Quantitative perfusion diagnostics in esophageal cancer surgery

Jansen, S.M.

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CHAPTER 2

Optical Techniques for Perfusion Monitoring of the Gastric Tube after Esophagectomy: a review of technologies & thresholds.

S.M. Jansen, D.M. de Bruin, M.I. van Berge Henegouwen, S.D. Strackee, D.P.Veelo, T.G. van Leeuwen, S.S. Gisbertz

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ABSTRACT

Introduction: Anastomotic leakage is one of the most severe complications after esophageal resection with gastric tube reconstruction. Impaired perfusion of the gastric fundus is seen as the main contributing factor for this complication. Optical modalities show potential in recognizing compromised perfusion in real-time, when ischemia is still reversible. This review provides an overview of optical techniques with the aim to evaluate the 1) quantitative measurement of change in perfusion in gastric tube reconstruction and 2) to test which parameters are the most predictive for anastomotic leakage.

Methods: A Pubmed, MEDLINE and Embase search was performed and articles on Laser Doppler Flowmetry (LDF), Near Infrared Spectroscopy (NIRS), Laser Speckle Contrast Imaging (LSCI), Fluorescence Imaging (FI), Sidestream Darkfield Microscopy (SDF) and Optical Coherence Tomography (OCT) regarding blood flow in gastric tube surgery were reviewed. Two independent reviewers critically appraised articles and extracted the data: Primary outcome was quantitative measure of perfusion change; secondary outcome was successful prediction of necrosis or anastomotic leakage by measured perfusion parameters.

Results: Thirty-three articles (including 973 patients and 73 animals) were selected for data extraction, quality assessment and risk of bias (QUADAS-2). LDF, NIRS, LSCI and FI were investigated in gastric tube surgery; all had a medium level of evidence. IDEAL stage ranges from 1-3. Most articles were found on LDF (n=12), which is able to measure perfusion in arbitrary Perfusion Units with a significant lower amount in tissue with necrosis development and on FI (n=12). With FI blood flow routes could be observed and flow was qualitative evaluated in rapid, slow or low flow. NIRS uses mucosal oxygen saturation and hemoglobin concentration as perfusion parameters. With LSCI a decrease of Perfusion Units is observed towards the gastric fundus intra-operatively. The Perfusion Units (LDF, LSCI), although arbitrary and not absolute values, and low flow or length of demarcation to the anastomosis (FI) both seem predictive values for necrosis intra-operatively. SDF and OCT are able to measure microvascular flow, intra-operative prediction of necrosis is not yet described.

Conclusion: Optical techniques aim to improve perfusion monitoring by real-time, high-resolution and high-contrast measurements and could therefore be valuable in intra-operative perfusion mapping. LDF and LSCI use Perfusion Units, and are therefore subjective in interpretation. FI visualizes influx directly, but needs a quantitative parameter for interpretation during surgery.

INTRODUCTION

Anastomotic leakage is a major complication after esophagectomy with gastric-tube reconstruction, with a high morbidity and even mortality rate (4%).[1] The development of poor blood perfusion is partially described to a lack of oxygen and nutrients, which are essential for cell metabolism. This is widely known as a contributing factor for anastomotic dehiscence.[2] The gastric-tube depends on the right gastric and right gastro-epiploic arteries, which usually terminate before the anastomotic site at the gastric fundus and this area is therefore prone to decreased perfusion (figure 1).

At present, perfusion is not quantitatively examined during surgery. If perfusion could be monitored and quantified, the surgeon could change the reconstructive design[3–5] and the anesthesiologists might improve perfusion with medication or adapting fluid administration.[6]

