silicon probe that can be sutured in place. Moisture under the probe or migration of the probe may cause some false alarms. The probe should also be covered to avoid any light disturbance. Furthermore, this system is not really suitable for buried flaps. (Kaariainen et al., 2018)

### 2.3.3 Invasive monitoring methods

Invasive monitoring methods mean minimally invasive techniques for free flap follow-up. Numerous methods have been described for experimental purposes and everyday clinical use. Among these are implantable Dopplers, tissue temperature monitoring, tissue PH monitoring, tissue oxygen monitoring, and microdialysis. (Abdel-Galil & Mitchell, 2009b) Even a Positron emission tomography (PET) scan has been used as a monitoring system in a clinical trial with good results (Schrey, Kinnunen, Grenman, Minn, & Aitasalo, 2008). Some of these methods are not suitable for monitoring intraoral flaps. For example, a temperature probe measures the inside natural cavity temperature, which does not change remarkably in cases of vascular compromise.

#### 2.3.3.1 Implantable Doppler

Implantable Doppler probes allow the continuous and direct monitoring of the flap vessels, and they can be attached to either pedicle veins or arteries. The cuff is made out of silicone and comprises a 20 MHz ultrasonic probe and an easily removable wire. In some cases, the probe wire may be accidentally detached leading to a false positive result. (K. P. Chang, Lin, & Lai, 2007; Um et al., 2014) The probe continuously provides a voice signal either from the venous or arterial pulse or both. Any weakening or loss of the sound may suggest vascular compromise. The decision whether to wrap the probe around an artery or vein is based on personal experience. Chang et al. studied 439 patients and found that arteries were superior to veins with better sensitivity and specificity. However, in cases of venous thrombosis, the artery may have a pulsation sound that lasts for hours, leading to false negative findings. No additional information was found on probes wrapped around both veins and arteries. (E. I. Chang et al., 2016) Wax studied 1142 flaps with implantable Doppler and found only 8 false positives but also 10 false negative flap compromises, and the overall flap survival rate was 97%. He found the system to be reliable enough for flap monitoring. (Wax, 2014) In buried flaps, implantable Doppler has been associated with numerous false positive findings that have led to unnecessary explorations (Rosenberg et al., 2006).

The ultrasound probe can also be attached to venous coupler sets, which is a device for making end-to-end venous anastomosis. This is called the flow coupler technique, which is easy to apply, simple to use, and monitoring is reliable. (D. P. Chubb, Rozen, Whitaker, & Ashton, 2011; Oliver, Whitaker, Giele, Critchley, & Cassell, 2005) The technique works as well as other implantable Doppler probes around veins. However, in a recent study, this system has been found to result in significantly more vascular thrombotic events than a coupler without the Doppler system. (Kempton, Poore, Chen, & Afifi, 2015)

### 2.3.3.2 Tissue oxygen monitoring

Tissue oxygen ($P_{ti}O_2$) monitoring has been widely used by neurosurgeons to measure brain oxygen levels. It comprises a Licox® touch-screen monitor, which shows tissue oxygen tension and trends in numerical values, together with a flexible probe. This method was first described in free flaps by Hirigoyen in a rabbit model (Hirigoyen et al., 1997), and it has since been used in several institutions including Tampere University Hospital. Several studies of its usefulness have been published. (Jonas et al., 2013; Kamolz, Giovanoli, Haslik, Koller, & Frey, 2002; Raittinen, Laranne, Baer, & Pukander, 2005; Wechselberger et al., 1997)

Oxygen dissolved in the interstitial fluid corresponds to the availability of oxygen at the cellular level in the flap. However, hemoglobin levels, microcirculation, and systemic oxygen levels also influence the levels of flap oxygenation. When the monitoring probe is inserted in the tissue, its oxygen diffuses through the polyethylene wall of the probe to a negatively polarized precious metal in the inner electrolyte chamber, resulting in $O_2$ molecules polarizing into $OH^-$ions. The polarization can be detected as an electric current. The current from the $O_2$-reduction is the raw signal of the sensor. The reactions in the probe are reversible making the measurements stable and continuous.

A major limitation of the $P_{ti}O_2$ monitoring system is the sensitivity of the probe to micro movements. The probe may be detached or it may lower $P_{ti}O_2$ readings, and therefore even lead to unnecessary re-operations. (Jonas et al., 2013; Wechselberger et al., 1997)

Tissue oxygen levels are considered to efficiently reflect the level of tissue perfusion. If the flap perfusion is increased, the $P_{ti}O_2$ levels approach that of systemic arterial blood. On the other hand, circulatory impairment of the flap quickly results in descending oxygen pressure. (Abdel-Galil & Mitchell, 2009b) The $P_{ti}O_2$ -levels are shown as mmHg and are in proportion to the measured temperature. The trend of $P_{ti}O_2$ -levels is important in the follow-up, but they are not the absolute value per se, which lengthens the learning curve of this method. (Kaariainen et al., 2018) Normally, after anastomosis, the $P_{ti}O_2$ -levels rise rapidly to the peak level before starting gradually to slide. However, the readings are reliable for the first few minutes after flap circulation is opened. A steeper slide or a simple drop under 10 mmHg predict vascular compromise, if it is not solved by controlling the probe and positioning the patient’s head or other conservative methods within 30 minutes (Hofer, Timmenga, Christiano, & Bos, 1993).

Lin et al. compared time before and after tissue oxygen monitoring in their study consisting of 614 free flap patients. Their percentage of re-operations was identical, but the rate of flap loss was significantly lower in the tissue oxygen monitoring group. These findings suggest that PtiO2 monitoring makes it possible to observe vascular compromises early enough to be able to save the flap with re-operation.(S. J. Lin et al., 2011)

Recently, Arnez et al. stated that the results of PtiO2 monitoring were similar to those of clinical bedside monitoring. Their study consisted of 87 patients, of whom 47 had head and neck tumors, and they reported 13% false positive results but no false negatives. For a flap monitoring device, this is a good feature and means that no flap compromises occur without an alarm. (Arnez et al., 2018)

#### 2.3.3.3 Microdialysis

Microdialysis (MD) is a method that continuously measures the extracellular molecules of individual tissues and organs. Its main principle is the gradient difference in extracellular space and flowing microdialysate by mimicking the blood flow in the capillaries. (Lonnroth & Smith, 1990; Ungerstedt, 1991)

Microdialysate (isotonic Ringer's solution) is circulated by a special pump through a thin dialysis tube inserted in tissue using a special probe. The molecules travel along gradient differences through a semipermeable membrane into the dialysate, which is then collected into a microvial. The collected fluid sample reflects the composition of the extracellular fluid in the investigated tissue. The samples can be collected continuously for hours or days and then analyzed chemically using a specific microdialysis device or other analyzers, such as radioimmunoassay and mass spectrometry. The gradient differences between the dialysis tube and the extracellular fluid are levelled both ways. This allows medication, for example, to be administered locally into the tissue via microdialysate. There are different commercial kits available for analyzing microdialysate. A commercial analysis kit has reagents that can measure oxygen dependent metabolite levels, such as glucose, lactate, and pyruvate, in the extracellular fluid, and thereby reflects the circulatory status of the investigated tissue. Pyruvate is produced from glucose by glycolysis, and therefore both of them reflect the amount of fresh blood circulating in the tissue. Lactate is produced as an end product in pyruvate breakdown. Small amounts are normal in extracellular fluid, but when levels are elevated considerably, it reflects anaerobic metabolism and suggests insufficient blood flow.

Microdialysis was first introduced to monitor free flap metabolism by Röjdmark et al. in 2002. Since then, it has been used in free flap follow-up both experimentally and nowadays also in everyday clinical use (Edsander-Nord, Rojdmark, & Wickman, 2002; Jyranki, Suominen, Vuola, & Back, 2006; Röjdmark, Heden, & Ungerstedt, 1998; Rojdmark, Blomqvist, Malm, Adams-Ray, & Ungerstedt, 1998; L. P. Setala et al., 2004; Udesen, Lontoft, & Kristensen, 2000). MD is able to measure true metabolic changes inside the flap tissue while other monitoring systems more or less reflect or measure blood flow inside the flap vessels or the flap itself (Su, Im, & Hoopes, 1982). Therefore, MD has been found to be extremely sensitive in noticing even small changes in the microenvironment of the flap. For example, the effect of hematoma around the probe has been seen to have an effect on MD metabolites: both lactate and glucose remain low, which itself is a confusing issue (Kristensen, Ladefoged, Sloth, Aagaard, & Birke-Sorensen, 2013). One major advantage in both MD and $P_{ti}O_2$ measuring devices is that they can be attached to muscle or fat and do not need a skin part to work in a free flap (Jyranki et al., 2006).

Frost et al. compared MD with implantable Doppler and clinical bedside monitoring in a 20-patient series. They found MD to be feasible but noticed many technical problems with the pump or analyzer and error measurements. They stated that all of the monitoring methods discovered flap compromises early enough for successful salvage surgery. However, MD and Doppler detected flap compromises sooner than clinical monitoring, MD with 100% specificity. (Frost et al., 2015)

### *Role of glycerol in flap monitoring*

Extracellular glycerol is thought to mirror the level of cellular injury, and levels can be detected by MD. Ischemia, and hence impaired energy production, is thought to result in calcium entering the cells. This activates phospholipids, which in turn hydrolyze cell membranes and release glycerol. (Allen, Chen, Seaber, & Urbaniak, 1995) According to Udesen et al., the normal course of surgery elevates MD glycerol levels only moderately before they normalize. However, in a failed free flap, glycerol levels rise rapidly, reflecting massive cellular destruction (Udesen et al., 2000). Confusingly, the reason for elevated glycerol levels post-operatively is thought to be adipose tissue lipolysis modulated by endogenous catecholamine, which is the result of sympathetic stress caused by the operation (Fellander, Eleborg, Bolinder, Nordenstrom, & Arner, 1996). However, Udesen et al. questioned this because they found glycerol levels were only elevated in the flap not in the control tissue. This leads to some confusion as to whether the slight elevation is caused by sympathetic tonus per se or only by cellular damage (Udesen et al., 2000).

*Role of lactate/pyruvate ratio in flap monitoring*

Tissue ischemia due to arterial or venous occlusion changes tissue metabolism from an aerobic to an anaerobic direction. This change is reflected by a decline of glucose and pyruvate and an elevation of lactate, and the lactate/pyruvate-ratio (L/P ratio) can be measured by MD.(L. Setala et al., 2006) Glucose and L/P ratio are the most sensitive to ischemia (Contaldo et al., 2005). Jyränki et.al studied microdialysis in intraoral free flaps. They found that in successful flaps the L/P ratio did not exceed 25, but in the case of vascular compromise it was elevated remarkably. After re-operation, however, the levels quickly returned to normal. Therefore, the L/P ratio is a reliable indicator for detecting ischemia. (Jyranki et al., 2006) Setälä et al. found the L/P ratio median to be 12, and 98% of all readings were under 32. (L. Setala et al., 2006)

#### 2.3.3.4 Multimodal monitoring

Multimodal monitoring means using two or more monitoring methods or devices in the same flap. As the results of single monitoring methods are more or less controversial, the idea of multimodal free flap monitoring with different devices along with clinical follow-up in clinical practice seems almost absurd. However, this is normal practice for critically ill patients in neurosurgical care. For example, $P_{ti}O_2$ monitoring and MD have been used together.(De Georgia, 2004) In theory, similar multimodal monitoring provides much more information about the flap tissue. For example, in cases where $P_{ti}O_2$ levels start to decrease slowly, even though the flap still looks good, MD could strengthen the decision to revise should the L/P ratio start to significantly increase. Similarly, color-duplex sonography has been used to confirm blood flow when an implantable Doppler probe was accidentally detached (Rosenberg et al., 2006).

In everyday practice, multimodal free flap monitoring is too complicated and too expensive. Yet, in clinical studies, it has been widely used to confirm suggested results or to control the feasibility of a new monitoring method. Schrey et al. used $P_{ti}O_2$ monitoring together with a PET scan and found that in estimating the need for revision surgery, a PET scan provides vital extra information cost-effectively. For example, PET could confirm low $P_{ti}O_2$ -levels as being real ischemia. (Frost et al., 2015; Nunes et al., 2007; Rosenberg et al., 2006; Schrey et al., 2008)

## 2.4 Maintaining perfusion pressure during postoperative period

### 2.4.1 Background

Head and neck microvascular surgery and the postoperative period are challenging for anesthesiologists. Operations last a long time, remarkable blood loss may occur, and patients often have comorbidities combined with heavy smoking and alcohol abuse (Blot et al., 1988). In many institutions, patients are sedated until the next morning to ensure flap survival. Prolonged sedation may, however, cause vasodilation and reduced mean arterial pressure (MAP), which in turn could be hazardous for the flap. To prevent this, actions to normalize the hemodynamic stability, such as elevating MAP by filling up the blood vessels or by increasing their tonus, should be taken. Traditionally, this has meant excessive IV liquid use, often leading to flap or even pulmonary edema. (Angelini, Ketzler, & Coursin, 2001; Hagau & Longrois, 2009; Sigurdsson & Thomson, 1995) To avoid these untoward side effects, the use of vasopressors, such as dopamine, dobutamine. or norepinephrine (NE), is often necessary (Massey & Gupta, 2007). On the other hand, there is a risk of possible vasoconstriction with flap ischemia. Hence, the use of vasopressors is still controversial, as shown by Gooneratne et al. (Gooneratne, Lalabekyan, Clarke, & Burdett, 2013) In a recent study from USA, Kovatch et al. asked microsurgeons for their opinions of vasopressors. Of those questioned, only 6% accepted them and 63% allowed them but preferred not to use them (Kovatch et al., 2018). Previously in Tampere University Hospital's guide for anesthesiologists, colloid was favored, and if any medication was needed, only dobutamine was allowed (Ingberg P, 2006).

### 2.4.2 Effects of autonomic nervous system

The human autonomic nervous system is responsible for many reactions vital for survival. It is anatomically and functionally divided into sympathetic and parasympathetic systems, both of which are active all the time. The sympathetic system predominates during emergency reactions and exercise and the parasympathetic system during quiet rest, when the body is supposed to conserve energy and regulate basic body functions. The one that is the more active depends on the balanced level of inhibition and activity in the end organs.

Circulating catecholamines, such as NE and epinephrine, act through adrenergic receptors that can be divided to alpha and beta receptors, both of which are divided into subtypes. Alpha receptors are situated in the heart, liver, brain, and arterioles causing vasoconstriction and glycogenolysis. Beta receptors are found in adipose tissue, the heart, and the lungs and cause an increased heart rate and force of contraction, bronchodilation, and lipolysis. Systemic blood pressure is increased by both alpha and beta receptor reactions by increasing the heart rate and contraction as well as vasoconstriction in the arterioles. These effects take place during sympathetic activity. During parasympathetic stimulation, the effects are the opposite. Many drugs have been used for both sympathetic and parasympathetic agonists and antagonists. The effects are mediated directly to the receptors or through sympathetic nerve endings, which in turn release NE to the receptors. (McCorry, 2007)

In previous studies, sympathectomy has been associated with vessel supersensitivity to catecholamines, especially NE, causing excessive vasoconstriction in sympathectomized areas when compared with control areas. Sympathectomy stops NE release in the nerve endings, and leaves the NE receptors free for circulating NE. This has been thought to be the reason for abnormally high vasoconstriction. (Banbury, Siemionow, Porvasnik, Petras, & Zins, 1999a; Godden, Little, Weston, Greenstein, & Woodwards, 2000; Rizzoni et al., 2000) Lecoq et al. investigated the flap vessel vasoconstriction caused by denervation as in microsurgery. No signs of denervation-induced vasoconstriction were noticed. They also suggested that surgical sympathectomy might protect cutaneous flaps from the vasoconstriction induced by the release of endogenous catecholamines. (Lecoq, Joris, Nelissen, Lamy, & Heymans, 2008)

According to Monroe et al., the risks of using vasopressors in free flaps seem to have been over emphasized. In the first of their two studies, they checked the patient records of 169 microvascular operations and found that vasopressors had been used in 82% of the operations intraoperatively "without permission". Later, they allowed anesthesiologists to use vasopressors intraoperatively with no adverse effects noticed. (Monroe, McClelland, Swide, & Wax, 2010; Monroe, Cannady, Ghanem, Swide, & Wax, 2011)

There seems to be four studies that aim to prove the safety of vasopressors in microvascular surgery for humans (Black et al., 2003; C. Chen et al., 2010; Monroe et al., 2010; Tuominen, Svartling, Tikkanen, & Asko-Seljavaara, 1997). Pattani et al. reviewed the literature on free flap complications. They found that intraoperative fluid administration, medical comorbidities, and prolonged operation time predispose patients to free flap disorders. However, no evidence supporting the hypothesis that free flap failure was caused by hypotension, colloids, and nitrous or vasopressor use was presented. (Pattani, Byrne, Boahene, & Richmon, 2010) Nevertheless, none of these nor most of the animal studies provided relevant information on the ideal therapeutic range of these vasopressors or the duration of safe administration (Ibrahim, Kim, Rabie, Lee, & Lin, 2014).

### 2.4.3 Dopamine and dobutamine

Dopamine is a sympathomimetic drug that has effects on organs that are clearly dose-dependent. A low dose selectively activates specific dopamine receptors, for example in the kidney, whereas a low dose has little or no effect on alpha or beta receptors. However, larger doses activate beta receptors more and result in vasoconstriction and increased heart rate systemically. (Koulu & Tuomisto, 2007) Dopamine has been used as a second option in treating hypotension after norepinephrine in patients with sepsis in the ICU (Rhodes et al., 2017).

Dobutamine is an agent whose primary activity results from the stimulation of beta 1receptors of the heart, and it increases contractility and cardiac output. However, it also has weak beta 2 and alfa 1 activity. Moreover, it has inotropic effects on the heart, and it is less hypertensive than dopamine or NE. (Tuttle & Mills, 1975)

In microvascular surgery, dopamine can cause vasoconstriction, and thus ischemia for free flaps. Three articles have been published on using dopamine in microvascular surgery. Both Cordeiro et al. and Suominen et al. measured direct arterial flow during operation simultaneously when dopamine was administered intravenously. (Cordeiro, Santamaria, Hu, & Heerdt, 1997; Singh, Fu Zhu, Dziegielewski, & Seikaly, 2012; Suominen et al., 2004) Similar results were reported with increased cardiac output after larger dopamine doses, but no increase in recipient flap artery flow. Cordeiro et al. stated that dopamine could be used with caution in free flaps, whereas Suominen et al. preferred dobutamine over dopamine should a vasoactive drug be needed. On the other hand, Singh et al. found high-dose dopamine safe in a rat model with no difference in free flap survival (dopamine vs. placebo) (Singh et al., 2012). In conclusion, in everyday clinical practice, both dopamine and dobutamine could be used if a vasopressor or inodilator is required during or after microvascular surgery. (Suominen et al., 2004)

### 2.4.4 Norepinephrine

Norepinephrine (NE) affects both alpha and beta receptors causing increased peripheral resistance, and thus increased MAP. On the other hand, NE decreases heart rate refractorily. (Koulu & Tuomisto, 2007) In addition, NE affects sympathetic nerve endings both directly and indirectly. The former is caused by the direct effect of circulating the drug to the receptors in the sympathetic nerve endings, and the latter is caused by sympathetic nerve activation, which in turn causes norepinephrine to be released from its reserve inside the nerve. The latter could be blocked by denervation as happens in microvascular surgery, causing the denervated nerve endings to hyperreact to the circulating norepinephrine. This is supposed to cause stronger vasoconstriction than in sympathetically intact vessels, and it is thought to cause circulation problems for free flaps. Some experimental studies have shown catecholamines to cause excessive vasoconstriction in sympathectomized free flaps. (Banbury, Siemionow, Porvasnik, Petras, & Zins, 1999b; Godden et al., 2000; Rizzoni et al., 2000) These theoretic findings have led microsurgeons to be extremely careful when using norepinephrine with free flaps. However, previous clinical experience may suggest otherwise. Hiltunen et al. studied the effects of hypotension and its correction with NE intraoperatively in pig free flaps. They reported no adverse effects to the flap in the case of moderate hypotension or its correction by NE infusion, even with high doses. (Hiltunen et al., 2011)

## 2.5 Postoperative sedation after microvascular surgery

### 2.5.1 Background

Standard postoperative sedation is achieved by using analgesics or sedatives. Many different drugs with different mechanisms, side-effects, and benefits are used. The main purpose of postoperative sedation in microvascular surgery is to ensure the vitality of the flap. However, a physician in the ICU should be careful not to increase patient morbidity or mortality and not harm the flap with the sedation instead. Fentanyl, morphine, and ketamine are the most used analgesic drugs. Midazolam, propofol, and haloperidol are the most widely used sedative agents. No universal recommendation is available, so treatment protocols vary a great deal between different ICUs and different countries. (Liu & Gropper, 2003)

There is growing evidence that too excessive sedation causes a lot of problems and leads to prolonged mechanical ventilation. However, inadequate sedation is also associated with risks, such as accidental extubation or restlessness, which is not optimal for free flap welfare. The goal of sedation should therefore be a tranquil and rousable patient. Hence, the level of sedation should be defined beforehand. It should be kept in mind, however, that there are some factors, i.e., bilateral neck dissection, massive blood transfusion, and a history of heavy smoking that support the use of more intensive sedation. (de Melo, Ribeiro, Kowalski, & Deheinzelin, 2001; Jacobi et al., 2002; Mantz, Josserand, & Hamada, 2011) Lighter sedation often lowers costs during intensive care because of reduced length of stay and shorter mechanical ventilation times. (Dasta et al., 2010)

Major reconstructive surgery, as in the operative treatment of head and neck cancers, is traditionally associated with a high postoperative risk for the patient and free flap survival. Therefore, these patients have generally been kept tracheostomized, sedated, and treated in the ICU for an average of 2 to 4 days. (Sigurdsson & Thomson, 1995; Spiegel & Polat, 2007) In the study by Spiegel and Polat, 88.9% of head and neck surgeons in the United States applied this protocol in 2007.

