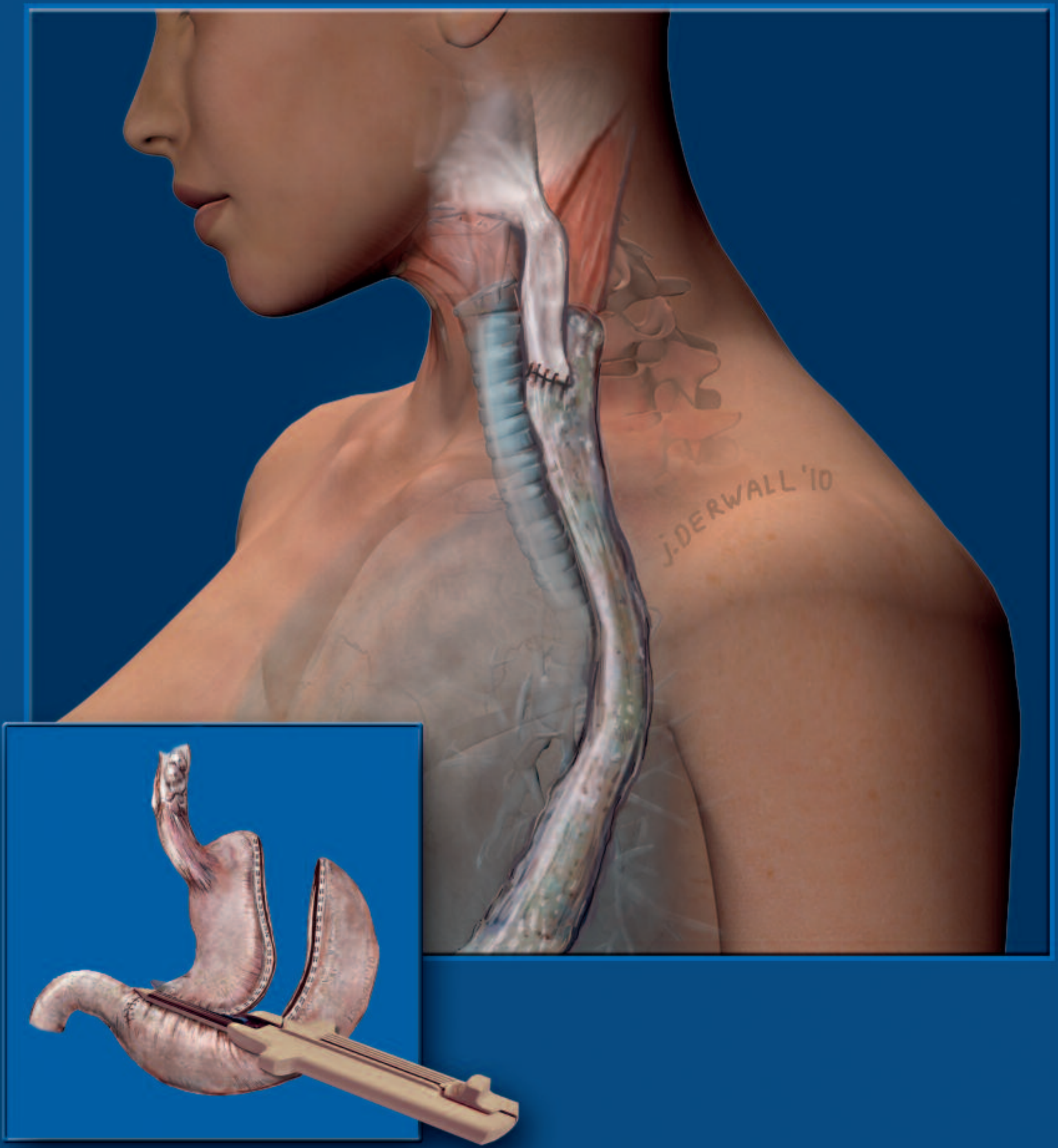
Gastric Microcirculation and Respiratory Morbidity following esophagectomy



Marc Buise

Gastric Microcirculation and Respiratory Morbidity following esophagectomy

Microcirculatie van de maag en respiratoire morbiditeit na slokdarm resectie.

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ERASMUS UNIVERSITEIT ROTTERDAM

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CONTENT

1. Introduction

1.1. INTRODUCTION

Advances in anesthesia during the last 4 decades have resulted in substantial decreases in morbidity and mortality after surgery[1]. Previously, anesthetists focused mainly on the assessment of anesthetic-related complications and traditional measures of postoperative morbidity. One of the challenges of modern anesthesia is the necessity to contribute to postoperative recovery and quality of life as part of a multidisciplinary team. The starting point for changing perceptions and standardizing approaches to perioperative management lies in improving communication within the team. For the anesthesiologist, this involves attention to the patient's wishes as well as to perioperative management, ventilation strategies, postoperative pain management, and early mobilization[2,3]. Similarly, surgeons should be willing to discuss and vary the operative technique according to patient physiology and characteristics[4].

Esophagectomy is a high-risk surgical procedure associated with tremendous postoperative morbidity and mortality[5] and provides a good example of a complicated procedure in which a multidisciplinary approach is required. For these patients, it is unlikely that a single intervention will show a benefit with respect to outcome; an approach that addresses several factors and shows effects on outcome or has promising benefits is necessary. A multimodal approach may improve the infrastructure for management of these patients in high-volume centers, resulting in earlier recognition and better treatment of complications [6,7]. Brodner described the first multimodal approach for esophagectomy 10 years ago[8]. He reported a significant decrease in intensive care unit stay after esophageal resection by combining thoracic epidural analgesia, early tracheal extubation, and forced mobilization and concluded that analgesia and blockade of the perioperative stress response, combined with other aspects of postoperative therapy, can improve recovery. These clinical pathways, along with restricted fluid management, are helpful when incorporated into a multimodal approach[9,10,11].

Clinical pathways succeed only if all parties feel that they are part of the process and take responsibility as a team for patient complications. Successful strategies for esophagectomy may improve morbidity and allow the emphasis to shift from postoperative survival to other factors such as cancer survival and quality of life[12]. Increased communication between anesthetists and surgeons has the potential to result in well-defined clinical pathways for patients with esophageal cancer. In this approach, the anesthetist plays a central role in the treatment of high-risk patients. We should remember that the postoperative recovery process begins when the decision to operate is made. A short history of esophagectomy is provided below. Complications and possible solutions are described in section 1.3.

1.2. EARLY HISTORY OF ESOPHAGECTOMY

The esophagus is a muscular tube through which food passes from the mouth and throat to the stomach. Esophageal cancer is a malignancy of the esophagus, and clinical features include difficulty swallowing, problems with passage of food, and pain. At the beginning of the 20th century, the German surgeon Ferdinand Sauerbruch (1875-1951), one of the leading surgeons of that era, considered that cancers in the mid-esophagus were inoperable for 3 reasons: (1) they were inaccessible; (2) damage or division of the nervi vagi resulted in instant death; and (3) closure of the upper stump of the esophagus was prohibitively dangerous. However, at the 1913 annual meeting of the surgical section of the American Medical Association, Franz J. A. Torek (1861-1938) reported the first successful resection of the thoracic esophagus in a 67-year-old female patient (Fig. 1). After posterolateral thoracotomy, the nervi vagi were carefully dissected, and the esophagus was lifted above the diaphragm and moved well into the neck. The upper stump of the esophagus was sutured to a separate anterolateral incision, which later served as the proximal end of a gastrostomy tube bridge to a previously constructed gastrostomy. At the end of the operation of 2 hours and 27 minutes, hot coffee, whiskey, and a strychnine-enema were administered, and the patient lived an additional 13 years[13]. Not every patient was that lucky, and high mortality in response to transthoracic resection led to attempts at different techniques of esophagectomy such as transhiatal esophageal resection and a 2-phase approach[14,15,16].

Figure 1. Torek's patient on the 12th postoperative day. The gastrostomy tube was introduced into the esophagus whenever the patient desired to swallow.

A breakthrough in thoracic operations occurred mainly as a result of developments in the field of anesthesiology, along with surgical courage. At the beginning of the 20th century, operations on the thorax continued to involve fatal complications such as pneumothorax. In 1904, Sauerbruch developed a negative-pressure chamber that maintained normal (spontaneous) respiration, allowing for safe operations of the thorax. However, the chamber was expensive, the surgical time window was limited, and use was restricted predominantly to animal research.

Surgical possibilities improved tremendously after the introduction of positive-pressure ventilation, developed in 1909 by Samuel Meltzer (1851-1920) and John Auer (1875-1948)[17]. To apply positive pressure ventilation, the patient's airway was connected to a ventilator via endotracheal intubation, a technique inspired by the work of Joseph O'Dwyer (1841-1898), who used a steel tube to intubate the trachea in children in cases of respiratory obstruction related to diphtheria. In the case of the first esophagectomy, intubation was performed with the use of a Chevalier-Jackson direct laryngoscope (Fig. 2), with the patient's head extending over the end of the table and supported by an assistant. A silk elastic catheter was placed within the trachea through the vocal cords and was positioned just above the tracheal bifurcation. The tube was then connected to a pressure bottle. Air pressure at 15 mm Hg to 20 mm Hg was pushed through the tracheal tube; a manometer and bottles for ether and humidification were also attached to the bottle (Fig. 3)[18]. After nearly a decade of debate, the Meltzer and Auer technique came into use worldwide[17].

Figure 2. Chevalier-Jackson laryngoscope.

Figure 3. Intratracheal insufflation apparatus, method of Meltzer and Auer. (50th anniversary book American Association for Thoracic Surgery)

1.3. ESOPHAGECTOMY AND ITS COMPLICATIONS TODAY

As described in section 1.2., esophagectomy is associated with a high incidence of complications, the two major ones being gastroesophageal anastomotic leakage or stenosis and respiratory morbidity[19]. High morbidity and mortality rates have led to national and international discussions of centralization of this high-risk surgery[5]. Although rates of complication are similar for lower- and higher-volume hospitals, the likelihood is that complications are dealt with more successfully in higher-volume centers[20,21]. In the Netherlands, centralization has taken place over the last 5 years.

1.3.1. Gastroesophageal anastomotic leakage

Complications associated with gastroesophageal anastomosis include anastomotic leakage (5-26%) and stenosis (12-40%)[22]. Although the causes of these complications are unknown, compromised microvascular blood flow and hypoxia within the gastric tube are believed to be important factors. The in-hospital mortality of patients with anastomotic leakage has been reported to increase to more than 7 times that of patients without leakage[23]. Several techniques have been used to measure gastric blood flow and tissue oxygenation after gastric tube construction[24,25,26].

The decrease in gastric microvascular blood flow after gastric tube reconstruction is a result of the diminished arterial supply to the gastric tube, owing to the ligation of several gastric arteries during the course of the procedure. However, ischemic preconditioning procedures aimed at increased collateral perfusion of the gastric tissue did not improve outcome[27,28]. Venous congestion of the gastric tissue has also been suggested to play an important role[29]. In this respect, it is remarkable that impairment of gastric fundus blood flow occurs in all patients during gastric tube reconstruction, but only a minority of patients develop anastomotic dysfunction. At this point, we can only speculate as to an explanation for this phenomenon[30]. The question that arises is whether it is possible to induce/improve recovery.

1.3.2. Respiratory morbidity

Pulmonary complications, such as pneumonia and respiratory insufficiency, are among the most frequently reported complications that occur after esophagectomy[31]. In 1992, Crozier and colleagues reported the development of pneumonia in half of their patient population[32]. The incidence of pulmonary complications is associated with age, operation duration, proximal tumor location, and surgical technique[23,33]. There is emerging evidence that anesthetic management directly influences the incidence of complications[34]. In 1997, deficiencies in the recognition and management of poorly positioned double-lumen tubes during esophagectomy were noted as a serious contribution to perioperative morbidity[35]. In response to this UK-based enquiry, leading British anesthetists called for the routine use of fiberoptic bronchoscopy and alternative ventilation strategies during 1-lung ventilation for esophagectomy[36,37]. It is recognized that prolonged perioperative hypoxemia and hemodynamic instability are associated with an increased occurrence of pulmonary complications (eg, acute lung injury, adult respiratory distress syndrome)[38].

Esophagectomy is marked by a significant inflammatory response involving proinflammatory cytokine (interleukin-6) release, likely leading to pulmonary morbidity. However, there is no clear cause-and-effect relation between interleukin-6 and the development of lung injury. Nonetheless, the use of a protective ventilatory strategy of low tidal volume during 1-lung ventilation decreases the interleukin-6 level and improves postoperative lung function, often resulting in earlier extubation and perhaps in decreased morbidity[39].

Since 1993, early extubation has been preferred over prolonged mechanical ventilation, although it is not standard practice in every clinic[40]. It has been shown that early extubation decreases the incidence of pulmonary complications, but successful early extubation requires adequate postoperative analgesia[41,42]. Thoracic epidural analgesia is superior to intravenous opiates in achieving adequate analgesia after major abdominal and thoracic surgery[43]. Although evidence is lacking as to its effects on the stress response and immune function after esophagectomy, there are clear benefits of epidural analgesia with regard to pain relief, decreased respiratory complications, decreased length of intensive care stay, and possibly decreased costs. In addition, postoperative epidural analgesia after esophagectomy appears to have beneficial effects on morbidity and mortality[44,45]. Effective thoracic epidural analgesia not only improves postoperative pulmonary function, it increases tissue oxygenation during abdominal surgery, and it might improve gastric blood flow after esophagectomy[46,47].

Current standards for fluid therapy and standard fluid-replacement algorithms for patients undergoing esophagectomy are not evidence-based[48,49]. To prevent compromise of gastric-tube perfusion, hypotensive episodes after esophagectomy have historically been treated with fluid administration, thereby avoiding the use of vasoactive (ie, adrenergic) medications. As a result, the net fluid balance occasionally increases greatly, up to 10 liters in some cases, in the first 24 hours after operation. Previous studies indicated that decreased fluid administration reduced pulmonary complications after esophagectomy without increasing the incidence of anastomotic leakage[8,9,10]. The theory of fluid transposition to an imaginary third space, and the influence of insensible loss during major surgery were discussed in these studies, and the calculated fluid deficit was not replaced. In contrast, studies using goal-directed fluid therapy (based on optimization of stroke volume) during major abdominal surgery found a decrease in postoperative morbidity and hospital stay. However, additional fluid had to be administered to reach this goal[50,51]. The effect of the goal-directed hemodynamic protocol remains unclear at this time.

1.4. THESIS OUTLINE

In the first part of this thesis, we focus on interventions to improve microvascular blood flow after gastric tube reconstruction. **Chapter 2** provides a review of the clinical utility of reflection spectrophotometry for measurement of microvascular hemoglobin oxygen saturation. **Chapters 3 and 4** present results of reflection spectrophotometry and laser Doppler flowmetry studies on the effect of the vasodilating compound nitroglycerin on microvascular blood flow in the gastric tube. **Chapter 5** describes the effect of the combined use of vasopressors and vasodilators on gastric microcirculation in a pig model of gastric-tube reconstruction. In the second part of this thesis, we focus on pulmonary complications. **Chapter 6** describes results of a new anesthetic regimen based on restricted fluid management and early extubation. **Chapter 7** demonstrates the effect of 2-lung, high-frequency jet ventilation on gas exchange and postoperative morbidity after esophagectomy. In **Chapter 8**, questions arising from our research are discussed, and future perspectives are considered.

The studies in this thesis were performed at Erasmus Medical Center (Rotterdam, the Netherlands), a University hospital performing more than 80 esophagectomies annually.

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2. Reflectance spectrophotometry and tissue oxygenation in experimental and clinical practice

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2.1 INTRODUCTION

Maintenance of adequate tissue oxygen delivery (DO2) to the tissue cells can be considered a primary objective in intensive care and peri-operative patient management. Generally, it is believed that tissue hypoxia plays a significant role in the development of organ failure in critically ill patients and is a major factor in the pathogenesis of multi-organ dysfunction. The introduction of regional measurement techniques has highlighted the inadequacy of the information being generated by global measurements of hemodynamic and oxygen-related variables and has focused attention on the processes underlying microcirculatory oxygenation. It should be obvious that an adequate transport of oxygen by the cardiovascular system does not guarantee its delivery to the critical tissues of the body[1]. For this reason, assessment of tissue oxygenation is essential.

The ideal technique for the assessment of tissue oxygenation should provide quantitative, accurate, and reproducible information. In addition, it should clearly distinguish which compartment is being sensed, i.e. arterial, venous microcirculatory or tissue compartments[2,3].

One of the techniques currently in use in both clinical and experimental practice is reflection spectrophotometry. Reflection spectrophotometry, based on absorption and scattering of reflected visible light, can provide information about hemoglobin oxygen saturation and hemoglobin concentration in tissue. Reflection spectrophotometry has been used in animal and clinical studies and is a non invasive technique without the use of special indicator dyes. Basically, reflection spectrophotometry, records the difference in absorption (and partly in scattering) between a standard reference and a sample (tissue) as a form of relative absorbency. Diffuse reflection spectra from biological pigmented structures located in cells can provide us with information concerning basic mechanisms of tissue function. The first measurements of such reflection spectra were performed by Chance in the intact mitochondria[4]. In order to collect a spectrum from oxygenated or partly deoxygenated hemoglobin out of the combined spectra from divers cellular pigments, e.g. cytochromes, an algorithm is needed to extract the relevant information from the raw data. In the past, various types of reflection spectrophotometers have been developed for the assessment of tissue oxygenation, each working with a somewhat different algorithm. The next section will describe the theoretical background and technical details of two types of reflection spectrophotometers. Essentially two classes of devices exist: those working with an algorithm based on the principle of isobestic points (these wavelengths where the curves of oxygenated and deoxygenated hemoglobin intersect), using discreet excitation wavelengths[5], and those reflection spectrophotometers based on the analysis of the full reflection spectra using the theory of Kubelka and Munk as developed in Erlangen[6]. This paper will review the use of reflection spectrophotometry in the experimental and clinical assessment of tissue oxygenation. In our discussion of the literature we will focus on investigations concerning the liver and gastrointestinal tract due to the role of splanchnic dysfunction in the pathogenesis of sepsis, leading to multi-organ failure (MOF)[7,8].

2.2 TECHNIQUE AND THEORETICAL BACKGROUND

A decisive breakthrough in the application of reflection spectro-photometry was achieved by the development of highly flexible micro-lightguides which solved the problem of optimal adaptation of the optical instrument to the organs. Before that time, application of tissue photometry was restricted to completely immobilized organs due to the use of lenses which had to be adjusted. Another major improvement was made by the development of microcomputers with the capacity to perform the required calculations in a short time frame. Nowadays, all the reflectance spectrophotometers are build on the same principal: the visible light of a halogen lamp is passed through a photodiode or bandpass-filter and guided by a micro-lightguide fiber to the tissue of interest. Light waves irradiated into tissue are altered along their course by absorption and scattering within the tissue. Both physical phenomena decrease the intensity of incident light penetrating the tissue. The reflected light from the tissue is collected by detecting micro-lightguide fibers in the same probe and led to a detection unit. With this information, it is possible to calculate a reflection spectrum.

In the late 1970s, Sato and co-workers developed a tissue spectrophotometer (Tissue spectrum analyzer TS-200, Sumitomo Electric Industries, Osaka, Japan)[5,9,10,11]. A reflectance spectrum is obtained in a region between 502 to 687 nm. Ten spectra that have been taken sequentially with variable intervals are stored in a memory system. The computer is programmed to subtract from these data a spectrum obtained from standard white material. In this way, the spectrophotometer records the difference in absorption between a standard reference (absorption almost zero) and a tissue sample according to:

$$[E_{r(tissue)}] = \log I_{r(standard)} / I_{r(tissue)}$$

Where [$E_{r(tissue)}$] is the relative absorbency and $I_{r(standard)}$ and $I_{r(tissue)}$ are the intensity of the diffusely reflected light from the white standard and the tissue, respectively. In order to assess the hemoglobin concentration, the difference between the Er at 569 nm and at 650 nm is determined: $\Delta E_{r(569\text{-}650)}$. Because 569 nm is the isobestic point of oxy- and deoxyhemoglobin (fig.1), at this wavelenght absorption is dependent on the concentration but not on the oxygen saturation status of hemoglobin. At 650 nm there is no hemoglobin absorption at all in this spectrum. Therefore, $\Delta E_{r(569\text{-}650)}$ can be considerd an estimate of the hemoglobin concentration.