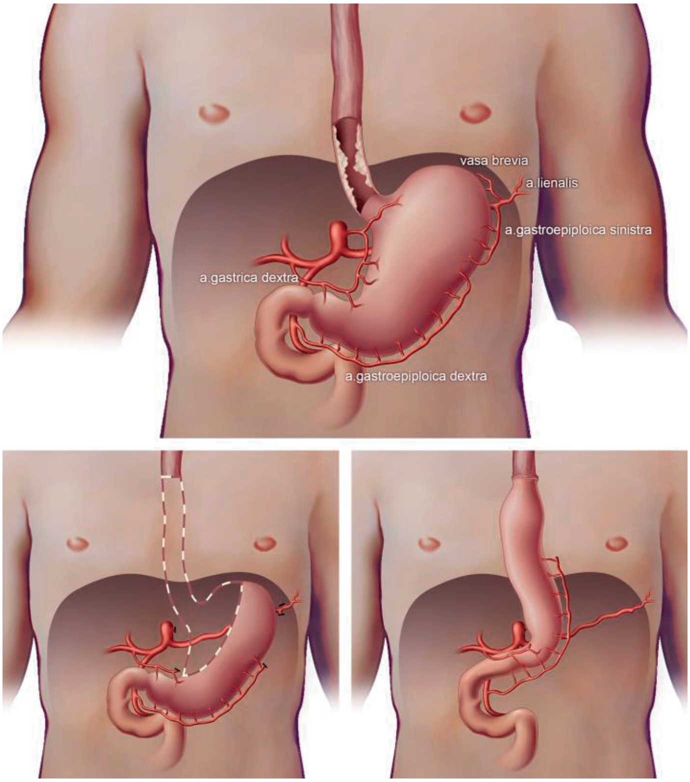

Figure 1. Esophagectomy with gastric-tube reconstruction.

Over the past decades, innovative optical techniques have been developed that use the interaction of light with tissue. Different optical techniques have been tested to monitor perfusion in gastric tube surgery (table 1).

The aim of this systematic review is to evaluate 1) technical background of optical modalities that are tested in gastric tube surgery, 2) quantitative parameters that are used to monitor (micro)vascularization at the anastomotic site and 3) which parameters are the most predictive for anastomotic leakage.

Table 1. Perfusion imaging methods. LDF: Laser Doppler Flowmetry, NIRS: Near InfraRed Spectroscopy, LSCI: Laser Speckle Contrast Imaging, IRT: InfraRed Thermographic imaging, FI: Fluorescence Imaging, OCT: Optical Coherence Tomography.

PERFUSION IMAGING METHODS					
Optical Imaging Method	**Optical principle**	**Imaging resolution**	**Physiology assessment**	**Maximal imaging depth**	**dye administration?**
LDF	Scattering	-	Perfusion in (Perfusion Units)	0.5 mm	No
NIRS	Absorption	-	Oxygenation	mm?	No
LSCI	Scattering	10 µm	Perfusion in (Flux)	1 mm	No
IRT	Scattering	1.2 mm	Temperature	2 mm	No
FI	Fluorescence	0.45mm	Perfusion in blood flow routes	1 cm	ICG, MB …
OCT	Scattering	1-15 µm	Perfusion in speckle decorrelation	2-3 µm	No

METHODS

Methodology was developed from standard guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[7] and the Standards for the Reporting of Diagnostic accuracy studies (STARD) Statement.[8]

Search strategy and study selection

A detailed electronic search was carried out on optical techniques and gastric tube surgery from the following databases: MEDLINE, Embase and Pubmed (table 2).

No timeline limitation was applied to the search, so all articles published before October 26th 2017 were included for analysis.

Table 2. Medline, Embase and Pubmed Electronic Search Strategies

SEARCH STRATEGY
"Digestive System Surgical Procedures"[Mesh:NoExp] OR "Esophagectomy"[Mesh] OR "Esophageal Neoplasms"[Mesh] OR (reconstructive[tiab] AND surgery[ti]) OR esophagus surgery[tiab] OR oesophagus surgery[tiab] OR esophageal surgery [tiab] OR oesophageal surgery[tiab] OR esophageal resection[tiab] OR oesophageal resection[tiab] OR oesophagus resection[tiab] OR cardia cancer[tiab] OR cardia carcinoma[tiab] OR esophagectom*[tiab] OR oesophagectom*[tiab] OR esophageal reconstruct*[tiab] OR oesophageal reconstruct*[tiab] OR gastrointestinal surgery[tiab] OR Gastric Tube*[tiab] OR Gastric conduit*[tiab] OR Gastric Reconstruct*[tiab] OR esophagogastrostomy reconstruct*[tiab] OR oesophagogastrostomy reconstruct*[tiab] OR esophagus cancer*[tiab] OR oesophagus cancer*[tiab] OR esophageal neoplasm*[tiab] OR oesophageal neoplasm*[tiab] OR cancer esophagus[tiab] OR esophagus neoplasm*[tiab] OR esophageal cancer*[tiab] OR oesophageal cancer*[tiab] OR esophagus neoplasm*[tiab]
AND
"Tomography, Optical Coherence"[Mesh] OR "Indocyanine Green"[Mesh] OR "Laser-Doppler Flowmetry"[Mesh] OR OCT[tiab] OR Optical Coherence Tomography [tiab] OR Indocyanine green[tiab] OR ICG[tiab] OR Sidestream dark field[tiab] OR SDF[tiab] OR Laser speckle[tiab] OR Speckle contrast [tiab] OR LSI[tiab] OR LSCI[tiab] OR Laser-Doppler Flowmetry[tiab] OR Laser Doppler Imaging[tiab] OR LDI[tiab] OR doppler laser flowmetry[tiab] OR laser doppler velocimetry[tiab] OR velocimetry laser doppler[tiab] OR laser doppler velocimetry[tiab] OR doppler laser flowmetry [tiab]
AND
"Blood Flow Velocity"[Mesh] OR "Perfusion Imaging"[Mesh:NoExp] OR "blood supply" [Subheading] OR perfusion[tiab] OR blood flow[tiab] OR blood supply[tiab]