Although there are only a few papers that promote this kind of treatment protocol, it nevertheless seems to be more or less the “standard of care” (Arshad et al., 2014). Moreover, postoperative sedation prolongs hospital stay and increases the risk of pneumonia and use of antiagitative drugs (Allak et al., 2011). Ideally, a patient in the ICU should also be easy to arouse and be able to communicate the need for analgesia (Mantz et al., 2011). Therefore, recent guidelines prefer a light sedation associated with shorter ICU stay and fewer complications (Barr et al., 2013a). In 45% of US hospitals, the main reason for ICU treatment after microvascular surgery was a lack of adequately trained nursing personnel to control the status of the flap (Haddock, Gobble, & Levine, 2010). Nkenke et al. studied prospectively the differences between a special ward with specialized nurses and an ICU after head and neck surgery. They found no significant difference in ICU readmissions or flap survival between the groups. (Nkenke, Vairaktaris, Stelzle, Neukam, & St Pierre, 2009) Similar findings have also been reported in other studies. Indeed, specially trained nurses and close medical support in an intermediate level ward seems to have similar results as treatment in an ICU (Morton, 2002; To, Tsang, Lai, & Chu, 2002).

The postoperative care of head and neck patients is under constant pressure to shift towards less costly treatments including less intensive care. However, to date, there have been no prospective and only a few studies that prove any difference in outcomes between normal ward and ICU treatment. (Dort et al., 2017; Morton, 2002; Nkenke et al., 2009; To et al., 2002) Treatment in the ICU is quite expensive. For example, the price of a single day could be as much as 2000 to 3000 euros, which is much more expensive than in a normal ward, which is approximately 500 euros. As cost-effectiveness is considered to be more and more important, an increasing number of critical studies argue against routine postoperative sedation and treatment in an ICU. (Allak et al., 2011; Arshad et al., 2014; Nkenke et al., 2009; L. Setala et al., 2009; Yu et al., 2018) In a recent survey in the United States, Kovatch et al. found that 75% of all head and neck free flap patients are still treated in an ICU for an average of 2 to 3 days. However, of these, only 11% needed postoperative sedation. Patient observation was mostly done on a clinical monitoring only basis, keeping in mind that there was on average 3 surgeons trained in microsurgery/institute. (Kovatch et al., 2018)

### 2.5.2 Propofol

Propofol is an intravenous anesthetic drug that is widely used for sedation during general anesthesia or as an induction agent for general anesthesia. As in many other anesthetics, the mechanism of action of propofol is poorly understood. It is, however, thought to be related to GABA-mediated chloride channels in the brain. Propofol has a few adverse effects with hypotension, caused by inhibiting sympathetic vasoconstriction, being the most important (Folino & Parks, 2017). During the intra- or postoperative period, this hypotension can cause a dilemma for anesthesiologists as to whether to use vasopressors or to use more IV-fluids. However, excessive amounts of both are potentially hazardous to the patient and the flap (Sigurdsson & Thomson, 1995).

Barr et. al. reported that propofol accumulates unpredictably in some patients and leads to delays in extubation after postoperative sedation. They also found remarkable hypotension in 17% of their patients. However, when used carefully and the sedation level adjusted to need, propofol acted predictably. (Barr et al., 2001)

Previous studies have reported that propofol affects blood coagulation by inhibiting blood clotting (Aoki, Mizobe, Nozuchi, & Hiramatsu, 1998; De La Cruz, Paez, Carmona, & De La Cuesta, 1999; Dogan, Ovali, Eti, Yayci, & Gogus, 1999;

Law, Ng, Irwin, & Man, 2001). Even though the effect of propofol on platelet aggregation appears to be clear, its effect on bleeding time has not been shown (Aoki et al., 1998).

### 2.5.3 Dexmedetomidine

Dexmedetomidine (DEX) is a highly specific alpha2 agonist used for sedation in the ICU. The alpha2 receptors are found in the central nervous system and in the spinal cord, where their activation lead to sedation and to some degree of analgesia by decreasing activity of noradrenergic neurons. DEX is as effective as propofol or midazolam in maintaining light postoperative sedation, but there has not been much evidence of its long-term safety. (Ahmed & Murugan, 2013; Ebert, Hall, Barney, Uhrich, & Colinco, 2000; Iirola et al., 2012; Jakob et al., 2012; Nguyen, Tiemann, Park, & Salehi, 2017; Ruokonen et al., 2009; Venn, Hell, & Grounds, 2000)

DEX seems to be ideal for light sedation with fewer analgesics needed. It produces a natural sleep-like condition from which patients can be easily aroused. (Nelson et al., 2003) Nevertheless, it does not cause sleep deprivation during sedation in patients in the ICU, which appears to lessen the risk of delirium.(Figueroa-Ramos, Arroyo-Novoa, Lee, Padilla, & Puntillo, 2009; Huupponen et al., 2008; Shehabi et al., 2009) This makes DEX even more suitable for head and neck postoperative follow-up because many patients have an increased risk of delirium due to heavy alcohol consumption and old age. In a large meta-analysis, Peng et al. reported that DEX may reduce 30-day mortality, length of hospital and ICU stay, incidence of delirium, duration of assisted mechanical ventilation, risk of atrial fibrillation, and cardiac arrest (Peng et al., 2018).

Alpha2 receptors are also found in blood vessels, where they mediate vasoconstriction, and in sympathetic nerve terminals, where they inhibit NE release. (Bloor, Ward, Belleville, & Maze, 1992; Drew & Whiting, 1979; Langer, 1980)

DEX has dual cardiovascular effects. At low-plasma concentrations, it decreases MAP and heart rate, but at higher levels it deepens sedation and elevates MAP because of increased vascular resistance. (Bloor et al., 1992; Ebert et al., 2000; Keating, 2015)

DEX is found to cause vasoconstriction in denervated vasculature, for instance, after microvascular surgery. (Bloor et al., 1992; Hogue et al., 2002; Talke et al., 2003) Used as a single sedative agent after reconstructive surgery, DEX yields higher systemic blood pressures compared with propofol and better perfusion pressures in the transplanted flaps. To prove this hypothesis, Nunes et al. simulated the harvest of musculocutaneous flaps in twelve domestic pigs and monitored flap oxygenation and microdialysate metabolism during a postoperative sedation period. They reported that DEX increased systemic blood pressures by raising systemic vascular resistance, but it did not seem to have any negative impact on the local perfusion or viability of the denervated flaps. Tissue oxygenation and microdialysate metabolites did not differ between the study groups. (Nunes et al., 2007)

In a recent study, DEX has also been found to attenuate the risk of blood coagulation after gastric surgery. It lowered fibrin degradation products and thrombin-antithrombin complex formation. The reason for this was thought to be lowered catecholamine levels which, in turn, inhibit platelet function. This finding was considered to be beneficial in preventing, for example, postoperative pulmonary embolisms. (Z. Chen et al., 2018)

## 2.6 Theory synopsis

Microvascular flaps are nowadays routinely used for reconstructions in head and neck cancer surgery. As previously noted, many flap monitoring systems have been described and are in varying degrees of use around the world. The pros and cons of each method and the reasons for using them are mainly based on the traditions of an institution or the personal opinion of an individual surgeon. Even the best monitoring system has limitations and confusing factors. Therefore, it is very difficult to set standards for the monitoring of free flap follow-up. Every patient and every flap must be taken as individuals with multiple confusing factors, leaving room for good clinical skills and assessment.

The postoperative course of care is as crucial as operative techniques per se, while free microvascular flaps are vulnerable to vascular compromises. Therefore, optimal postoperative care that ensures flap survival and avoids re-operations is of the utmost importance. There seems to be no generally accepted gold standard for the ideal postoperative sedation, flap follow-up method, or postoperative medication. According to the current literature, most microsurgeons prefer ICU follow-up with sedation using propofol and avoiding the use of vasopressors. Flap follow-up is mostly done by clinical assessment together with hand-held Doppler ultrasound.

During this study, the postoperative follow-up of head and neck free flap surgery at Tampere University Hospital was carried out in the ICU. Previously propofol was administered until the first postoperative morning. The aim was to have a MAP of

>70 mmHg. To reach this, anesthesiologists are nowadays allowed to use vasoactive medication if required, and only necessary fluids are administered. Previously more IV-fluids were used. Tissue oxygen levels were monitored using the Licox® monitoring system for more than 72 h postoperatively together with clinical signs of the flap confirming arterial pulsation using handheld Doppler when needed. In case of any doubt, an immediate re-operation and anastomosis revision was performed.

# 3 AIMS OF THE PRESENT STUDY

The purpose of this study was to find out more about the optimal circulation and monitoring methods of free vascular flaps in head and neck cancer surgery

The specific aims were as follows:

1. To find out the tissue oxygen levels that indicate the circulation problems of free microvascular flaps, and to study the feasibility of tissue oxygen monitoring during the postoperative period after free microvascular flap surgery

2. To estimate the role of microdialysate glycerol in tissue ischemia and the confounding effect of denervation in MD glycerol levels

3. To find out whether or not the use of sympathomimetics or dexmedetomidine causes signs of vasoconstriction and flap ischemia during microvascular flap surgery in the head and neck area

4. To compare propofol and dexmedetomidine postoperative sedation considering flap ischemia and survival in head and neck cancer surgery

# 4 MATERIALS AND METHODS

## 4.1 Studies I-IV

### 4.1.1 Study I

In study I, the material comprised 118 head and neck cancer patients operated in the department of Otolaryngology, Head and Neck Surgery, Tampere University Hospital, Finland during the years 1999 to 2009. All patients underwent radical removal of the tumor and a selective neck dissection followed by a free flap reconstruction. (Table 1) In study I, the microvascular transfers were mostly radial forearm flaps (92), fibular (11), and scapular (3). A few other flaps were also used (Table1). A Licox® probe was inserted into the subcutaneous tissue or muscle before reconstruction and vessel anastomosis.

Postoperative care was according to the usual protocol in the ICU, with no special requirements for medication. The analyses were made retrospectively based on medical records and $P_{ti}O_2$ monitor readings.

**Table 1.** . Patient demographics in studies I, III and IV

| | Study I | Study III | Study IV | Together |
|---|---|---|---|---|
| Patient demographics | | | | |
| Sex M (F) | 70 (48) | 13 (12) | 14 (6) | 97 (66) |
| Age (mean) | 56 | 61 | 60 | |
| Tumor site | | | | |
| Oral cavity | 84 | 14 | 13 | 111/163 |
| Oropharynx | 24 | 11 | 7 | 42/163 |
| Hypopharynx | 5 | | | 5/163 |
| Other | 5 | | | 5/163 |
| Flaps | | | | |
| Radial forearm flap | 92 | 25 | 20 | 137/163 |
| Fibular flap | 11 | | | 11/163 |
| Other flaps | 15 | | | 15/163 |
| Re-operation | 8 | 0 | 2 | 10/163 |

M=male, F=female

### 4.1.2 Study II

In study II, 12 domestic pigs were anesthetized and mechanically ventilated. Two identical rectus abdominis musculocutaneous flaps from both sides of each pig were raised by an experienced plastic surgeon. In A-flaps, the adventitia with its sympathetic nerves was carefully stripped from the artery. The adventitia in the B-flaps was left intact. The flaps were then sutured in their original position and left intact during the experiment.

Flap ischemia was induced by clamping both flap arteries for 60 minutes to mimic ischemia during a microvascular operation. (Figure 1) Ischemia was confirmed by measuring the tissue oxygen pressure of the flaps. The extracellular L/P ratio indicated the degree of anaerobic metabolism locally in the flap tissue. Thereafter, the flaps were followed carefully for the 60 minutes reperfusion period.

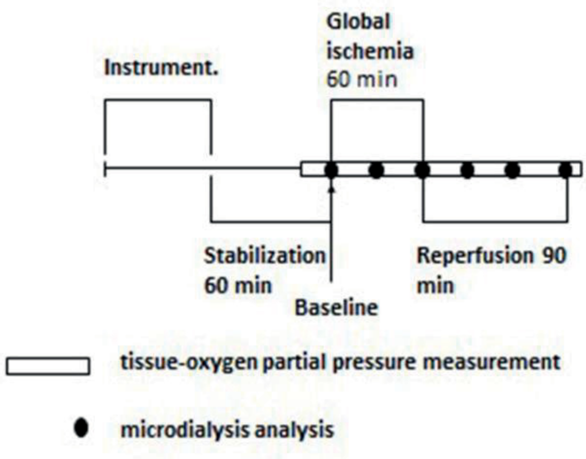



**Figure 1.** Study II protocol

### 4.1.3 Study III

Study III comprised 27 consecutive head and neck cancer patients (15 oral, 12 oropharyngeal). The patients were enrolled in an unblinded, randomized, controlled trial. Patient demographics are shown in Table 1. The patients were randomized in three groups of nine: NE, dopamine, and control group. Blocks of nine patients, three from each group, were used for the randomization, and the allocation was performed after the operation by the medical/research nursing staff in the intensive care unit. The patients were allocated into dopamine, norepinephrine, and control group for the postoperative period in the ICU. The groups were unblinded, so the ICU physician knew which drug had been given. In the control group, no medication was given unless MAP dropped below 60 mmHg. In the two medication groups, MAP was maintained between 80 and 90 mmHg with vasoactive drugs if needed. The medication used was determined according to the randomization protocol.

All the operations were carried out using a two-team approach. An experienced head and neck surgeon performed the tumor removal, selective neck dissection, and reconstruction as well as microvascular anastomoses. A plastic surgery team harvested the flap simultaneously. Only radial forearm flaps were used. The microdialysis and Licox® catheters were inserted into the subcutaneous tissue side-by-side and sutured or clipped in place before reconstruction. (Figure 2)

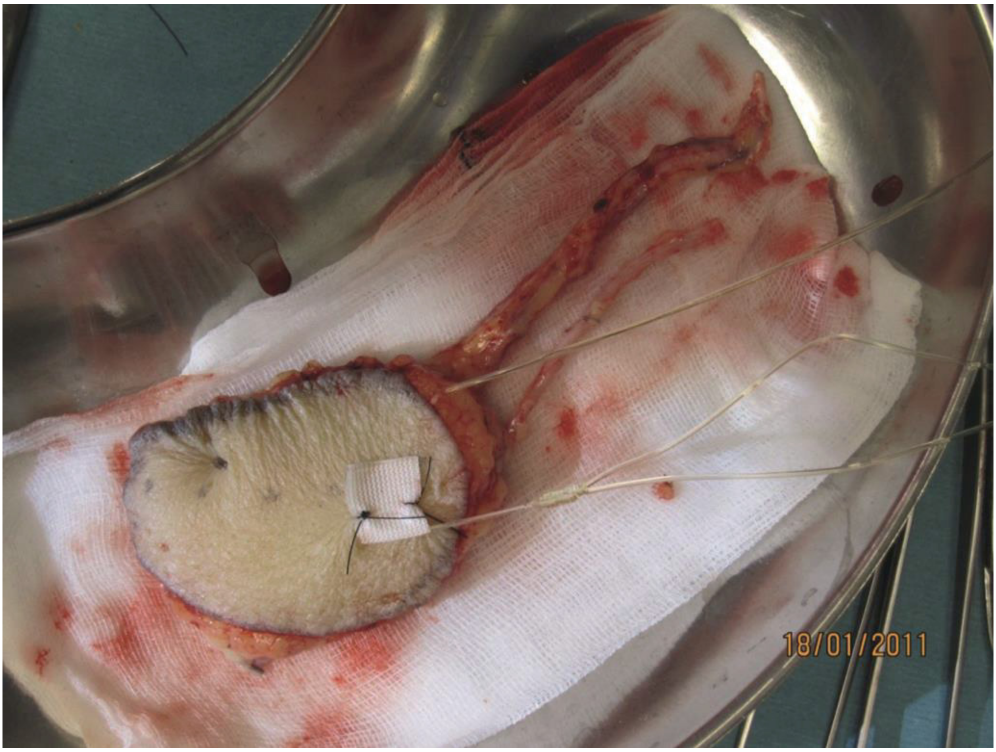



**Figure 2.** Microdialysis (divided catheter) and tissue oxygen monitoring catheter sutured side by side in radial forearm flap

The postoperative follow-up protocol was identical. (Figure 3) MAP, heart rate, and central venous pressure (CVP) were monitored and reported every hour. The levels of analgesic, sedative, and cardiovascular medications were followed.

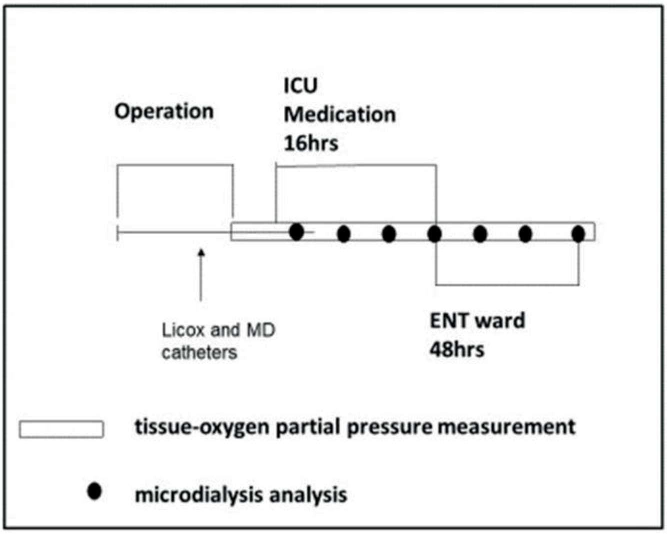



**Figure 3.** Study protocol in studies III and IV

### 4.1.4 Study IV

Twenty consecutive head and neck cancer patients were allocated in 2 equal groups: propofol group and DEX group. Blocks of four patients, two from each group, were used for the randomization and the allocation was performed after the operation by the medical/research nursing staff in the intensive care unit. The code of one patient had to be opened in the ICU, and therefore the groups were not equal in number.

The operations, reconstructions, and postoperative follow-up protocol were identical to study III.

Study IV had two groups: the DEX-group and the propofol group (control). The study was double-blinded, and the medication was administered by nontransparent IV-lines postoperatively in the ICU. The treatment group was sedated with DEX and the control group with Propofol as usual. Sedative agents were infused according to a six-step study protocol, which was also used in the Prodex study (Table 2) (Jakob et al., 2012). Two pumps were used. One pump was used to administer saline-placebo or propofol and the other to administer saline-placebo or DEX. Both pumps were adjusted simultaneously to ensure the medical personnel were unaware which medication was used. The sedation level was controlled hourly and, when necessary, changes to medication levels were made.

**Table 2.** The six dose levels of both medicines in study IV

| Dose Level | Dexmedetomidine rate (ug/kg/h) | Propofol rate (mg/kg/h) |
|---|---|---|
| 1 | 0.2 | 0.3 |
| 2 | 0.45 | 0.8 |
| 3 | 0.7 | 1.6 |
| 4 | 0.95 | 2.4 |
| 5 | 1.2 | 3.2 |
| 6 | 1.4 | 4 |

## 4.2 Tissue oxygen monitoring (Studies I-IV)

Tissue oxygen was monitored with standard Licox® CC1.2 probes that were carefully inserted into the flap tissue via a standard catheter and secured with a clip or suture. The 2 cm long sensor area situated at the tip of the probe was confirmed to be wholly inside the flap, and thereafter the flap with a Licox® O2 probe was sutured into the proper place before anastomosis. The readings were displayed on a Licox®-device (Integra Life Sciences, Dublin, Ireland), and the data were automatically saved on to a linked laptop computer. The monitoring of the flaps was continuous. In the analysis, readings were taken at 2 to 3 hour intervals. The Licox® device was used in all four studies.

## 4.3 Microdialysis (Studies II-IV)

MD catheters (20000 molecular weight cut off) were inserted into the tissue. Then, microdialysate was pumped through the catheter with a CMA100 microinjection pump at a constant speed of 0.1 μl/min. The dialysate was collected in microvials and analyzed every 2 to 3 hours with microdialysis (CMA 600 Microdialysis Analyzer, CMA/Microdialysis AB, Solna, Sweden) devices.

A commercially available metabolite kit (Iscusflex, Microdialysis, Solna, Sweden) was used for lactate, pyruvate, glucose, and glycerol analyses, and the readings were saved. L/P ratio as well as lactate/glucose ratio (L/G ratio) was calculated.