Based on the spectral data of the reflected light, an index of the oxygen saturation (ISO_2) of the hemoglobin is generated. The ISO_2 is estimated by a computer using the different degrees of absorption at three wavelengths: 569, 577, and 586 nm. Wavelengths of 569 and 586 nm are isobestic points and 577 is the wavelength of peak absorption of oxyhemoglobin. The following equation is used:

$$ISO_2 = \{ 0.673 \times [E_{r(577\text{-}586)} - 9/17 \times E_{r(569\text{-}586)}] / E_{r(569\text{-}586)} \} \times 100\%$$

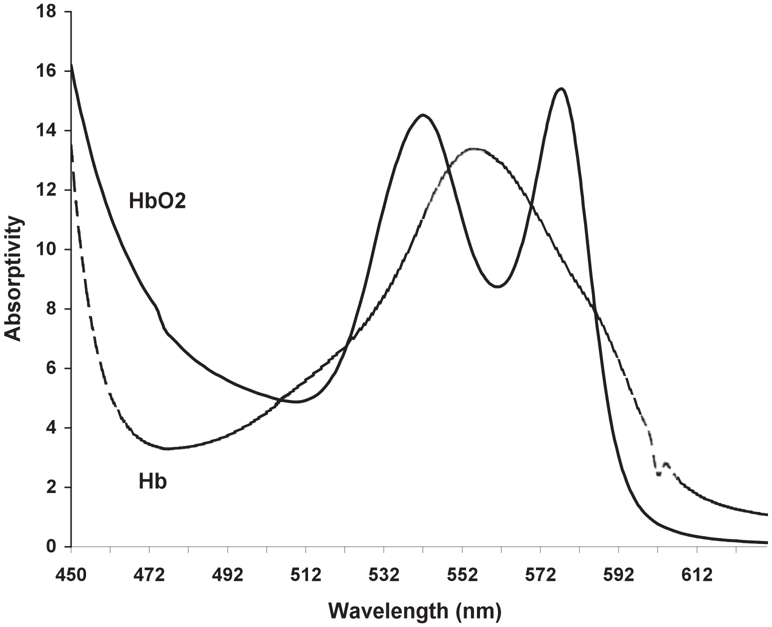

Figure 1. Absorption spectra of oxy- and deoxyhemoglobin.

The spectra of these forms of hemoglobin have their own characteristics with isobestic points at wavelengths of 569 and 586 nm.

In this way, this spectrometer does not use the reflection spectra of all different wavelengths but instead works with the spectra of only three discrete wavelengths.

In the other class of spectrophotometers, such as the Erlangen Micro-lightguide spectroPHOtometer (EMPHO), monochromatic visible light with a wavelength between 502-630 nm is used. By transmission of the remitted light through a rotating interference bandpass-filter disk with a resolution of 2 nm, a diffuse reflection spectrum of 64 wavelengths is obtained. The bandpass-filter allows a sampling velocity of 100 spectra per second. Due to the high sampling rate and the small measuring tissue volume, the device enables measurements of remission spectra in tissue volumes containing only a few capillaries[12]. The algorithm used in the EMPHO is based on the two-flux theory of Kubelka and Munk, describing the optical properties of an absorbing and scattering medium[13,14]. According to this theory, the radiation flux directed inwards a sample is diminished along its path by scattering and absorption. Therefore, the reflectance of light by a medium is dependent on its absorption coefficient and on its scattering coefficient. The two- flux theory was evaluated by Hoffman, who concluded that with some modification the theory is a good approximation to describe tissue reflectance[15,16]. In 1988 Dümmler developed an algorithm for the online evaluation of quantitative hemoglobin oxygenation ($HbSO_2$)[17].

For the quantitative evaluation of $HbSO_2$ out of diffuse reflection spectra from tissues, a mathematical procedure is required, involving the back scattering properties of the tissue and the absorption by hemoglobin and other tissue pigments. Following the derivation of the differential equations used in the Kubelka and Munk two-flux theory, the relation between the wavelength-dependent absorption A(λ) and wavelength- dependent scattering S(λ) of the tissue is formulated as:

$$A(\lambda)/ S(\lambda) = (A0 + C1\varepsilon 1(\lambda) + C2\varepsilon 2(\lambda) / (S0+S1(\lambda))$$

Where A0 is the basic absorption of the tissue, C1 is the concentration of oxygenated hemoglobin, C2 is the concentration of deoxygenated hemoglobin, $\varepsilon 1(\lambda)$ is the wavelength dependent extinction coefficient of oxygenated hemoglobin, $\varepsilon 2(\lambda)$ is the wavelength- dependent extinction coefficient of deoxygenated hemoglobin, S0 is the basic scattering of the tissue and S1 is the wavelength-dependent scattering of the tissue. This relation depends on four parameters A0/S0, C1/S0, C2/S0 and S1/SO.

Based on these four parameters and on the fact that oxygenated hemoglobin has two absorption maxima while deoxygenated has only one single absorption maximum (fig 1.), the determination of spectra from fully oxygenated and fully deoxygenated hemoglobin suffices to calculate the oxygenation state from mixed spectra of unknown saturation:

$HbO_2 = C1 / C1 + C2$

The hemoglobin concentrations are calculated as relative values because only the ratios C1/S0 and C2/S0 can be determined:

$Hbcon = C1 + C2$

Using these calculations, a raw curve is collected, influenced by a lot of noise from the tissue surroundings. To obtain a corrected spectrum, the microcomputer has to compare these raw data with a dark spectrum and a white standard spectrum. Before each measurement, a response spectrum from a standard white subject is obtained. The calculation for the determination of the collected spectrum is shown in the following equation:

$CS = DC – RS / DC – WSt$

where CS is the corrected spectrum, DC is the dark Curve, RS is the raw spectrum and WSt is the spectrum of the white standard. This Dümmler algorithm and its usability in the EMPHO, was validated and improved by Kessler and co-workers (EMPHO II Bodenseewerk Gerätetechnik, Überlingen, Germany)[18,19].

In another spectrophotometer of the same class (O_2C, Lea Medizin Technik, Giesen, Germany), the same algorithm is used as in the EMPHO but the interference bandpass filter disk is replaced by a photodiode, allowing a higher sampling rate of the spectra. Simultaneously, the perfusion of the same volume of tissue can be determined by combining this spectrophotometer with Laser Doppler Flowmetry (LDF). Theoretically, there is no interference between these techniques because of the different ranges of light used in these two optical techniques.

2.3 EXPERIMENTAL AND CLINICAL UTILITY

Reflectance spectrophotometry has been applied in many studies focused on the oxygenation of the microcirculation in the gastrointestinal tract and liver, due to the importance of this region in for instance the development of disease processes in critically ill patients. Sato and coworkers introduced reflection spectrophotometry for the assessment of tissue hemoglobin concentration[5]. It was demonstrated that in the intestine, the penetration depth (the catchment volume) of the spectroscopic reflectance was limited to mucosal and, to a lesser degree, submucosal vessels. They also showed that a change in gastric mucosal Hb concentration reflected a corresponding change in mucosal blood volume, and therefore in gastric mucosal blood flow[5,20,21]. In this way RS was used to assess the perfusion state of tissues. In patients with liver disease, it was observed that the spectral intensity in a normal liver is higher than in cirrhotic livers, indicating that in cirrhotic livers the regional hepatic blood volume was decreased. It also seems that the estimated saturation value in the hepatic tissue capillary blood remained stable until the local blood hemoglobin concentration decreased to 0.55 absorbance. A further decrease in absorbance accompanies the lowering of the estimated saturation values which suggests that, concomitant with the decrease in blood supply, the amount of oxygen available for the liver decreases. They concluded that reflection spectrophotometry measures both qualitatively and quantitatively the absorption of hemoglobin, thereby determining the hemoglobin concentration and the hemoglobin oxygen saturation. Compared to regional hepatic blood flow measurements by radioisotope clearance technique, chemical liver function, and indocyanin green tests (ICG), reflection spectrophotometry can be used to assess local hepatic blood flow[10 11].

Expanding on the possibilities to determine tissue blood flow using reflection spectrophotometry, Leung and coworkers compared reflection spectrophotometry to gastric mucosal blood flow measurements with hydrogen gas clearance, laser Doppler flowmetry, and intravital microscopy flow measurements[22]. The aim of their studies was to validate reflection spectrophotometry against other measurement techniques of mucosal blood flow, and to define the limitations of reflection spectrophotometry in assessment of gastroduodenal mucosal perfusion. Having studied the patterns of mucosal Hb concentration and saturation under conditions of well defined hemodynamic changes in the mucosa, they concluded that different local hemodynamic conditions generate characteristic changes in mucosal Hb concentration and saturation as measured with reflection spectrophotometry.

Hyperemia causes an increase in mucosal Hb concentration and mucosal saturation; mucosal ischemia due to congestion leads to an increase in mucosal Hb concentration and a decrease in mucosal saturation; and ischemia without congestion causes a decrease in both mucosal Hb concentration and saturation. Other flow measurement techniques, such as laser Doppler flowmetry, hydrogen gas clearance, and microspheres cannot distinguish between ischemia associated with congestion and ischemia without congestion. This can be considered a major advantage of reflection spectrophotometry[23,24]. However not under all conditions reflection spectrophotometry correlates well with tissue blood flow; during changes of hemoglobin saturation, due to hypoxia and hyperoxia, laser Doppler flowmetry but not reflection spectrophotometry provided a good reflection of gastric microvascular blood flow. During acute normovolemic anemia neither laser Doppler flowmetry or reflection spectrophotometry corresponded with changes in gastric mucosal blood flow[25,26].

Reflection spectrophotometry is used in many investigations concerning the local autoregulatory mechanisms in the microcirculation under septic conditions, independent of systemic cardiopulmonary effects[27]. For instance, Radermacher and coworkers observed an autonomous behavior of the hepatic and intestinal microvascular $HbSO_2$ during endotoxemia, irrespective of simultaneous changes in the systemic circulation[28,29]. Local hemodynamics are regulated by mechanisms independent of the systemic circulation. In order to gain insight in these mechanisms, for instance in the microcirculation of the intestinal serosa and mucosa, the effect of vaso-active medication on the mucosal and serosal microvascular oxygenation has been studied[30,31,32,33,34,35,36]. A discrepancy between intestinal microvascular blood flow and $HbSO_2$ during sepsis has also been found: the mucosal capillary hemoglobin saturation was well preserved, despite a marked heterogeneity of the microcirculatory blood flow as observed with Orthogonal Polarization Spectral (OPS) Imaging[37,38]. These results demonstrate that the relation between microvascular blood flow and tissue oxygenation is influenced by local regulatory processes. Although these mechanisms are not yet fully understood, it is clear that with data provided by reflection spectrophotometry, more insight can be gained in the regulation of tissue oxygenation during disease processes.

Reflection spectrophotometry has also been used to investigate the effects of therapeutic interventions, such as mechanical ventilation, on tissue oxygenation. Fournell and coworkers demonstrated that the use of Positive End Expiratory Pressure (PEEP) during mechanical ventilation can have a detrimental influence on the oxygenation of the gastric mucosa[39]. In a clinical study they expanded on this research by the use of combination of RS and LDF, the so-called oxygen to see: O_2C (Fournell et al., unpublished data). With this device, oxygenation (reflection spectrophotometry) and blood flow (laser Doppler flowmetry) in tissue can be measured simultaneously in the same place.

Our research group has recently started to use the O_2C during the intra-operative assessment of hepatic microvascular oxygenation during liver transplantation. The rapid changes in microvascular blood flow and hemoglobin saturation during the reperfusion-phase could be recorded in real-time and are shown in figure 2. The portal vein and the hepatic artery were opened simultaneously after 24 seconds in the recorded time frame. In the absence of blood flow and hemoglobin in the preservation fluid, the saturation value of 35% is produced by the reflection spectra of intracellular cytochromes. Although RS appears to have more problems with very fast changes compared to laser Doppler flowmetry, in ten seconds a stable signal was obtained during these measurements.

The O_2C was also applied by our group for the assessment of tissue oxygenation and microvascular blood flow in the upper part (fundus) of the stomach during gastric-tube reconstruction after esophagectomy, a treatment for esophageal cancer.

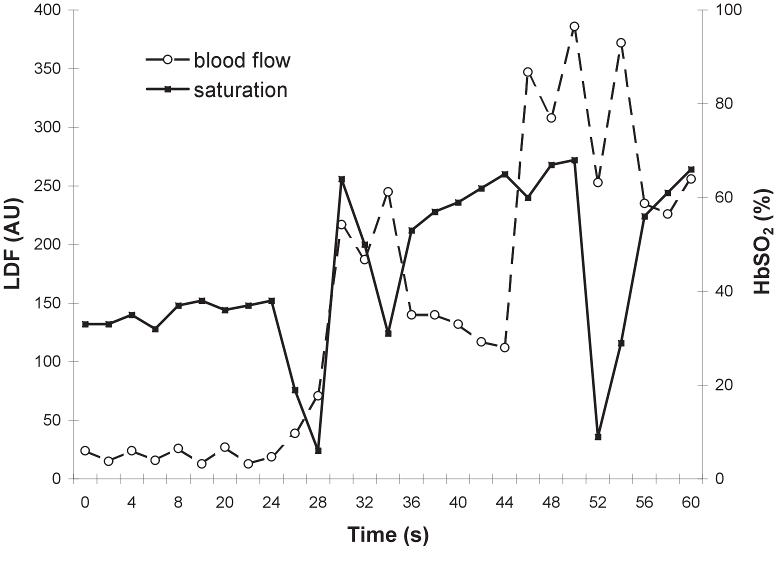

Figure 2. Hepatic microvascular blood flow and $HbSO_2$ during reperfusion after liver transplantation in real time. To create a rapid recirculation of the transplanted liver the hepatic artery and portal vein were opened simultaneously. Both LDF and RS were able to follow these changes.

This part of the esophagal tube in particular is notorious for its insufficient circulation following the reconstruction, leading to anastomotic leakage and the development of strictures[40,41]. In figure 3, we show the data of one patient during five steps of the reconstruction. T0, is the baseline measurement, is the phase before manipulation of the vascularisation of the stomach. T1 is when the stomach, normally dependent for its blood supply on four big arteries, has to survive on only one artery: i.e. the right gastro-epiploïc artery. Then, a gastric tube is created from the stomach with stapling devices, impairing microvascularistion (T2). During surgery, the stomach is pulled up through the thorax, to the neck of the patient. At T3 the gastric tube has been pulled up to the cervical end of the esophagus, and the anastomosis is made. In an attempt to improve gastric microcirculatory blood flow, nitroglycerine has been applied topically (T4). Although the microvascular blood flow decreased tremendously during the procedure; $HbSO_2$ actually increases during the procedure. The local application of an NO-donor increased microvascular blood flow but it showed no impressing changes in $HbSO_2$. These simultaneous measurements of flow and oxygenation on the gastric tube have not been performed before, and more research into the nature and the consequences of these findings is planned for the future.

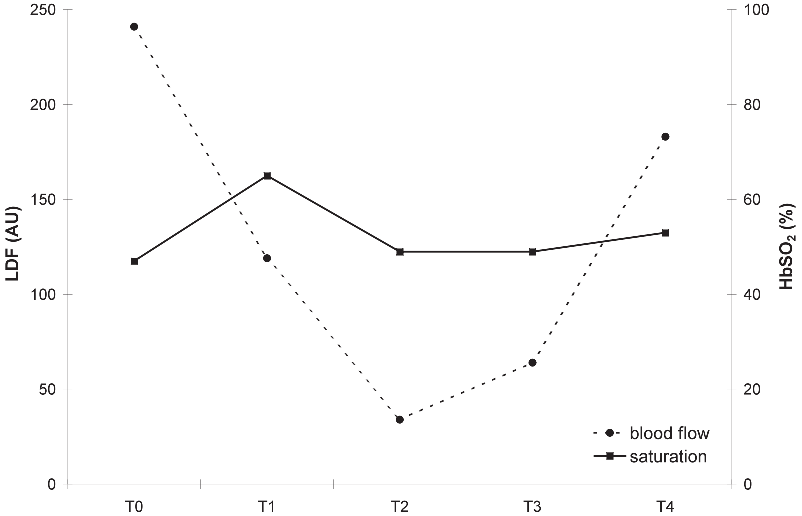

Figure 3. Gastric fundus microvascular blood flow and $HbSO_2$ during gastric tube reconstruction. In the first 4 steps creation of the gastric tube showed a decrease in microvascular blood flow as measured with LDF, but an increase in $HbSO_2$ as measured with RS. Local application of nitroglycerine (T4) is increasing microvascular blood flow but has very less effect on HbO_2.

Since its introduction in 1979, reflection spectrophotometry has been used in many studies as a clinically applicable technique for the measurement of hemoglobin O_2 saturation and hemoglobin concentration in the microcirculation. Meanwhile, validation of reflection spectrophotometry has been proven very difficult due to problems with both the definition of a golden standard, and the creation of an *in vitro* model with similar absorption and scattering properties as living tissue but without oxygen extraction. Only two authors have claimed the *in vitro* validation of this technique. Krug and Kessler have validated the EMPHO using a solution of intralipid and erythrocytes in a model existing of a micro-oxygenator and microflow chamber[18]. In this study, the aim was to validate the algorithm and its accuracy with different absorbency and scattering properties. After some modifications of the Dümmler algorithm, which had been adjusted by other researchers already, they created hemoglobin spectra that correlate with the remission spectra from isolated hemoglobin as known from literature[42]. Validation of the algorithm of the EMPHO for the splanchnic region was performed in 1994 by Hasibeder and coworkers[31]. They used a suspension of homogenized hemoglobin free intestinal mucosa in heparinized pig blood and simultaneously recorded tissue pO2 and hemoglobin saturation. They demonstrated a correlation between oxygen measurements with Clark-type surface electrodes, reflection spectrophotometry and hemoglobin oxygen saturation measurements with a hemoximeter for $HbSO_2$ values between 20 - 80%. Our group has applied a similar approach by combining the O_2 dependent quenching of palladium (Pd)-porphyrin phosphorescence, a technique described in previous papers[2], with $HbSO_2$ measurements in the pig intestine using O_2C.

In figure 4 it is shown that an *in vivo* hemoglobin oxygen saturation curve can be created. Independent of the tissue PO_2, the maximum saturation of the tissue hemoglobin appears to be ± 80 %. By combining these data, more information is provided on the relation between hemoglobin oxygen binding and tissue oxygenation. The available reflection spectrophotometry devices however do have limitations. For instance, not all investigations show corresponding results. The baseline saturation measurements of Haisjackl et al. do not correspond with those from Leung et al.[22], although the relative changes after comparable interventions were similar. This might be due to three reasons. The penetration depth being dependent on the intensity of the incident light and the distance between incident and detected lightguides, the lights and lightguided fibers were not identical. In addition, the optical properties of the tissue of each organ will result in different scattering and absorption properties of the incident and reflected light, making it difficult to extrapolate parameters

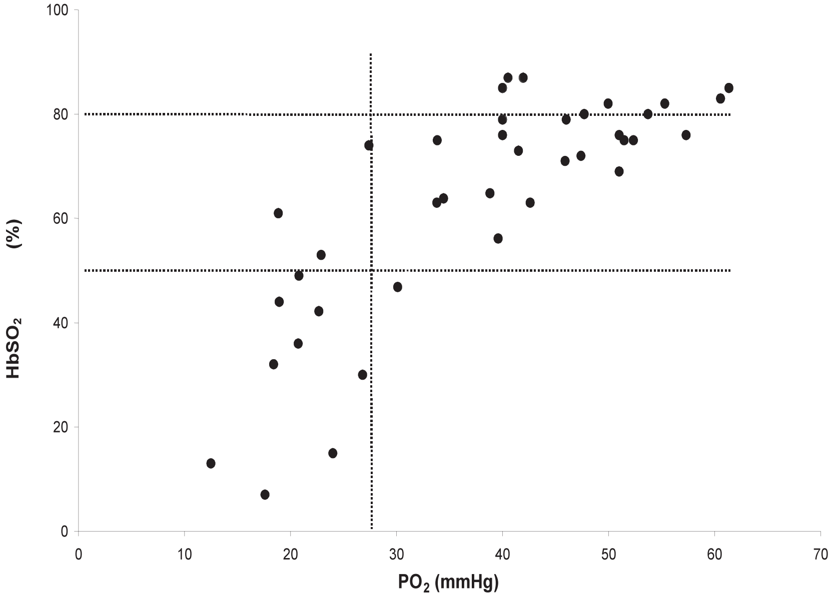

Figure 4. Microvascular HbSO$_2$ (O$_2$C) vs Microvascular PO$_2$(Pd-Porphyrin)
An in vivo hemoglobin oxygen saturation curve can be created between 20 and 80 % saturation.

such as catchment volume between different tissues. Another reason may be the difference between the two methods (algorithms) used in the two reflection spectrophotometers. To our knowledge there is no study comparing these two forms of algorithms and technical devices.