Abstracts of publications with potential relevance based on titles were analyzed and selected full text articles were reviewed for analysis and quality assessment by two authors (DMB, SMJ).

Inclusion and exclusion criteria

Inclusion criteria were: perfusion or blood flow and use of optical techniques and gastric tube reconstruction as subject of study. Exclusion criteria were: articles not available, articles not in English, study designs (reviews, case reports) and reviews.

Endpoints

Primary outcome was quantitative measurement of change in perfusion in gastric tube reconstruction; secondary outcome was successful prediction of necrosis or anastomotic leakage by measured perfusion parameters.

Data extraction

Data extraction on year of publication, study design, inclusion and exclusion criteria, type of technique (index test), reference standard, target condition, number of participants in each group, types of surgery, variables and outcomes (data on efficacy) was done by two reviewers (SMJ, DMB). In vivo studies were reviewed according to QUADAS-2 standards.[9]

Development of techniques was staged by IDEAL (Idea-Development-Exploration-Assessment-Long-term Study).[10]

Assessment of risk of bias

Two reviewers (SMJ, DMB) independently assessed the quality of methodology by using the QUADAS-2 quality tool for assessing risk of bias.[9] This includes patient selection, index test, reference standard, flow and timing. A representative spectrum was defined as any cohort of patients or animals with oesophageal cancer treated with esophagectomy and gastric tube reconstruction.

RESULTS

Our search identified 953 articles. After removal of duplicates 577 unique articles were screened by title and abstract and 43 articles were selected based on the inclusion and exclusion criteria (figure 2).

Eleven articles were excluded after reading full text for 3 reasons; cancer as subject of the study, trachea as subject of the study, no optical modality used. We included 32 articles for analyses on study quality and data extraction (table 3-5).

After screening references for original articles, 1 article was added to our search (n=33). Twelve articles studied Laser Doppler Flowmetry, 12 Fluorescence Imaging and 1 Fluorescence imaging & Laser Doppler Flowmetry, 3 studied Spectroscopy & Laser Doppler Flowmetry, 3 Laser Speckle Contrast Imaging and 1 Laser Speckle Contrast Imaging & Thermographic Imaging, 1 Sidestream Dark field Microscopy & Laser Doppler Flowmetry and 0 articles on Optical Coherence Tomography.

Quality assessment

All studies are in the initial phase of research, according to the IDEAL-stage (1-3) (table 6). Quadas-2 analysis for diagnostic accuracy showed a level of bias, due to lack of a reference test to measure perfusion.

Statistical analysis

Due to the experimental set-up of studies, heterogeneity in outcome parameters and lack of randomized controlled trials, a meta-analysis could not be performed of the selected articles. Studies were evaluated on IDEAL-stage and quality (QUADAS-2) and an overview is given on optical techniques, working mechanism, measurement parameters and interpretation of parameters.