MD was used in studies II, III and IV to investigate free flap extracellular fluid metabolism in order to observe any possible changes due to denervation or medication. Catheters were easy to insert in the flap tissue and the pump was easy to use. Microvials were collected and analyzed every 30 minutes in study II and every two hours in studies III and IV.

The L/P ratio was considered to be the main variable in studies III and IV, with expected cut-off point at 20. As the L/P ratio showed unexpected variance and abnormally high levels in a clinical setting, the L/G ratio was also used in study IV.

## 4.4 Ethics

All the studies were approved by the Ethics Committee of Tampere University hospital. Study II was approved by the Ethics Committee for Animal Experiments at the University of Kuopio. Studies III and IV were also approved by the Finnish National Agency of Medicine. Study IV was also approved by European Clinical Trials Database (Eudra CT).

## 4.5 Statistics

Study I was retrospective, so all operated patients with relevant data were accepted.

In study I, the data were analyzed with receiver operating characteristics (ROC) analysis. In addition, negative and positive predictive values were calculated together with sensitivity and specificity.

In study II, power calculation for sample size was not performed. Instead, a convenient sample size was chosen. The normality of the data was tested with Kolmogorof-Smirnof test (K-S test). T-test was used for all statistical analyses. Bonferroni correction was used due to multiple testing

In studies III and IV, statistical power was calculated (80% power, $\alpha$ 5%) by using PS power and sample size calculator.

In study III, data were analyzed by Wilcoxon and Friedmann and Mann-Whitney tests using SPSS (IBM SPSS Statistics, version 21).

In study IV, linear mixed-effect models with L/P ratio, L/G ratio, or $P_{ti}O_2$ as dependent variables were fitted using function lme in R (Software environment for statistical computing and graphics, version 2.13.0, The R Foundation for Statistical Computing). Due to skewed distributions, natural logarithm transformation was applied for dependent variables.

# 5 RESULTS

## 5.1 Studies I-IV

### 5.1.1 Study I

The Licox® monitoring method detected all cases with circulatory problems. ROC-analysis showed high negative predictive values and good efficiency for the alarming criteria to predict the need for a re-operation. There were no false negative cases in the whole material. The overall success rate with the reconstructions was 99.2% (117/118), and the salvage rate for the re-operated cases was 88% (7/8) (Table 3).

**Table 3.** ROC -analysis of $P_{ti}O_2$ -monitoring in 163 patients

| Alarm | Re-operation | | |
|---|---|---|---|
| | Yes | No | Sensitivity 100% |
| Yes | TP=10 | FP=14 | Spesifity 92% |
| No | FN=0 | TN=139 | Positive predictive value 0.42 |
| Total | 10 | 153 | Negative predictive value 1 |

TP/FP=True/false positive, TN/FN= true/false negative

A typical $P_{ti}O_2$ curve shows a rapid response to the opening and closing of the artery during the vascular anastomosis phase of the operation (Figure 4). An average normal $P_{ti}O_2$ curve reaches a steady state within two hours postoperatively, followed by a slow descent. At the starting point, the mean readings were slightly higher in septocutaneous flaps than in muscular flaps - 75 mmHg vs. 52 mmHg, respectively. After 24 hours, the same readings were 60 mmHg and 40 mmHg, and at 72 hours 36 mmHg and 30 mmHg, respectively (Figure 5).

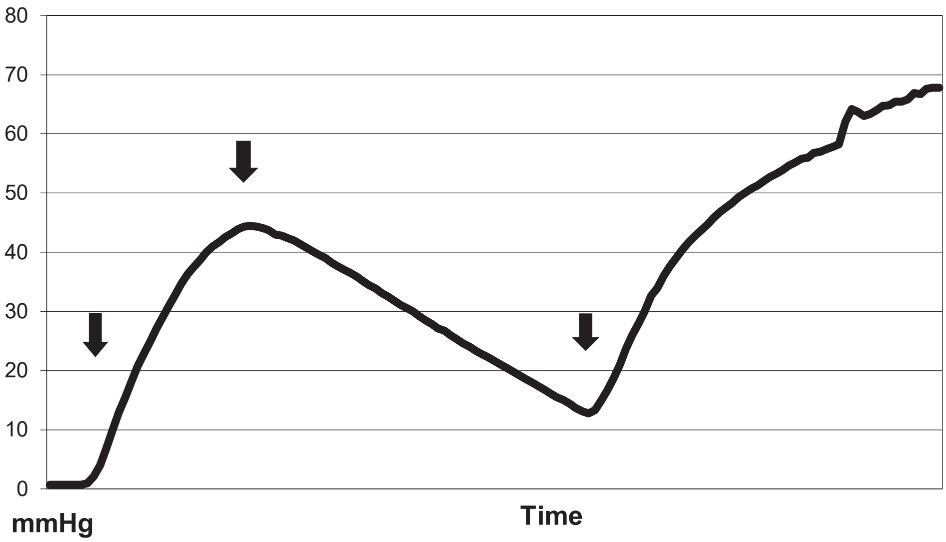



**Figure 4.** Typical $P_{ti}O_2$ -curve during arterial and venous anastomosis. Arrows indicate the unclamping (1st and 3rd) and clamping (2nd) of the artery.

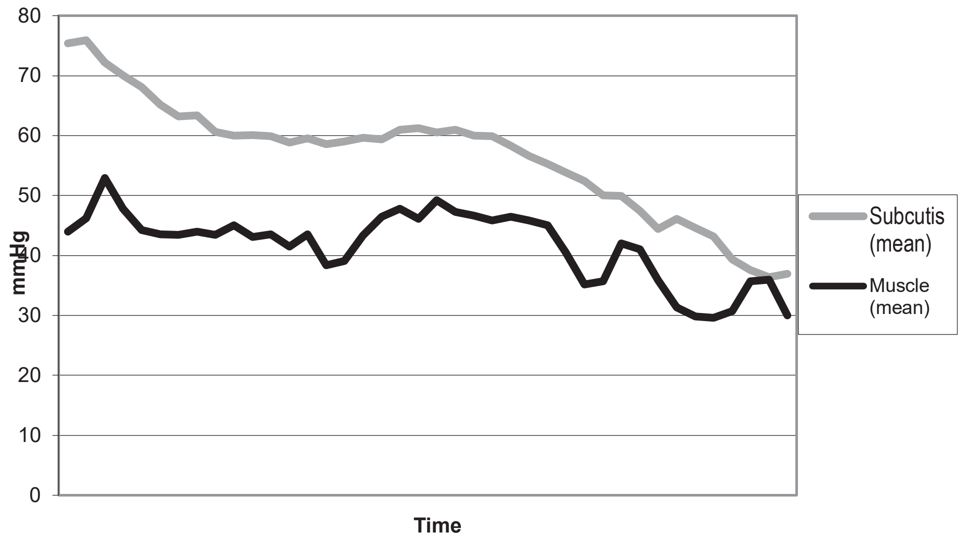



**Figure 5.** Mean $P_{ti}O_2$-levels in 118 patients. Black line shows constantly lower values in muscular flaps in comparison with subcutaneous flaps (grey line)

In twenty-one patients (18%), there was a clear change in the trend of the curve, a decline of 50% in less than an hour or a decline below 10 mmHg in the $P_{ti}O_2$ readings (Table 3). After subsequent analysis of the flap's clinical signs, a decision to re-operate was made in 8 cases. Thus, 13 / 21 (62%) of the alarms were false positive. Six patients were operated during the first 24 hours and two during the first 72 hours. Two patients had to be re-operated twice. One flap did not survive and had to be replaced with a new one. In 7 patients, a venous blockage occurred due to a compressing hematoma, and there was one arterial thrombosis. A typical curve leading to a re-operation caused by a venous blockage is shown in Figure 6.

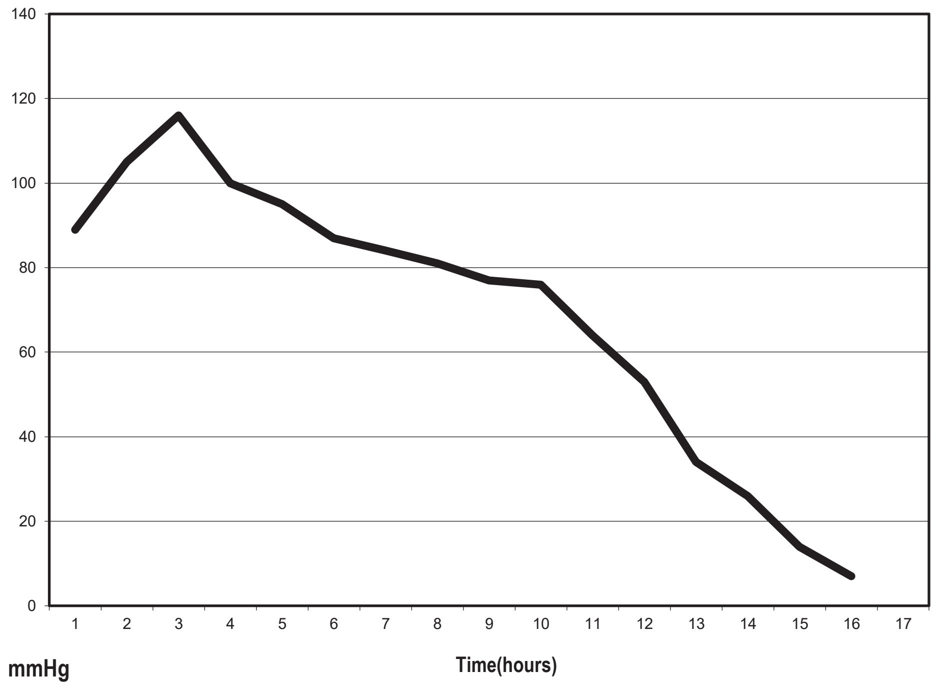



**Figure 6.** Typical $P_{ti}O_2$-curve with venous thrombosis with a noticeable angle in the curve leading to a decrease close to 0 mmHg

### 5.1.2 Study II

In study II, MD-glycerol was measured and analyzed in both denervated and intact flaps. After 60 minutes of ischemia, a significant increase in levels of MD glycerol was noticed in both denervated subcutaneous and intramuscular flaps ($P=0.0002$ and $P=0.016$, respectively) and in neurologically intact subcutaneous and intramuscular flaps ($P=0.0002$ and $P=0.0002$, respectively). There was, however, no significant difference between these groups (Figure 7). Also, subcutaneous and intramuscular glycerol levels reacted equally. The reason for the elevated MD glycerol levels of the flaps was tissue ischemia and an early phase of flap necrosis independent of whether the sympathetic innervation was removed or left intact. No sign of possible confounding effects of sympathetic stimulus was observed.

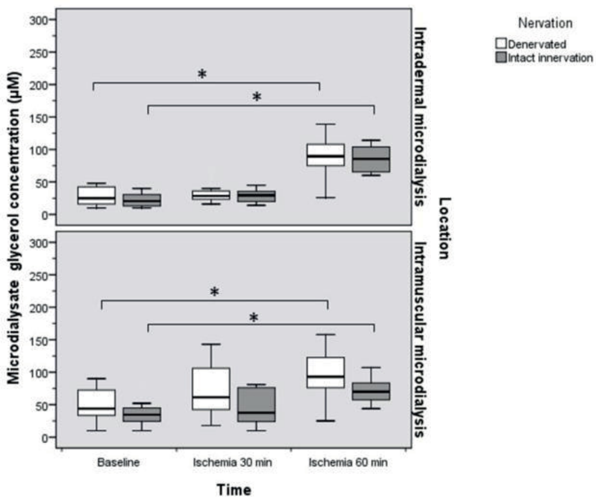



**Figure 7.** No statistical difference was seen in MD -glycerol levels between flaps with intact enervation and denervated flaps (Study II)

The elevation of MD glycerol was also observed in one patient in study IV as a marker of the cell destruction during ischemia shown in Figure 8.

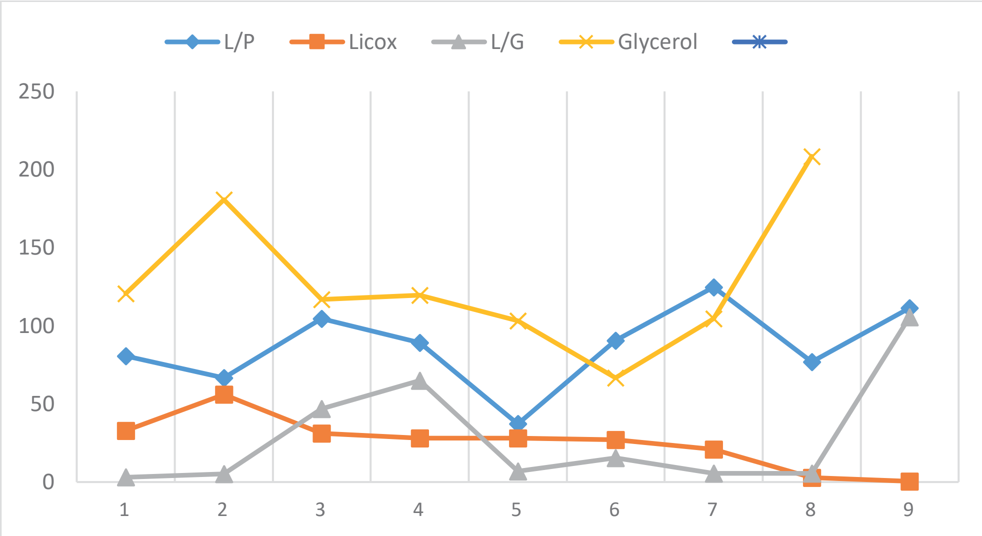



**Figure 8.** $P_{ti}O_2$ (mmHg) and MD -metabolites in a patient with two re-operations. In L/G and L/P - curves, the two peaks can be easily noticed. MD -glycerol (µmol/L) also started a steep incline showing an imminent flap loss. However, the second re-operation was successful.

### 5.1.3 Study III

In study III, 25 patients were analyzed. Of these, 9 belonged to the norepinephrine group, 8 to the dopamine group, and 8 to the control group. All operations and postoperative recoveries in both the intensive care unit and a normal ward were uneventful. No flap losses or major complications leading to re-operations in any of the groups were observed. The number of drugs used in the study are shown in Table 4.

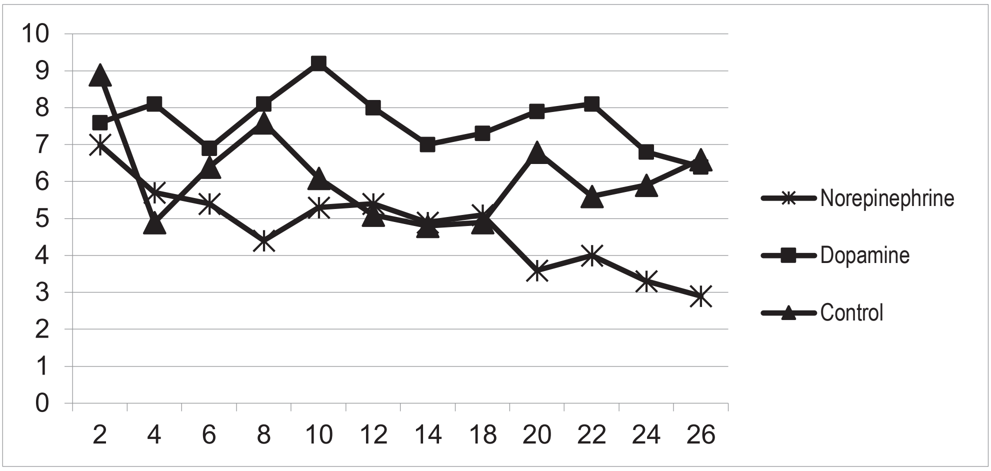
**Table 4.** The amount of vasoactive medication given in study III.

| Study group | Vasoactive drug | MAP (mmHg) | HR |
|---|---|---|---|
| Norepinephrine n=9 | Levophed 9.8 mg (3-21) | 83(±2) | 73(±9) |
| Dopamine n=8 | Abbodop 558 mg (144-1710) | 79(±7) | 86(±20) |
| Control n=8 | Levophed 2.9 mg (1-4)*<br>Abbodop 8.8 mg** | 82(±8) | 89(±15) |

* 3 patients

** 1 patient

Heart rate, CVP, and MAP are shown in Figure 7. MAP measurements showed the most stability in the norepinephrine group. The dopamine group had the greatest variation in MAP levels and heart rate (Figure 9).



10
9
8
7
6
5
4
3
2
1
0
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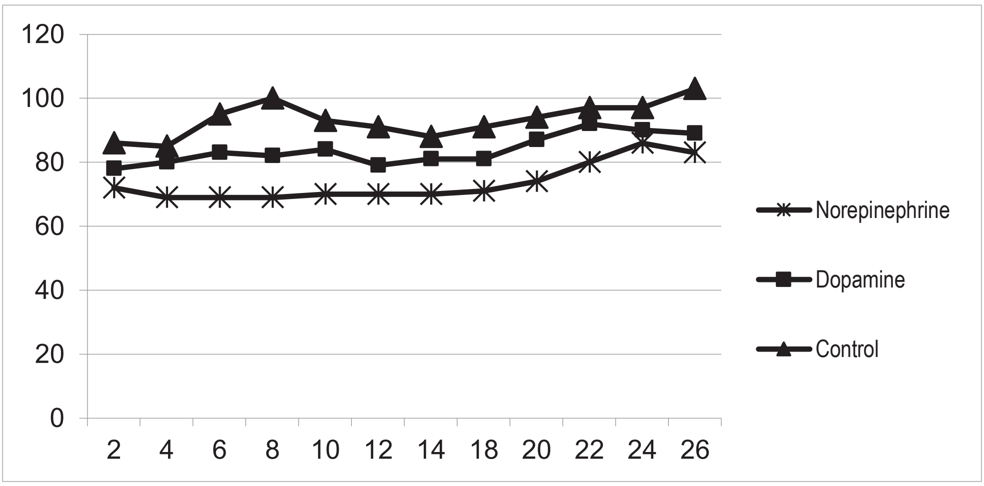
12
14
18
20
22
24
26
Norepinephrine
Dopamine
Control


A.



120
100
80
60
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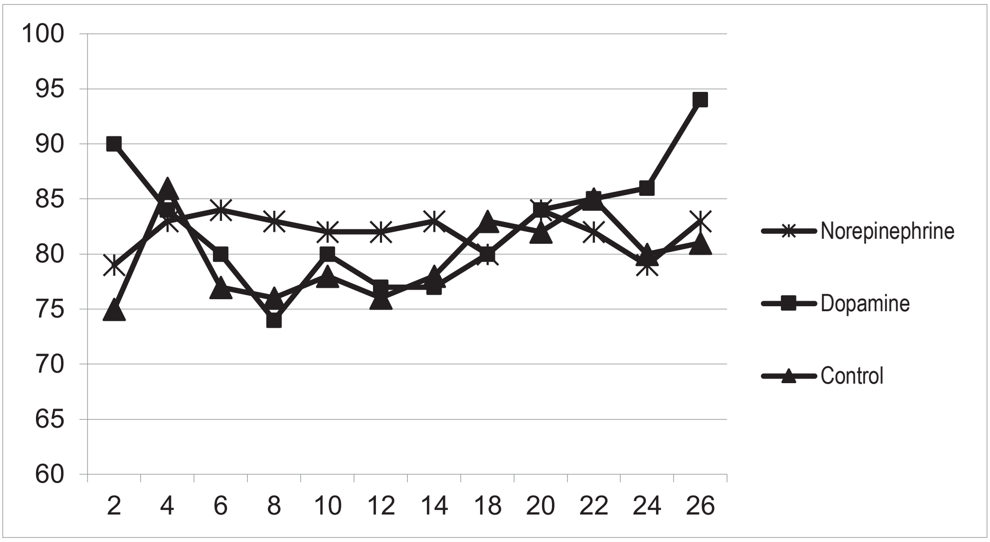
26
Norepinephrine
Dopamine
Control


B.