CONCLUSION

Reflectance spectrophotometry is a powerful technique for the assessment of hemoglobin oxygenation in tissue. Despite its limitations it can be concluded that reflection spectrophotometry allows detection of changes in capillary hemoglobin saturation and that this technique can be applied in patients suffering from sepsis. Therefore, this may be a useful clinical resuscitation tool, especially in the light of the recent microcirculatory measurements of sublingual microcirculation performed by us and De Backer et al. using OPS imaging. De Backer et al. have shown that microcirculatory shut down is a characteristic of sepsis, with the severity of shutdown correlating with patient outcome. We have confirmed this view in pressure resuscitated septic shock patients, and showed that such microcirculatory shut down can be reversed by recruitment of the microvessels by vasodilator therapy[43,44]. Whether such techniques will provide clinically useful resuscitation end points still has to be determined.

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3. The effect of nitroglycerin on microvascular perfusion and oxygenation during gastric tube reconstruction

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Anesth Analg. 2005;100:1107-11.

ABSTRACT

Background

Esophagectomy followed by gastric tube reconstruction is the surgical treatment for patients with esophageal cancer. Complications of the cervical anastomosis are associated with impaired microvascular blood flow (MBF) and ischemia in the gastric fundus. Aim of the present study is to differentiate whether the decrease in MBF is a result of arterial insufficiency or is due to venous congestion by the simultaneous assessment of MBF, microvascular hemoglobin O2 saturation ($\mu HbSO_2$), and microvascular hemoglobin concentration (μHbcon), during different stages of gastric tube reconstruction.

Methods

In 14 patients, MBF was determined with laser Doppler flowmetry, and $\mu HbSO_2$ and μHbcon with reflectance spectrophotometry. Following completion of the anastomosis, nitroglycerin was applied at the fundus.

Results

Although MBF did not change significantly in the pylorus, in the fundus MBF decreased progressively during surgery from 210 ± 18 AU at baseline (normal stomach) to 52 ± 9 after completion of reconstruction (mean ± SEM; $p<0.05$). There was no change in $\mu HbSO_2$ and μHbcon during the reconstruction. Following application of nitroglycerin, MBF doubled.

Conclusion

We conclude that MBF but not $\mu HbSO_2$ and μHbcon decreased during gastric tube reconstruction. This decrease might be due to venous congestion which can partly be counteracted by application of nitroglycerin.

This study was awarded in a poster session at the annual meeting of the European Society of Intensive Care Medicine, Amsterdam NL, 2003

INTRODUCTION

Esophagectomy followed by gastric tube reconstruction is the surgical treatment of choice for patients with cancer of the esophagus[1]. This operation is associated with high morbidity and mortality rates; complications associated with the gastro-esophageal anastomosis are anastomotic leakage (5-26%) and stenosis (12-40%)[2]. Although the cause of these complications is still unknown, compromised microvascular blood flow and hypoxia of the gastric tube are thought to be important factors. Perioperative evaluation of the tissue perfusion of the gastric tube is mainly based on clinical signs and therefore subject to the judgement of the operating surgeon. Monitoring of systemic hemodynamic and oxygenation parameters is not sufficient to ensure that the gastric tissue is provided with an adequate amount of oxygen. Therefore monitoring at the level of the tissue itself is necessary[3]. In order to establish an objective measurement of both tissue blood flow and tissue oxygenation, accurate and clinically applicable techniques are required.

In the past, the microvascular blood flow (MBF) in the cervical esophagogastrostomies has been studied with laser Doppler flowmetry (LDF), showing a decrease in MBF and an association between decreased MBF and impaired anastomotic healing[4,5,6]. A perioperative decrease in tissue oxygen tension was observed using Clark-type tissue electrodes[7,8], suggesting that MBF and tissue PO_2 are related during gastric tube surgery. This is supported by the results from a pig model of gastric tube reconstruction in which a simultaneous decrease in MBF and tissue oxygen tension was observed in the perioperative period, using LDF and Clark-type electrodes, respectively[9]. These observations have been attributed to arterial insufficiency of the gastric tube, due to the technique of gastric tube reconstruction. However, we think that there is also a role for venous congestion in the decrease of MBF. An impaired arterial blood supply would lead to a pale appearance of the tissue whereas venous congestion gives a more dark character of the tissue. It is our observation that the fundus of the stomach has a blue color at the end of gastric tube reconstruction.

To our knowledge, no clinical study combining the assessment of MBF and tissue oxygenation has been performed to date. The aim of the present study is to differentiate if the decrease in MBF is a result of arterial insufficiency or is due to venous congestion by the simultaneous assessment of MBF, microvascular hemoglobin O_2 saturation ($\mu HbSO_2$) and microvascular hemoglobin concentration (μHbcon) at the gastric serosa, during different stages of gastric tube reconstruction. We hypothesized firstly that a decrease in MBF, in combination with a decrease in $\mu HbSO_2$ and μHbcon would be caused by arterial insufficiency. Secondly, a decrease in MBF with a simultaneous increase in μHbcon and a preservation of $\mu HbSO_2$ would be due to venous congestion. Finally, in the case of venous congestion the topical application of NTG may restore MBF by vasodilatation but may not restore the MBF in case of impaired arterial blood supply due to ligation of the arteries during reconstruction. More insight into the pathophysiological processes underlying microvascular disturbances will be helpful in the prevention of complications in patients undergoing esophageal resection.

METHODS

With approval of the local institutional human investigations committee, and after obtaining written informed consent, microvascular measurements were performed in 14 patients. Twelve male and two female patients were scheduled for elective esophageal resection and reconstruction. All patients were American Society of Anesthesiologists physical status I and II, and were aged between 42 and 78 year.

Anesthesia

General anesthesia was induced with propofol (1-2 mg/kg) or etomidate (0.15-0.3 mg/kg) sufentanil (0.2-0.4 μg/kg) or fentanyl (5-10 μg/kg) and a non-depolarizing muscle relaxant. Anesthesia was maintained by inhalation anesthesia with a combination of isoflurane (0.8-1.2 end-tidal %) and air in all patients. No patient received nitrous oxide. Before the induction of general anesthesia, a thoracic epidural catheter was placed to provide peri- and postoperative analgesia. In all patients epidural blockade was started with a bolus of 12 mls, 1.5 ml per segment from T4 to T12, bupivacaine 0.175 % and sufentanil (2 μg/ml), before starting the operation. After 90 minutes bupivacaine 0.125% combined with fentanyl 2.5 μg/ml was started in a dosage of 10 ml/h.

All patients were ventilated with volume control, 8 ml/kg and a frequency to achieve an end-tidal CO_2 of 4.5 – 5.5 kPa. FiO_2 was 40% and PEEP was set at 5 cm H_2O. In all patients standard hemodynamic monitoring was used including radial arterial blood pressure and right atrial pressure (RAP) measurements through a central venous catheter placed in the left internal jugular vein. Fluid management was performed using hydroxyethyl starch (Voluven®, Fresenius Kabi, ‘s Hertogenbosch, the Netherlands) and lactated ringer's solution in order to maintain mean arterial pressure above 60 mm Hg and RAP between 12-16 mmHg (measured RAP – 1/3 of ventilation plateau pressure). Arterial oxygen and carbon dioxide partial pressures, hemoglobin concentration and hemoglobin saturation were determined (ABL 707, Radiometer, Copenhagen, Denmark).

Operation technique

Two operation techniques were used; transhiatal- (13 patients) and transthoracic esophagectomy (1 patient). In both techniques, the gastric tube is constructed by means of ligation of the left gastric artery, the right gastric artery, the short gastric arteries, and the left gastroepiploic artery and then fashioned along the greater curvature. The arterial supply of the gastric tube depends on the right gastroepiploic arterial arcade[10].

Reflection spectrophotometry

Microvascular hemoglobin saturation ($\mu HbSO_2$) is measured using reflectance spectrophotometry (RS). The tissue is illuminated with visible white light (500-630 nm) which is back-scattered mainly by mitochondria and changed in color by hemoglobin according to the oxygen saturation status. This reflected spectrum is detected and analyzed by a spectrophotometer with a frequency of more than 100 times per second. The $\mu HbSO_2$ can be determined according to the equation Hbsat = Cox / Cox + Cdeox, in which Cox is the concentration of oxygenated hemoglobin and Cdeox is the concentration of deoxygenated hemoglobin, expressed as a percentage (%). In addition, the relative microvascular hemoglobin concentration (µHbcon) is calculated as a relative value: Hbcon = Hbox + Hbdeox, in Arbitrary Units (AU)[11,12]. Previously, we have described the clinical usability of RS and its value for the assessment of microvascular oxygenation[3,13].

Laser Doppler Flowmetry

LDF is a well-established technique for the assessment of microvascular blood flow[3,14] which has been used frequently during gastric tube reconstruction[2,4,15]. MBF is determined by analysis of the power spectra of backscattered laser light (820 nm). All moving blood cells in the tissue generate Doppler frequencies that are displayed as powerspectra. The powerspectra show the complete distribution of Doppler shifts, hence a histogram of erythrocyte velocities is measured. The microvascular blood flow value is defined mathematically as the first moment of the Doppler power spectra so it relates to the velocity of the erythrocytes times the number of moving erythrocytes and is described in AU.

The microvascular parameters MBF, $\mu HbSO_2$, and µHbcon were determined simultaneously using the O2C® (Lea Medizin Technik, Giesen, Germany). This device combines the two optical techniques, LDF and RS, in one optic fiber so the measurements were obtained at the same time and in the same place. There is no interference between the two techniques because they are operating in a different lightwave range. We used a flat probe, which contains five optic fibers (fig. 1). The measurement depth is determined by the distance between the illuminating and detecting fibers and by the absorption and reflection capacity of the tissue. The surface diameter of the probe was 14 mm and the distance between the fibers was 6 mm, corresponding with a measurement depth of 4-6 mm.

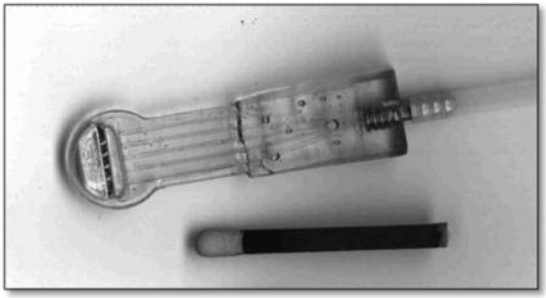

Figure 1. Photograph of the flat probe used in combination with a normal match. The outer diameter of the probe is 14 mm and the distance between the illuminating and detecting fibers is 6 mm (used with permission of Lea Medizin Technik, Giesen, Germany).

STUDY PROTOCOL

After opening the abdomen but before compromising the vascularisation of the stomach, baseline values (T=0) of MBF, μHbSO$_2$, and μHbcon were determined. An average of four measurements (with a time interval of 30 seconds) was obtained from three positions: the pre-pyloric antrum, the corpus at the greater curvature and the fundus of the stomach where the future anastomosis of the gastric tube was expected. The probe was placed by the surgeon, gently touching the surface of the serosal side of the stomach. Pressure artifacts were detected by an obvious decrease in signal in both LDF and RS curves, and a change in configuration of the RS signal. After T=0 the measurements were repeated four times: T=1 after ligation of the left gastric artery, the gastric short vessels, and the left gastroepiploic artery; T=2 after construction of the gastric tube; T=3 after pulling up the gastric tube to the neck. At T=3, measurements at the corpus were not performed due to the intrathoracic position of the reconstruction. At T=4 nitroglycerin (NTG) was applied locally after the completion of the anastomosis. 25 ml of nitroglycerin 10 mg/ml (Nitro Pohl, Transmedico BV, Weesp, the Netherlands) was sprinkled over a 10 x 10 cm gauze. The gauze was then placed at the anastomotic side. After two minutes, the gauze was removed and the microvascular measurements were repeated. Parallel with the microvascular measurements arterial blood samples were taken and systemic hemodynamics were recorded.

Statistical analyses

Values are reported as mean +/- SEM. Each parameter was analyzed using analysis of variance (ANOVA) for repeated measurements. Measurements at the different sites were compared at each stage using one way ANOVA. When appropriate, post-hoc analyses were performed with the Student-Newman-Keuls test. P values < 0.05 were considered significant. All analyses were performed with Graphpad Prism (version 3.0, Graphpad Software, San Diego USA).

RESULTS

Systemic hemodynamic parameters

Mean arterial pressure (MAP) was 71 ± 5 mmHg at T=0 and did not change significantly during the procedure. In 3 patients vasopressors were administered at different stages of the procedure to maintain a MAP above 60 mmHg: once dopamine at T=0, twice phenylephrine at T=1 and T=2. Right atrial pressure (RAP) was 15 ± 1 mmHg at all measurements. Volume resuscitation was performed with mean volumes of 1500 ± 35 ml of colloid and 6430 ± 140 ml of crystalloid solutions. Mean arterial hemoglobin concentration was 9.6 ± 0.3 g/dl at T=0, and decreased to 8.1 ± 0.2 g/dl at T=4. Mean blood loss was 1392 ± 185 ml. Four patients received a blood transfusion, two patients received 1 unit of packed cells and two patients received 2 units. At baseline, mean arterial hemoglobin saturation was 99 ± 0.2%; arterial oxygen tension was 24 ± 3 kPa. Both parameters did not change significantly during the operation. Systemic parameters are shown in table 1. All patients were kept normothermic throughout the procedure.

Table 1. perioperative hemodynamic and blood gas values.

	T=0	T=1	T=2	T=3
Hb	9,6 ± 0,3	9,6 ± 0,3	9,6 ± 0,2	8,1 ± 0,2
PaO_2	23 ± 2,7	23 ± 3,0	25 ± 3,3	25 ± 3,2
$PaCO_2$	4.8 ± 0,4	4.9 ± 0,2	4,8 ± 0,1	4.8 ± 0,2
$HbSO_2$	99 ± 0,0	99 ± 0,0	99 ± 0,0	99 ± 0,0
MAP	71 ± 2,3	76 ± 2,7	77 ± 2,6	70 ± 4,9
RAP	15 ± 1,2	13 ± 0,9	14 ± 1,2	12 ± 1,1

Hb: arterial hemoglobin concentration (g/dl); PaO_2: arterial oxygen tension (kPa); $PaCO_2$: arterial carbondioxide tension (kPa); $HbSO_2$: arterial hemoglobin oxygen saturation (%); MAP: mean arterial pressure (mmHg); RAP: right atrial pressure (mmHg). Data represent mean ± SEM.

Microvascular measurements

Baseline measurements of the gastric microcirculation showed a μ$HbSO_2$ of 65 ± 4% at the pylorus, 66 ± 4% at the corpus and 56 ± 5% at the top of the fundus. The μ$HbSO_2$ values at the pylorus, the corpus and the fundus were the same and did not change significantly during the operation (fig. 2).

At baseline, MBF showed no significant difference at the three measurement sites: 200 ± 18 AU at the pylorus, 207 ± 8 AU at the corpus and 210 ± 11 AU at the fundus. During the following three stages of the operation, only the MBF at the top of the fundus decreased significantly to 52 ± 9 AU. At the pylorus there was no change in MBF (fig. 2). The μHbcon at baseline was 70 ± 4 AU at the pylorus, 66 ± 5 AU at the corpus and 70 ± 2 AU at the fundus. These values were not statistically different and did not change significantly during the operation (fig. 2). For reasons of clarity, only the data from the pyloric part and the fundus are shown because there was no difference between the values from the pyloric part and the corpus.

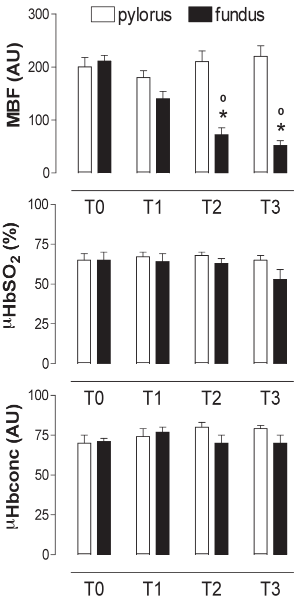

Figure 2. Microvascular blood flow (MBF), ~ hemoglobin saturation (μ$HbSO_2$), and ~ hemoglobin concentration (μHbconc) measured at the gastric pylorus and fundus during gastric tube reconstruction. Only the MBF at the fundus and pylorus decreased, whereas no significant change was observed in μ$HbSO_2$ and μHbconc. Data from the corpus are not shown, but were identical to those from pylorus.

Values represent mean ± SEM. $P<0.05$; * vs T0, ∘ vs other.

When the gastric tube reconstruction was finished, the topical application of NTG at the fundus (T=4) doubled MBF from 52 ± 9 AU to 100 ± 14 AU ($p < 0.05$). The increase in MBF was not accompanied by a statistically significant change in the other microvascular and systemic parameters (fig. 3)

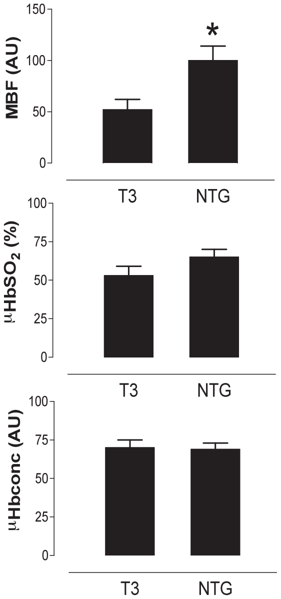

Figure 3. Microvascular blood flow (MBF), ~ hemoglobin saturation (μHbSO$_2$), and ~ hemoglobin concentration (μHbconc) measured near the cervical anastomosis following completion of the gastric tube reconstruction (T3) and after local application of nitroglycerin (NTG). Only MBF could be improved with administration of NTG.
Values represent mean ± SEM. * $P<0.05$ vs T3.

DISCUSSION

The main result of the present study is that during gastric tube reconstruction a decrease in MBF of almost 75% occurs at the fundus without significant change in μHbSO$_2$ and μHbcon. A decrease in gastric MBF has been reported in previous clinical studies[4-6], but this was never related to a simultaneous measurement of μHbSO$_2$ and μHbcon.

According to our hypothesis an increase in μHbcon and gradual decrease in μHbSO$_2$ would be expected to occur in the presence of venous congestion. However, in this respect the short interval of measurement, which was restricted by the limited access to the gastric tissue during surgery, may be a limitation of our study: this effect may be more profound in the postoperative period. Based on these results, it can be concluded that venous congestion plays a role in the decrease of MBF during gastric tube reconstruction.

The importance of venous congestion has already been demonstrated by Murakami et al., who showed a significant increase of MBF after performing a venous anastomosis between the short gastric vein and the internal and external jugular veins[16]. Venous congestion has often been attributed to intra-thoracic compression and twisting of the gastric tube[17]. The results of the present study demonstrate that MBF is already compromised before closure of the thorax, and can be improved without changing the pressure inside the thorax or repositioning of the gastric tube.