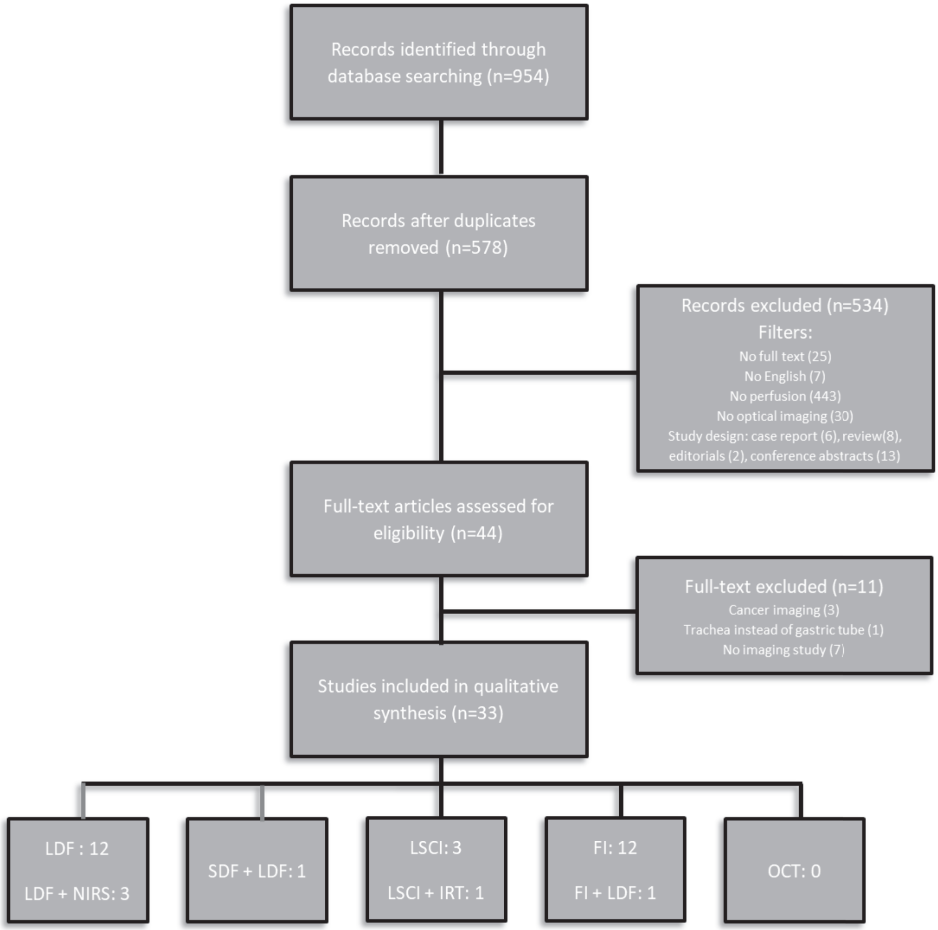

Figure 2. Flow diagram

Optical techniques

Laser Doppler Flowmetry (LDF)

LDF was first introduced by Sheperd and Riedel in 1982, and utilizes laser light to measure velocities of red blood cells by their Doppler shifts.[11] LDF makes point measurements. Perfusion is measured in Perfusion Units, an arbitrary unit. In gastric-tube surgery LDF was studied the most widely. It is the oldest technique, developed in 1980.

There were three animal studies (1 rat study n = 20, 2 pig studies n = 32), and nine prospective patients studies (n = 209) on LDF included in our analysis (table 3). Studies were conducted between 1995 and 2013. Outcomes were change in blood flow in perfusion units (PU) in all studies and leakage in two.[12–14]

Table 3. Details of the study characteristics in LDF studies. (ND=not done)

STUDY CHARACTERISTICS (Laser Doppler Flowmetry)							
AUTHOR	YEAR	STUDY DESIGN	PTN	OUTCOME	Significant difference in perfusion?	Predicting necrosis?	Predicting anastomotic leakage?
Urschel J.D.	1995	Animal study	20	Perfusion Units	Yes	ND	ND
Schilling M.K.	1996	Cohort study	11	Perfusion Units	Yes	ND	ND
Boyle N.H.	1998	Cohort study	16	Perfusion Units, Phi	Yes	ND	ND
Boyle N.H.	1998	Cohort study	16	Perfusion Units	Yes	ND	ND
Boyle N.H.	2000	Cohort study	10	Perfusion Units	Excellent correlation between LDF & SLDF of 0.955 CC (p<0.01)	ND	ND
Ikeda Y.	2001	Cohort study	43	mL/min/100g	Yes	ND	Yes
Schroder W.	2002	Animal study	17	Perfusion Unis, ptO2 in mm/Hg	Yes	ND	ND
Miyazaki T.	2002	Clinical Trial	44	Perfusion Units	No	ND	Yes
Tobari S.	2005	Animal study	15	Perfusion Units	Yes	Yes	ND
Michelet P.	2007	Cohort study	27	Perfusion Units	Yes	ND	No (n=1)
Al-Rawi O.Y.	2008	Cohort study	12	Perfusion Units	Yes	ND	ND
Pathak D.	2013	Cohort study	10	Perfusion Units	Yes	ND	ND

Table 4. Details of study characteristics in NIRS studies.

STUDY CHARACTERISTICS (Near Infrared Reflectance Spectroscopy)							
Buise M.	2006	Randomized controlled trial	32	Perfusion Units, µHbSO2, µHbcon	No	ND	No (n=7)
Bludau M.	2008	Cohort study	18	Perfusion Units, MOS, SO2 in %	PU no, MOS yes	ND	ND
van Bommel J.	2010	Animal study	12	Perfusion Units, µHbcon, µHbSO2	PU yes, µHbcon yes, µHbSO2 no	ND	ND

Four of twelve studies (n = 67) found a significant decrease in PU after vessel ligation of the stomach for gastric-tube reconstruction. One study (n = 11) found a significant decrease of PU only in the fundus after stomach mobilization and not in the antrum.[15] PU's had a variety in amounts (23 – 1109) compared between studies, emphasizing the fact that this is an arbitrary parameter, and not an absolute parameter.