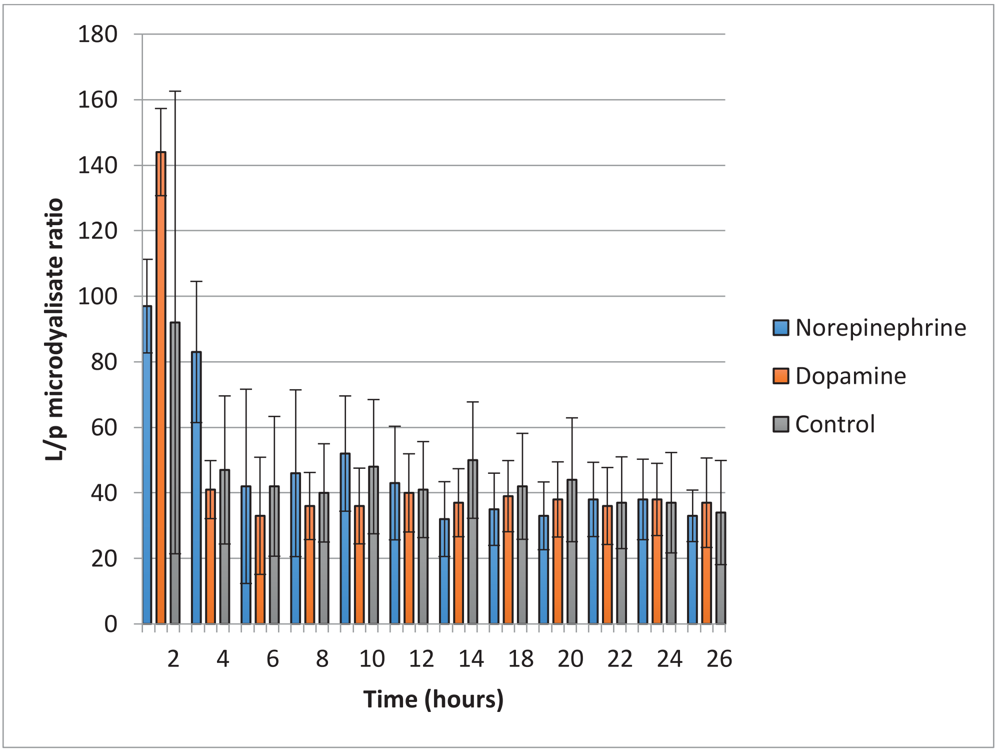



C.

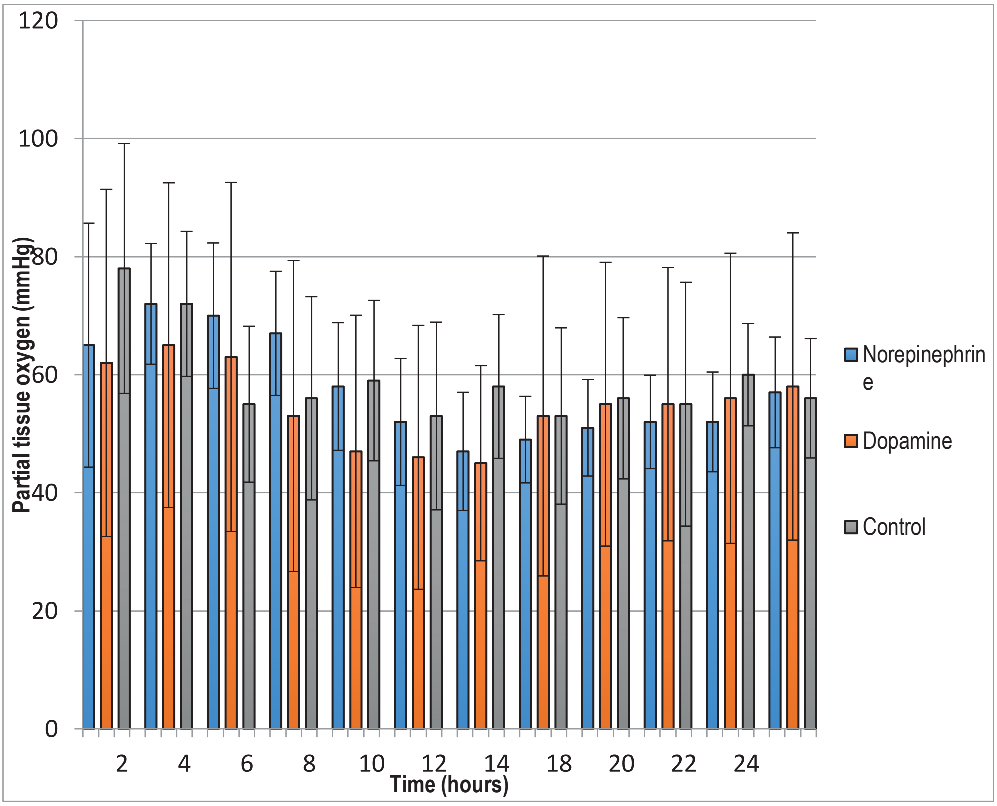
**Figure 9.** Mean values of A) CVP (mmHg), B) Heart rate, and C) MAP (mmHg) in different groups shown in study III.

In the control group, three out of eight patients required small amounts of both vasopressor agents to maintain the pre-set MAP levels >60 mmHg (Table 4).

The L/P ratio and $P_{ti}O_2$ measurements showed a similar pattern in all study groups (Figure 10). The behavior of these values was similar in all three groups during continuous monitoring for 72 h. No significant differences in partial tissue oxygenation and L/P ratio levels at any time-point between the NE and dopamine groups were observed.


180
160
140
120
100
80
60
40
20
0
L/p microdyalisate ratio
2
4
6
8
10
12
14
18
20
22
24
26
Time (hours)
Norepinephrine
Dopamine
Control

A.




B

**Figure 10.** In study III, the different study groups are shown in A: MD -L/P -ratio and B: $P_{ti}O_2$

### 5.1.4 Study IV

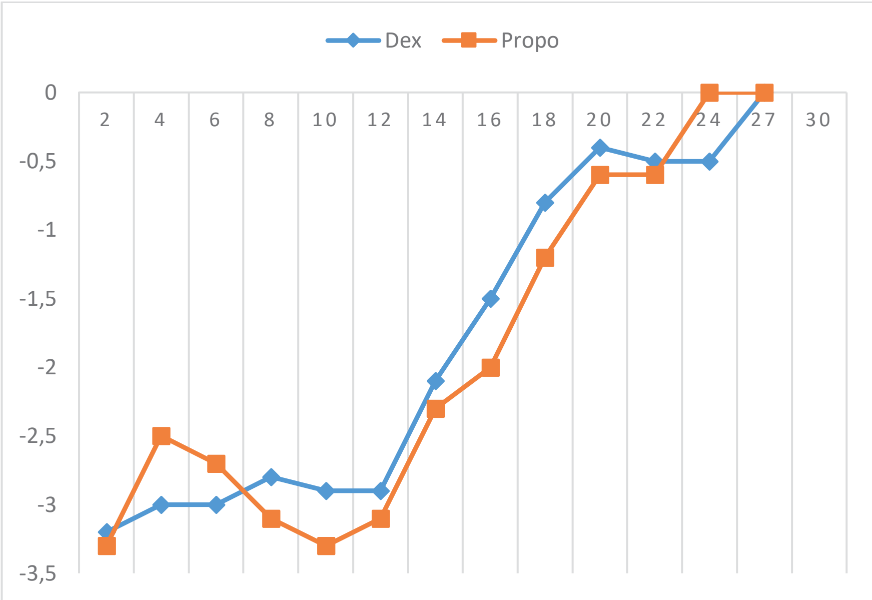
In study IV, 20 patients were divided into a propofol group (n=9) and a DEX group (n=11) (Table 5). Their hemodynamic parameters were monitored during postoperative sedation and they remained similar (Figure 11). Richmond agitation sedation score (RASS-scores) were also identical, indicating adequate sedation. In the propofol group, the patients tended to need a little more of the rescue medicine midazolam and equal amounts of analgesic agents during sedation (Table 6).

**Table 5.** Patient demographics in study IV

| | Propofol-group | Dex-group |
|---|---|---|
| Patient demographics | 7 | 6 |
| Oropharyngeal cancer, n | 2 | 5 |
| Age, mean, y | 60 (21-77) | 60 (26-82) |
| Sex (M/F), | (7/2) | (7/4) |
| Apache, median | 14 | 14 |
| SOFA, median | 5 | 5 |
| Sedation time, median, h | 15 | 14 |
| Lactate highest during sedation, median | 1,4 | 1,2 |
| Diuresis, median ml/kg/h | 1,2 | 1 |

n=number, y=years, h=hours, SOFA=sequestial norgan failure assesment

Apachce=Acute physiology age and chronic health evaluation score


Dex
Propo
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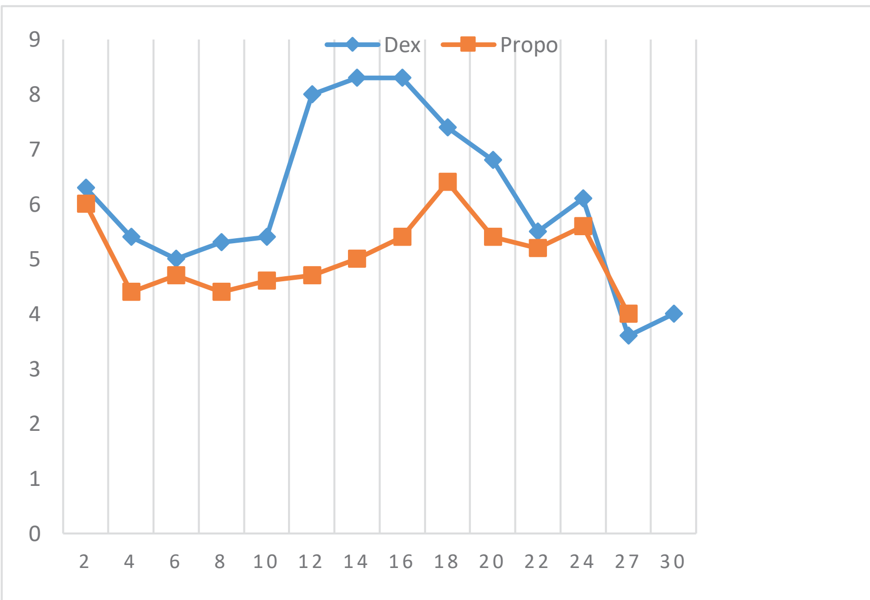
A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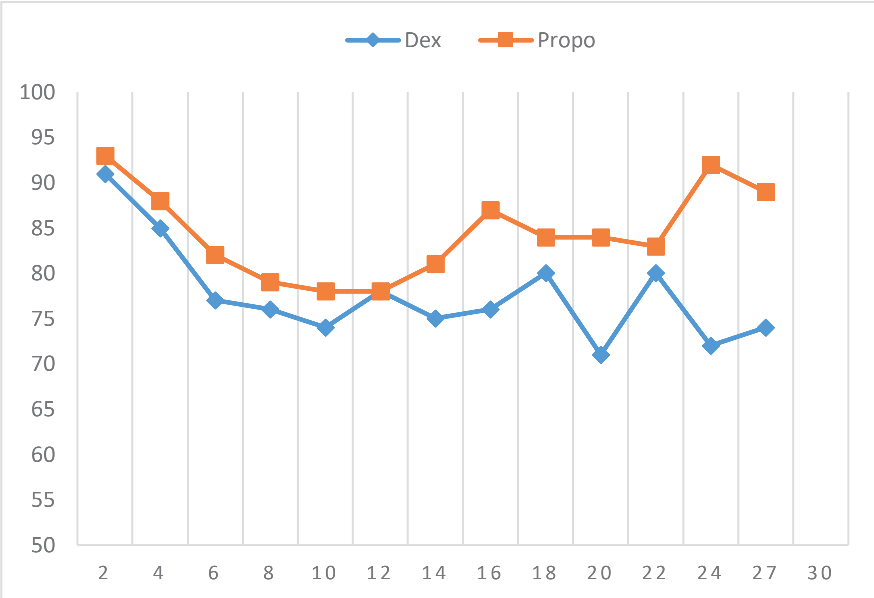


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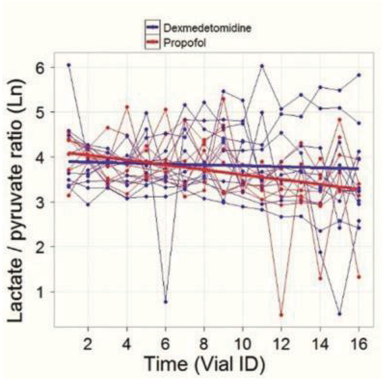
**Figure 11.** Level of sedation and hemodynamic parameters in study. IV A) RASS -score, B) CVP (mmHg), C) MAP (mmHg) Dex=dexmedetomidine, Propo=propofol

**Table 6.** Amounts of rescue medicine in study IV

| Medication | Propofol-group | Dex-group | P-value |
|---|---|---|---|
| Propofol, mean, mg/kg/h | 22 | 0 | |
| Dexmedetomidine, mean, µg/kg/h | 0 | 1.3 | |
| Midazolam, mean, µg/kg/h | 17 | 12 | 0.63 |
| Dormicum, mean, µg/kg/h | 10 | 9 | 0.98 |
| Fentanyl, mean, µg/kg/h | 0,53 | 0,56 | 0.89 |
| Norepinephrine, mean, µg/kg/h | 2.4 | 1.8 | 0.49 |

No significant difference was observed in either $P_{ti}O_2$ or L/P and L/G values between the groups. In other words, no signs of untoward vasoconstriction in the flaps (Figure 12). Altogether, all flaps were successful. There were two re-operations due to hematoma in the propofol group with a 100% salvage rate. These results show that DEX is comparable with propofol in the postoperative sedation of head and neck free flap patients.

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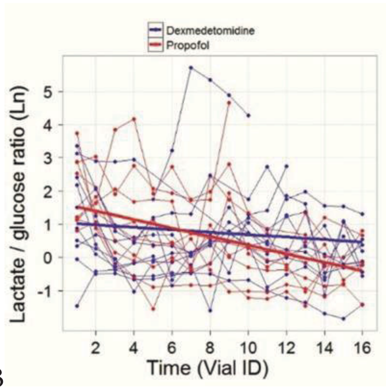


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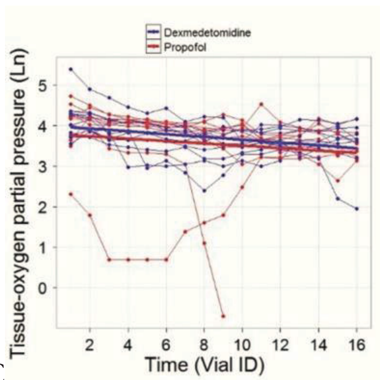


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**Figure 12.** No statistical difference was shown in A) L/P-ratio B) L/G-ratio and C) $P_{ti}O_2$ between DEX and Propofol in Study IV.

## 5.2 Free flap monitoring methods

### 5.2.1 Tissue oxygen monitoring

$P_{ti}O_2$ monitoring with the Licox® system was used in all the present studies. In clinical studies (I, III, IV), the system detected all the vascular compromises, i.e., 10 of 163 patients (Table1). One flap was lost, resulting in a total free flap survival rate of 99.4% and a salvage rate of 90%. The Licox® system alarmed the surgeon beforehand in every case, leading to revision with a sensitivity of 100% (Table 3) with a typical curve (Figure 6). One re-operation was performed because of a large hematoma with no ischemia signs in the $P_{ti}O_2$ curve. This was detected during a routine clinical follow-up visit by the surgeon and evacuated. In the re-operation, no signs of vascular compromise were observed. In other words, the flap circulation was still working, and the hematoma was successfully evacuated before it caused any ischemia to the flap. Therefore, this case was not considered a real true negative. The sensitivity of the Licox® system was 90% with a total of 14 false alarms, which were confirmed by clinical observation and meticulous clinical follow-up. No flap losses or even re-operations happened due to a vascular compromise which was not seen in the tissue oxygen pressure curve, yielding a false negative rate of zero.

In study II in an experimental animal setting, $P_{ti}O_2$ readings reacted to a clamped artery (total ischemia) as expected. At the baseline, the mean $P_{ti}O_2$ reading was 20 mmHg, decreasing to 5 mmHg and 0.5 mmHg after 30 minutes and 60 minutes, respectively (Figure 13). This is precisely similar with the curve seen normally in microvascular operations when an artery is clamped for any reason. (Figure 4)

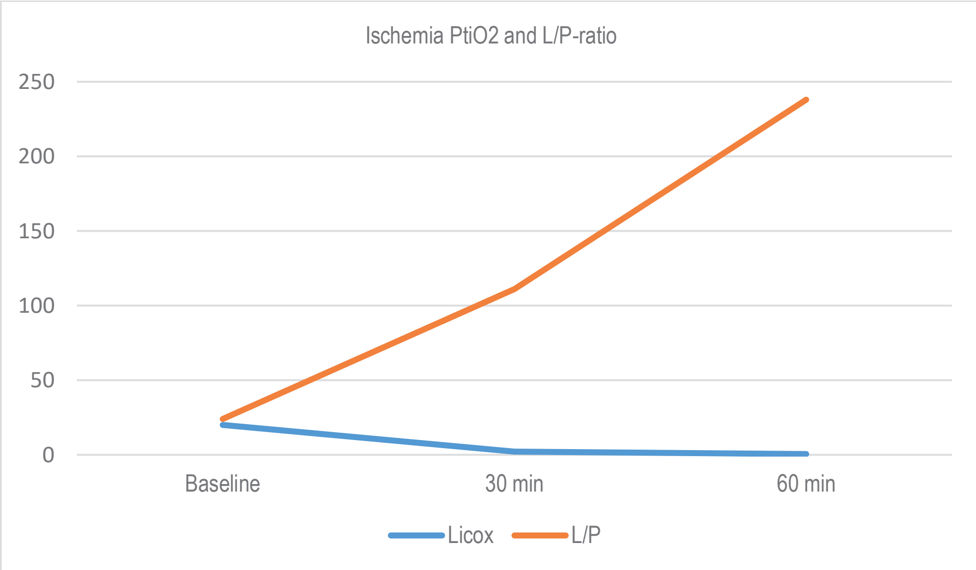


**Figure 13.** The $P_{ti}O_2$ -readings together with L/P -ratio are shown during clamp induced ischemia in study II

In studies II to IV, the Licox® system was used together with MD to double check the outcome of the flaps during the administering of the study drugs in the ICU. Both methods adequately reacted to flap problems: the Licox® system noticed ischemia, and MD confirmed a shift from aerobic to anaerobic metabolites in the extracellular fluid (Figure 7).

### 5.2.2 Microdialysis

### 5.2.3 Lactate/pyruvate-ratio

The lactate/pyruvate ratio was used as the main variable to express ischemia in our hypothesis. In studies III and IV, its values were higher than the expected range (>22-25) but remained constant throughout the observation period (Figure 8). As in $P_{ti}O_2$ monitoring, the trend seems to be a mild downwards shift after operation.

Figure 8 shows the L/P curve together with the $P_{ti}O_2$, glycerol, and lactase/glucose (L/G) curve in a re-operated patient, and all of these reacted to ischemia as expected. The L/P ratio and the L/G ratio were elevated, and the $P_{ti}O_2$

curve approached zero. The L/P curve seems to react quickly to ischemic changes, indicated by the arrows, but also remained high after the first re-operation. Evacuating the hematoma and re-anastomosing the vessels in a re-operation eventually saved the flap.

In a controlled animal setting in study II, the L/P ratio quickly reacted as expected, rising significantly high after clamping, and therefore led to total ischemia (Figure 12). However, no absolute alarm limits can be given according to the findings of this study.

### 5.2.4 Lactate/glucose-ratio

In studies III and IV, the L/G ratio was found to be more stable than the L/P ratio, still reacting to ischemia precisely. In a re-anastomosed flap before vascular compromises, the L/G ratio was constantly below ten (Figure 6), but when problems with circulation appeared, it increased tenfold or even more. Even though no absolute alarm limits could be given, the trend of the curve should be taken into account.

# 6 DISCUSSION

## 6.1 General discussion

Patients undergoing ablative and reconstructive head and neck surgery are treated with free microvascular flaps, which have almost entirely replaced pedicled flaps. Free flaps are used in the reconstruction of defects and to restore functions, such as chewing, speaking, and swallowing. Nowadays, there are more indications for free flaps other than malignancies, and the number of head and neck cancer patients is increasing all the time. Hence, free flap reconstructions are performed more and more frequently. There are several different transfers available ranging from soft tissue flaps to composite structures. However, in a single institution only a few of them are routinely used, although individualized treatments with various different flaps have been found feasible (Husso et al., 2016; Steel & Cope, 2015). In the present study, septocutaneous radial forearm flaps were mostly used, but also a few osseomuscular fibula and scapula flaps and musculocutaneous ALT-flaps. Normally, the flap tissue is totally dependent on only one artery and one or two veins. This makes flaps susceptible to vascular problems during the first postoperative days. According to the literature, a meticulous microvascular technique, an optimized postoperative setting, and follow-up with timely re-operation to save the flap are the key reasons for the current flap success rate of over 95%, as was also seen in the present study. Yet, flap failure leads to re-operation, prolongs hospitalization, and increases both patient morbidity and costs. (Cervenka & Bewley, 2015)

### 6.1.1 Free flap postoperative follow-up

Even though the free flap success rate is high, the need for reliable postoperative monitoring during the first postoperative days, which are the most critical for free flap survival, is widely accepted. Clinical follow-up together with a hand-held Doppler device is considered to be so effective that it is not possible to achieve better results using other monitoring methods. However, this method demands hourly bedside visits during the first days and is therefore time consuming. Therefore, it is not ideal for smaller hospitals. (Cervenka & Bewley, 2015; D. Chubb et al., 2010) A reliable monitoring system reduces the need for regular routine check-ups. As reported in the present study, the most remarkable practical advantage of using the Licox® $P_{ti}O_2$ monitoring system is the possibility to lessen the need for continuous clinical follow-up of the flap during the immediate postoperative period. Instead of having the surgeon regularly checking for clinical signs during the first 72 postoperative hours, nurses can easily monitor continuous real-time data on blood circulation in the flaps and only alert the surgeon if needed.