Our observation of a preserved $\mu HbSO_2$ seems to be contradictory to previous studies showing tissue oxygen tension of the gastric tube to decrease during the operation[7,8]. The accuracy of our technique is confirmed by the comparison of our baseline measurements to the results of previous studies applying reflectance spectrophotometry on gastric tissue[18]. If both techniques, RS and tissue electrodes, are compared, a few remarks can be made that might explain the apparent differences. In the assessment of microvascular oxygenation it is difficult to determine which compartment is really being measured[3]. The catchment depth of the oxygen electrode has been estimated to be about 15-20 μm, compared to a penetration depth of 4-6 mm with reflection spectrophotometry. A limitation of oxygen electrodes is their sensitivity to oxygen. Vessels carrying high pO_2 blood in the catchment volume of the electrode can bias the electrode value despite the surrounding tissue being hypoxic; tissue electrodes are sensitive to changes in arterial pO_2. Presumably, the $\mu HbSO_2$ measured with RS originates from another compartment than the pO_2 measured with tissue electrodes[3].

The second observation made in our study is the increase in microvascular blood flow by 100% following local application of nitroglycerin (NTG). NTG has been shown to improve MBF during septic shock[19]. The use of topical application of vasodilators to reverse disturbances in microvascular blood flow in septic patients was recently described by DeBacker[20]. In addition, MBF in the gastric tube fundus has been observed to increase following systemic administration of prostaglandin E1 as well (21). These observations suggest that vasoconstriction in the gastric tube, leading to a decrease in MBF, can be counteracted by administration of a vasodilator[21]. This is confirmed by our results and emphasizes the role of venous congestion in this process. In arterial insufficiency a local application of a vasodilator could not be expected to restore the effect of vascular ligation in another part of the gastric tube. Whether vasodilating substances as NTG can influence the metabolism of the tissue itself, and thereby affect parameters of microvascular oxygenation, remains to be determined.

Finally, we have demonstrated the clinical applicability of a device combining reflection spectrophotometry with laser Doppler flowmetry for the simultaneous measurement of microvascular hemoglobin saturation and microvascular blood flow during major surgery. To our knowledge, no clinical study combining the assessment of tissue oxygenation and MBF has been performed to date.

In conclusion, MBF but not μHbSO$_2$ and μHbcon, was decreased during gastric tube reconstruction. Topical administration of the vasodilator NTG improved MBF, possibly due to general vasodilatation and decreased venous congestion. Further research will be required to provide more insight into the relation between MBF and μHbSO$_2$ and μHbcon in gastric tissue and the effect of perioperative administration of systemic NTG on these parameters as well as patient outcome.

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4. Intravenous nitroglycerin does not preserve gastric microcirculation during gastric tube reconstruction: a randomized controlled trial

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ABSTRACT

Introduction

Complications of esophagectomy and gastric tube reconstruction include leakage and stenosis, which may be due to compromised microvascular blood flow (MBF) in gastric tissue. We recently demonstrated that decreased MBF could be improved perioperatively by topical administration of nitroglycerin. The aim of the present study was to investigate whether nitroglycerin, administered intravenously during gastric tube reconstruction, could preserve tissue blood flow and oxygenation in the gastric fundus, and reduce the incidence of postoperative leakage.

Methods

In this single-centre, prospective, double-blinded study, we randomized 32 patients scheduled for esophagectomy into two groups. The intervention group received intravenous nitroglycerin during gastric tube reconstruction, and the control group received normal saline. Baseline values for MBF, microvascular hemoglobin oxygen saturation and microvascular hemoglobin concentration were determined at the gastric fundus before and after gastric tube construction and after pulling up the gastric tube to the neck.

Results

MBF and microvascular hemoglobin oxygen saturation decreased similarly in both groups during gastric tube reconstruction and were comparable. The esophageal anastomosis was controlled by contrast radiography before discharge from the hospital; leakage was observed in two patients (13%) in the nitroglycerin group and five patients (31 %) in the control group (not significant).

Conclusion

Under stable systemic hemodynamic conditions, continuous intravenous administration of nitroglycerin could not prevent deterioration in gastric microvascular perfusion and microvascular hemoglobin saturation during gastric tube reconstruction.

INTRODUCTION

Esophagectomy with direct reconstruction of the digestive tract remains the most successful therapy for esophageal cancer. Frequent complications of the gastro-esophageal anastomosis include leakage (5–26%) and anastomotic stenosis (12–40%), which have been attributed to decreased microvascular blood flow (MBF) and concomitant compromised oxygenation of the gastric tube[1,2].

The decrease in MBF is accounted for predominantly by diminished arterial supply of the gastric tube caused by ligation of several gastric arteries during the course of the procedure. On the other hand, venous congestion has been proposed to contribute to this reduced MBF as well[3]. We recently demonstrated a decrease in MBF but not in microvascular haemoglobin oxygen saturation ($\mu HbSO_2$) during gastric tube reconstruction, using simultaneous measurement of MBF and $\mu HbSO_2$[4]. We showed that the decreased MBF could be improved with topical administration of nitroglycerin.

This effect of nitroglycerin, which must be considered temporary because of the short half-life of nitroglycerin, depends entirely on the accessibility of gastric tube tissue. Therefore, we considered this observation proof of principle, and hypothesized that it should be possible to establish a similar effect with intravenous administration of nitroglycerin. If so, then the effect could easily be prolonged during the days following surgery. Our hypothesis was supported by data reported by other investigators, who were able to improve tissue perfusion in septic patients[5] or during cardiopulmonary bypass[6] with intravenous administration of nitroglycerin. Based on these observations, we hypothesized that systemic administration of nitroglycerin can preserve gastric MBF and $\mu HbSO_2$ during gastric tube reconstruction.

Materials and Methods

With the approval of the local institutional human investigation committee, and after obtaining written informed consent, 32 patients were included between May 2004 and March 2005. All patients were in physical status I and II, according to the American Society of Anesthesiologists classification[7].

General anaesthesia was induced with propofol (1–2 mg/kg), sufentanil (0.1–0.3 μg/kg) and rocuroniumbromide (0.6 mg/kg). Anaesthesia was maintained with isoflurane (0.8–1.2 end-tidal %) in all patients. Before induction of general anaesthesia, a mid-thoracic epidural catheter was placed (between Th6 and Th8) to provide peroperative and postoperative analgesia. In all patients epidural blockade was started with a bolus of 10 ml bupivacaine

0.25%, before starting the operation. After 90 min, a mixture of bupivacaine 0.125% with fentanyl 2.5 µg/ml was administered through the epidural catheter at a dosage of 10 ml/hour.

All patients were mechanically ventilated to achieve an arterial carbon dioxide tension of 4.5–5.5 kPa. Fractional inspired oxygen was initially set at 40%, but this was increased to 70% before fashioning the gastric tube. Positive end-expiratory pressure was set at 5 cmH_2O. In all patients standard haemodynamic monitoring was used, including radial arterial blood pressure and right atrial pressure (RAP) measurements. Fluid management was performed using crystalloids and hydroxyethyl starch (Voluven®; Fresenius Kabi, 's-Hertogenbosch, The Netherlands) in order to maintain mean arterial pressure above 60 mmHg and RAP above 10 mmHg. The attending anaesthesiologists were advised to use vasopressors when the volume of colloids exceeded 2 l; the agent of choice was phenylephrin. Arterial and central venous oxygen and carbon dioxide partial pressures, haemoglobin concentration and haemoglobin saturation were determined (ABL 707; Radiometer, Copenhagen, Denmark).

Operation technique

Two operation techniques were used: transhiatal and transthoracic oesophagectomy. Although these approaches differ, in both techniques the gastric tube is constructed in a similar manner by ligation of the left gastric artery, the right gastric artery, the short gastric arteries and the left gastroepiploic artery, and it is then fashioned along the greater curvature. As a consequence, the arterial supply of the upper part of the gastric tube depends exclusively on the right gastroepiploic arterial arcade. After transecting the oesophagus in the neck and stripping of the oesophagus, the gastric tube was pulled up via the prevertebral route where an oesophagogastrostomy was created. In all patients an end-to-side anastomosis was hand sewn with a single layer using absorbable monofilament suture (PDS 3–0, Ethicon; Johnson & Johnson, Amersfoort, The Netherlands).All operations were performed by the same surgical team (KT and HT).

Reflection spectrophotometry and laser Doppler flowmetry

The microvascular parameters MBF, µ$HbSO_2$ and microvascular haemoglobin concentration (?Hbcon) were determined simultaneously using the O_2C® (Lea Medizin Technik, Giesen, Germany). This device combines two optical techniques, namely laser Doppler flowmetry (LDF) and reflectance spectrophotometry (RS), in one optic fibre. There is no interference between the two techniques because they operate at different light wave ranges. In the present study a flat probe was used, with a measurement depth of 4–6 mm.

μHbSO$_2$ was measured using RS. The tissue is illuminated with visible white light (500–630 nm), which is backscattered mainly by mitochondria and changed in colour by haemoglobin according to its oxygen saturation status. This reflected spectrum is detected and analyzed by a spectrophotometer with a frequency of more than 100 Hz; a mean of these values is provided every 2 s. In addition, the μHbcon is calculated as a relative value in arbitrary units (AU). The clinical usability of RS and its value for the assessment of microvascular oxygenation were demonstrated previously[8].

LDF is a well established technique for the assessment of microvascular perfusion, and has been used frequently during gastric tube reconstruction[3,4,9]. Using LDF, MBF is determined by analysis of the power spectra from moving blood cells, generated by Doppler frequencies of backscattered laser light (820 nm). The MBF value is defined mathematically as the first moment of the Doppler power spectra, so it relates to the velocity of the erythrocytes multiplied by the number of moving erythrocytes, and it is described in AU. Changes in MBF have been qualitatively related to the occurrence of intestinal tissue ischaemia. For instance, Pierie and coworkers demonstrated that a reduction in gastric MBF of more than 70% from baseline values was a predictor of impaired healing of the cervical esophagogastrostomy[9]. Similarly, during intestinal hypotension a comparable decrease in jejunal mucosal perfusion was associated with increased lactate production[10].

Study protocol

Patients were randomized into two groups of 16 patients each. Randomization was performed by drawing closed envelopes. The treatment group received intravenous nitroglycerin (Nitro Pohl; Transmedico BV, Weesp, The Netherlands) at a dosage of 1 μg/kg per min, started immediately following induction of anesthesia. The control group received intravenous NaCl 0.9% at a similar infusion rate, started at the same time. The researcher and the attending anesthesiologist were blinded as to the content of the syringe.

After opening the abdomen, but before compromising the vascularization of the stomach, baseline values (T0) of MBF, μHbSO$_2$ and μHbcon were collected. An average of measurements over 1 min (30 values) was obtained from two gastric areas; the pre-pyloric antrum and the fundus of the stomach where the future anastomosis of the gastric tube was expected. The probe was placed by the surgeon, gently touching the surface of the serosal side of the stomach. Pressure artifacts were identified by an obvious decrease in signal in both LDF and RS curves, and a change in configuration of the RS signal. After T0 the measurements were repeated two further times: after construction of the gastric tube (T1) and after pulling up the gastric tube to the neck (T2). Arterial and central venous blood gas analysis was performed simultaneously. At the end of the operation the study medication was stopped.

As part of clinical practice following gastric tube reconstruction, all patients underwent a contrast radiography examination of the esophagogastrostomy after at least 7 days or before leaving the hospital.

Statistical analyses

In our previous study, in which patients served as their own controls, we found an increase in MBF from 52 AU to 100 AU after application of nitroglycerin, with a standard deviation of 34.8 and 53.4, respectively[4]. A sample size of 16 in each group has 80% power to detect a difference between means of 45 with a significance level (α) of 0.05 (two-tailed).

Values are reported as mean ± standard error. Each variable was analyzed using analysis of variance for repeated measurements. When appropriate, *post hoc* analyses were performed using the Bonferoni test. Differences between treatment and control groups at each time point were analyzed using an unpaired *t*-test. Incidences of postoperative leakage in the groups were compared using a Fischer test. $P < 0.05$ was considered statistically significant. All analyses were performed using Graphpad Prism (version 3.0; Graphpad Software, San Diego, CA, USA).

RESULTS

Demographic and operation characteristics are summarized in Table 1. In the nitroglycerin group 15 people were operated on using the transhiatal approach as compared with 12 patients in the control group. There was a significant difference in fluid volume administration: 6.5 ± 1.3 l in the nitroglycerin group versus 7.7 ± 1.7 l in the control group. Total perioperative blood loss was similar in the two groups. Both groups received equal amounts of vasoactive medication. Mean arterial blood pressure was comparable throughout the procedure and did not change significantly in either group. Heart rate was higher in the nitroglycerin group during the entire operation than in the control group. RAP was significantly higher in the control group than in the nitroglycerin group at baseline, and decreased compared with baseline at T2 (Table 2).

Table 1. Demographic and operative characteristics.

	NTG	NaCl
Male/Female	14/2	13/3
Age (year)	62 ± 11	61 ± 9
Operation time (min)	236 ± 52	245 ± 55
Infusion in (L)	6.5 ± 1.3*	7.7 ± 1.7
Blood loss (L)	1.1 ± 0.1	1.4 ± 0.2

Values represent mean ± SEM. *) p<0.05 NaCl vs. NTG

Table 2. Hemodynamics.

		T0	T1	T2
MAP	NTG	70 ± 2	72 ± 3	70 ± 2
	NaCl	75 ± 4	73 ± 3	72 ± 2
RAP	NTG	13 ± 1*	12 ± 1	11 ± 1
	NaCl	16 ± 1	14 ± 1	13 ± 1 **
HR	NTG	86 ± 3*	83 ± 3*	88 ± 3*
	NaCl	74 ± 3	71 ± 3	75 ± 4

Values represent mean ± SEM. MAP = mean arterial pressure (mmHg), RAP = right atrial pressure (mmHg), HR = heart rate (beats per minute)

*) P<0.05 NTG vs. NaCl **) P<0.05 vs. baseline

There was a significant difference in the central venous oxygen saturation between the control and the nitroglycerin groups at baseline. The arterial oxygen tension values were similar between groups throughout the procedure. There were significant differences in arterial hemoglobin concentration between baseline and subsequent time points in the two groups, and there was a difference in hemoglobin concentration between groups at T1 (Table 3).

Table 3. Blood gas analysis.

		T0	T1	T2
S_aO_2	NaCl	99 ± 0	99 ± 0	99 ± 0
	NTG	99 ± 0	99 ± 0	99 ± 0
$S_{cv}O_2$	NaCl	83 ± 0*	85 ± 0	87 ± 0
	NTG	88 ± 0	86 ± 0	89 ± 0
P_aO_2	NaCl	23 ± 2	34 ± 3 **	36 ± 3**
	NTG	23 ± 2	32 ± 2**	37 ± 5**
Hb	NaCl	6.4 ± 0.7	6.3 ± 0.5*	5.9 ± 0.8**
	NTG	6.2 ± 0.3	5.6 ± 0.2**	6.0 ± 0.2

Values represent mean ± SEM. S_aO_2 = arterial hemoglobin oxygen saturation (%), $S_{cv}O_2$ = central venous hemoglobin oxygen saturation (%), P_aO_2 = arterial partial oxygen pressure (kPa), Hb = arterial hemoglobin concentration (mmol/l)
*) P< 0.05 NTG vs. NaCl **) P<0.05 vs. baseline

With respect to microvascular parameters, baseline values were similar in the two groups for all parameters at the gastric fundus and pylorus. There was no significant change in or difference between the two groups in MBF, μ$HbSO_2$ and μHbcon at the pyloric part of the stomach during the procedure (data not shown).

As can be seen in Figure 1, fundus MBF was 210 ± 17 AU in the nitroglycerin group and 216 ± 13 AU in the control group at baseline (not significant). There was a decrease at T1 in both the nitroglycerin group and the control group, but there was no further decrease from T1 to T2 in the two groups. μ$HbSO_2$ at T0 was 91 ± 2% in the nitroglycerin group and 86 ± 3% in the control group (not significant). There was no significant change in μ$HbSO_2$ in the two groups between T0 and T1. At T2, however, μ$HbSO_2$ decreased significantly in both groups, to 63 ± 5% in the nitroglycerin and 51 ± 7% in the control group. The μHbcon increased significantly between baseline and T1, from 72 ± 3 AU to 80 ± 3 AU in the nitroglycerin group and from 65 ± 3 AU to 78 ± 3 AU in the control group. There was no difference between T1 and T2.

All patients underwent a contrast radiography examination of the esophago-gastrostomy. Two cases of anastomotic leakage occurred in the

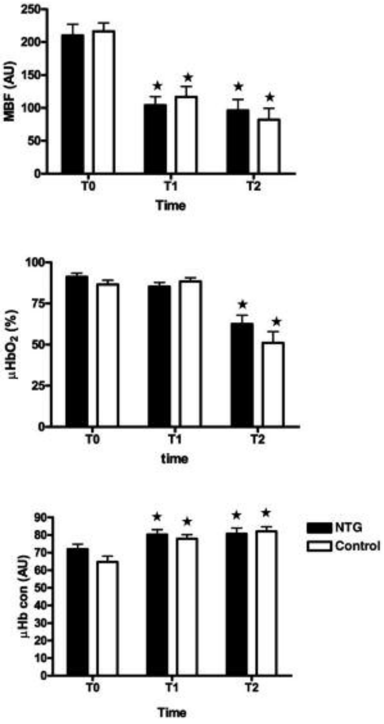

Figure 1. Microvascular parameters

Microvascular parameters; microvascular bloodflow (MBF), microvascular hemoglobin saturation ($\mu HbSO_2$) and microvascular hemoglobin concentration (µHbcon) measured at the fundus of the stomach during gastric tube reconstruction. The MBF decreased between T0 and T1 and the $\mu HbSO_2$ decreased between T1 and T2. Values represent as mean ± SEM. * P<0,05 vs. baseline

nitroglycerin group (12%) and five occurred in the control group (31%); this difference was not statistically significant (*P* = 0.19). We did not differentiate between minor or major, clinically relevant leakage.

DISCUSSION

In the present study we were unable to prevent a decrease in gastric fundus microvascular perfusion and oxygenation during gastric tube reconstruction with continuous intravenous administration of nitroglycerin. This substance acts as a nitric oxide (NO) donor; in the vascular endothelium NO functions as a regulator of vascular tone, and thereby of microvascular perfusion[11]. NO plays an important role in the autoregulation of gastric mucosal blood flow, and it is likely that NO plays a role in protecting the gastric mucosa and preserves mucosal integrity[12,13]. During conditions of decreased flow, use of nitroglycerin was shown to be effective in improving tissue perfusion[4,6].

Nevertheless, the present results are in contrast with the findings of our previous study[4], in which gastric MBF could be improved with application of nitroglycerin locally on the gastric tube tissue. It cannot be ruled out that the dose of nitroglycerin used in the present study might have been insufficient to establish effective tissue concentrations in the gastric tube. We opted for a dosage of 1 μg/kg per min, which was in the same range as that used in the studies of conducted by Spronk and coworkers [5] (0.5 mg bolus followed by 33.3 μg/min) and Iribe and colleagues 6 (0.5–2.0 μg/kg per min). In both studies tissue perfusion could be significantly improved with intravenous nitroglycerin.

With topical administration, tissue concentrations must have been relatively high. If we had aimed to establish similar tissue concentrations or used an improvement in MBF as a therapeutic end-point, then greater amounts of nitroglycerin might have been required. On the other hand, during gastric tube reconstruction perfusion pressure (arterial blood pressure) is considered critical for adequate tissue perfusion and thus healing of the proximal anastomosis. Therefore, we decided not to use higher concentrations of nitroglycerin in our study to prevent its systemic effects.