Table 5. Details of study characteristics in LSCI, FI and SDF studies.

STUDY CHARACTERISTICS							
Laser Speckle Contrast Imaging							
Klijn E.	2009	Animal study	9	Flux, Celcius	Yes	ND	ND
Milstein D.M.	2016	Cohort study	11	Laser Speckle Perfusion Units	Yes	ND	ND
Ambrus F.	2017	Cohort study	25	Laser Speckle Perfusion Units	Yes	ND	ND
Ambrus F.	2017	Cohort	45	Laser Speckle Perfusion Units	Yes	ND	ND
Fluorescence Imaging							
Shimada Y.	2011	Cohort study	40	ICG detection	ND	ND	No (n=3)
Kubota K.	2013	Cohort study	5	Blood flow: good versus sparse	ND	ND	ND (n=0)
Kumagai Y.	2013	Cohort study	20	Blood flow: good versus sparse	No	No (n=3)	ND (n=0)
Rino Y.	2014	Cohort study	33	Blood flow routes	ND	ND	No (n=5)
Zehetner J.	2014	Cohort study	150	Perfusion: Good versus less robust	Yes	ND	Yes (n=24)
Campbell C.	2015	Retrospective study	90	Anastomotic leakage	Yes	Yes	Yes
Yukaya T.	2015	Cohort study	27	Arterial blood flow & venous return	Yes	No	No (n=9)
Koyanagi K.	2016	Cohort	40	Blood flow: simultaneous versus delayed	Yes	No	Yes (n=7)
Kitagawa H.	2017	Retrospective cohort	45	Linemarking	Yes	Yes	ND (n=0)
Ohi M.	2017	Retrospective cohort	120	Blood flow: rapid, slow, low	Yes	Yes	Yes (p=0.0057)
Schlottmann F.	2017	Cohort	5	Blood flow	Yes	ND	ND
Sidestream Darkfield Microscopy							
Jhanji S.	2010	Randomized controlled trial	135	Vessel density, Blood flow: present, intermittent or absent, Perfused vessel density, Microvascular Flow Index (MFI)	Yes	ND	**ND**

Ikeda et al. (n = 43) evaluated the effect of tissue blood flow on the incidence of anastomotic leakage following esophagostomy with gastric tube reconstruction. He found that blood flow measured with LDF in patients with leakage was significantly lower (9.1 +- 2.0 mL/min/100g) when compared to patients without leakage (13.7 +- 2.9 mL/min/100g) ($p<0.01$, unpaired t-test). To change the arbitrary unit of PU to this parameter of mL/min/100g tissue, Ikeda et al. used the theory of Bonner (Physicist) [16]. However, Rajan et al. showed that Bonner and Nossal use assumptions for light scattering and Doppler shift in this theory, which are difficult to apply on human tissue.[17]