Many different monitoring methods are presented in the literature, although some are more suitable for free flap monitoring than others. All of these methods have pros and cons, and there is a learning curve for each method in interpreting the results. As seen in the literature and in this study with $P_{ti}O_2$ monitoring and MD, after the proper learning level has been reached, all of the methods are suitable for the monitoring of free flaps. However, the possibility of false alarms should be kept in mind. The choice of flap monitoring method depends on the subjective opinion and previous experience of the surgeon as well as the availability of the different methods. (Abdel-Galil & Mitchell, 2009a; Abdel-Galil & Mitchell, 2009b; Cervenka & Bewley, 2015; Kaariainen et al., 2018)

The cost-effectiveness of a monitoring system is a complex equation of hospital, operating theatre and monitoring costs. In Tampere University Hospital an average cost of an ICU-treatment is 2000€/day, which is four-times more than treatment in normal ward. During this study the prices for both the $P_{ti}O_2$ monitoring probe and MD-analyzers was around 500€/patient. In this study both were used so the cost for one patient was ca. 1000€. In previous literature the cost of an implantable Doppler probe was 275€ (Rozen, Chubb, Whitaker, & Acosta, 2010) and clinical monitoring 193€ /patient (Subramaniam et al., 2016). In Tampere University Hospital the cost of an operating theatre is around 700€ an hour. Normally the re-operation leads to multiple extra ICU-days and several hours in operating theatre with a total cost of minimum 5000€. If the flap is lost a new flap is usually used, meaning total costs of 15000€, with new microvascular operation, ICU-days and prolonged treatment in normal ward. Although the free flap success rate is high, one must consider the salvage rate being more important in calculating cost-effectiveness because with a successful salvage estimated 10000€ could be saved. It can be estimated that monitoring is cost effective if at least one out of 20 flaps (5%) can be salvaged with a 500€ monitoring cost/ flap. In this study the salvage rate is 9 out of 163 (5,5%), therefore in our series the $P_{ti}O_2$ monitoring can be considered cost-effective.

Nevertheless, when the monitoring methods fail, the surgeon still has the possibility to use clinical evaluation based on the color and turgor of the flap together with a needle pinprick test. Moreover, this type of evaluation is still thought to be the gold standard or at least the closest to it in free flap follow-up (Abdel-Galil & Mitchell, 2009a; Abdel-Galil & Mitchell, 2009b; Cervenka & Bewley, 2015; Chae et al., 2015; D. Chubb et al., 2010). This was also the case in the present study. When $P_{ti}O_2$ monitoring alerted the surgeon in charge, the final decision whether to re-operate or not was based on additional clinical evaluation, if possible.

Flaps can be monitored in many ways. The basic method is hourly clinical observation by nurses, who alert the surgeon in charge when something may already be wrong in the flap. More advanced methods are able to predict that something is about to go wrong. However, closer and more advanced monitoring requires more sophisticated devices and a lot of experience. For example, Setälä and Gudaviciene analyzed 268 flaps with MD lactate, glucose, and L/G ratio and found out how patient temperature changes or degree of vasoconstriction showed minimal signs of ischemia in the flap and still did not affect its outcome (L. Setala & Gudaviciene, 2013). In the present study using $P_{ti}O_2$ monitoring, there seem to be flaps that tend to have low O2 readings but have no clinical signs of flap failure. Thereafter, the levels return to normal without any noticeable specific reason. This could be a sign of minor problems in flap perfusion, as observed in Setälä's study. In these cases, the decision whether to re-operate or merely observe requires special expertise. In other words, to decide whether a flap perfusion failure is going to lead to inevitable flap loss or is only a temporary disorder.

## 6.2 Studies

### 6.2.1 Study I

Study I is a retrospective analysis of 118 head and neck reconstructions operated at Tampere University Hospital since the year 1999. The main finding in the study was that the Licox® $P_{ti}O_2$ monitoring system is a good postoperative monitoring method that helps to achieve a free flap success rate of 99%. During the study period, only one flap was lost, although eight re-operations were performed. This result is slightly better than reported in the previous literature with different monitoring methods (Disa et al., 1999; Hidalgo et al., 1998; Spiegel & Polat, 2007).

The $P_{ti}O_2$ values are shown on a monitor from which the trend of the curves can be seen. Although the Licox® probe is easy to insert into the flap, the meticulous insertion and fixing of the probe are also highly important. Indeed, before carefully suturing the probe, a few were accidentally dislocated. Moreover, in the beginning, some patients managed to bite the probe. Later, the probe was inserted in such a way that made this impossible.

Tissue oxygen tension of a free flap follows a typical curve during and after the operation. Usually, after arterial anastomosis is accomplished and the clamp opened, there is an immediate rise in oxygen pressure. After a few hours postoperatively, the levels reach their steady state and start to slowly decline during the following days. In this study, the reactions of the $P_{ti}O_2$ curve were similar to the ones reported in previous studies. (Hirigoyen et al., 1997; Jonas et al., 2013)

High readings immediately after surgery may be due to ischemia and local microtrauma, which damages the mitochondria of the cells and results in high extracellular $O_2$ concentrations. However, these readings can also be explained by the fact that the afferent artery is a branch of the carotid artery and produces a high volume of arterial blood into the flap tissue. During the first two postoperative hours, it is not uncommon to notice a slight dip in the in $P_{ti}O_2$ levels, which is probably due to the tissue edema in the flap. Later, the $P_{ti}O_2$ levels stabilize and reach a steady level. Since the system reacts rapidly to changes in $P_{ti}O_2$ levels, any possible ischemia is naturally detectable also during this stabilization period. During the following 72 hours, the readings start to slowly decline even without any circulatory problems. This decline is due to tissue autoregulation that is thought to be caused by both circulating metabolites and the vasoconstriction of the flap arterioles (Morff & Granger, 1982).

When this study started, there were only rough alarming limits for imminent ischemia, and the trend of the curve together with clinical check-up was considered more important than single readings. Based on the results of the present study, alarm limits could be set so that a 50% drop in $P_{ti}O_2$ readings or a simple drop below 10 mmHg with no spontaneous recovery in 30 minutes predicts vascular problems. These flaps should be meticulously controlled and re-operated if no spontaneous recovery occurs. These findings are similar to those previously published in the literature. (Hirigoyen et al., 1997; Hofer et al., 1993; Kamolz et al., 2002)

According to the findings of the current study, the Licox® $P_{ti}O_2$ monitoring system can be used as an alarming monitoring system for microvascular free flaps.

The system identifies imminent ischemia early enough and appears to be as useful as expected based on previous clinical experience (Kamolz et al., 2002; Raittinen et al., 2005). The main disadvantage of this method mentioned in previous studies is the number of false positives caused by technical problems (Jonas et al., 2013). In this material, the reason for the relatively high number of false positive alarms seems to have been the high sensitivity of the probe to movement and mechanical manipulation.

It is important to understand the importance of false alarms for overall flap survival: a false positive result may lead to unnecessary revision, while a false negative will lead to flap failure. Since the specificity of the system is 88%, one has to acknowledge that this system is not an absolute monitoring system but an alarm system that still requires clinical observation and decision making. However, it should be pointed out that all false alarms were false positive, and thus this makes the system highly sensitive to any actual circulatory problems. The fact that the system has good specificity, i.e., no false negatives occurred, is one of the best features of $P_{ti}O_2$ monitoring. This was observed in the present study as well as in the study by Arnez et al. (Arnez et al., 2018)

### 6.2.2 Study II

MD-glycerol has been used as a marker of disintegrating cell membranes. However, lipolysis only, as induced by sympathetic stimulus, may increase the extracellular concentration of glycerol. Thereby, variation in sympathetic drive is potentially a confounding factor for glycerol as a marker of ischemic cell membrane disintegration. Surgical procedures cause lipolysis either due to ischemia or sympathetic stress. (Arner, 1988; Fellander, Nordenstrom, Tjader, Bolinder, & Arner, 1994; Rojdmark et al., 1998) The main finding of study II was the opposite to the original hypothesis, i.e., intact innervation of the microvascular flap did not contribute to intramuscular extracellular glycerol release as compared to denervated flap after 60 minutes of ischemia.

Sympathetic stress or tissue destruction are thought to be reasons for elevated extracellular glycerol levels in free flaps.(Fellander et al., 1996; Udesen et al., 2000) In the present study, the MD-glycerol levels were identical both in denervated flaps and in flaps with intact sympathetic innervation. This led to the conclusion that sympathetic innervation does not interfere with MD glycerol levels, leaving ischemic damage as the only reason for elevation in MD glycerol concentrations.

Therefore, MD glycerol may add to the diagnostics of a tissue perfusion defect indicated by low $P_{ti}O_2$ and high L/P ratio equally in free microvascular flaps and pedicled flaps with intact innervation. Thus, a stepwise diagnostic approach is possible, where low $P_{ti}O_2$ indicates early perfusion (O2 supply) failure, an increasing L/P ratio confirms metabolic derangement, and an increasing glycerol concentration indicates cell injury related to ischemic conditions has already started.

Study II was done under strict laboratory conditions, which makes it easily repeatable. There were two different flaps in the same animal serving as a control group for each other. A small sample size with no power calculated and randomization could be considered as a minor weakness of this study.

### 6.2.3 Study III

Head and neck cancer patients who undergo tumor ablation and microvascular reconstruction often experience systemic changes due to prolonged major surgery with tissue trauma, fluid loss, and possible hypothermia. This is one of the reasons for intensive postoperative care and even sedation. Sedatives have a tendency to cause hypotension and sometimes lead to a need for corrective actions.(Barr et al., 2001; Bloor et al., 1992; Ebert et al., 2000) The control of intra- and postoperative blood pressure and the avoidance of hypotension is a determining factor for adequate microvascular flap perfusion. If the need to elevate MAP occurs, the clinical dilemma exists between anesthesiologists and microsurgeons as to whether to add circulating plasma volume or to use vasopressors to improve cardiac output, which in turn may cause unwanted vasoconstriction. (Gooneratne et al., 2013; Kovatch et al., 2018; Sigurdsson & Thomson, 1995) A recent Finnish recommendation suggests the clinical judgement of the liquid balance and possible repair primarily with vasopressors to increase MAP. Extra fluids should be considered later according to secondary judgement together with inotropes. (Wilkman & Kuitunen, 2018)

Autonomic nerve fibers running along the anastomosed vessels are disrupted in microvascular surgery, which changes the response of the vasodilated flap vessels to vasopressors. This phenomenon is significant and emphasizes the importance of studying metabolic and circulatory changes in the flap itself during treatment with different vasopressors. The results of recent studies measuring graft blood flow together with the results of the present study indicate that the vasoconstrictive effect of systemically administered norepinephrine in denervated flaps is markedly attenuated in the acute phase after microvascular reconstruction (Eley, Young, & Watt-Smith, 2012). A lack of denervation-induced hypersensitivity to vasoconstriction produced by α-adrenergic agents is also observed in pedicled grafts (Lecoq et al., 2008).

Ibrahim et al. reviewed four human studies of vasopressor use in free flap surgery. None of them showed any significant adverse reactions. According to the present and previous studies, there seems to be no evidence that vasopressor use should be contraindicated. However, the majority of the literature supports limited and careful use of vasopressors in microvascular surgery. (Ibrahim et al., 2014)

These findings also support the safe use of norepinephrine and dopamine as vasopressors if necessary, at least during the first 72 h after microvascular anastomosis. MAP was successfully increased with both agents. The $P_{Ti}0_2$ and L/P ratio values in the flaps did not significantly differ among the norepinephrine, dopamine, and control groups. These results provide further evidence that the use of norepinephrine and dopamine to maintain sufficient MAP does not have adverse effects on free flap metabolism and circulation. The results indicate that norepinephrine and dopamine may be safely used during the immediate postoperative period after reconstructive head and neck microvascular surgery using the radial forearm flap. However, dopamine doses must be significantly higher to maintain an optimal MAP, and therefore the risk of side effects is greater, and dopamine should be used with caution.

Study III was prospective and randomized but not blinded. The nature of the study was intention-to-treat, so the amount of vasoactive medication varied between patients, which can be considered a minor weakness of the study. However, in routine intensive care, the amounts have to be titrated individually taken into account patient weight and response, etc. The results of the present study only apply to head and neck patients undergoing reconstruction with radial forearm flaps. Further research should be carried out to study the effect of vasopressors on perforator flaps and in other anatomical areas, such as the lower limbs, to support its generalized use.

MD has been used to measure numerous metabolites and even drug concentrations in different tissues, e.g., blood and brain. It also seems to be useful as a postoperative monitoring system for free flaps.(Edsander-Nord et al., 2002; Jyranki et al., 2006; Nielsen, Gutberg, & Birke-Sorensen, 2011; L. Setala et al., 2006) The MD pump could be set in advance to the desired speed and during monitoring only microvials are sampled and analyzed. In a free flap follow-up, the suggested monitoring interval is hourly in the first postoperative day, every 2 hours on the second day, and every 3 hours on the third day.(Jyranki et al., 2006; L. Setala et al.,

2006) In this study, MD was used together with $P_{ti}O_2$ monitoring, which gives continuous information about the flap. MD was found to be slower to react to ischemia than $P_{ti}O_2$ levels. Similar findings have been published previously with implantable Doppler, which also detects the flaps continuously (Frost et al., 2015)

### 6.2.4 Study IV

In these studies, we have observed that external manipulation of the probe triggers immediate changes in the subsequent $P_{ti}O_2$ readings. Suctioning, restlessness of the patient, or manipulation of the reconstruction can cause a sharp temporary rise or decline in the curve. It has been found to be beneficial to keep the patient under sedation for the first 12 to 18 postoperative hours and to try to minimize mechanical manipulation of the reconstructed area. In the early part of this series in study I, variation in the $P_{ti}O_2$ curves, caused by the previously discussed reasons, quite understandably resulted in several alarms. These problems seem to relate to the clinical surroundings. No problems occurred in study II conducted under strict laboratory conditions with no movement of the animals, and therefore no malfunction of the $P_{ti}O_2$ probe. This finding supports the assumption that restlessness and movements of the patient could dislocate or even break the probe. Therefore, the proper postoperative setting with optimal sedative medication is important not only for the survival of the flap but also for the success of the $P_{ti}O_2$ monitoring.

The American College of Critical Care Medicine recommends the use of non-benzodiazepine sedatives, such as propofol or DEX, in the ICU (Barr et al., 2013b). Propofol is traditionally used for sedation together with midazolam boluses. However, recent studies have shown that DEX could also be feasible in short term sedation.(Barr et al., 2013a; Martin, Ramsay, Mantz, & Sum-Ping, 2003) There seems to be neither consensus nor ideal agent for moderate sedation. However, it should be rapid in onset, have a predictable pharmacodynamic profile, and it should allow quick recovery of the cognitive and physical functions of the patient.(Gan, 2006) As a postoperative sedative, DEX offers a few advantages compared with propofol. These include shorter ICU and mechanical ventilation time due to lighter sedation, fewer analgesics needed, and lower postoperative delirium risk. DEX is also more cost-effective than midazolam.(Bloor et al., 1992; Dasta et al., 2010; Ebert et al., 2000; Keating, 2015; Shehabi et al., 2009; Talke et al., 2003) The better analgesic feature of DEX was not, however, observed in the present study. DEX is superior not only from the clinicians' but also from the patients' point of view, causing less anxiety than propofol during ICU stay (Venn & Grounds, 2001) .

Flap complications due to uncontrolled vasoconstriction in denervated vessels are a concern during DEX sedation (Bloor et al., 1992; Talke et al., 2003). Nevertheless, the present study indicates that DEX is an ideal drug for the postoperative sedation of head and neck microvascular patients. No sign of flap vasoconstriction with ischemia was observed in the present study and in a previous animal study with free flaps.(Nunes et al., 2007) Study IV was randomized, double blind, and double dummy making it easily repeatable.

Previous studies have reported that propofol also has an effect on blood coagulation, yet no effect on bleeding time has been shown (Aoki et al., 1998; De La Cruz et al., 1999; Dogan et al., 1999; Law et al., 2001). A similar effect was also observed with DEX in a study by Chen (Z. Chen et al., 2018). In study IV, two bleeds (one from the pedicle artery branch and one from the facial artery branch) occurred in the propofol group, whereas none occurred in the DEX group. Whether this was just coincidence or caused by propofol per se remained unclear.

According to the present studies, strict guidelines for MD values cannot be given. Setälä et al. used glucose level <2 mmol/l, lactate >6 mmol/l, and an L/P ratio of more than 25 as alarms to the microsurgeon.(L. Setala et al., 2006) In Jyränki's study, the L/P ratio never exceeded 25 in a successful flap.(Jyranki et al., 2006) In studies III and IV, the L/P ratio was higher than 25, but no flap failures or even circulatory problems were found. The lactase/glucose (L/G) curve seemed to be more consistent, yet in this study there were not enough patients or true flap failures to give exact limits for the readings. The trend of the curve should be checked, and a significant increase should be seen as an alarm signal indicating circulatory problems.

In study IV, one patient had to be re-operated because of a hematoma, and the $P_{ti}O_2$ and MD curves are shown in Figure 8. Here, the differences in L/P and L/G ratios are shown. Both react accurately to the first signs of ischemia; however, the L/P ratio remains higher after the first ischemic period while the L/G ratio is rapidly normalized back to the original level. Prolonged elevation of lactate after ischemia has been detected previously (Edsander-Nord et al., 2002). However, the reason why a difference in L/P and L/G ratio was observed in this study remains unclear. The reason could be a slower increase in pyruvate levels, which is a metabolite of glucose, and therefore its levels depend not only on the level of glucose but also on whether there are aerobic or anaerobic circumstances in the tissue.

## 6.3 Future applications

### 6.3.1 Free flap monitoring

Considering the difficulties in the field of free flap monitoring, tissue oxygen monitoring with the Licox® $P_{ti}O_2$ monitoring system seems to be useful method. Moreover, the small size of the equipment makes it easy to use bedside in even smaller patient rooms. The trend of the curve is visible, and alarms can be set to notify the staff of circulatory compromises. The alarm limits shown in study I help the nursing staff and novices to notice problems while more experienced users look at the trend of the curve rather than simple limits. Therefore, it would be optimal that someday the $P_{ti}O_2$ readings could be sent to a mobile app to ease the work load of the surgeon in charge. However, to make it more useful in everyday practice, the learning curve of the system should be easier, and the costs should be a lot less than they are now.

MD alone as a postoperative monitor is also feasible, but some extra criteria should be fulfilled. The monitor needs more space, and it is not easily moved. Subsequently, the equipment must be apart from the patient room requiring extra personnel to interpret the analysis. However, the system per se is much more informative in free flap follow-up than a simple Doppler or $P_{ti}O_2$ monitor. The system provides exact metabolite information at half hourly intervals and, according to the present and previous studies, even hints of imminent flap disorder due to the elevation of MD glycerol levels. One of the extra advantages of MD is the possibility to monitor several other molecules, such as drug levels in the flap, which could, for example, be used in clinical studies.

There seems to be room for both $P_{ti}O_2$ monitoring and MD. Both monitoring methods allow easy monitoring by nurses and lessen the control visits of the surgeon from. Furthermore, as shown in these studies, both can also be useful in clinical experiments.

Perhaps in future, these two monitoring systems could be used together in hospital to provide more accurate data on the status of the flap. For example, the $P_{ti}O_2$ monitor would follow the oxygenation continuously, and if there is a suspicion of a decline in levels, this could be confirmed with MD. A decline in glucose and pyruvate levels together with an elevation in lactase and glycerol levels should be noticed. If ischemia continues, a marked elevation in glycerol level signals imminent flap loss. With double-monitoring it would be easier to create more simple follow-up guides with different algorithms for even inexperienced personnel to use. However, to make this happen, both monitoring methods would need to be remarkably cheaper and MD monitoring would need to be made easier for the personnel to use.

### 6.3.2 Postoperative care

Traditionally, patients have been postoperatively sedated in the ICU to optimize flap outcomes. This protocol has also been used at Tampere University Hospital. The sedation time has ranged between 12 and 18 h until the first postoperative morning, and the sedative agent used has previously been propofol with no vasopressors. Gradually, as a result of the present study, there has been a shift towards lighter post-operative sedation. The patients are still followed in the ICU, but nowadays the primary sedative is DEX and the patients are arousable in a few hours postoperatively. The light sedation lasts on average for 12 to 16 h enabling earlier removal to a normal ward. If a vasopressor is needed, norepinephrine and dopamine are allowed.

Perhaps in future, postoperative patients will be treated in a specialized head and neck ward without sedation. This would enable patients to recover faster and shorten the length of postoperative ICU and even hospital stay. Flaps will be followed by a reliable monitoring method and specially trained nurses effectively with no routine follow-up visits by the surgeon.