Hemodynamic stability is demonstrated by the unchanged mean arterial pressure and RAP during the entire study protocol in the nitroglycerin group. There was a difference in the central venous hemoglobin oxygen saturation between the nitroglycerin and NaCl groups at T0, but this was not related to a difference in microvascular saturation. We did not measure cardiac output because we believe that there is no relation between changes in cardiac output and changes in microvascular blood flow, as was recently demonstrated by De Backer and coworkers[14].

Although one might assume that systemic circulatory capacitance is increased by nitroglycerin, the experimental group received less fluid during the procedure. Several reasons can have contributed to this finding. One is that in this study hypotension was primarily treated with fluids instead of vasopressors. As a result, too much fluid was administered in both groups with regard to the end-points for fluid administration. Looking at RAP, it can be seen that in all patients RAP was well above 10 mmHg during the entire procedure. If we had adhered to these end-points more strictly, then less fluid might have been administered, certainly in the control group, and differences in venous capacitance between the two groups might have been more marked. In the experimental conditions employed, only at baseline was RAP lower in the nitroglycerin group.

Another reason is that we cannot rule out the possibility that the dosage of nitroglycerin was simply too low to cause an effect on systemic circulatory capacitance, and therefore did not lead to increased administration of fluids in the experimental group. Whether a higher dose of nitroglycerin in combination with more fluids would have an effect on the microcirculation remains speculative.

Despite the differences in fluid administration, hemoglobin concentrations in the two groups were in the same range throughout the study period. Based on the American Society of Anesthesiologists guidelines for blood transfusion, a permissive anemia strategy was used. Acute anemia in the absence of hypovolemia is known to have an effect on tissue perfusion. Microvascular perfusion is augmented by an increase in the amount of perfused capillaries in the tissue (capillary recruitment) and by vasodilatation of microvessels already perfused[15,16,17]. As a result, the absolute amount of oxygen transported by the capillaries can be maintained. In the splanchnic tissues, NO is thought to play an important role in this process[18,19]. It can be hypothesized that, under these circumstances, administration of an NO donor such as nitroglycerin might not have as much an effect as when there are higher hemoglobin levels. This mechanism might have interfered with the effect of nitroglycerin administration.

The simultaneous decrease in MBF and increase in μHbcon, followed by a decrease in $\mu HbSO_2$ at a later stage, implies that venous congestion plays an important role in the decrease in gastric tissue perfusion during gastric tube reconstruction. This mechanism has been proposed by others as well [3]. Blood flow in the mucosal and serosal layers of the gut is known to behave differently under certain circumstances. In addition, the distinct effects of NO donors such as nitroglycerin on the various layers of the gastric tissue during this kind of surgery are unknown. For obvious reasons, we were only able to apply the $O_2C^{®}$ probe on the serosal side of the gastric tube. Because the measurement depth of this probe is in the 4–6 mm range, we cannot distinguish between the different layers of the gastric tissue. It is therefore very difficult to draw any conclusions regarding differential tissue blood flow changes in our study.

Finally, the incidence of anastomotic leakage is relatively high in the total study population (22%); this included clinically relevant leakage as well as leakage restricted to radiological signs only. Although not supported by the microvascular data, we observed a tendency toward a lower incidence of anastomotic leakage in the nitroglycerin group. This result did not achieve statistical significance, but the study was not designed for that purpose either. Larger patient numbers might be required to evaluate this

CONCLUSION

Intravenous administration of nitroglycerin at a dosage of 1 μg/kg per min does not prevent the decrease in gastric MBF and $\mu HbSO_2$ that occur following gastric tube reconstruction. Further research is necessary to gain more insight into the effect of NO donors on impaired microvascular perfusion and oxygenation in general, and its relation to anastomotic complications following esophagogastrostomy specifically.

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5. The effects of intravenous nitroglycerine and noradrenaline on gastric microvascular perfusion in an experimental model of gastric tube reconstruction

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ABSTRACT

Background

Esophagectomy with gastric tube reconstruction is the surgical treatment for cancer of the esophagus. Perfusion of the anastomotic site of the tube depends exclusively on the microcirculation, making it susceptible to hypoperfusion. It is unknown whether vasodilatation is superior to increased perfusion pressure to improve gastric tissue perfusion of the anastomosis.

Methods

We performed a gastric tube reconstruction in 12 pigs, mean bodyweight 32 ± 2 kg. Besides systemic hemodynamic parameters, gastric microvascular blood flow (MBF) was assessed with laser Doppler flowmetry and gastric microvascular HbO2 saturation (mHbSO$_2$) and Hb concentration (mHbcon) with spectrophotometry. Animals were randomized over two groups: with and without intravenous nitroglycerin (NTG). In both groups mean arterial pressure was increased from 50 to 110 mmHg with infusion of norepinephrine; in the NTG group central venous pressure was maintained below 10 mmHg throughout the experiment with NTG.

Results

Except for central venous and pulmonary capillary wedge pressures, all hemodynamic parameters were similar in both groups. Especially in corpus and fundus, MBF decreased following surgery. However, overall MBF was significantly higher in the NTG group. Increasing MAP had no effect on fundus MBF. Gastric mHbSO$_2$ and mHbcon were not different between groups and did not change at higher MAP levels.

Conclusion

In our experimental model of gastric tube reconstruction, tissue perfusion is severely compromised; this effect is aggravated by systemic hypotension independent from cardiac output. Impaired venous outflow might contribute to this effect and can be counteracted with infusion of nitroglycerine.

INTRODUCTION

Esophagectomy with direct reconstruction of the digestive tract remains the most successful therapy for esophageal cancer. Formation of the gastroesophageal anastomosis can be complicated by leakage and stenosis, which have been attributed to decreased microvascular blood flow (MBF) and concomitant tissue hypoxia[1-4].

The decrease in MBF, which occurs immediately during surgery, is easily attributed to the partial ligation of the feeding arteries of the stomach: as a result the upper part of the gastric tube is indirectly perfused through the microcirculation. However, venous congestion might contribute to the reduction in MBF as well, as suggested by studies performing venous vascular grafts[5], venous blood letting[6] or with administration of nitroglycerin[7].

Other strategies that exert a beneficial effect on gastric MBF are administration of prostaglandins[8,9] and the use of thoracic epidural analgesia[10,11], which can both be assumed to have a direct interaction with local gastric vasomotor tone. Although it is evident that these interventions can only have an effect under stable systemic circulatory conditions, it is as yet unclear whether systemic hemodynamic parameters, especially arterial blood pressure, have an individual effect on gastric MBF following gastric tube reconstruction.

We hypothesized that gastric tube perfusion depends on arterial perfusion pressure and that, assuming the role of venous congestion, this effect can be augmented with infusion of nitroglycerine. For this purpose we developed an experimental model of gastric tube reconstruction, in which we were able to combine a clinically relevant surgical model with measurements of systemic hemodynamics as well as gastric tissue perfusion parameters.

METHODS

With permission of the local Animal Experimental Committee and in accordance with the National Guidelines for Animal Care and Handling, 12 female Landrace pigs, mean bodyweight 32 ± 2 kg were included in our study.

Anesthesia

After an overnight fast with free access to water, the animals were sedated with an intramuscular injection of ketamine (30 mg/kg), midazolam (1 mg/kg) and azaperon (2,5 mg/kg). Intravenous access was obtained by cannulation of an ear vein; anesthesia was maintained with a combination of intravenous infusion of midazolam (0,2 mg/kg bolus, followed by 0,3 mg/kg/h), propofol (2 mg/kg/h) and fentanyl (20 μg/kg bolus, followed by 20 μg/kg/h). Muscle relaxation was obtained with infusion of pancuronium bromide (0,1 mg/kg bolus, followed by 0,2 mg/kg/h).

Through a midline cervical tracheostomy, an endotracheal tube (9,0 Fr) was placed in the trachea. Ventilation was performed (AV-1; Drägerwerke, Lübeck, Germany) with oxygen in air (FiO_2 of 0,40) and the frequency was set to achieve normocapnia; positive end-expiratory pressure (PEEP) was set at 5 cm H_2O. As maintenance fluid crystalloid solution was administered at a rate of 10 ml/kg/h. Central body temperature was maintained at approximately 37 °C with a heating pad.

Catheters were placed in the right carotid artery for the measurement of arterial blood pressure and collection of arterial blood samples, and in the right jugular vein for the administration of fluid. A pulmonary artery thermodilution catheter (Edwards Lifesciences, Irvine CA, USA) was positioned in the pulmonary artery for the continuous measurement of cardiac output, central venous pressure [CVP], pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), mixed venous hemoglobin oxygen saturation (SvO2) and central body temperature.

Microvascular measurements

Microvascular blood flow (MBF), - hemoglobin oxygen saturation ($\mu HbSO_2$) and - hemoglobin concentration (μHbcon) were determined simultaneously using the O2C($^{®}$) (Lea Medizintechnik, Giesen, Germany). This device combines two optical techniques: laser Doppler flowmetry (LDF) and reflectance spectrophotometry (RS) in one optic fiber. There is no interference between the two techniques because they operate at different light wave ranges. In the present study a flat probe was used, with a measurement depth of 4-6 mm.

The $\mu HbSO_2$ was measured with RS: the tissue is illuminated with visible white light (500-630 nm), which is backscattered mainly by mitochondria and changed in color by hemoglobin according to its oxygen saturation status. This reflected spectrum is detected and analyzed by a spectrophotometer with a frequency of more than 100 Hz; a mean of these values is provided every 2 seconds. In addition, the μHbcon is calculated as a relative value in arbitrary units (AU). The clinical usability of RS and its value for the assessment of microvascular oxygenation have been described previously[12].

LDF is a well-established technique for the assessment of microvascular perfusion, and has been used frequently during gastric tube reconstruction[3,4,9].

Using LDF, MBF is determined by analysis of the power spectra from moving blood cells, generated by Doppler frequencies of backscattered laser light (820 nm).

The MBF value is defined mathematically as the first moment of the Doppler power spectra, so it relates to the velocity of the erythrocytes multiplied by the number of moving erythrocytes, and it is described in AU. Changes in MBF have been qualitatively related to the occurrence of intestinal tissue ischemia. For instance, Pierie and coworkers[1] demonstrated that a reduction in gastric MBF of more than 70% from baseline values was a predictor of impaired healing of the cervical oesophagogastrostomy[1].

Surgery

Following a median laparotomy, the vasculature of the stomach was identified and baseline measurements of the microcirculation were performed. Then, the stomach was completely mobilized, which included ligation of the short gastric arteries, the right and left gastric artery and the left gastro-epiploic artery. The right gastro-epiploic artery along the greater curvature was carefully preserved. After opening of the hiatus, the esophagus was dissected and transected at the gastro-esophageal junction. Finally, a 3 centimeter wide gastric tube was formed by dissection of the lesser curvature and the gastro-esophageal junction with a linear stapler (Proximate 55 mm TLC linear cutter, Ethicon, Johnson&Johnson, the Netherlands). In this way, the perfusion of the gastric tube was completely dependent on the right gastro-epiploic artery, comparable to the clinical setting.

The use of the pig as a model for gastric tube formation has been described previously (8, 13-15). It is important to note that, as has been demonstrated by Schröder and coworkers, the porcine gastric vascularization differs from the human situation in that the left instead of the right gastro-epiploic artery is dominant[14]. The left gastro-epiploic artery originates from the splenic hilus and serves as the main feeding artery for the gastric fundus, especially after ligation of the short gastric artery. Because dissection results in profound ischemia of the gastric fundus, the length of the gastric tube is limited and not enough to perform a transthoracic pull-up in order to restore continuity. For this reason, and because gastric pull-up would clearly limit accessibility for our measurements, measurements were performed with the gastric tube in the abdomen.

Experimental protocol

Before surgery, animals were randomized over two groups of 6 animals each: one to receive nitroglycerine (NTG) during the experiment and one control group. In the NTG group continuous intravenous administration of nitroglycerine was started immediately following induction of anesthesia. During the experiment, the dosage was adjusted in order to keep central venous pressures below 10 mmHg. We hypothesized that at this pressure venous blood flow would be augmented and that the required dosage of NTG would not lead to systemic hypotension, either through decreased cardiac output or arterial vasodilatation.

After opening the abdomen, but before compromising the vascularization of the stomach, baseline values (T0) of MBF, μHbSO$_2$ and μHbcon were collected. An average of measurements over 1 min (30 values) was obtained from three gastric areas: the pylorus (pre-pyloric antrum, where vascularization remains intact), the corpus (where the right gastro-epiploic artery ends), and the fundus of the stomach (the top of the gastric tube where the anastomosis could be made). In the fundus, we discriminated between the ultimate top of the gastric tube, which appeared clearly congested and ischemic, and the area just below the top, which remained clearly more vital and was deemed suitable for the formation of a possible anastomosis by visual identification of the surgeon. At this site the measurements were performed.

The O2C probe was placed gently on the surface of the serosal side of the stomach. Pressure artifacts were identified by an obvious decrease in signal in both LDF and RS curves, and a change in configuration of the RS signal.

Subsequent measurements were made after a stabilization period of at least 30 minutes following surgery and then repeated at different blood pressure levels, ranging from a mean arterial pressure (MAP) of 50 mmHg to 110 mmHg with intervals of 10 mmHg. First, MAP was lowered with infusion of propofol; after a stabilization period of 30 minutes hemodynamic and microvascular parameters were recorded. MAP was increased first by reducing the dosage of propofol, then with infusion of norepinephrine to increase MAP above 70 mmHg. Every time the target MAP was reached, a 30-minute stabilization interval was used before measurements were made. Between measurements, the abdomen was temporarily closed with moist surgical gauzes and semi-occlusive drape to prevent hypothermic disturbances of the blood flow. When all measurements were performed, the experiment was terminated by intravenous administration of 30 mmol potassium chloride.

Statistical analysis

Values are reported as mean ± standard deviation. Each variable was analyzed using analysis of variance for repeated measurements. When appropriate, post hoc analyses were performed using the Bonferroni test. Differences between NTG and control group at each time point were analyzed using an unpaired t-test. $P < 0.05$ was considered statistically significant. All analyses were performed using Graphpad Prism (version 4.0; Graphpad Software, San Diego, CA, USA).

RESULTS

Table 1. Hemodynamic parameters

	BL	S	50	60	70	80	90	100	110
MAP									
CTRL	86 ± 11	83 ± 17	48 ± 5	60 ± 2	70 ± 3	80 ± 3	90 ± 3	101 ± 2	109 ± 6
NTG	79 ± 7	79 ± 10	51 ± 2	59 ± 4	71 ± 2	80 ± 2	89 ± 2	101 ± 2	109 ± 2
HR									
CTRL	99 ± 35	110 ± 34	113 ± 34	117 ± 34	125 ± 31	113 ± 13	123 ± 17	126 ± 12	124 ± 9
NTG	108 ± 19	110 ± 14	107 ± 16	128 ± 23	133 ± 26	124 ± 23	110 ± 30	116 ± 28	120 ± 30
CVP									
CTRL	11 ± 2	11 ± 1	11 ± 1	11 ± 1	11 ± 1	11 ± 2	11 ± 1	11 ± 2	11 ± 2
NTG	8 ± 1#	8 ± 2#	8 ± 1#	9 ± 1#	9 ± 1#	9 ± 1#	9±1#b	9±1#bs*	10±1#bs*
PCWP									
CTRL	11 ± 2	12 ± 2	12 ± 2	12 ± 1	12 ± 1	12 ± 1	12 ± 2	12 ± 1	12 ± 1
NTG	8 ± 1#	9 ± 1#	8 ± 1#	9 ± 1#	9 ± 1#	9±1#b	10±1#b	10±1#s*$	10±1#s*
CO									
CTRL	4,1 ± 0,6	3,8 ± 0,3	3,5 ± 0,4	3,8 ± 0,5	3,7 ± 0,7	4,3 ± 0,8	4,6 ± 1,1	4,4 ± 0,9	4,1 ± 0,5
NTG	4,8 ± 1,0	4,6 ± 1,1	4,3 ± 1,1	3,9 ± 1,1	3,9 ± 0,9	3,9 ± 0,7	3,9 ± 0,6	4,1 ± 0,9	4,2 ± 0,9
SvO_2									
CTRL	73 ± 6	72 ± 9	69 ± 12	70 ± 9	74 ± 9	75 ± 11	77 ± 14	75 ± 12	76 ± 14
NTG	81 ± 8 #	82 ± 8 #	75 ± 16	79 ± 16	78 ± 12	77 ± 11	74 ± 13	77 ± 14	76 ± 15

P < 0.05: # vs CTRL; b vs baseline; s vs surgery; * vs 50; $ vs 60

Systemic hemodynamic data are shown in Table 1. Baseline MAP values were similar in both groups. Both central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) were significantly lower in the NTG group at baseline and throughout the experiment (Table 1). Although we aimed to keep CVP below 10 mmHg in the NTG group, we could not prevent a small but significant increase at the end of the experiment (Table 1). During baseline and directly after formation of the gastric tube, cardiac output values were higher, but not significantly, and mixed venous oxygen saturation was significantly higher in the NTG group compared to controls. The volume of fluids administered during the experiment was similar in both groups. Likewise, similar dosages of norepinephrine were administered in both groups, with a maximum dose of 0,5 mcg/kg/min at MAP 110 mmHg. In the NTG group, nitroglycerine was administered at a rate of 2,5-3,5 mcg/kg/min.

MBF measurements at baseline and following gastric tube formation are displayed in Figure 1.

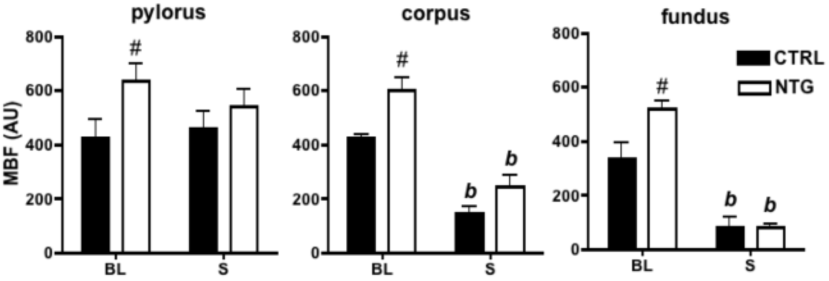

Figure 1. Microvascular blood flow (MBF) measurements on gastric pylorus, corpus and fundus at baseline (BL) and immediately following surgery (S). Data represent mean ±SEM; # P<0,05 vs CTRL, b P<0,05 vs BL.

At baseline, MBF was significantly higher in the NTG group all over the stomach. MBF in corpus and fundus decreased severely directly after surgery in both groups. Parallel with the decrease in MBF, µHbcon increased significantly in corpus and fundus (Fig 2).

In figure 3 the effect of MAP on MBF is shown: MBF does not change significantly with increasing MAP. Only in the corpus we found that MBF at MAP > 90 was significantly higher compared to MBF at MAP < 60 mmHg. Especially in the fundus, and to a lesser extent in the corpus as well, MBF was significantly higher in the NTG group (Fig. 3).

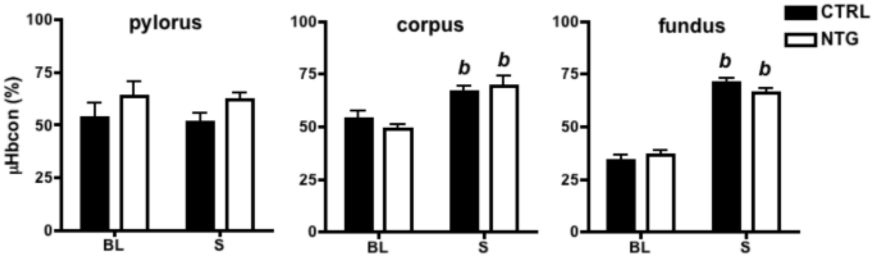

Figure 2. Microvascular hemoglobin concentration (µHbcon) measurements on gastric pylorus, corpus and fundus at baseline (BL) and immediately following surgery (S). Data represent mean ±SEM; b P<0,05 vs BL.