Table 6. QUADAS-2 results and IDEAL-stage

QUADAS-2 RESULTS AND IDEAL-STAGE

	RISK OF BIAS				APPLICABILITY CONCERNS			IDEAL
Study	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**	**PATIENT SELECTION INDEX TEST REFER**	**INDEX TEST**	**REFERENCE STANDARD**	
Study 1 Urschel 95	☹	?	?	?	☹	☺	?	1
Study 2 Schilling 96	☺	☺	?	?	☺	☺	?	2a
Study 3 Boyle 98	☺	☹	☹	☺	☺	☺	☺	2a
Study 4 Boyle 98	?	?	?	?	☺	☹	?	2a
Study 5 Boyle 00	?	☹	☺	☺	☺	☺	☺	2b
Study 6 Ikeda 01	☺	☺	?	☺	☺	☹	☺	2b
Study 7 Schroder 02	☹	☹	?	☺	☹	☺	☺	2a
Study 8 Miyazaki 02	?	?	?	☺	☺	☺	?	2b
Study 9 Tobari 05	☹	☺	☹	☺	☹	☺	☹	2b
Study 10 Michelet 07	☺	?	?	?	☺	☹	?	2b
Study 11 Al-Rawi 08	☹	☹	?	?	☺	☹	?	2b
Study 12 Pathak 13	☺	☹	?	?	☺	☺	?	2b
Study 13 Buise 06	☹	☺	☺	☺	☺	☺	☺	2b
Study 14 Bludau 08	☹	?	☺	☺	☺	☺	☺	2a
Study 15 v Bommel 10	☹	?	☺	☺	☹	☺	☹	2b
Study 16 Klijn 09	☹	?	☹	☺	☹	☺	☺	2b
Study 17 Milstein 16	?	?	?	?	☺	☺	?	2a
Study 18 Shimada 11	☺	?	?	?	☺	☺	?	2a
Study 19 Kubota 13	☹	?	?	?	☺	☺	?	1
Study 20 Kumagai 13	☺	?	?	?	☺	☺	?	2a
Study 21 Rino 14	☺	?	?	?	☺	☺	?	2a
Study 22 Zehetner 14	?	☺	☺	☺	☺	☺	☺	2b
Study 23 Campbell 15	☺	☺	☺	☺	☹	☺	☺	3
Study 24 Yukaya 15	?	?	☺	☺	☺	☺	☺	2b
Study 25 Koyanagi 16	☺	☺	?	?	☺	☺	☺	2b
Study 22 Jhanji	☹	☺	☺	?	☺	☺	☺	2b
Study 23 Schlottmann	☺	☹	☹	☺	☺	☺	☺	1
Study 24 Ambrus	☺	☹	?	☺	☺	?	☺	2b
Study 25 Katigawa	☺	☺	☺	☺	☺	☺	☺	2b
Study 26 Ambrus	☺	☹	?	☺	☺	☺	☺	2b
Study 27 Ohi	☺	☺	☺	☺	☺	☺	☺	2b

☺Low Risk ☹High Risk ? Unclear Risk

Miyazaki et al. (n = 44) compared intraoperative blood flow in PU between leakage and non-leakage groups.[13] However, groups were not comparable due to unmatched group sizes (low power: n=5 leakage patients, compared to n=39 non-leakage patients). Postoperative blood flow was significantly lower in the leakage group after three days.

Boyle et al. validated Scanning Laser Doppler Flowmetry (2000) based on LDF (n = 16).[18] They found a significant fall in gastric perfusion (PU) of 41% in all subjects after mobilization of the stomach. Also, a greater decrease of perfusion in the fundus (55%) compared to the antrum (25%) measured with Scanning Laser Doppler Flowmetry was found.

In general; LDF is able to measure perfusion in Perfusion Units with a significant lower amount of perfusion units in tissue with necrosis development compared to healthy tissue.

Near Infrared Spectroscopy (NIRS)

NIRS is based on the absorption of laser light by tissue properties, and it was first described by MacMunn in 1885.[19] The absorption spectrum of light is different for diverse chromophores in tissue. This could i.e. be used to measure oxygenated or deoxygenated haemoglobin.

We found three articles on NIRS in gastric perfusion evaluation, of which one animal study of van Bommel et al. in pigs (n = 12), all using one type of optical device. Outcome parameters were mucosal oxygen saturation (MOS) and haemoglobin concentration (Hbcon).

Van Bommel et al. found no difference in MOS and Hbcon between nitro-glycerine and norepinephrine in a pig study.[20] Buise et al. also evaluated the influence of nitro-glycerine on gastric tube microcirculation and found no difference in MOS between intervention with nitro-glycerine and saline.[21] Measured MOS decreased significantly in both groups after pulling up the gastric tube to the neck (91% to 63% in nitro-glycerine group, 86% to 51% in saline group). In general; NIRS is able to measure perfusion in mucosal oxygen saturation and haemoglobin concentration, however the predictive value of necrosis development is not described yet.

Laser Speckle (Contrast) Imaging (LSCI)

The principle of speckle intensity fluctuations to measure skin perfusion is developed by many researchers using different techniques around 1970-1980.[22,23]

We found one animal study (n = 9 pigs) on LSI by Klijn et al.[24] and three patients studies (n = 81). Klijn combined LSI and thermographic imaging to evaluate blood flow changes after increase of mean arterial blood pressure (MAP) from 50-110 during gastric tube surgery. An increasing MAP had no effect on perfusion at any location in the gastric tube measured by LSI and thermography. A decrease in PU (arbitrary units) was found between top and the base and medial side of the gastric tube, this difference however was not significant. Milstein et al. evaluated 11 patients using LSCI intra-operatively. They found a high inter-rater reliability of blood flow measurements in Laser Speckle Perfusion Units (LSPU) , with a progressive decrease of LSPU towards the fundus of the gastric tube.[25] Ambrus et al. showed a decrease of LSPU towards the fundus after gastric pull-up of 25% in 25 patients.[26] In another study of 45 patients they used LSCI to investigate the influence of phenyl ephedrine on gastric microcirculation and they observed no difference between the group with phenyl ephedrine (n=20) compared to the group without phenyl ephedrine (n=25).[27]

In short; LSCI measures perfusion in Perfusion Units and a decrease of PU is observed towards the fundus intra-operatively. However, no predictive value for necrosis is found yet.