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# 8 PUBLICATIONS

# PUBLICATION
# I

**Early recognition of ischaemia with continuous real-time tissue oxygen monitoring in head and neck microvascular flaps**

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ORIGINAL PAPER

# Early recognition of ischaemia with continuous real-time tissue oxygen monitoring in head and neck microvascular flaps

**Lassi Raittinen · Juhani Pukander · Jussi Laranne**

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**Abstract** Aim of this study was to evaluate the reliability of a continuous real-time tissue oxygen monitoring method (Licox®) for postoperative follow-up of free microvascular flaps after ablative head and neck tumour surgery. We also wanted to establish and test accurate alarm levels for this monitoring method. One hundred eighteen head and neck cancer patients, operated in Tampere University Hospital, Finland, were analysed. Tissue oxygen ($P_{ti}O_2$) levels were continuously monitored with the Licox® system. Receiver operating characteristic analysis was performed considering following alarming signals: a clear change in the trend of the curve leading to a decline more than 50% in 1 h or a decline below 10 mmHg in the $P_{ti}O_2$ level. Licox® recognized all the patients who needed re-operation with sensitivity of 100% and specificity of 88%. The overall success rate was 99.2% (117 of 118) and flap salvage rate 88% (seven of eight), respectively. The Licox® tissue oxygen pressure monitoring system is a reliable method for detecting early postoperative circulation problems in free microvascular flaps. The suggested alarm signals are a clear change in the trend of the curve leading a decline more than 50% in an hour or a decline below 10 mmHg.

**Keywords** Tissue oxygen monitoring · Free flaps · Postoperative monitoring · Head and neck cancer

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## Introduction

Free microvascular flap reconstruction is a standard part of modern head and neck tumour surgery. Although the success rate of these reconstructions is high in experienced hands [2, 4], postoperative circulatory impairment of the flap is still a potential complication and leads to failure of the whole reconstruction. A major re-operation is required with an increased risk of complications and high cost. If a circulatory problem can be detected early, salvage procedures can be started without delay. In most cases, the reconstruction can be saved with a simple revision of the anastomoses.

The importance of careful postoperative monitoring has been emphasised in many reports [1, 3]. Clinical observation and handheld Doppler ultrasound are the most common methods while more sophisticated techniques—for example, microdialysis—are seldom used.

In head and neck reconstructions, vitality of the flap is often difficult to observe especially in reconstructions of the posterior oral cavity or hypopharynx. Clinical observation and Doppler ultrasound both require experienced personnel and multiple regular inspections of the flap during the first 72 postoperative hours. Several methods for monitoring circulation in these flaps have been introduced, but no golden standard exists. The ideal system should be easy to use, reliable and harmless to the flap, and it should promptly alarm in case of circulatory problems.

In Tampere University Hospital, a continuous, real-time Licox® (GMS, Kiel-Mielkendorf, Germany) tissue oxygen monitoring device has been used for postoperative free flap monitoring in head and neck reconstructions since 1999. We report our experience with this system.

**Table 1** One hundred eighteen patients with head and neck tumours

| | |
|---|---|
| Sex male/female | 70 (59%)/ 48 (41%) |
| Age | Mean 56 years (17–88) |
| Oral cancer | 84 (71%) |
| Tonsillar cancer | 24 (20%) |
| Hypopharyngeal cancer | 5 (4%) |
| Sinonasal cancer | 2 (2%) |
| Epithelioid sarcoma | 1 (1%) |
| Mucoepidermoid sarcoma | 1 (1%) |
| Ameloblastoma | 1 (1%) |

## Materials and methods

### Patients

The material comprised 118 head and neck tumour patients operated at the department of Otolaryngology, Head and Neck Surgery, Tampere University Hospital, Finland (Table 1). All patients underwent radical removal of the tumour, a selective neck dissection followed by a free flap reconstruction. The donor tissue sites for reconstruction are shown in Table 2.

### Tissue oxygen monitoring

Principle of the Licox® $O_2$ probe is based on measuring partial oxygen pressure in tissue ($P_{ti}O_2$). Oxygen dissolved in the interstitial fluid corresponds to the availability of oxygen at the cellular level. When the monitoring probe is inserted in the flap, tissue oxygen diffuses through the polyethylene wall of the probe to a negatively polarized precious metal in the inner electrolyte chamber resulting the $O_2$ molecules to polarize into $OH^-$ ions. This current from the $O_2$ reduction is the raw signal of the sensor. The 2-cm sensitive area lies at the tip of the probe. Reliable readings are obtained when all the sensors are inside the flap. The reactions in the probe are reversible making the measurements stable and continuous.

Tumour resections and reconstructions were done with standard techniques. During the operation, the monitoring $O_2$ probe was inserted through skin and into the septocutaneous part of the flap ($n=104$) or into muscular tissue ($n=14$).

**Table 2** Flaps used for reconstruction

| | |
|---|---|
| Radial forearm | 92 (78%) |
| Fibula | 11 (9%) |
| Crista iliaca | 5 (4%) |
| Rectus abdominis | 4 (3%) |
| Scapula | 3 (2,5%) |
| Latissimus dorsi | 2 (2%) |
| RFA + fibula | 1 (1%) |

**Table 3** The ROC analysis for alarming signals, which were $P_{ti}O_2$ level less than 10 mmHg, a clear change in the trend of the curve leading to a decline more than 50% in 1 h

| | Re-operation | | Sensitivity | 100% |
|---|---|---|---|---|
| Alarm | Yes | No | Specificity | 88% |
| Yes | TP=8 | FP=13 | Positive predictive value | 0.38 |
| No | FN=0 | TN=97 | Negative predictive value | 1 |
| | 8 | 110 | | |

Postoperatively, $P_{ti}O_2$ level in the flaps was continuously observed for 72 h, first in the intensive care unit and later in the normal ward. The $P_{ti}O_2$ curve was analysed continuously. The flaps were additionally monitored by a physician with traditional methods (i.e. colour, turgor, vital reaction and a needle puncture if needed) once during the first postoperative evening and later during regular office hours. Nurses caring for the patients were instructed to alarm the surgeon if there was a clear change in the trend of the curve leading to a decline more than 50% in 1 h or if the $P_{ti}O_2$ level dropped altogether below 10 mmHg. When one or more of these criteria was met, the operating surgeon was called to evaluate the flap's condition. Decision to re-operate was based on the $P_{ti}O_2$ curve and clinical signs of the flap.

### Statistics

Receiver operating characteristic (ROC) analysis was performed to confirm the reliability of the above mentioned $P_{ti}O_2$ limits. Negative and positive predictive values were calculated together with sensitivity and specificity.

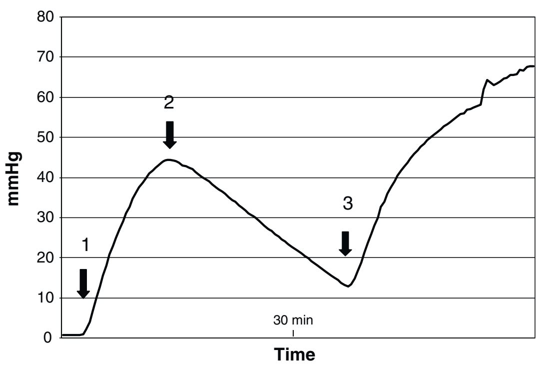


**Fig. 1** $P_{ti}O_2$ curve during the vascular anastomosis phase. *1* Opening of the arterial anastomosis. *2* Arterial clamp during venous anastomosis. *3* Arterial and venous clamp off

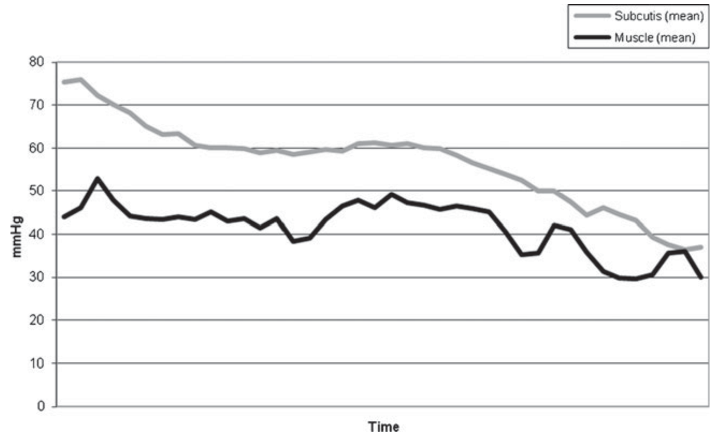


**Fig. 2** Mean $P_{ti}O_2$ level in septocutaneous (*grey*) and muscular (*black*) free flaps

## Results

This monitoring method detected all cases with circulatory problems. ROC analysis showed high negative predictive values and good efficiency for the alarming criteria to predict the need for a re-operation. There were no false negative cases in the whole material. The overall success rate with the reconstructions was 99.2% (117 of 118), and salvage rate for re-operated cases was 88% (seven of eight) (Table 3).

Typical $P_{ti}O_2$ curve shows a rapid response to opening and closing of the artery during the vascular anastomosis phase of the operation (Fig. 1). An average normal $P_{ti}O_2$ curve reaches a steady state within 2 h postoperatively followed by a slow descend. At the starting point, the mean readings were slightly higher in septocutaneous flaps than in muscular flaps—75 vs. 52 mmHg, respectively. After 24 h, the same readings were 60 and 40 mmHg and at 72 h 36 and 30 mmHg, respectively (Fig. 2).

In 21 patients (18%), there was a clear change in trend of the curve, a decline of 50% in less than an hour or a decline below 10 mmHg in the $P_{ti}O_2$ readings (Table 3). After subsequent analysis of the flap's clinical signs, a decision to re-operate was done in eight cases. Thus, 13 of 21 (62%) of the alarms were false positive. Six patients were operated during the first 24 h and two later during the first 72 h. Two patients had to be re-operated twice. One flap did not survive and had to be replaced with a new one. In seven patients, a venous blockage occurred due to a compressing haematoma, and there was one arterial thrombosis. A typical curve leading to a re-operation caused by venous blockage is shown in Fig. 3.

## Discussion

Our material with 118 patients shows that this monitoring method based on continuous $P_{ti}O_2$ measurement is reliable and useful in the clinical follow-up of free flap reconstructions. To our knowledge, this is the largest published material of head and neck patients monitored with this system. It is remarkable that in the whole series, there were no false negative cases and the system detected all cases with

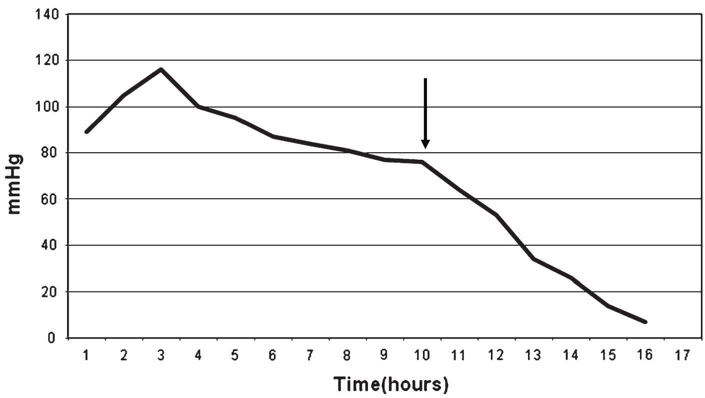


**Fig. 3** A typical $P_{ti}O_2$ curve leading to re-operation, showing a typical slow decline followed by a clear change of trend (*arrow*) leading to readings below 10 mmHg after beginning of the venous thrombosis due to a haematoma in the surgical field

circulatory problems. The alarm criteria—a clear change in the trend of the $P_{ti}O_2$ level leading to a decline more than 50% in an hour or $P_{ti}O_2$ level declining below 10 mmHg—proved to be useful in clinical practise. These limits were originally suggested by Hofer et al. [5]. There seem to be two reasons for the relatively high number of false positive alarms in this material, namely normal physiological events occurring in the flaps' circulation during the immediate postoperative period and high sensitivity of the $P_{ti}O_2$ probe.

The variability of postoperative $P_{ti}O_2$ levels may cause some confusion. High readings immediately after surgery are due to ischaemia and local microtrauma, which damages mitochondria of the cells and results in high extracellular $O_2$ concentrations. During the first two postoperative hours, $P_{ti}O_2$ stabilizes and reaches a steady level. Since the system reacts rapidly to changes in $P_{ti}O_2$ levels, possible ischaemia is naturally detectable also during this stabilization period. In the following 72 h, the readings start to decline slowly even without any circulatory problems. This decline is due to tissue autoregulation, which is thought to be caused by both circulating metabolites and vasoconstriction of the flap arterioles [7]. Also, the fact that in subcutaneous flaps the initial $P_{ti}O_2$ readings are higher and the decline of the curve steeper than in muscular flaps might cause some uncertainty. This, however, can be explained by the differences in distribution of microcirculation and oxygen uptake in subcutaneous and muscular tissue. The $P_{ti}O_2$ reaches an equal level in both flaps within 72 h (Fig. 1). Although the readings vary somewhat individually, the trend seems to be the same in all cases. These findings are in accordance with those of Kamolz et al. [6].

We have noticed that external manipulation of the probe triggers immediate changes in the subsequent $P_{ti}O_2$ readings. Suctioning, restlessness of the patient or manipulation of the reconstruction can cause a sharp temporary rise or decline in the curve. To eliminate this, we find it beneficial to keep the patient under sedation for the first 12–18 postoperative hours and try to minimize mechanical manipulation of the reconstructed area. It is also important to fix the probe so that it does not move out of place when the reconstruction is observed or suction is applied.

In the early part of this series, variation in the $P_{ti}O_2$ curves, caused by the previously discussed reasons, quite understandably resulted in several alarms. Clinical experience and comprehension of the flaps physiology and circulation greatly diminishes the false positive interpretations of the $P_{ti}O_2$ readings.

Since the specificity of the system is 88%, one has to acknowledge that this system is not an absolute monitoring system but an alarm system still requiring clinical observation and decision making. However, we would like to point out that all false alarms were false positive and thus makes this system highly sensitive to any actual circulatory problems.

As we stated earlier, a monitoring system should be easy to use, reliable and harmless to the flap, and it should promptly alarm in case of circulatory problems. This system seems to accomplish those requirements. A most remarkable practical advantage is the possibility to basically abandon continuous clinical follow-up of the flap during the immediate postoperative period. Instead of having the surgeon checking clinical signs regularly during the first 72 postoperative hours, nurses can easily monitor continuous real-time data of the flaps circulation and alarm the surgeon only if needed.

## Conclusion

The Licox® tissue oxygen monitoring system is a sensitive and reliable tool for monitoring microvascular reconstructions in the head and neck area. It enables continuous real-time observation of circulation in microvascular free flaps. This can easily be done by the nursing staff thus remarkably reducing clinicians work. With the suggested alarm criteria, 100% of the vascular events threatening the flap could be noticed, and measures to prevent flap loss started without delay.

**Conflict of interest** I would like to point out that the authors of "Early Recognition of Ischemia With Continuous Real-time Tissue Oxygen Monitoring In Head and Neck Microvascular Flaps" to be published soon in European Journal of Plastic Surgery have no conflicts of interest.

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# PUBLICATION
# II

**Sympathetic innervation does not contribute to glycerol release in ischemic flaps**

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**ORIGINAL ARTICLE**

# Sympathetic innervation does not contribute to glycerol release in ischemic flaps

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**Abstract**

***Background.*** Extracellular glycerol as detected by microdialysis has been used as a surrogate marker for (ischemic) tissue damage and cellular membrane breakdown in the monitoring of free microvascular musculocutaneous flaps. One confounding factor for glycerol as a marker of ischemic cell damage is the effect of lipolysis and associated glycerol release as induced by sympathetic signalling alone. We hypothesized that extracellular glycerol concentrations in a microvascular flap with sympathetic innervation would be confounded by intact innervation per se as compared to denervated flap. Clinical relevance is related to the use of both free and pedicled flaps in reconstructive surgery. We tested the hypothesis in an experimental model of microvascular musculocutaneal flaps. ***Methods.*** Twelve pigs were anesthetized and mechanically ventilated. Two identical rectus abdominis musculocutaneal flaps were raised for the investigation. In the A-flaps the adventitia of the artery and accompanying innervation was carefully stripped, while in the B-flaps it was left untouched. Flap ischemia was induced by clamping both vessels for 60 minutes. The ischemia was confirmed by measuring tissue oxygen pressure, while extracellular lactate to pyruvate ratio indicated the accompanying anaerobic metabolism locally. ***Results.*** Intramuscular and subcutaneal extracellular glycerol concentrations were measured by microdialysate analyzer. Contrary to our hypothesis, glycerol concentrations were comparable between the two ischemia groups at 60 minutes ($p = 0.089$, T-test). ***Conclusions.*** In this experimental model of vascular flap ischemia, intact innervation of the flap did not confound ischemia detection by glycerol. Extrapolation of the results to clinical setting warrants further studies.

**Key Words:** *Glycerol, microdialysis, postoperative monitoring, free flaps, pedicled flaps, flap ischemia*

## Introduction

Free microvascular flaps and pedicled flaps with intact innervation are routinely used for reconstruction of large tissue defects during tumor surgery. Postoperative circulatory impairment of the flap leads to failure of the reconstruction and often a major reoperation is required with an increased risk of complications. Even though the frequency of postoperative circulatory failures may be low, the consequences for the individual patient are devastating with costly reoperations and prolonged hospitalization. If the tissue perfusion defect is detected early enough, attempts to salvage the flap can be started immediately and in most cases the reconstruction can be restored with a revision of the anastomoses [1–3].

The clinical estimation of the vitality of the tissue may be difficult especially in buried flaps in the posterior oral cavity or hypopharynx. Clinical observation requires repeated inspections of the flap by experienced personnel during the first 72 postoperative hours with obvious inter-individual variation. There have been attempts to find more objective methods for monitoring tissue perfusion but no golden standard is yet available [2–4].

Tissue partial pressure of oxygen ($P_{Ti}O_2$) measured continuously and directly from the tissue

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reflects best the circulatory status, and more precisely, balance between oxygen supply and extraction in the tissue [2,5].

Microdialysis (MD) is used for cerebral monitoring in intensive care units and also in free flaps both in research and in clinical setting [6–8]. It enables sampling of extracellular fluid for measurement concentrations of intermediary metabolites such as glucose, lactate, and pyruvate. In addition, microdialysate glycerol has been used as a marker of disintegrating cell membranes. However, lipolysis only, as induced by sympathetic stimulus may increase extracellular concentration of glycerol. Thereby, variation in sympathetic drive is potentially a confounding factor for glycerol as a marker of ischemic cell membrane disintegration. Surgical procedures cause lipolysis either due to ischemia or sympathetic stress [9–11]. Finally, lactate alone [12] and the lactate to pyruvate ratio could be related to enzyme activity changes without tissue hypoxia. Therefore, combining more than one parallel measure of tissue perfusion and metabolism (multimodal monitoring) may offer more reliable results for study purposes and for decision making in the clinical setting.

While decreasing $P_{Ti}O_2$ and glucose concentration or increasing the lactate/pyruvate-ratio (L/P-ratio) have been considered somewhat straightforward measures of inadequate substrate supply and altered metabolism [14], extracellular glycerol could depict the cellular damage. The remaining drawback is that glycerol can be confounded by the degree of sympathetic inflow to the local vasculature. The role of adrenergic regulation of lipolysis mediated via β-adrenoceptors is unclear in free flaps. Previously glycerol has been measured both in free flaps and in pedicled flaps, but the effect of sympathetic denervation was not compared [15].

In this paper we report the effect of sympathetic denervation on the extracellular glycerol concentrations during experimental flap ischemia as compared to the flaps with intact innervation.

## Material and methods

The results for the present publication come from a larger trial from which some of the results were published recently [16]. The present report does not repeat the data presented earlier. While the previous report described a comparison of the sedation methods, the present report focuses on the time period in the experiment which was not reported therein. In general terms, in order to minimize the risk for experimental animals and promote efficient use of research funds and experimental animals it is ethically justified to report all different aspects from a single experimental study while specifically clarifying that no attempt to unjustified splicing or repetition of data occurs.

### *Animals and anesthesia*

After the approval from the institutional committee of care and use of experimental animals, 12 domestic pigs (25–40 kg) were deprived of food but not water 24 h prior to experiments. Premedication with atropine 0.05 mg/kg of body weight, azaperone 8 mg/kg and ketamine 5–10 mg/kg intramuscularly were followed by cannulation of an ear vein and intravenous administration of 2 mg/kg propofol before tracheotomy. Anesthesia was maintained with propofol (15–20 mg/kg/h) and fentanyl (30 μg/kg/h until the end of surgery, 5 μg/kg/hour thereafter). Vecuronium bolus injections of 4 mg were given when necessary. The animals were ventilated with a volume-controlled mode (Servo 900, Siemens, Elema AB, Solna Sweden) with 5 $cmH_2O$ of positive end-expiratory pressure (PEEP). $FIO_2$ (0.3–0.6) was adjusted to keep $PaO_2$ levels between 13.3 kPa (100 mmHg) and 20 kPa (150 mmHg). Tidal volume ($V_T$) was kept at 10 mL/kg and the minute ventilation adjusted to maintain $PaCO_2$ levels between 4.5 and 5.5 kPa (34–41 mmHg).