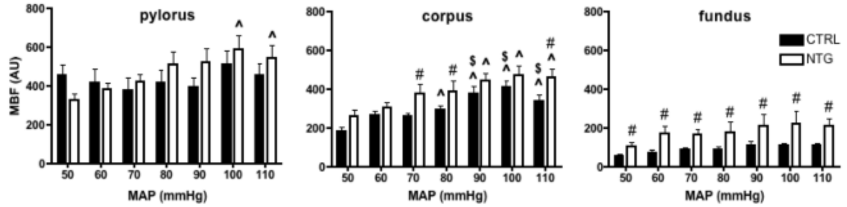

Figure 3. Microvascular blood flow (MBF) measurements on gastric pylorus, corpus and fundus at increasing MAP levels. Data represent mean ±SEM; # P<0,05 vs CTRL, b P<0,05 vs baseline, ^ P<0,05 vs MAP 50, $ P<0,05 vs MAP 60.

The µHbcon in the pylorus did not change at different MAP levels (Fig. 4). A similar lack of effect was observed in fundus and corpus, however especially in the fundus µHbcon was significantly lower in the NTG group from MAP 60 through 110.

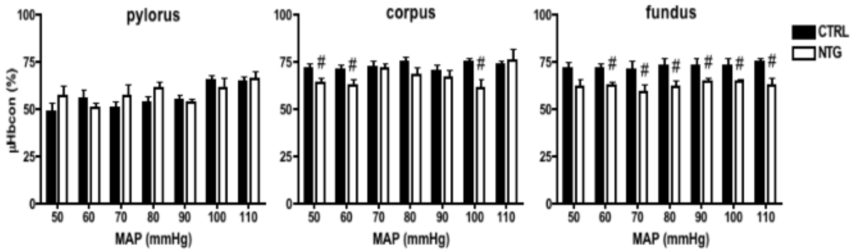

Figure 4. Microvascular hemoglobin concentration (µHbcon) measurements on gastric pylorus, corpus and fundus at increasing MAP levels. Data represent mean ±SEM; # P<0,05 vs CTRL

In contrast to the other parameters, $\mu HbSO_2$ values in pylorus, corpus and fundus remained stable between 65-80 % throughout the experiment in both groups. Only in the fundus, $\mu HbSO_2$ temporarily decreased immediately following surgery in both groups from about 75 % to 50 %.

Discussion

The main finding of our study is that the deterioration of the microvascular perfusion of the gastric tube following surgery is not improved with higher perfusion pressures but can partly be prevented with administration of nitroglycerine. According to our hypothesis, being that a decrease in MBF and a simultaneous increase in μHbcon would be expected to occur in the presence of venous congestion, our observations imply that prevention of venous stasis is more important for the gastric tube perfusion than increased arterial perfusion pressure.

Although it is generally accepted that gastric tube formation leads to a major reduction in gastric tissue blood flow, only few studies have investigated the effect of systemic hemodynamic parameters on gastric tube perfusion. The importance of venous congestion has been proposed previously[5,7]; now we have clearly demonstrated that this mechanism is independent from cardiac output and arterial blood pressure.

However, systemic hemodynamic parameters were not completely similar in both groups. First, central venous and pulmonary capillary wedge pressures were lower in the NTG group. In a previous study we found that the use of a fixed NTG dosage (1 mcg/kg/min) does not have any effect on gastric tube MBF(16). Therefore we concluded that it would be preferable to titrate the infusion of NTG on a determinant of venous outflow. Because we needed a parameter that is often and easily used in clinical practice as well, we chose for central venous pressure. Conform our hypothesis, a lower systemic venous pressure should facilitate venous drainage of the gastric tube, thereby increasing gastric tissue blood flow. Second, the higher mixed venous hemoglobin saturation values at baseline indicated that the ratio between systemic oxygen delivery and uptake was increased in the NTG group. Because arterial oxygen content was similar in both groups and cardiac output showed a trend towards higher values, we conclude that administration of NTG caused a more dynamic circulation. Apparently, this was accompanied by an increased tissue blood flow; it remains speculative whether this was caused by the increase in cardiac output or vice versa.

Although the effect of NTG is immediately visible in the higher MBF baseline values, the surgical procedure decreased MBF in the corpus and fundus to comparable low levels. Subsequently, recovery occurred in the NTG group over time: throughout the experimental protocol fundus and corpus MBF values were significantly higher than in the control group (Figs. 1 and 3). This is supported by the µHbcon data: increased in both groups following surgery but significantly lower corpus and fundus values in the NTG group during the actual experiment (Figs. 2 and 4). In retrospect, we could have shown this effect even better with a longer stabilization interval before the post-surgery measurements and addition of a second baseline measurement before the start of the experimental protocol.

Nitroglycerine is a nitric oxide (NO)-donating compound; in the vascular endothelium NO functions as a regulator of vascular tone, and thereby of microvascular perfusion. NO plays an important role in the autoregulation of gastric mucosal blood flow, and it is likely that NO plays a role in protecting the gastric mucosa and preserves mucosal integrity[17]. During conditions of decreased flow, use of nitroglycerin or another NO-donor was shown to be effective in improving tissue perfusion[18-20]. In the present study we chose for nitroglycerine because of its alleged venodilating properties. Nevertheless, based on our observations, it might be assumed that any vasodilating substance can improve gastric tube tissue perfusion as long as venous outflow is improved and arterial hypotension is avoided, i.e. the balance between the arterial and venous vasodilating properties of the substance is in favor of the latter. We are not aware of commonly used vaso-active agents with similar properties.

Although the beneficial effect of vasodilators on MBF seems to be clear, it must be noted that the design of our study makes it difficult to judge the effects of norepinephrine and nitroglycerine separately. We could only assume that, because norepinephrine did not have a significant effect on tissue perfusion in itself, it did not interfere with the effect of nitroglycerine either. Furthermore, the significantly higher MBF at MAP 70 and higher is independent from the infusion of nitroglycerine and is the result of insufficient perfusion pressures during systemic hypotension than improved tissue perfusion at supra-normal MAP levels.

Clearly, systemic arterial hypotension must be avoided. This has been suggested previously by gastric tube MBF measurements in experimental[15] and clinical[21] setting as well. On the other hand, our data also show that aiming for supra-normal blood pressure has no effect on gastric MBF in the anastomotic area and, maybe even more important, that the use of vasoconstrictive substances under normovolemic conditions has no detrimental effect on gastric MBF. Similar observations have been made in patients suffering from septic shock: for instance LeDoux and coworkers demonstrated that increasing mean arterial pressure from 65 to 85 mmHg with norepinephrine had no effect on systemic oxygen metabolism or splanchnic perfusion[22].

Having demonstrated that gastric MBF deteriorates severely during gastric tube formation (which can be prevented to a certain extent), the question remains why $\mu HbSO_2$ did not change concomitantly. Assuming tissue oxygen metabolism to be constant, a decrease in tissue blood flow would be accompanied by an increase in oxygen extraction and a decrease in tissue hemoglobin oxygen saturation. We have observed this apparent discrepancy in patients as well[7], and it seems to contradict previous studies showing that the tissue PO2 decreases during the operation[23-25].

However, we have no reason to doubt our own measurements. First, the accuracy of our technique is confirmed by the comparison of our own data with the results of previous studies applying reflectance spectrophotometry in gastric tissue[7,26]. Second, for technical reasons it can be assumed that the $\mu HbSO_2$ measured with reflectance spectrophotometry originates from another tissue compartment than the tissue PO_2 measured with oxygen electrodes[27].

Finally, it can also be speculated that there is no relation between gastric tube MBF and $\mu HbSO_2$. Due to manipulation and denervation it is likely that gastric tissue oxygen demand is very low following surgery. And although decreased MBF has been correlated to impaired anastomotic healing[1,2,3,4], no such relation could be found for e.g. gastric tissue PO_2[24]. This is certainly not typical for an arterial flow insufficiency, and indirectly it argues for the occurrence of venous congestion in the tissue leading to much slower changes, which fell beyond the time limit of our study.

In an uncomplicated postoperative course, it takes about 4 days for tissue blood flow in the anastomotic region to recover to preoperative values[28]. Considering that this occurs in all patients, then why do only a minority of them suffer from impaired anastomotic healing? Factors other than vascular perfusion may play a role in this process, such as for instance conduit width, intrathoracic pressure changes and inflammatory reactions to surgery.

In conclusion, we were able to demonstrate in an experimental gastric tube model that the deterioration of the microvascular perfusion of the gastric tube following surgery can at least partly be prevented with administration of nitroglycerine if titrated at a reduction of central venous pressures and started before surgery. Hypotension should best be avoided whereas supra-normal arterial pressures do not improve gastric tissue perfusion. These findings imply that reducing venous congestion, while maintaining an adequate circulation, is more important for restoration of gastric tube perfusion than increasing arterial perfusion pressure. Clinical studies are required to investigate whether interventions aiming at improved gastric venous outflow actually result in improved anastomotic healing.

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6. Pulmonary morbidity following esophagectomy is decreased after introduction of a multimodal anesthetic regimen

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ABSTRACT

Background

Respiratory morbidity is the most frequent complication after esophagectomy, which can occur in 50% of the patients treated for esophageal cancer. We tested the hypothesis whether an anesthetic regimen, emphasizing intraoperative fluid restriction and early extubation could, positively influence postoperative morbidity, without affecting the gastric tube reconstruction.

Methods

We introduced an anesthetic regimen, based on early extubation and a controlled intraoperative fluid management (net fluid balance < 4 L) in combination with the use of norepinephrin to maintain mean arterial blood pressure > 65 mmHg. Postoperative morbidity and mortality were compared with a similar group of patients operated one year before.

Results

From June 2005 till September 2006, 83 patients were treated according to the new regimen (NR) and compared to a similar number of patients from the same period in 2003-2005 (standard regimen: SR). Applying the NR resulted in significantly less fluid administration (balance of 3.5 ± 0.2 L NR vs. 5.1 ± 0.2 L SR, $p<0.05$) resulting in fewer patients developing pneumonia (26% in the NR group vs. 42 % in the SR group, $p<0.05$). Similar per operative blood loss and urine output and occurrence of leakage or ischemia of the gastric tube anastomosis occurred in both groups.

Conclusion

Respiratory morbidity is significantly reduced with the introduction of a new anesthetic regimen directed at intraoperative fluid restriction and early extubation, without increasing anastomotic leakage of the gastric tube reconstruction.

INTRODUCTION

Esophageal resection with gastric tube reconstruction is a major intervention with considerable postoperative morbidity. Despite improvements in surgical techniques and perioperative care, the postoperative course is often complicated, with respiratory morbidity as the most frequent (30-50%) non-surgical complication[1,2].

Brodner and co-workers have shown that a multimodal approach consisting of thoracic epidural analgesia, early tracheal extubation and forced mobilization postoperatively resulted in improved outcome after surgery[3]. In our institution, the anesthetic regimen for esophagectomy consisted of general anesthesia in combination with thoracic epidural analgesia, followed by prolonged sedation and mechanical ventilation in the ICU. In order not to compromise gastric tube perfusion, hypotensive episodes were treated with administration of fluid, avoiding vasoactive medication. As a result, the net fluid balance largely increased in the first 24 hours, up to 10 L in some cases. It is not unlikely that this affects postoperative recovery. Recently, a reduction in per operative fluid administration has been shown to benefit patient recovery following abdominal surgery[4-6].

In an attempt to reduce our own morbidity rates, we decided to adjust our anesthetic regimen directed at early extubation and intraoperative fluid restriction in combination with the use of a vasopressor to maintain mean blood pressure above 65 mm Hg. To evaluate the effect of this regimen on postoperative morbidity, patients were compared with a similar number of patients operated one year earlier.

METHODS

Institutional Ethical Review Board (Erasmus University Hospital, Rotterdam) and written informed consent for the use of their data for scientific purposes were obtained.

Anesthesia

In both the standard (SR) and new regimen (NR), general anesthesia was induced with propofol, fentanyl or sufentanil, and a non-depolarizing muscle relaxant, and maintained by inhalation anesthesia using sevoflurane and air. All patients were mechanically ventilated with a mixture of oxygen in room air (FiO_2 of 0.40) and a positive end expiratory pressure at 5 cm H_2O. In all patients hemodynamic monitoring consisted of radial arterial blood pressure and right atrial pressure measurements.

Before induction of general anesthesia, an epidural catheter was inserted at the mid-thoracic inters pace (T6-T8) tested with 3 ml bupivacaine 0.5 %. Before starting surgery, the epidural block was topped up with 10 ml bupivacaine 0.25%, directly followed by a continuous administration of a mixture of bupivacaine 0.125% with fentanyl 2.5 µg/ml at a rate of 10 ml/h throughout the operation and continued on the ICU. If no effective epidural block could be established per operatively, analgesia was provided with fentanyl intravenously, followed in the ICU by continuous administration of fentanyl 50-100 µg/hr i.v. in case of postoperative mechanical ventilation (in the SR group), or patient-controlled analgesia with morphine i.v. (bolus of 1 mg, lockout of 6 - 10') when extubated (in the NR group). In both groups, the presence of postoperative pain was continuously evaluated by an acute pain service using numeric rating scales. If necessary, infusion rates were adjusted or alternative forms of analgesia were used, until pain scores (Visual Analogue Scale) were less than four on a scale from zero (no pain) to ten (maximum pain).

In the SR group, propofol sedation and mechanical ventilation were continued overnight in the ICU. Depending on respiratory function, extubation occurred on postoperative day one. In the NR group, patients were extubated at the latest two hours after arrival at the ICU. To be extubated, the patient must be awake, cooperative, hemodynamic stabile, and having a temperature above 35,5°C and an oxygen saturation higher than 93 % on 40% inspired oxygen.

Fluid and vasopressor therapy

In the SR group, fluid therapy was not strictly regulated. Each patient received 500-1000 ml colloid (Voluven, hydroxyethylstarch 130 kD, Fresenius,'s Hertogenbosch, the Netherlands) at the start of the procedure to compensate for the epidural induced vasodilatation. Maintenance infusion throughout the procedure was set at 10-15 ml/kg bodyweight/hr of crystalloid solution (saline or lactated Ringer's solution), aiming at mean arterial blood pressures (MAP) above 65 mm Hg and right atrial pressures (RAP) between 10 and 15 mm Hg. Persisting hypotension (MAP below 65 mm Hg) was first treated with administration of additional amounts of colloid, and if no adequate reaction (RAP>15 mm Hg and MAP<65 mm Hg) was obtained, vasopressors were administered.

In the NR group, we aimed to reduce of the net per operative fluid balance below 4 liters. Crystalloids were administered in a maintenance infusion of 250 ml/h and additional amounts were given until a diureses of minimal.0,5 ml/kg/h is achieved. Mean arterial pressure was maintained at or above 65 mm Hg with administration of norepinephrin if necessary. No compensation for epidural related vasodilatation was administered and colloids were used 1:1 to compensate for blood loss. Blood loss was calculated as the surgical aspirations and the weight of the used gauses with a correction for fluid used for flushing the surgical area. ASA guidelines for erythrocyte transfusion were used[6].

Standard fluid administration in the ICU consisted of 2 litres of fluid per 24 hours, 1500 ml crystalloid solutions and enteral feeding, which was started after arrival on the ICU at a 21 ml / h through a naso-jejunal feeding tube (positioned during surgery).

Data collection

Data were collected retrospectively (November 2003 - April 2005) and prospectively (June 2005 until September 2006). As such, 84 patients were included in the SR and 83 in the NR group. Patient characteristics, operation characteristics, total per operative blood loss, urine production and the types and volumes of infusion fluids that were administered during the procedure and the total per operative fluid balance were obtained for each patient. In addition, the daily fluid balance on the ICU was recorded until the fourth postoperative day.

Postoperative surgical and cardiopulmonary 30 day-morbidity were scored in all patients. Surgical morbidity included leakage and/or ischemia of the gastric tube (determined by endoscopy or esophageal contrast videography), hemorrhage, chylothorax, recurrent nerve paresis, wound infection and pleural empyema. Cardiopulmonary morbidity included pneumonia (based on chest X-ray and positive sputum culture), arrhythmias, myocardial infarction, decompensatio cordis, lung emboli and cerebral infarction. Additionally, the frequency of re-intubation and re-admission to ICU, and in-hospital and 30 day mortality were scored. Finally, duration of intensive care and total hospital stay were recorded.

Statistical analysis

All continuous variables are described as mean ? SEM or as median and range if not normally distributed; binominal variables are described in percentages. For analysis of between group differences an unpaired t-test, analysis of variance or a $\chi 2$ test was performed. $P < 0.05$ was considered significant. All analyses were performed using SPSS 11.5 for Windows (SPSS inc, Chicago, USA).

RESULTS

Patient and procedural characteristics (Table 1) and tumour classification characteristics (data not shown) were similar in both groups.

Table 1. Patient and surgical characteristics.

	SR (n=84)	NR (n=83)
Male /Female (%)	73 / 27	69 / 31
Age (year)	63 ± 2	62 ± 1
Bodyweight (kg)	81 ± 3	79 ± 2
ASA I/II/III	29 / 50 / 21	23 / 58 / 19
Type surgery: THE/TTE (%)	83 / 17	78 / 22
Successful TEA (%)	96	92
Time surgery (min)	235 ± 7	229 ± 7
Time total procedure (min)	328 ± 11	329 ± 9

SR = standard regimen; NR = new regimen. ASA: American Society of Anesthesiologists classification; type of surgery: transhiatal (THE) and transthoracic (TTE) esophagectomy; TEA: thoracic epidural analgesia. Data are expressed as percentage of total or as mean ± SEM.

Table 2. Peroperative fluid therapy

	SR (n=84)	NR (n=83)
Fluids In		
Crystalloids (ml)	5630 ± 189	3670 ± 266 *
Colloids (ml)	1917 ± 94	1460 ± 77 *
Packets Cells (ml)	589 ± 43	600 ± 133
Fluids out		
Blood loss (ml)	1432 ± 92	1129 ± 115
Urine production (ml/kg/hr)	1.77 ± 0.15	1.17 ± 0.10
Total Fluid balance (ml)	+ 5100 ± 277	+ 3683 ± 241 *

SR = standard regimen; NR = new regimen. Data are expressed as mean ± SEM.

* P < 0.05 vs. Standard Regimen

Significantly less crystalloid and colloid fluids were administered in the new regimen (NR) group, leading to a significantly less positive fluid balance at the end of the operation procedure, i.e. 3683 ± 241 ml (NR) vs. 5100 ± 277 ml (SR) (Table 2). Per operative urine production was 1.77 ± 0.15 in the SR-group vs. 1.17 ± 0.10 ml/kg/hr in the NR-group. There were no differences in both groups according to the per operative hemodynamics.

Vasopressors were used in 79% (SR) versus 75% (NR) considered not significant. In the ICU, daily fluid balance was less, only in the NR group on the day of surgery (Fig. 1).

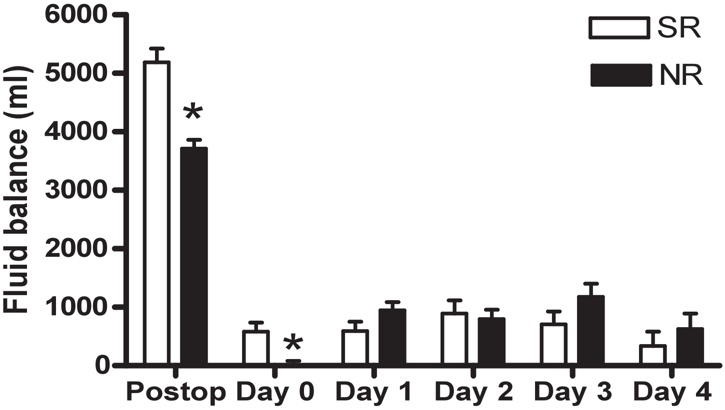

Figure 1. Fluid Balance following esophagectomy.
SR= standard regimen, NR= new regimen. Postoperative reflects the fluid balance directly following surgery whereas Day 0 reflects the fluid balance on the ICU from the remaining part of the day. Data expressed as mean ± SEM; *P<0.05 vs SR

All patients in the NR group were extubated, according the protocol, in the operation room or in the 2 hours after entering the ICU.