Fluorescence Imaging

In Fluorescence Imaging (FI) a laser illuminates the tissue. An intrinsic or extrinsic fluorescent molecule is excited by this light from the ground state to a higher energy level. When the molecule returns to the ground state a photon is emitted with a lower energy (higher wavelength) than used for excitation. Filtering separates the emitted light from the excitation light, enabling discrimination between the two types of light. This creates an image with a high-contrast. In the past years there has been an exponential grow of FI studies, mostly qualitative.[28]

Twelve articles on FI were included all with use of indocyanine green (ICG) (n = 556). Different qualitative outcome measures were determined cognitively: detection of microcirculation, blood flow (good vs. sparse or absent) and blood flow routes. Rino et al. used FI to evaluate blood supply routes and found 66.7% located in the greater omentum and 'splenic hiatal route' (n=22).[29] Shimada et al. found that microcirculation detected by ICG does not necessarily provide enough blood flow to maintain a viable anastomosis.[30] Kubota et al. also describe the possibility to observe venous perfusion with FI.[31] However, they did not quantify this perfusion. Kumagai et al. measured enhancement of the route to the cranial branch in seconds and found no difference in 'enhancement time' between 'good or 'sparse or absent' flow (p = 0.24).[32]

Yukaya et al. reported a quantitative assessment of blood flow with ICG in luminance over time, however no significant correlation was found.[33] Hodari et al. described the decrease of anastomotic leakage incidence from 20 to 0% after the introduction of robotic-assisted esophagectomy with gastric tube reconstruction, using integrated FI (n=54).

Zehetner et al. correlated the distance of the point of demarcation assessed by FI of the gastric tube towards the anastomosis with leakage and found a significant correlation: the longer this distance the higher risk of anastomotic leakage.[34] Also, Koyanagi et al. found a significant difference in anastomotic leakage development based on ICG stream. They divided patients into two groups based on the ICG fluorescence stream: a simultaneous group where the blood stream was fast and a delayed group where the blood stream was slow (n=40). In the delayed group 7 patients developed anastomotic leakage, whereas 0 patients developed leakage in the simultaneous group.[35] Kitagawa et al. showed in a retrospective study (n=72) that FI was associated with post-operative endoscopic assessment of the anastomosis after gastric tube reconstruction. In the group that used FI for line marking, only 6,5% anastomotic leakage occurred, compared to 15,4% in the group without FI.[36] Ohi et al. showed a correlation between a surgical intervention in case of low perfusion area and the development of anastomotic leakage. They described FI depicted low flow as an independent risk factor for the development of anastomotic leakage (p=0.0057).[37] Finally, Schlottmann et al. imaged gastric tube perfusion using FI in 5 patients. In 2 of the 5 patients (40%) low FI intensity was visible in the fundus of the gastric tube and a surgical intervention was made. They describe that there was no anastomotic leakage in this group of patients.[38]

In short; FI is able to measure the quality of perfusion. No quantitative parameter is described yet. However, with FI the length of the demarcation to the anastomosis seems a predictive value for necrosis intra-operatively.

Sidestream Dark field Microscopy

In Sidestream Dark field (SDF) Imaging tissue is illuminated by green light emitting diodes (LEDs). Haemoglobin in red blood cells is absorbing this 530 nm light, producing a high contrast compared to surrounding tissue. To image movement of flowing RBSs, light is pulsed stroboscopicly into the tissue and is detected with a camera.[39]

We found one article on SDF imaging in gastric tube surgery.[40] However, instead of gastric tissue SDF was performed sublingually to calculate microvascular parameters like vessel density and blood flow velocity. Sublingual microvascular flow significantly increased in patients after stroke volume guided fluid therapie and dopexamine.

In short, based upon these findings, SDF is able to measure microvascular flow. However, intra-operative prediction of necrosis is not yet described.

Optical Coherence Tomography

Optical Coherence Tomography (OCT) is an imaging method that was developed in 1991 by Fuijimoto.[41] It is the optical equivalent of ultrasound, except instead of sound near infrared light waves are shined into the tissue. Light intensity changes are caused by differences in backscattered light and measured in an interferometer, which allows for the depth resolved visualization of tissue layers. With OCT It is possible to image tissue in real-time, in high-resolution and in depth and potentially blood flow could be imaged by this technique. OCT is able to image the internal lumen of the esophagus during gastroscopy, as described by multiple studies.[42,43] Additionally, perfusion could be measured by OCT in different tissues.[44,45] However, in our analysis we did not find any article on OCT imaging of perfusion in gastric tube surgery.