### *Animal preparation*

A fluid filled catheter was inserted into the left femoral artery (single-lumen central venous catheter, Arrow) and a pulmonary artery catheter (7.5F flow-directed, Arrow, Arrow International Inc, Reading, PA) introduced via the right internal jugular vein. Kefuroxim 750 mg IV was administered before instrumentation as antibiotic prophylaxis. During instrumentation the animals received 5 mL/kg/h infusions of saline, Ringer's acetate and hydroxyethyl starch. Additional fluid was administered if necessary to keep pulmonary artery occlusion pressure (PAOP) between 5 and 8 mmHg. Body temperature of the animals was kept above 38°C using an operating table heater and warmed fluids when necessary. After the experiment, the animals were put down with a lethal dose of intravenous magnesium sulphate.

### *Experimental protocol*

Two symmetrical rectus abdominis myocutaneous flaps (7 × 10 cm) were raised on each side of the upper abdomen with blood supply by superior epigastric vessels. The adventitia with its sympathetic nerve fibers was carefully stripped from the arteries in one flap (A-flap), while innervation was left untouched in the B-flap. Flaps were fixed in their original positions with skin sutures. Sixty minutes of hemodynamic stabilization was allowed after surgical preparation. Finally, 60 min global flap ischemia was induced by occluding the pedicular vessels with Ackland V2 or V3 clamps. Ischemia was followed by 90 min of reperfusion (Figure 1). The data describing

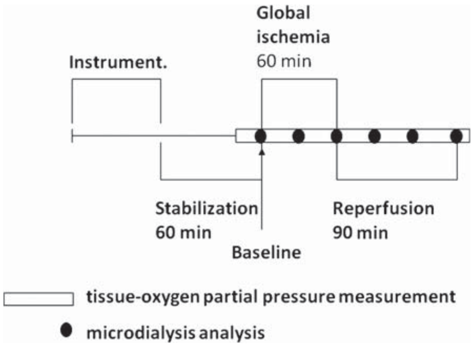


Figure 1. The study setting: Instrumentation was followed by stabilization, ischemia and reperfusion. The microdialysis measurement time points are shown as black dots, while $P_{ti}O_2$ was followed continuously.

the immediate reperfusion period following the ischemic time for 60 min is reported herein. These data were not reported in the previously published report focusing on comparison between two sedative protocols. In addition, we explicitly state that the sedation protocol was identical until the 60 min reperfusion.

### *Monitoring*

Femoral arterial pressure, pulmonary arterial pressure (PAP) and central venous pressure (CVP), were recorded with quartz pressure transducers and displayed continuously on a multimodular monitor (S/5 Compact Critical Care Monitor, Datex-Ohmeda@, Helsinki, Finland). Data were collected and afterwards filtered into 2-min medians and stored through a dedicated information management system (Clinisoft, Datex-Ohmeda@, Helsinki, Finland). All pressure transducers were calibrated simultaneously to the level of the heart. Cardiac output (L/min) was measured by a thermodilution technique (mean value of three measurements, cardiac output module, Datex-Ohmeda@, Helsinki, Finland). Heart rate was measured from the ECG, which was also continuously monitored.

### *Microdialysis*

A microdialysis catheter (CMA 20 Microdialysis Catheter, CMA/Microdialysis AB, Stockholm, Sweden) was used with precision perfusion pump (CMA 100 Microinjection Pump, CMA/Microdialysis AB, Stockholm, Sweden). The methodology has been described elsewhere [17–19]. Two catheters were inserted just under the dermal layer of the skin (one in each rectus abdominis myocutaneous flap) and another two catheters were inserted into the muscle (one in each flap). The dialysate samples with 1 μl/min flow rate and 30-min time interval were collected. The dialysate samples were analyzed for glucose, lactate and pyruvate and glycerol concentrations at the end of stabilization and at 30 and 60 min after global flap ischemia by a microdialysis analyzer (CMA 600 Microdialysis Analyzer, CMA/Microdialysis AB).

### *Tissue-oxygen partial pressure*

We used a $P_{Ti}O_2$ probe that is routinely used in clinical setting for the monitoring of brain tissue oxygenation and in free-flap surgery [2,13]. Standard CC1.2 microcatheter tissue-oxygen partial pressure ($P_{ti}O_2$) probes (Licox, Integra, Hampshire, UK) were used for the measurements. Two $P_{Ti}O_2$ probes were used intramuscularly, one in each rectus abdominis myocutaneous flap. No catheters were inserted under the dermis. Tissue-oxygen pressure was intermittently monitored from each probe in periods of 5 min from the end of the stabilization period until the end of the experiment (Licox, GMS, Kiel-Mielkendorf, Germany). Repeated $P_{ti}O_2$ values were graphically displayed on a linked laptop and data was automatically registered every 20 seconds.

### *Data analysis and statistics*

Power calculation for sample size was not performed. Instead a convenience sample size was chosen. The normality of the data was tested with the Kolmogorov-Smirnov test (K-S test). Thereafter the data are presented as mean ± standard deviation (SD) unless otherwise mentioned. The T-test was used for all statistical analyses (intramuscular and subcutaneous glycerol in A-, B-flaps and control). Bonferroni correction was used due to multiple testing. A value of $p < 0.05$ was considered significant.

## Results

The data were normally distributed according to the K-S test. Systemic hemodynamics and arterial oxygenation were stable at the end of the stabilization and after 60 min of the local flap ischemia (Table I). Decreasing muscle tissue $O_2$ tension ($P_{Ti}O_2$) confirmed flap ischemia and increasing L/P ratio suggested anaerobic metabolism at 30 and 60 min during the occlusion of vessels (Table II). At 30 min after occlusion of arterial supply and venous return to the flap, the L/P ratio was higher in denervated flaps' muscle tissue in comparison to the flaps with intact innervation (Table II, $p = 0.014$).

Before and during ischemia (baseline, 30 and 60 min) extracellular glycerol concentrations were comparable in denervated flaps and in flaps with intact innervation. After 60 min of ischemia no significant differences between the two groups were detected

Table I. The hemodynamic parameters remained stable throughout the experiment.

| | Baseline ($n = 12$) | 30-min ischemia ($n = 12$) | 60-min ischemia ($n = 12$) |
|---|---|---|---|
| MAP (mmHg) | 77 ± 11 | 77 ± 10 | 77 ± 7 |
| CO (L/min) | 4 ± 1 | 4 ± 1 | 4 ± 1 |
| Arterial $PO_2$ (kPa) | 23 ± 4 | 22 ± 4 | 22 ± 4 |
| Arterial L/P ratio | 11 ± 2 | 11 ± 3 | 11 ± 3 |

MAP, mean arterial pressure; CO, cardiac output.

($p = 1.0$ and $p = 0.18$, subcutaneal and intramuscular samples, respectively, Figure 2). A marked increase over time only occurred after 60 min in both denervated flaps' subcutaneal and intramuscular microdialysate ($p = 0.0002$ and $p = 0.016$, respectively) and in the flap with intact innervation; subcutaneal and intramuscular microdialysate ($p = 0.0002$ and $p = 0.0002$, respectively). Subcutaneal or intramuscular microdialysate glycerol concentration at 60 min of ischemia were not different between the groups ($p = 0.94$ and $p = 0.84$). A comparable behaviour of intramuscular $P_{ti}O_2$ in relation to extracellular glycerol concentration over time is depicted in Figure 3.

After 60 min of reperfusion, intramuscular microdialysate glycerol concentration was comparable in the two groups, 62 ± 31 micromol/L and 48 ± 27 micromol/L in the denervated flap and in the flap with intact innervation, respectively ($p = 0.5$).

## Discussion

The main finding of the present experiment was that opposite to our original hypothesis, intact innervation of the microvascular flap did not contribute to intramuscular extracellular glycerol release as compared to the denervated flap after 60 min of ischemia. Surprisingly, we found that the L/P ratio increased to a higher extent earlier on in the denervated flap.

Sympathetic stress and ischemia during operation are known to increase lipolysis [10,22,23]. This can be detected as elevated extracellular glycerol concentrations by microdialysis. Accepting the notion that sympathetic activity alone is one of the stimuli for glycerol release, we hypothesized that the confounding effect of lipolysis due to intact sympathetic drive rather than ischemia could be measured as higher or variable levels of glycerol in microvascular flaps with intact innervation [24]. Contrary to the hypothesis our experiment showed no significant difference between denervated and the flaps with intact innervation. Glycerol concentrations increased only moderately (as compared to baseline) even after 60 min of no blood flow while the lactate to pyruvate ratio was already several-fold (5–10 times SD of the baseline setting) higher after 30 min as compared to the baseline measures.

From the clinical perspective, postoperative monitoring of the viability of free microvascular flaps is important. In particular, head and neck cancer surgery portends high risks for adverse events; flaps are usually buried or otherwise difficult to observe. Several monitoring methods have been introduced to clinical use such as $P_{ti}O_2$ and microdialysis [5,8,11,13,14]. $P_{ti}O_2$ measurement provides the clinician with on-line information of tissue oxygen levels. The method however supplies the clinician with variable baseline absolute $P_{ti}O_2$ level. Thereby adding metabolic monitoring along $P_{ti}O_2$ measurements could offer additional information for clinical decision-making. While the L/P ratio is considered as a clear indicator of anaerobic metabolism locally, glycerol release from cells is a less robust indicator of ischemia. The present study indicates that glycerol is minimally confounded by the sympathetic innervation or lack of it. Thereby it may add to the diagnostics of the tissue perfusion defect indicated by low $P_{ti}O_2$ and high L/P ratio equally in free microvascular flaps and pedicled flaps with intact innervation. Thus a stepwise diagnostic approach is possible: $P_{ti}O_2$ indicates the early perfusion ($O_2$ supply) failure, increasing L/P ratio confirms metabolic derangement and finally, increasing glycerol concentration indicates already the start of cell injury related to ischemic conditions. In the present experiment we obtained results which, contrary to our hypothesis, suggest that glycerol release was not modified by the sympathetic innervation either in muscle tissue or in

Table II. The mean/SD values for the muscle preparates showing clearly the signs of ischemia and reperfusion in the study groups.

| | Baseline ($n = 12$) | 30-min ischemia ($n = 12$) | 60-min ischemia ($n = 12$) |
|---|---|---|---|
| *Muscle* $PtiO_2$ *(mmHg)* | | | |
| Denervated | 20 ± 10 | 2 ± 5† | 0.5 ± 1† |
| Innervated | 24 ± 13 | 3 ± 4† | 1 ± 2† |
| *Muscle MD- Lactate/Pyruvate* | | | |
| Denervated | 24 ± 10 | 111 ± 63*,† | 238 ± 119† |
| Innervated | 19 ± 10 | 52 ± 27† | 183 ± 95† |

*Denotes the difference between the groups (T-test, $p < 0.05$). †Denotes the difference to the baseline (Paired T-test < 0.05). Bonferroni correction for repeated measurements was used.

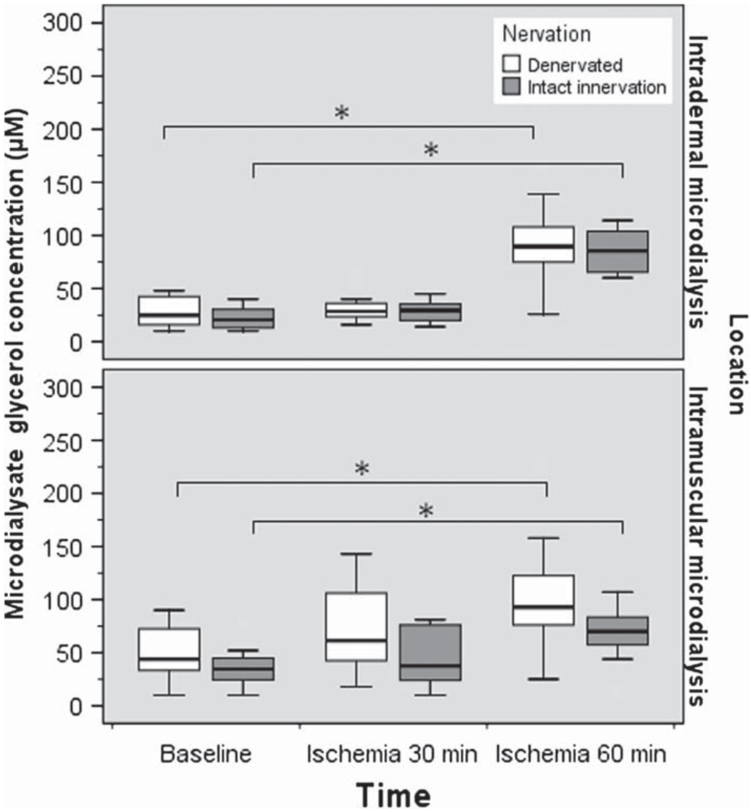


Figure 2. No statistical difference was observed between innervated and denervated glycerol-levels at baseline or during ischemia at 30 min or 60 min in subcutaneal (intradermal) or intramuscular microdialysate. Data is shown as median, quartiles and 95% confidence intervals. The asterisk denotes $p<0.05$, within the group comparison from baseline to 60-min, paired T-test, $n=12$ at each timepoint in each group.

subcutis. Previously, Navegantes and colleagues showed in a human model of sympathetic excitation that glycerol release was not increased in skeletal muscle by sympathetic activation alone. Conversely,

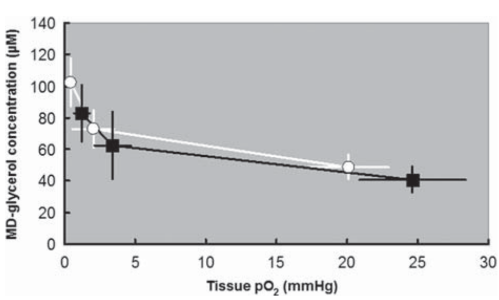


Figure 3. The effects of ischemia on muscle tissue $pO_2$ ($P_{Ti}O_2$) and muscle microdialysate glycerol concentration (MD-glycerol) is depicted as an x-y plot with mean (squares and circles) ± standard deviations (error bars) at the baseline (right-most), 30 min of ischemia (second to left) and after 60 min of ischemia (left-most) in denervated flaps (○) and the flaps with intact innervation (■).

in adipose tissue sympathetic activation alone increased glycerol release [25]. Finally, the early, pronounced increase of the L/P ratio 30-min time point during ischemia in denervated flap is in contrast to the report by Qvist and colleagues. They showed that sympathetic activation in human skeletal muscle increases lactate concentration in the intramuscular extracellular compartment [26]. We cannot explain the differences between the present report and previous studies. The role of the potential confounding effect of sedation in an animal model as opposed to the awake state in human volunteer trials can be speculated.

There are limitations to our study. One weakness of the methods is the lack of objective measures of sympathetic activity locally. However, we aimed to simulate closely the clinical setting for perioperative conditions. Even though we used the most precise atraumatic surgical technique in preparation of the flaps and the most delicate surgical clamps, we cannot definitely exclude the possibility that clamping of the vessels (and the surgical manipulation) may have affected the sympathetic innervation leading to an abnormal innervation on flap-B. Importantly, the adventitia of the supplying artery was carefully stripped off from one of the flaps, while the other was left intact. Secondly, the experiment was performed on anesthetized pigs. This may limit the physiological relevance of the results. Deep sedation may have effects on the metabolism and therefore on, for example, glycerol release. However, here we suggest that the conditions mimic the clinical setting including the use of propofol as the anaesthetic. In addition, the sedation was identical between the groups. Finally, as this was a convenience sample size instead of power calculated to detect a certain difference between the groups we cannot fully rule out the possibility of erroneous negative findings.

In summary, decreasing $P_{ti}O_2$ and increasing the L/P-ratio indicated ischemia and anaerobic metabolism in both the denervated flap and the flap with intact innervation. Surprisingly, denervation was associated with a more pronounced increase in intramuscular L/P ratio at 30 min of vascular occlusion. Contrary to our hypothesis glycerol release was not altered by the presence or absence of flap innervation.

Bearing in mind the limitation of a small sample size we suggest in conclusion that glycerol release from cells into the extracellular space is not confounded by the sympathetic innervation during deep sedation.

## Acknowledgements

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Some of the data were presented as a poster at The Annual Congress of ESICM, Barcelona 2006. Other sections of the experiment have been reported previously (Nunes S et al., Anesthesia & Analgesia 2007).

***Author roles:*** Leena Berg, Heikki Ahonen, and Ilkka Parviainen: Data collection and conduct of the work. Lassi P. Raittinen, Silvia Nunes, Jussi Laranne, and Jyrki J. Tenhunen: Manuscript preparation, data analysis and study design.

***Declaration of interest:*** JT was an invited speaker in a Microdialysis users' meeting in Cascais, Portugal 2004 (organizer and the payment of flights: CMA Microdialysis, Stockholm, Sweden). The other authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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# PUBLICATION
# III

**The Effect of Norepinephrine and Dopamine on Radial Forearm Flap Partial Tissue Oxygen Pressure and Microdialysate Metabolite Measurements: A Randomized Controlled Trial**

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# The Effect of Norepinephrine and Dopamine on Radial Forearm Flap Partial Tissue Oxygen Pressure and Microdialysate Metabolite Measurements: A Randomized Controlled Trial

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**Background:** Patients undergoing ablative and reconstructive head and neck surgery with a microvascular flap have multiple factors that potentially decrease postoperative mean arterial pressure, which may endanger flap survival. The safety of vasopressor use has long been a topic of discussion. The authors analyzed the effect of vasopressors on microvascular flap perfusion after head and neck cancer reconstruction.

**Methods:** A total of 27 patients were enrolled in a randomized, controlled, clinical trial. A microvascular radial forearm flap was used for reconstruction. Patients were allocated into one of three groups: dopamine, norepinephrine, and control. The intervention groups received the vasoactive drug, aiming to maintain the mean arterial pressure between 80 and 90 mmHg. Normovolemia was maintained according to central venous pressure. Flap perfusion was monitored with continuous tissue partial pressure of oxygen and microdialysate metabolite (lactate-to-pyruvate ratio) measurements.

**Results:** No adverse effects were observed, and postoperative recovery was free of complications in all groups. Neither the lactate-to-pyruvate ratio nor continuous tissue partial pressure of oxygen values differed significantly between groups during the first 24 hours of the vasoactive drug infusion period or during the 72-hour follow-up.

**Conclusions:** Norepinephrine and dopamine are safe and effective vasopressors for use during the postoperative period following head and neck cancer surgery with microvascular reconstruction. Dopamine should be used with caution, however, because of the risk of side effects. (*Plast. Reconstr. Surg.* 137: 1016e, 2016.)

**CLINICAL QUESTION/LEVEL OF EVIDENCE:** Therapeutic, II.

Microvascular flaps are used for head and neck area reconstruction after extensive tumor surgery. Comorbidities and the duration of surgery, anaesthesia, and sedation may lead to decreases in the mean arterial pressure intraoperatively and postoperatively, requiring the use of vasopressors.[1] Treatment with vasopressors is controversial, however, because of the possibility of a vasoconstriction-induced decrease in flap perfusion, leading to flap ischemia and thrombosis. Therefore, up to 52 percent of surveyed anesthesiologists prefer to manage blood pressure decreases with crystalloid infusion; only 36 percent of them considered vasopressors to be safe, and 46 percent of them regarded the use of norepinephrine to be contraindicated.[2] The

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*This trial is registered under the Finnish National Agency of Medicine and the Tampere University Hospital Ethics Committee, identification number R05114M; and under the name "The Effect of Norepinephrine and Dopamine on Radial Forearm Free Flap Tissue Oxygen Pressure and Microdialysate Metabolite Measurements," ClinicalTrials.gov identification number NCT02241083 (https://clinicaltrials.gov/ct2/show/NCT02241083).*



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use of massive fluid infusions may have negative pulmonary and circulatory effects, and prolong the hospital stay.[2,3] Preferred drugs for managing mean arterial pressure are sympathomimetic amines, or mixed alpha-/beta-adrenergic drugs titrated to the patient's needs.

Recent reports indicate that the use of vasopressors does not pose a negative threat to flap vitality.[1,3–5] In a study by Eley et al., norepinephrine caused vasoconstriction in the flap but to a lesser extent than in the control tissue.[1] Therefore, flap skin blood flow increased with an increase in arterial blood pressure. Dobutamine modestly increased the flap blood flow. In a study by Scholz et al., dobutamine was used for head and neck microvascular flap patients, and blood flow measured at the arterial anastomosis site indicated that dobutamine improved free-flap perfusion.[3]

Different protocols are followed during the first 24 hours postoperatively to ensure optimal patient care.[2,3] Because the operation is extensive, patients may have moderate blood loss, requiring a period of fluid and airway monitoring, repositioning, and adjustment, and it is considered that these patients are better cared for in an intermediate or intensive care unit. Furthermore, although there is some disagreement, it is common practice to maintain the patient under sedation and ventilation during the first 24 hours.[1,6,7] Sedation may cause systemic vasodilation, leading to decreased mean arterial pressure, and potentially compromise flap survival.[2,3] In addition, flaps undergo a series of inflammatory and circulatory adjustments for which careful monitoring is advised. The aim of this randomized clinical study was to analyze, by continuous tissue partial pressure of oxygen monitoring and microdialysis metabolite measurements, the effect of norepinephrine and dopamine on microvascular radial forearm flaps after head and neck cancer ablation and reconstruction.