Postoperative data are shown in Table 3. The incidence of postoperative pneumonia was significantly reduced in the NR group compared to SR group ($p<0.01$) while the reintubation rate was not significantly different between groups. Total cardiopulmonary morbidity was significantly reduced in the NR group, which is attributed in particular to the decreased occurrence of pneumonia (Table 3). Overall 30-day morbidity was significantly less in the NR group (50 %) compared to the SR group (68%) (Table 3). Although in-hospital mortality was lower (5%) in the NR group than in the SR group (9%), this was not significantly different. ICU and hospital stay were comparable in both groups (Table 3).

Table 3. Morbidity and mortality following esophagectomy.

	SR (n=84)	NR (n=83)	P-value
Surgical morbidity			
Leakage anastomosis	13	14	1.000
Recurrens nerve paresis	10	5	0.274
Wound infection	8	5	0.767
Chylothorax	3	1	0.360
Pleural empyema	7	3	0.322
Bleeding/haematoma	3	1	0.360
Total	**33**	**24**	0.285
Cardio-pulmonal morbidity			
Arrhythmias	9	10	1.000
Pneumonia	42	16	<0.01
CVA	1	4	0.369
Decompensatio cordis	5	2	0.436
Pulmonary Embolism	2	2	1.000
Myocardial infarction	1	0	0.489
Total	**44**	**26**	0.012
ICU Re-admission	7	7	1.000
Re-intubation	23	14	0.177
Mortality			
Overall 30 days morbidity	68	50	0.023
30 days mortality	4	3	0.398
In hospital mortality	9	5	0.398
Duration			
ICU stay	4 (2 – 65)	4 (1 – 57)	0.062
Hospital stay	17 (9 – 94)	14 (8 – 72)	0.095

SR= standard regimen; NR= new regimen. Data expressed as percentage of group total or as median (range).

DISCUSSION

With the introduction of an adjusted anesthetic regimen, directed at early extubation and conservative fluid management, based on the patients' urine output, postoperative pulmonary morbidity in patients undergoing esophagectomy could be significantly reduced. Our fluid management resulted in a lower positive fluid balance less then four liters.

The role of intraoperative fluid therapy in major abdominal surgery patients is subject of an ongoing debate. Recent clinical trials investigating the effect of a restrictive fluid management found a significant reduction in postoperative complications[4-6]. In contrast, studies using the goal directed fluid therapy (based on optimization of stroke volume) found a reduction in postoperative morbidity and hospital stay but to reach this goal more fluid had to be administered[7,8]. Looking specifically at esophagectomy patients, several studies actually favour fluid restriction[9,10]. Neal and colleagues used an intraoperative fluid replacement therapy, guided by urine output of minimal 0.5 ml/kg/h in 56 patients undergoing esophagectomy. If urine output fell below these parameters, extra fluid was administered. In addition, vasopressors and extra volume were used to maintain blood pressure. Limited fluid administration was not associated with high morbidity rates but it was shown to reduce the need for postoperative bronchoscopy and tracheotomy[11].

These observations can be explained by the systemic inflammatory response induced by esophagectomy, leading to a fluid shift, accumulation of fluids in the extra vascular space and hence pulmonary edema[12]. Administration of steroids, suppressing the inflammatory response and the concomitant fluid shift, was shown to reduce postoperative respiratory morbidity and organ dysfunction in these patients[13,14]. However, their benefit is not undisputed and steroids are not used for this purpose in our institution[15].

In our study we did not only apply restrictive fluid management but we also extubated the patients earlier. Several studies have already shown that a short interval between surgery and extubation is associated with lower morbidity rates[16-18]. It can be hypothesized that early extubation actually contributed to less postoperative pulmonary morbidity because it led to a significantly smaller positive fluid balance due to less sedation-related hypotensive episodes. This is supported by the observation that after the operation day, daily fluid balances were similar in both groups.

The incidence of pulmonary complications varies in literature. Recently Orringer reported 2% pneumonia/atelectasis in two thousand transhiatal esophagectomies, describing the clinically significant pneumonia prolonging the hospital stay beyond 10 days[19]. In an English multi-centre study, pulmonary complications occurred in 40.5 % of the patients following esophagectomy[20]. These variations can be due to the use of definitions. Defining pneumonia is difficult in patients after surgery because increased temperature, numbers of leukocytes and levels of C-reactive protein are usually increased. In addition, the postoperative chest X-ray leads to confusing results with atelectasis, pleural effusion, pulmonary contusion and venous congestion interfering with infectious infiltrates. We defined pneumonia as an infiltrate on the chest X-ray in combination with a positive sputum culture. Using this definition our incidence in pneumonia decreased significantly from 42% to 16%.

Our incidence of leakage of the cervical esophagogastrostomy is relative high (13% (SR) and 14% (NR)) but it is within the normal range (5-26%)[21]. Results of anastomotic leakage reported in literature are confusing because in trans-thoracic esophagectomy it is not always clear if a cervical- or intrathoracic anastomosis is studied. Also the discrimination between clinical significant and radiological findings is confusing. In this study, all the anastomotic leakages, determined by endoscopy or esophageal contrast videography, are reported.

CONCLUSION

In conclusion an anesthetic regimen directed at a restricted preoperative fluid management, using a well-defined haemodynamic endpoint of fluid resucitation and early extubation, could reduce the pulmonary morbidity rates following esophagectomy. Because of the complexity of perioperative management of esophagectomy with gastric tube reconstruction the introduction of standardized clinical care pathways should be encouraged by hospital administration and healthcare authorities.

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7. Two-Lung High-frequency Jet Ventilation as an alternative ventilation technique during Trans Thoracic Esophagectomy

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ABSTRACT

Objective

The aim of this study is to evaluate 2-lung high-frequency jet ventilation during esophagectomy and evaluate the influence of high-frequency jet ventilation on pulmonary complications as compared with 1-lung ventilation.

Design

A retrospective study.

Settings

A single centre study in a university hospital.

Participants

We analyzed the data of patients who had undergone an elective esophagectomy by transthoracic esophagectomy between January 2000 and December 2006.

Intervention

The patients had undergone a cervicothoracoabdominal subtotal esophagectomy via a right-sided thoracotomy. Patients with high-frequency jet ventilation were intubated with a single lumen endotracheal tube, and an oxygen insufflation catheter was placed inside the endotracheal tube and connected to a high-frequency jet ventilator.

Measurements and main results

Eighty-seven patients were enrolled; 30 with high-frequency jet ventilation and 57 with 1-lung ventilation. Both groups were adequately oxygenated, but patients in the 1-lung ventilation group had a higher $PaCO_2$ (42.75 ±7.5 mm Hg) compared with that for the high-frequency jet ventilation group (35.25 ± 8.25 mm Hg) ($P < .05$). There was no difference in postoperative respiratory complications between the 2 groups. Mean blood loss was significantly lower for patients in the high-frequency jet ventilation group (1243 ± 787 mL).

Conclusions

High-frequency jet ventilation to two lungs, using a single lumen tube, is a safe and adequate ventilation technique for use during esophagectomy. High-frequency jet ventilation has no influence on the incidence of postoperative pulmonary complications but reduced perioperative blood loss and leads to a decreased need for fluid replacement.

INTRODUCTION

Transthoracic esophagectomy with one-lung ventilation (which leads to a total collapse of the contra-lateral lung) surgically exposes the esophagus. During this procedure, hypoxemia may occur due to shunting of the blood via the nonventilated lung as well as by surgery-induced compression of the mediastinum[1]. In some cases of severe hypoxemia, the collapsed lung must be reinflated to restore tissue oxygenation, thus interrupting the surgical procedure. Operative hypoxemia and the duration of one lung ventilation, is even related to the development of post-operative adult respiratory distress syndrome[2].

Pulmonary complications such as pneumonia and respiratory insufficiency are among the most frequently reported complications that develop after esophagectomy[3]. In 1992, Crozier reported an incidence of pneumonia in half of his patients[4]. The occurrence of pneumonia depends on many factors e.g., pulmonary complications are associated with the surgical approach used for esophagectomy. A Dutch study demonstrated that limited transhiatal esophagectomy is associated with lower morbidity than is transthoracic esophagectomy with extended en bloc lymphadenectomy[5].

In 1997 the British national confidential enquiring into perioperative death (NCEPOD) reported deficiencies in the management of double lumen tubes during esophagectomy[6].

High-frequency jet ventilation (HFJV) to two lungs has been successfully used in several fields of thoracic surgery[7]. To reduce the problems of hypoxemia and malpositioning of the double lumen tube and in an attempt to decrease the incidence of postoperative pneumonia after esophagectomy (by decreasing the areas of atelectasis and shunting) we have begun using HFJV during esophagectomy at our institution[1,8].

The aim of this study is to evaluate HFJV to two lungs, through a single endotracheal tube, during esophagectomy and the influence of HFJV on early postoperative pneumonia and compare our findings with patients getting one-lung ventilation by a double lumen tube.

METHODS

The Institutional Ethical Review Board of Erasmus University Hospital in Rotterdam, The Netherlands, approved the use of the data for scientific purposes. Data from 30 elective esophagus resections by transthoracic esophagectomy, ventilated with two-lung HFJV, between January 2000 and

December 2006 were reviewed. These data were compared to those of 57 patients selected for transthoracic esophagectomy, getting one-lung ventilation by a double lumen tube, during the same period. Operations were done with curative intent using a cervicothoracoabdominal subtotal esophagectomy (3-hole esophagectomy). A right-sided posterolateral thoracotomy was used in all patients.

During the reviewed period of 6 years, anesthesia was following a clinical protocol. Before the induction of anesthesia, a thoracic epidural catheter was placed between T6 and T8 to provide perioperative and postoperative analgesia. After a test dose of 3 mL bupivacaine 0.5%, an epidural blockade was started with a bolus of bupivacaine and sufentanil. General anesthesia was induced with propofol (1-2 mg/kg) or etomidate (0.15-0.3 mg/kg), sufentanil (0.2-0.4 µg/kg), and rocuronium (0.5-1.0 mg/kg). Patients were intubated in the supine position and then placed in the left lateral decubitus position. Anesthesia was maintained using a propofol infusion, and bolus sufentanil was administered as indicated. In all patients, standard hemodynamic monitoring was used including radial arterial blood pressure and, in the supine position, right atrial pressure measurements through a central venous catheter placed in the left internal jugular vein. In both groups arterial blood gas analysis was performed during the thoracotomy at between 10 and 20 minutes following stabilization of hemodynamics and ventilation. Fluid management was liberal and was done using hydroxyethyl starch (HAES sterile 6% or Voluven®; Fresenius Kabi, 's-Hertogenbosch, The Netherlands), and crystalloids were given to maintain a mean arterial pressure above 60 mm Hg and a right atrial pressure between 10 and 12 mm Hg. Arterial oxygen and carbon dioxide partial pressures, hemoglobin concentration, and hemoglobin saturation were determined (ABL 707, Radiometer, Copenhagen, Denmark). Blood transfusions were given if the hemoglobin level was below 5.0 mmol/L (8.0 g/dL). Vasopressors were avoided in an attempt not to influence the microvascular blood flow of the constructed gastric tube.

Patients in the high-frequency jet ventilator (HFJV) group were intubated with a normal, single lumen, endotracheal tube (male size, 8.5 and female size, 7.5; Portex). After the thoracotomy incision, the ventilator (Draeger Physioflex, Dräger Medical AG & Co. KG, Lübeck, Germany) was disconnected, and an oxygen insufflation catheter (Baxter Healthcare Corporation, New Providence, NJ, USA) was placed inside the endotracheal tube and connected to a Jet Ventilator (AMS 1000, Acutronic Medical Systems AG, Hirzel, Switzerland). The HFJV was set at a frequency of 100/minute with a driving pressure of 2.0 atm, FiO_2 was set at 0.6 to 1.0 to maintain adequate oxygenation. The surgeon gently manipulated the right lung outside the operative field to create exposure on the esophagus.

Patients in the one-lung ventilation group, received a left-sided double-lumen tube (male size, 39, and female size, 37; Portex, Smiths Medical International LTD, Watford, United Kingdom); correct placement was checked by auscultation and, if in doubt, by fiberoptic analysis. Tube position was checked after every repositioning of the patient. The right lung collapsed after the right lateral thoracotomy and one-lung ventilation of the left lung was started (Draeger Physioflex). Tidal volume of 8 to 10 mL/kg and a frequency of 12 to 15/minute were adjusted to achieve an end-tidal CO_2 of 35 to 45 mm Hg with plateau pressure lower than 35 cm H_2O. Positive end expiratory pressure (PEEP) was set at 5 to 7 cm H_2O, inspiration; expiration was set at 1:2, and FiO_2 was between 0.6 and 1 to maintain oxygen saturation (plethysmography) above 95%.

After thoracotomy, the patient was returned to the supine position before starting the abdominal part of the operation. In the two-lung ventilation group, the HFJV catheter was removed, and conventional mechanical ventilation was restarted at the same settings as described above. In the one-lung ventilation group, the double lumen tube was replaced by a normal endotracheal tube before transport to the intensive care unit. All patients at the intensive care unit were sedated and ventilated until the following morning (Draeger Evita 2 or Evita 4) at the following settings: Bilevel Positive Airway Pressure mode, 5 cm of H_2O PEEP, a peak pressure of 10 to 15 cm H_2O above PEEP to achieve tidal volume of 8 to 10 mL/kg, and a frequency of 15 to 25 needed to achieve normocapnic ventilation. The inspiration:expiration ratio was set at 1:2 and FiO_2 was chosen to keep oxygen saturation above 95%

In our hospital, clinicopathologic data from all patients who are operated on are collected in a database. Pulmonary morbidity was scored including pneumonia (based on positive findings on a chest radiograph and a positive results of a sputum culture), and adult respiratory distress syndrome (based on characteristic findings on a chest radiograph in combination with a PaO_2/FiO_2 ratio lower than 200 mm Hg.

Statistical analyses

To compare categorical data, the Fisher exact test was used. The Mann-Whitney U test was used to compare continuous variables. Two-tailed P values less than .05 were considered statistically significant. When variables were normally distributed, the mean and standard deviations are reported in the Tables. All analyses were performed with Graphpad Prism software (version 3.0, Graphpad Software Inc, San Diego, CA, USA).

RESULTS

Thirty patients for elective transthoracic esophagectomy, received two-lung mechanical ventilation by HFJV. This group was compared with 60 patients, receiving one-lung ventilation by a double lumen tube. From 3 patients, data considering anesthesia were incomplete and therefore they were excluded. There was no difference in the patients' characteristics (Table 1).

Mean operation time was comparable between the groups. The mean length of stay in the intensive care unit for patients in the HFJV group was 11 ± 13 days (median, 6 days) compared with 13 ± 23 days (median, 7 days) for patients in the one-lung ventilation group(not significant; NS).

During thoracotomy, the oxygen saturation was higher in the HFJV group than in the one-lung ventilation group. However, arterial oxygen tension was comparable between both groups during thoracotomy (Table 2). Both groups were normocapnic perioperatively, but the HFJV ventilation group had a significantly lower, Pa_{CO2} of 35.25 ± 8.25 mm Hg versus Pa_{CO2} of 42.75 ± 7.5 mm Hg (Table 2).

There was significantly less blood loss in patients in the HFJV group (1243 ± 787 mL) compared with the one-lung ventilation group (1883 ± 941 mL) (P = 0.002). This resulted in smaller red blood cell transfusions (0.8 ± 1.1 units vs 1.6 ± 1.5 units; P = .007) and smaller crystalloid administrations (6031 ± 1793 mL vs 7333 ± 2164 mL; P = .001) (Figure 1).

In the HFJV group, pneumonia occurred in 11 patients (37%) compared with 20 patients (35%) in the 1-lung ventilation group (NS). Adult respiratory distress syndrome does not occur. There were no differences in surgical complications such as chylothorax, recurrent nerve pareses, or gastric tube leakage (data not shown).

DISCUSSION

In this retrospective observational study we demonstrated adequate ventilation of both lungs by high-frequency jet ventilation (HFJV) during transthoracic esophagectomy using a single lumen endotracheal tube. We compared the HFJV group to patients receiving one-lung ventilation by a double lumen tube (DLT). The NCEPOD report (1997) noted deficiencies in the recognition and management of badly positioned tubes during esophagectomy[8]. In an editorial of the British Journal of Anesthesia, Sherry noted that even the most experienced anesthetist continue to have problems with double lumen tube positioning and she asked for an alternative ventilation strategy[9]. In our data analysis no problems or complications were reported with double tube positioning but this can be due to the retrospective study design[10]. However, using HFJV with a single lumen tube avoids the problems associated with DLT as malpositioning, tube migration, laryngeal damage and perforation of the bronchi[7]. Also the need to change tubes before transport to the ICU is avoided.

Although the technique has been successfully used in other fields of thoracic surgery, to the best of our knowledge, this is the first study to describe a cohort of patients treated with two-lung HFJV during esophagectomy[7]. Other authors have described HFJV in combination with conventional one-lung ventilation, as an additional support in the dependent lung, to restore decreased oxygenation during one-lung ventilation[11]. While using high-frequency positive pressure ventilation, using a conventional ventilator (tidal volume, 300 mL; frequency, 100/min); Tsui found less hypoxemia in patients treated with two-lung ventilation than in those treated with one-lung ventilation[12]. HFJV to both lungs during esophageal surgery was successfully used to manage a patient having a transesophageal fistula[13].

All previously mentioned additional ventilation strategies were made in an attempt to avoid hypoxic periods, because perioperative hypoxemia and prolonged duration of one-lung ventilation most likely lead to an increased incidence of postoperative pulmonary complications after esophagectomy[2].

In our study, although there was no hypoxemia in either of our groups, gas exchange was better using two-lung ventilation than one-lung ventilation during thoracotomy. In other thoracic operations than esophagectomy, the use of HFJV compared with one-lung ventilation has led to prolonged improvement in oxygenation up to even 7 days after surgery[6].

There was no difference in length of stay in hospital or ICU between our groups. Other studies have shown that patients with HFJV had a reduced mean hospital stay. This reduction could be attributed to a lower incidence of postoperative chest infections (as recognized by the findings of pyrexia, purulent sputum, and positive culture results)[6]. In our patients, there was no difference in postoperative pneumonia.

The length of ICU stay in both groups is relative long (11 ± 13 days (median, 6 days) vs. 13 ± 23 days (median, 7 days)). This is partly due to the strategy to ventilate the patients for the night on the day of surgery and the policy not to send this particular patient group to a step down unit.

Although not the focus of our study, we observed a greater need for fluid replacement and more blood loss in patients in the one-lung ventilation group. Blood loss is mainly dependent on surgical technique. No extended lymphadenectomy was performed and in both groups the same technique was used by the same surgeon (HWT). Previous studies have shown no change in cardiac output during one-lung ventilation; however, those studies showed an increase in pulmonary wedge pressure and pulmonary vascular resistance due to hypoxic pulmonary vasoconstriction[14,15]. Tachibana et al. showed that the effect of pulmonary vasoconstriction and shunting provides a relative flow obstruction to the left ventricle and this, in combination with compression of the mediastinum, leads to a greater need for fluid replacement and an increased central venous pressure. In his study, no change in outcome between one-lung or two-lung conventional ventilation was found[1]. We did not analyze the central venous pressure because of the unreliability of this measurement during lateral positioning[16]. However, an increased central venous pressure, and thus, splanchnic congestion, may be an explanation for the blood loss in patients in the one-lung ventilation group. The influence of the higher central venous pressure on operative blood loss is well-known during hepatic surgery[17]. The observed decrease in blood loss in the HFJV group resulted in a decreased need for transfusions. Blood transfusions during radical esophagectomy are associated with a poorer prognosis[18]. Additionally, when used as part of a multimodal approach to reduce the high morbidity and mortality after esophagectomy, decreased blood transfusions and a restrictive fluid management seems to be beneficial[19,20].