## PATIENTS AND METHODS

The Ethics Committee of Tampere University Hospital and the Finnish National Agency of Medicine approved the study. Written informed consent was obtained from the patients. A total of 27 consecutive head and neck cancer patients (15 oral and 12 oropharyngeal) were included in our unblinded randomized controlled trial. Patient demographics are listed in Table 1. Blocks of nine patients were used for randomization, and the allocation was performed by the medical/research nursing staff in the intensive care unit. Operations were performed using a two-team approach in which tumor removal, functional neck dissection, and microvascular reconstructions were performed by one senior ear, nose, and throat surgeon with standard techniques. An experienced plastic surgeon performed the harvesting of the radial forearm flap. The preferred receptor vessels for anastomosis were the facial artery and the venous tributaries in proximity to the internal jugular vein in all study patients.

Flap perfusion and vitality were monitored continuously using a continuous tissue partial pressure of oxygen monitoring catheter (Licox; Integra, Hampshire, United Kingdom) and a microdialysis catheter (CMA 20 Microdialysis Catheter; CMA/Microdialysis AB, Stockholm, Sweden) inserted into the subcutaneous tissue of the flaps before performing the flap insertion and microvascular anastomosis. Clinical parameters such as flap temperature, color, turgor, and capillary filling were also followed by the nursing staff. Postoperatively, patients were monitored in the intensive care unit under sedation with propofol (infusion at a maximum dose of 4 mg/kg/hour) for 24 hours, which is the regular practice in our department. Normovolemia was maintained with central venous pressure between 6 and 10 $cmH_2O$. Patients were randomized into one of three unblinded groups: control, dopamine, and norepinephrine. In the control group, no attempts to increase mean arterial pressure were made provided that it remained greater than 60 mmHg. In both intervention groups, mean arterial pressure was maintained between 80 and 90 mmHg with either dopamine [Abbodop (Abbott, Cherry Hill, N.J.; Electra-Box Pharma, Stockholm, Sweden); maximum dose, 13.3 μg/kg/minute] or norepinephrine [Levophed (Hospira, Lake Forest, Ill.); maximum dose, 0.33 μg/kg/minute]. Preset mean arterial pressure limits were followed with an intention-to-treat principle. Infusion rates of the study medications were titrated, if needed, during the first postoperative 24 hours. Mean arterial pressure and central venous pressure were measured simultaneously.

Postoperative flap follow-up, in addition to a thorough clinical evaluation, was performed by continuous tissue partial pressure of oxygen monitoring (Licox; GMS, Kiel-Mielkendorf, Germany) and microdialysis metabolite measurements (CMA 600 Microdialysis Analyzer; CMA/Microdialysis AB) for 72 hours postoperatively.

Continuous tissue partial pressure of oxygen readings were recorded continuously on computer software, and microdialysis metabolites were analyzed every 2 hours for the first 24 hours, and then every 3 hours for the next 48 hours. A

**Table 1. Patient Demographics**

| | Dopamine | Norepinephrine | Control | Total |
|---|---|---|---|---|
| No. of patients | 8 | 9 | 8 | 25 |
| Mean age ± SD, yr | 63 ± 14 | 65 ± 8 | 55 ± 16 | |
| Sex | | | | |
| Male | 4 | 5 | 4 | 13 |
| Female | 4 | 4 | 4 | 12 |
| Chronic renal insufficiency | 0 | 0 | 0 | 0 |
| Diabetes mellitus | 1 | 1 | 0 | 2 |
| Hypertension | 4 | 2 | 0 | 6 |
| Chronic pulmonary disease | 0 | 0 | 1 | 0 |
| Cerebrovascular disease | 0 | 0 | 1 | 0 |
| Coronary artery disease | 0 | 0 | 1 | 0 |
| Peripheral vascular disease | 0 | 0 | 0 | 0 |
| Hypercholesterolemia | 2 | 1 | 0 | 3 |
| Previous radiation therapy | 0 | 1 | 0 | 1 |
| Smoking | 3 | 4 | 4 | 11 |
| Localization | | | | |
| Oral | 4 | 5 | 5 | 14 |
| Oropharyngeal | 4 | 4 | 3 | 11 |
| Tumor size | | | | |
| T1 | 1 | 1 | | 2 |
| T2 | 4 | 6 | 5 | 15 |
| T3 | 2 | 1 | 2 | 5 |
| T4 | 1 | 1 | 1 | 3 |
| Lymph node status | | | | |
| N0 | 5 | 5 | 5 | 15 |
| N1 | 0 | 3 | 1 | 4 |
| N2 | 3 | 1 | 2 | 6 |

commercially available metabolite kit was used (Iscusflex; M Dialysis AB, Johanneshov, Sweden) for analysis of lactate, pyruvate, glucose, and glycerol levels. The lactate-to-pyruvate ratio was calculated every 2 hours by the computer software. A remarkable increase (up to the hundreds) in the lactate-to-pyruvate ratio or a decrease in continuous tissue partial pressure of oxygen to less than 10 mmHg after achieving a plateau was considered to indicate compromised flap circulation.

The sample size was calculated (80 percent power; $\alpha = 5$ percent) by using PS Power and sample size calculator. The main variable was lactate-to-pyruvate ratio, with values ranging from 30 to 40 considered significant. Two patients were excluded from the analysis because of missing microdialysis or continuous tissue partial pressure of oxygen data. Data were analyzed by the Wilcoxon and Friedmann and Mann-Whitney tests using IBM SPSS Version 22 (IBM Corp., Armonk, N.Y.).

## RESULTS

This study included 14 men and 11 women with a mean age of 61 ± 13 years. Table 1 shows the patient characteristics per study group. The overall treatment time in the three study groups was 1900 minutes (1815 to 1954 minutes).

All surgical interventions and postoperative recoveries in the intensive care unit and ear, nose, and throat ward were free of complications. Heart rate, central venous pressure, and mean arterial pressure are shown in Figure 1. Mean arterial pressure measurements showed greater stability in the norepinephrine group. The dopamine group had the greatest variation in mean arterial pressure levels and heart rate (Fig. 2, *below*). In the control group, three of eight patients required small amounts of both vasopressor agents to maintain the preset mean arterial pressure levels greater than 60 mmHg (Table 2).

Lactate-to-pyruvate ratio and continuous tissue partial pressure of oxygen measurements followed a similar pattern in every study group (Fig. 2). The behavior of these values was similar in all three groups during continuous monitoring for 72 hours. There were no statistically significant differences in partial tissue oxygenation and lactate-to-pyruvate ratio levels at any time point between the study groups undergoing treatment with vasoactive drugs.

There were no flap losses or major complications leading to reoperations in any of the groups. One patient in the dopamine group developed significant tachycardia that required a medication dose decrease.

## DISCUSSION

Patients with head and neck cancer undergoing tumor ablation and microvascular

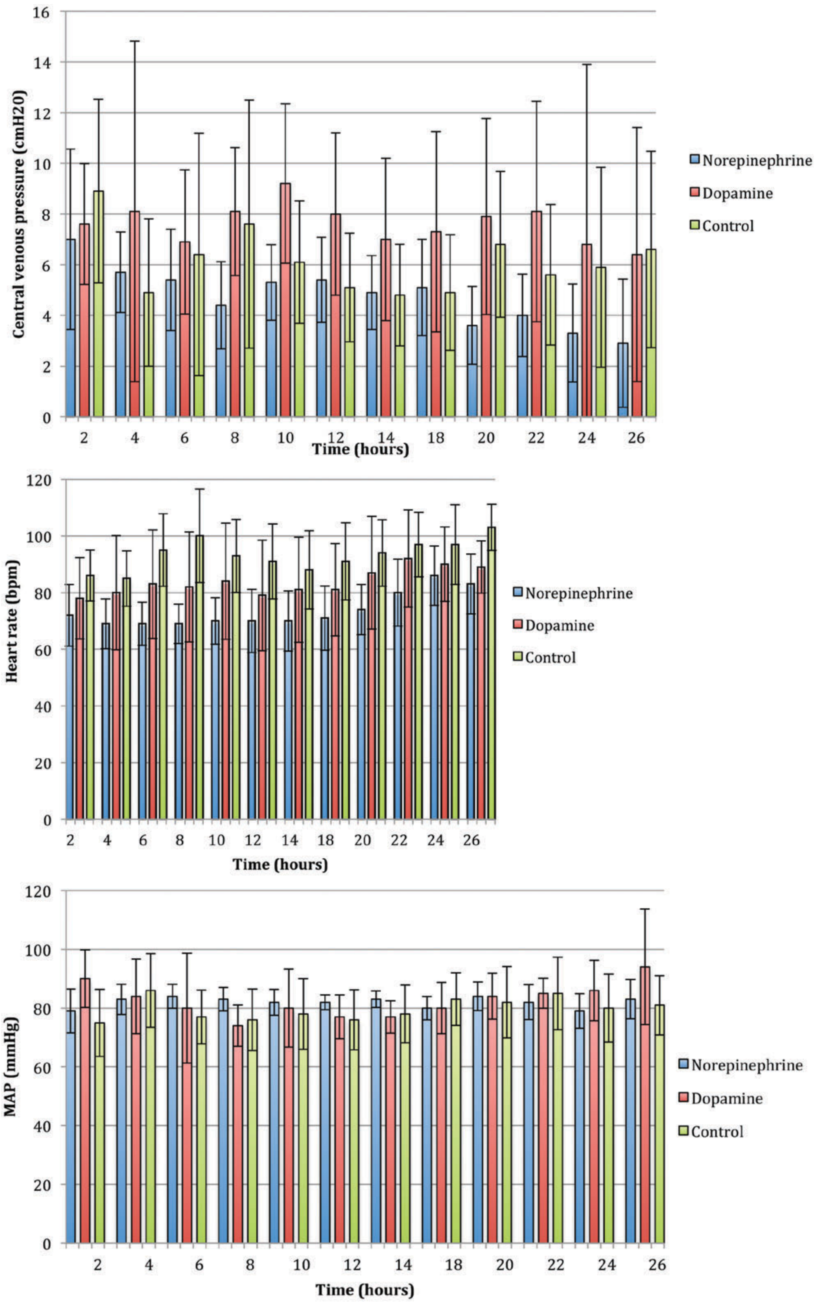
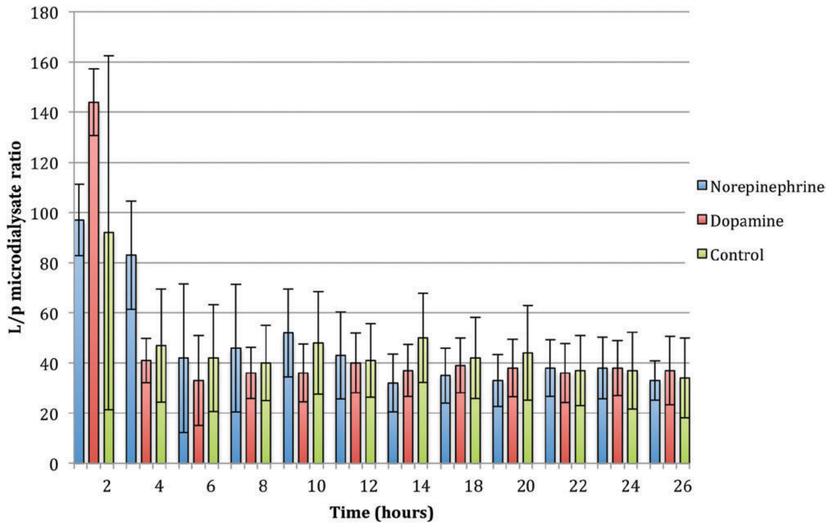



**Fig. 1.** (*Above*) Mean central venous pressure measurements and confidence intervals per unit of time among the study group patients after head and neck cancer ablative surgery and microvascular reconstruction. (*Center*) Mean heart rate measurements and confidence intervals per unit of time among the study group patients after head and neck cancer ablative surgery and microvascular reconstruction. (*Below*) Mean arterial pressure (*MAP*) measurements and confidence intervals per unit of time among the study group patients after head and neck cancer ablative surgery and microvascular reconstruction.



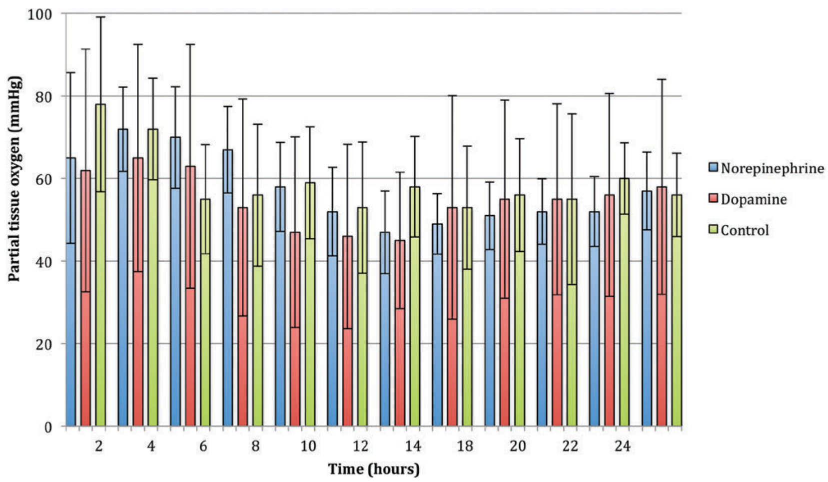




**Fig. 2.** (*Above*) Mean microdialysate flap lactate-to-pyruvate (*L/P*) ratio values and confidence intervals per unit of time in study groups of patients undergoing head and neck cancer ablation and microvascular flap reconstruction. (*Below*) Mean partial tissue oxygen readings and confidence intervals per unit of time in study groups of patients undergoing head and neck cancer ablation and microvascular flap reconstruction.

reconstruction often experience systemic changes caused by prolonged major surgery with tissue trauma, fluid loss, and possible hypothermia. These factors, combined with patient comorbidities and use of vasodilator sedatives such as propofol, place patients at a great risk for hypotension. Control of intraoperative and postoperative blood pressure and avoidance of hypotension is a determining factor for adequate microvascular flap perfusion.[2,8] Patient postoperative management has been a matter of debate in the reviewed literature. In our clinic, the protocol is patients undergoing a standard period of 24 hours of postoperative sedation for adequate resuscitation, pressure management, and comfort.

The use of vasopressors to maintain sufficient blood pressure in reconstructive surgery without adverse effects has been actively studied.[9-15] The physiopathology of the actions of vasopressors is well known. Norepinephrine reacts very specifically with α-receptors in the peripheral vessels as opposed to the β-receptors in the heart. In contrast,

**Table 2. Mean Arterial Pressure and Heart Rate Measurements among the Study Group Patients after Head and Neck Ablative Surgery and Microvascular Reconstruction**

| Study Group | Vasoactive Drug (mg) | MAP | HR |
|---|---|---|---|
| Norepinephrine | Levophed, 9.8 (range, 3–21) | 83 ± 2 | 73 ± 9 |
| Dopamine | Abbodop, 558 mg (range, 144–1710) | 79 ± 7 | 86 ± 20 |
| Control | Levophed, 2.9 (range, 1–4*) Abbodop, 8.8† | 82 ± 8 | 89 ± 15 |

MAP, mean arterial pressure; HR, heart rate.
*Three patients.
†One patient.

dopamine has both adrenergic and dopaminergic actions. Whereas the effects of dopamine are more dose-dependent, smaller doses almost exclusively affect the β-receptors of the heart, which raises the heart rate, whereas larger doses mainly affect the peripheral vasculature. Dopamine has properties distinct from dobutamine in that it is a naturally occurring catecholamine with fewer inotropic and arrhythmogenic effects and greater effects on blood pressure.

The use of vasopressors is considered a danger to flap survival and thus crystalloid infusion is generally preferred to maintain the mean arterial pressure level.[2] Early experimental animal models with free flaps showed that the use of vasopressors could potentially lead to vasoconstriction in the flap microcirculation.[16,17] This is based on the fact that denervated tissue seems to preserve some of its previous adrenergic control with higher vasoconstrictor reactivity to α-adrenergic drugs such as norepinephrine.[9,18] In contrast, some clinical studies have demonstrated that intraoperative use of vasopressors has no negative effects on the microvascular flap success rate.[10,11]

The results of recent studies measuring flap blood flow together with our results indicate that the vasoconstrictive effect of systemically administered norepinephrine in denervated free flaps is markedly attenuated in the acute phase after microvascular reconstruction.[1] A lack of denervation-induced hypersensitivity to vasoconstriction produced by α-adrenergic agents is also observed in pedicled flaps.[18] Autonomic nerve fibers running along the anastomosed vessels are disrupted in free-flap surgery, which changes the response of the vasodilated flap vessels to vasopressors. This phenomenon is significant and emphasizes the importance of studying metabolic and circulatory changes in the flap itself during treatment with different vasopressors. The results of our study apply only to head and neck patients undergoing reconstruction with radial forearm flaps. Further research should be performed to study the effect of vasopressors on perforator flaps and in other anatomical areas such as lower limbs, to support its generalized use.

Scholz et al. evaluated the effect of dobutamine on free-flap blood flow in arterial anastomosis with an ultrasonic flowmeter.[3] Dobutamine improves free-flap perfusion. Eley et al. reported promising results demonstrating that norepinephrine causes less vasoconstriction in the free flap than in the control skin during the perioperative period.[1] Thus, the flap skin blood flow increases with an increase in the arterial blood pressure. Eley et al., however, also stated that acceptance of a small vasoconstrictor effect in return for a significant improvement in flap perfusion requires further validation to fully address concerns about the adverse effects of α-adrenergic agents on free tissue transfer. In their study, laser Doppler velocimetry was used to measure the skin blood flow. Our findings support the safe use of norepinephrine and dopamine as vasopressors if necessary, at least during the first 72 hours after microvascular anastomosis. Mean arterial pressure was successfully increased with both agents. The continuous tissue partial pressure of oxygen and lactate-to-pyruvate ratio values in the flaps did not differ significantly between the norepinephrine, dopamine, and control groups. These results provide further evidence that the use of norepinephrine and dopamine to maintain sufficient mean arterial pressure does not have adverse effects on free-flap metabolism and circulation.

The patients in our study were treated with the objective of minimizing complications and side effects. Therefore, the infusion speed of the vasoactive drug was monitored tightly to maintain a preset mean arterial pressure range. In contrast, the drug dosage was fixed beforehand in most of the previous studies, independent of the mean arterial pressure measurements.[1,13,14,19] Even with close monitoring of the infusion speed, adverse effects were observed in the present study. We observed a heart rate increase in the dopamine group, which required a reduction in the dose of the vasoactive drug. In three patients treated with dopamine, the preset maximum dosage of infusion was reached and yet the mean arterial pressure measurements remained low. This phenomenon was not observed in the norepinephrine group. For volume maintenance, all study patients were treated with crystalloids. Blood derivatives were administered based on the patient's hemoglobin values, comorbidities, estimated blood loss during surgery, and overall condition. The study patients' blood loss was minimal and none required blood transfusion.

The Licox polarographic probe has gained great popularity in the neurosurgical field and is a surgically implanted probe through which electrochemical changes allow for measurements of oxygen partial pressure of the tissue.[20] Use of this method has become standard for head and neck free flaps in our unit. Reconstructive surgeons quickly adopted the method for monitoring microvascular flaps, especially buried flaps. Our team has published a positive experience with this valuable tool.[21] Microdialysis allows for measurement of tissue glucose, pyruvate, and lactate concentrations, and analysis of their ratio predicts the presence of ischemia and aids the plastic surgeon in deciding whether the patient requires reoperation. In this method, a minicatheter is placed in the flap subcutaneous tissue and the metabolites are sampled at various time intervals.[22,23] The Licox and microdialysate probes located in the flap subcutaneous tissue provide uniform information about flap perfusion. Interestingly, the metabolite lactate-to-pyruvate ratio values found in our study were higher than the expected range (>22 to 25) but remained constant throughout the observation period. The reason for this is unknown.

## CONCLUSIONS

Although the use of vasopressors after microvascular flap reconstruction remains controversial, there are few prospective studies in this area. Our research provides new information on free-flap metabolism and circulation when norepinephrine or dopamine is used as a vasopressor to maintain sufficient mean arterial pressure in patients undergoing head and neck reconstruction. Microvascular flaps were monitored using two strongly sensitive methods that quantify tissue perfusion by partial tissue oxygenation and microdialysate metabolites, making our findings reproducible. The results indicate that norepinephrine and dopamine may be safely used during the immediate postoperative period after reconstructive head and neck microvascular surgery with the radial forearm flap. Dopamine doses must be significantly higher to maintain an optimal mean arterial pressure. Therefore, the risk of side effects is greater, and dopamine should be used with caution.

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# PUBLICATION
# IV

**The effect of dexmedetomidine on microvascular flap perfusion as depicted by tissue oxygen tension and microdialysis after reconstruction in head and neck cancer surgery**

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Submitted