CONCLUSIONS

High-frequency jet ventilation to two lungs, using a single lumen tube, is a safe and adequate ventilation technique for use during esophagectomy. Using HFJV the problems associated with double lumen tubes are avoided. High-frequency jet ventilation has no influence on the incidence of postoperative pulmonary complications but reduced perioperative blood loss and leads to a decreased need for fluid replacement. Our retrospective study suggests that a prospective, multicenter randomized study of HFJV on postoperative outcomes in transthoracic esophagectomy is warranted.

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8. General Discussion and Future Perspectives

GENERAL DISCUSSION

The incidence of esophageal malignancies is increasing tremendously in the western world[1]. Esophagectomy followed by gastric tube reconstruction is the surgical treatment of choice for patients with cancer of the esophagus. Esophagectomy and gastric tube reconstruction has a high incidence of complications[2]. This operation is an example of a complicated procedure in which a multidisciplinary approach is necessary.

The two major complications are leakage of the new created gastro-esophageal anastomosis and early postoperative respiratory insufficiency. In the following part we will discuss these complications and give some perspectives for the near future.

The surgeon; impaired anastomotic healing

The most frequent surgical complications are associated with the gastro-esophageal anastomosis and are anastomotic leakage (5-26 %) and stenosis (12-40 %)[3]. Although the cause of these complications is not exactly clear, compromised gastric tissue blood flow and concomitant tissue ischemia are thought to play a key role. This is easily explained by the way the surgeon forms the gastric tube, i.e. with ligation of the feeding blood vessels. On the other hand we have shown in the present thesis that venous congestion is also an important contributing factor to the impaired gastric tissue blood flow[4].

Assuming that the surgical technique leaves hardly any room for improved perfusion, administration of vasoactive medication might be the second best option to improve tissue perfusion. In this thesis we demonstrated that topical nitroglycerin (NTG) has a positive effect on gastric tube perfusion. NTG is clinically used as a (venous) vasodilatator but its effect on microvascular blood flow in general is still part of discussion. Unfortunately we failed to demonstrate a similar beneficial effect of intravenous NTG in a fixed dosage, but the results of our study in an experimental gastric tube model was promising for the future. In this model we considered the gastric tube as a system free of autonomic nervous regulation. In this model anastomotic microvascular blood flow is dependent on the driving pressure from the fundus and the vascular resistance of the tube. We have demonstrated that increasing the driving pressure alone is insufficient to increase tissue blood flow. However, the combination of sufficient driving pressure with administration of NTG as drug to lower vascular resistance through prevention of venous congestion, does lead to improved gastric blood flow. The importance of venous congestion has been demonstrated before by the positive effect of the performance of a venous anastomosis between the short gastric vein and the internal and external jugular veinsand by the effect of bloodletting from the gastric veins[5,6]. Future research could be directed at the search for other vasodilating drugs that might exert a similar positive effect on tissue perfusion.

However, in our opinion a more important issue that should be addressed first is how gastric tube tissue blood flow can be monitored in the postoperative period. This is necessary in order to titrate any therapy and evaluate its effect; administration of a fixed dosage is not successful as we have shown in this thesis but was also demonstrated by Boerma and coworkers in septic ICU patients[7]. Suitable techniques for postoperative monitoring are preferably endoluminal and minimally invasive, such as carbon dioxide tonometry, photospectrometry or laser Doppler flowmetry[8,9]. Measurements should be repeated for about 2-4 days, the estimated time for recovery of the gastric tube perfusion. As an alternative a more remote physiologic parameter can be used to monitor venous congestion, such as central venous pressure. In this thesis we have shown that this easily obtainable and often used clinical parameter, could very well be used to titrate the dosage of nitroglycerine. In fact, central venous pressure is used in a similar way in liver surgery to guide volume and vasodilator therapy in order to prevent congestion of the hepatic vascular bed and minimize preoperative blood loss[10].

On the level of the microcirculation, maybe a better accessible tissue surface can be found that also reflects the effect of vasodilator therapy. For instance, the sublingual microcirculation has been the subject of many recent studies investigating the systemic and local effects of vasoactive drugs[7,11]. One of these studies reported that the administration of 5μg/kg min dobutamine improved capillary perfusion in septic patients, independent of global hemodynamic parameters and cardiac index. This could also be studied in patients undergoing esophagectomy in order to improve the impaired microvascular blood flow. However, the question still arises whether improving tissue perfusion in the postoperative period can really prevent impaired anastomotic healing.

Although gastric tissue blood flow is decreased in all patients, only a minority suffers from impaired anastomotic healing. Factors other than vascular perfusion may play a role in this process, such as conduit width, intrathoracic pressure changes, and inflammatory reactions to surgery. Additionally, the surgeon can be assisted in the formation of a vital anastomosis with optical techniques that visualize the global tissue perfusion of the complete gastric tube[12]. In the end, we have no reason to doubt that skills and experience of the surgeon outweigh the effect of any supportive tissue perfusion therapy on clinical outcome.

The anesthesiologist; pulmonary complications

Although surgical complications certainly have an impact on outcome, they are relatively rare compared to the respiratory complications, occurring in 40-60 % of patients. These patients have a worse long-term outcome[13]. There are several reasons for decreased postoperative pulmonary function. During transthoracic esophagectomy the right lung is (partly) collapsed to create surgical exposure to the esophagus. Direct trauma leads to atelectasis and local contusion in this lung. Through a systemic inflammatory response to this trauma, the other lung is also affected, resulting in bilateral lung edema and atelectasis.

Second, the surgical trauma of an esophagectomy (including exploration of two or even three body compartments) induces an even stronger systemic stress response with subsequent release of inflammatory mediators causing global vasodilatation and capillary leakage. As a result, the likelihood of edema formation in the lung increases even more. In conjunction with decreased postoperative immune function this leads to an increased risk for postoperative pneumonia as well.

With this knowledge, it is evident how the perioperative anesthetic management can contribute directly to the postoperative course. Excessive fluid administration will lead to accumulation of fluid in the lungs; therefore a strict balance is required between the maintenance of systemic circulation with adequate perfusion pressure of the gastric tube and the prevention of edema formation. Because the patient's hemodynamic autoregulation is disturbed by the inflammatory response as well as by general anesthesia and thoracic epidural analgesia, additional hemodynamic monitoring can be very valuable for hemodynamic support. At least, the peroperative management should be aimed at restricted administration of fluid, as we have shown in this thesis.

An additional advantage of minimal fluid administration is that the volume of the systemic venous compartment remains limited and impaired regional venous outflow through venous congestion is less likely to occur. In our experimental study we demonstrated that a lower central venous pressure was associated with improved gastric tissue blood flow. Although it is currently generally accepted that there is no relation between volume of the central venous compartment and central venous pressures, it can be assumed that abundant fluid administration will at least increase the likelihood of venous congestion. In a similar way fluid administration is restricted during liver surgery to decrease peroperative blood loss[10].

Besides balanced hemodynamic management, the perioperative anesthetic management can be expanded with more measures to diminish pulmonary morbidity. Beneficial effects of steroids and of selective digestive tract decontamination [have been demonstrated[14,15]. Future research should look into the value of low-tidal volume mechanical ventilation. Although we did not find a positive effect of high frequency ventilation over single lung ventilation on pulmonary complications, it is very likely that a protective ventilation strategy (= low tidal volume and low airway pressures) can reduce the local pulmonary and systemic inflammatory response. Additionally, preoperative lung function assessment, perioperative respiratory muscle training and early forced mobilization with physical therapy might all contribute to decreased pulmonary morbidity.

Practical considerations

In conclusion, it is clear that a coordinated multidisciplinary approach is warranted for the patient undergoing an esophagectomy with gastric tube reconstruction. It is crucial to realize that the anesthetic management contributes directly to the postoperative course and probably to long-term outcome as well. From this perspective, the roles of surgeon and anesthesiologist during this procedure are complementary. Currently, most research efforts are focused on the oncological aspects of esophageal cancer. This is of course the most important way to improve patient cure and survival, however there is ample evidence that the perioperative course can still be improved in order to reduce postoperative morbidity and increase patient's quality of life.

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9. Summary / Samenvatting

SUMMARY

The incidence of cancer of the esophagus has increased markedly over the past 25 years. Clinical features of esophageal cancer are difficulty swallowing, problems with passage of food and pain. Surgical resection has remained the mainstay of treatment of esophageal cancer. Eshophagectomy with direct gastric tube reconstruction is associated with high morbidity and mortality. The two major groups of complications are respiratory morbidity and gastroesophageal anastomotic leakage. In this thesis we describe several studies aiming at a reduction of the incidence of the two major postoperative complications following esophagectomy. In **chapter 1** a historical review describes the development of the perioperative care from the first esophagectomy by Torek in 1913 and the challenges of esophagectomy nowadays.

In **chapter 2** we discuss the use of reflection spectrophotometry in clinical and experimental practice. Reflection spectrophotometry, based on absorption and scattering of reflected visible light, can provide information about hemoglobin oxygen saturation and hemoglobin concentration in tissue. Reflection spectrophotometry has been used in animal and clinical studies and is a non invasive technique without the use of special indicator dyes. Despite its limitations, reflection spectrophotometry allows detection of changes in capillary hemoglobin saturation.

In **chapter 3** we use reflection spectrophotometry in combination with laser Doppler flowmetry to evaluate the microcirculatory alterations in the gastric tissue during gastric tube reconstruction. Complications associated with the gastroesophageal anastomosis are anastomotic leakage and stenosis. Although the cause of these complications is unknown, compromised microvascular blood flow (MBF) and hypoxia of the gastric tube are thought to be important factors. In the present study, we observe a decrease in MBF of almost 75%, occuring at the fundus without significant change microvascular oxygen saturation, during gastric tube reconstruction. Another observation in this study is the increase in microvascular blood flow following local application of nitroglycerin (NTG). We conclude that MBF decreased during gastric tube reconstruction and that topical administration of the vasodilator NTG improved MBF, possibly due to general vasodilatation and decreased venous congestion.

The effect of systemic administration of nitroglycerin on gastric MBF is described in **chapter 4**. NTG acts as a nitric oxide (NO) donor; in the vascular endothelium NO is a regulator of vascular tone, and thereby of microvascular perfusion. NO plays an important role in the auto-regulation of gastric mucosal

blood flow and it is likely that NO plays a role in protecting the gastric mucosa and preserves mucosal integrity. During conditions of decreased flow, such as gastric tube formation, the use of NTG is shown to be effective in the improvement of gastric MBF. In this study we were not able to prevent a decrease in gastric fundus microvascular perfusion and oxygenation during gastric tube reconstruction with the continuous intravenous administration of NTG. Although intravenous NTG does not preserve microvascular blood flow or microvascular hemoglobin saturation, it might be important in the reduction of the incidence of early leakage of the esophagogastrostomy.

In **chapter 5**, we test the hypothesis that gastric tube perfusion depends on arterial perfusion pressure and that, assuming the role of venous congestion, this effect can be augmented with infusion of nitroglycerine. For this purpose we developed an experimental model of gastric tube reconstruction, in which we were able to combine a clinically relevant surgical model with measurements of systemic hemodynamics as well as gastric tissue perfusion parameters.

In this model we demonstrate that the deterioration of the microvascular perfusion of the gastric tube following surgery is not improved with higher perfusion pressures but can partly be prevented with administration of nitroglycerine. These findings imply that venous congestion is more important for the gastric tube perfusion than increasing arterial perfusion pressure.

Despite improvements in surgical techniques and perioperative care, the postoperative course is often complicated, with respiratory morbidity as the most frequent (30-50%) non-surgical complication.

In **chapter 6** we describe the effect of a new anesthesia regimen, based on restrictive fluid management (guided on the patients' urine output), early extubation and thoracic epidural analgesia. The incidence of postoperative pneumonia is significantly reduced in the new regimen group compared to standard treatment group. We conclude that an anesthetic regimen directed at a restricted preoperative fluid management, using a well-defined haemodynamic endpoint of fluid resucitation and early extubation, could reduce the pulmonary morbidity rates following esophagectomy. Because of the complexity of perioperative management of esophagectomy with gastric tube reconstruction, the introduction of standardized clinical care pathways should be encouraged by hospital administration and healthcare authorities.

Transthoracic esophagectomy with one-lung ventilation (which leads to a total collapse of the contra-lateral lung) surgically exposes the esophagus. During this procedure, hypoxemia may occur due to shunting of the blood via the nonventilated lung as well as by surgery-induced compression of the mediastinum. In some cases of severe hypoxemia, the collapsed lung must be reinflated to restore tissue oxygenation, thus interrupting the surgical procedure. Operative hypoxemia and the duration of one lung ventilation, is even related to the development of post-operative adult respiratory distress syndrome. In **chapter 7** we demonstrate adequate ventilation of both lungs by high-frequency jet ventilation (HFJV) during transthoracic esophagectomy using a single lumen endotracheal tube. Using HFJV the problems associated with double lumens tubes are avoided. High-frequency jet ventilation has no influence on the incidence of postoperative pulmonary complications but reduces perioperative blood loss and leads to a decreased need for fluid replacement.

SAMENVATTING

De incidentie van slokdarmkanker is de afgelopen 25 jaar fors gestegen. De symptomen van slokdarmkanker zijn slikklachten en problemen met voedsel passage en pijn. Tumoren zonder uitzaaiing op afstand worden bij voorkeur chirurgisch behandeld. Ook al is chirurgische behandeling succesvol in het verwijderen van de tumor, bij veel patiënten treedt er een recidief op en lange termijn overleving van de geopereerde patiënten groep is ongeveer 20%.

Na een slokdarm verwijding wordt de continuãteit van het maagdarm stelsel hersteld door middel van een buismaagprocedure. Hierbij wordt de maag tot een buis gevormd en aangesloten op de slokdarm rest, meestal in de hals. Slokdarmresectie en buismaagreconstructie gaan gepaard met een hoge morbiditeit en mortaliteit. In **hoofdstuk 1** wordt een overzicht van de hedendaagse problemen in het peri-operatieve traject in de behandeling van het slokdarmcarinoom gegeven. Tevens beschrijft een historisch overzicht de chirurgische en anesthesiologische ontwikkeling van de slokdarmoperatie.

In **hoofdstuk 2** wordt een introductie en overzicht gegeven van de klinische en experimentele toepasbaarheid van reflectiespectrophotometrie. Reflectiespectrophotometrie is gebaseerd op de absorptie en weerkaatsing van gereflecteerd zichtbaar licht en geeft informatie over de hoeveelheid verzadigd hemoglobine en de concentratie hemoglobine in weefsels. Reflectiespectrophotometrie is een niet-invasieve techniek en veel gebruikt in kliniek en experimentele setting.

In **hoofdstuk 3** beschrijven we het gebruik van reflectiespectrophotometrie in combinatie met laser Doppler flowmetrie in de evaluatie van microcirculatoire verandering van het maagweefsel tijdens een buismaagprocedure. Complicaties gerelateerd aan deze buismaagreconstructie zijn lekkage en stenose van de aanhechting van de maag aan de rest-slokdarm. De oorzaak van deze complicatie is niet precies bekend maar waarschijnlijk geassocieerd met een afname van de microvasculaire doorbloeding en weefseloxygenatie. In dit hoofdstuk laten we zien dat de doorbloeding met 75% afneemt in het bovenste deel van de buismaag zonder verandering van de weefseloxygenatie. Verder laten we zien dat de locale toediening van de vaatverwijder nitroglycerine (NTG) de doorbloeding kan verbeteren. Deze waarnemingen wekken de suggestie dat de afname van de microvasculaire doorbloeding kan worden verbeterd door vaatverwijding. Mogelijk dat veneuze stuwing van het maagweefsel hierbij een rol speelt.

Het effect van de intraveneuze toediening van NTG op de microcircualtie van het maagweefsel wordt beschreven in **hoofdstuk 4**. NTG is een stikstofoxide (NO) donor. NO speelt een belangrijke rol in de regeling van de vasculaire tonus van de vaatwand en daardoor de doorbloeding van het maagweefsel. NO speelt waarschijnlijk een belangrijke rol in de bescherming van maagslijmvlies. Deze studie kon echter geen positief resultaat van de continue intraveneuze toediening van NTG aantonen op de doorbloeding en oxygenatie van het maagweefsel. Mogelijk speelt NO wel een rol in de preventie van vroege lekkage van de nieuwe maag-slokdarm verbinding.

In **hoofdstuk 5** testen we de hypothese dat doorbloeding van de buismaag afhankelijk is van een arteriële drukgradiënt en dat, door een veronderstelde veneuze stuwing, dit effect kan worden versterkt met toediening van NTG. Voor dit doel werd een diermodel ontwikkeld, in dit model worden systemische hemodynamische parameters gekoppeld aan metingen van maag doorbloeding tijdens diverse chirurgische fasen van een buismaagreconstructie. Met behulp van dit model konden we aantonen dat ontsporing van de microvasculaire doorbloeding niet wordt hersteld met hogere bloeddrukken maar wel verbetert onder invloed van NTG. Deze observatie impliceert een belangrijke rol voor veneuze stuwing van de buismaag.

Ondanks verbetering in de chirurgische techniek en peri-operatieve zorg wordt het postoperatieve traject veelvuldig gecompliceerd door, voornamelijk, respiratoire complicaties. In **hoofdstuk 6** beschrijven we het effect van een nieuw anesthesieprotocol, gebaseerd op een terughoudend vochtbeleid (op geleide van de urineproductie), vroege extubatie, en thoracale epidurale pijnbestrijding. Longontsteking kwam in de groep, behandeld volgens het nieuwe protocol, significant minder voor. We concludeerden dat een terughoudend perioperatief vochtbeleid, met gebruik van eenvoudige, goed gedefinieerde eindpunten, in combinatie met vroeg extubatie een vermindering van respiratoire complicaties geeft. Transthoracale slokdarmresectie maakt gebruik van het laten samenvallen van één long om het zicht op de slokdarm voor de chirurg te verbeteren. Tijdens de periode van één long beademing ontstaat er hypoxemie door shunting van het bloed via de nietbeademde long en door druk van de chirurg op het mediastinum. In sommige gevallen moet de operatie worden onderbroken om beide longen weer te beademen om oxygenatie te herstellen. Hypoxemie tijdens de operatie, en de duur van één -long beademing zijn gerelateerd aan het optreden van postoperatieve pulmonale complicaties. In **hoofdtuk 7** laten we zien dat high-frequency jet ventilation (HFJV), door een normale, single lumen, tube, tijdens transthoracale slokdarmresectie adequate ventilatie geeft. Door gebruik van HFJV is er geen kans op problemen geassocieerd met het plaatsen en gebruiken van dubbel lumen tubes voor één long ventilatie. HFJV heeft geen invloed op de incidentie van postoperatieve pulmonale complicaties maar vermindert per-operatief bloedverlies en de hoeveelheid per-operatief toegediend vocht.

Appendices

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CURRICULUM VITAE

Marcus Paulus Buise was born on april 9, 1967 in Oosterhout (NBr). After MAVO an HAVO he finished Atheneum in 1987. After two years biology he started medical studies in 1989 and passed the final medical exam in 1996. He worked as a surgical resident in “de Lichtenberg” in Amersfoort and the ”Zuiderziekenhuis” in Rotterdam. From 2000 to 2005 he followed his specialist training in Anesthesiology in the Erasmus MC in Rotterdam (head of the department: Prof. dr. J Klein). In this period this research was started. After graduation he went to Leiden to become an intensivist (head Prof. dr. P.C.M. van den Berg). In 2006 he started in the Catharina-hospital, Eindhoven, working as an anesthetist-intensivist and recently become a member of the medical board.

He is married to Annick and together they have two children; Thomas and Floor.

ABBREVIATIONS

AU:	Arbitrary Units
MBF:	Microvascular Blood Flow
NTG:	Nitroglycerine
RAP:	Right Atrial Pressure
MAP:	Mean Arterial Pressure
LDF:	Laser Doppler Flowmetry
RS:	Reflection Spectrophotometry
NO:	Nitric Oxide
FiO_2:	Fraction of Inspired Oxygen
O_2:	Oxygen
$\mu HbSO_2$:	Microvascular hemoglobin O_2 saturation
μHbcon:	Microvascular hemoglobin concentration
THE:	Trans Hiatal Esophagectomy
TTE:	Trans Thoracic Esophagectomy

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