OCT could potentially measure perfusion in related parameters. However, no studies are there to proof this and show the relation between these parameters and the prediction of necrosis development.

DISCUSION

This systematic review describes the current literature on optical techniques and their (quantitative) parameters to measure perfusion and predict anastomotic leakage in gastric tube reconstruction after esophagostomy. The techniques differ in terms of field of view, resolution and perfusion parameter.

Recommendations for the intraoperative use of optical techniques

(Scanning) Laser Doppler Flowmetry (LDF)

Advantages of LDF are the real-time, non-invasive imaging in a relatively easy and fast way. Disadvantages are the inaccuracy of Doppler-shift measurements in angled movements, point measurements missing important information due to heterogeneity of capillary network and misinterpretation of parameters due to overlying vessels. Although articles show a relation between drop in perfusion units and development of anastomotic leakage, surgeons should understand this relative change of color within the image is arbitrary and therefore sensitive for misinterpretation.

Near Infrared Spectroscopy (NIRS)

Advantages of this technique are the small probe and the ability to monitor perfusion during and post-surgery. Disadvantages are the sensitivity for patient movements, which could influence the outcome during monitoring, the use of point measurements and the probing of overlying vessels, which results in misinterpretation due to probing of underlying arteries instead of the subsurface capillaries.

Articles show variance in MOS before and after gastric pull up, but also between antrum and fundus of healthy gastric tissue. In surgery tissue will always be deoxygenated due to the operation; therefor predication of necrosis with NIRS becomes difficult.

Laser Speckle (Contrast) Imaging (LSCI)

The advantage of LSCI is the directly available color-coded images. Moreover, speckle is more sensitive for motion than Doppler shift and does not relate to angle motions. The disadvantage is the parameter (Perfusion Units) which is arbitrary and therefore difficult to compare. Articles show the feasibility of LSCI diagnostics during surgery and a significant decrease of the quantitative parameter LSPU towards the fundus. Correlation of this parameter to patient outcome has not been showed yet and would improve the value of this technique in the clinical setting.

Fluorescence Imaging (FI)

Advantages of FI are the visual movie of influx of perfusion in real-time during surgery. It is very easy to interpret, however studies use qualitative parameters, which is a disadvantage. Although the correlation between the distance of ICG demarcation to the fundus and the patient outcome in terms of anastomotic leakage is described, a quantitative parameter is needed to determine perfusion problems intraoperatively on the spot. Luminance over time could be a useful parameter, but the significant correlation with anastomotic leakage development is not proven yet. At the moment, studies focus on the development of FI to a quantitative imaging technique, for example in the PERFECT trial for colorectal cancer (NCT02626091).

Sidestream Dark field Microscopy (SDF)

Advantages of SDF are the real-time visualization of RBCs in the capillaries; to see movement means that there is flow. Moreover, flow can be measured in a quantitative parameter (mm/sec, vessel density and vessel diameter).

Disadvantages are the contact that you have to make with tissue. Therefore patient movement by breathing or heartbeats will influence the image and artefacts can occur due to pressure. The validation of this quantitative parameter needs to be done, before we can adjust measurements to the clinic.

Optical Coherence Tomography (OCT)

This technique is the only optical depth-resolved imaging system that is able to make a cross-sectional image in millimeters. Advantages are the high-resolution, high-contrast and real-time imaging ability. Disadvantages are the post-processing that is needed to measure perfusion in a linear parameter. If OCT would be able to create measurements in quantitative parameters of mL/min/gram, it would be very promising to use this technique in gastric tube surgery.

Limitations

Our results show that there is lack of understanding of quantitative parameters and little consensus on which technique to use. Due to a missing gold standard in perfusion measurements, diagnostic accuracy at this stage cannot be tested and therefor overall quality of literature according to QUADAS-2 is medium.

Moreover, selected studies use optical techniques as a method to test an intervention, which makes it difficult to evaluate the optical technique itself. This is caused by the gap between the biomedical engineering and the clinic, the misinterpretation of quantitative parameters by clinicians and the force of companies to get their device into the clinic.

Almost all studies are in the initial phase of human research according to IDEAL-stage for surgical innovation. Human studies are needed to evaluate quantitative parameters of techniques and their ability to predict anastomotic leakage.

Because of the heterogeneity in parameters, a meta-analysis could not be conducted and overall appraisable on quantification is complicated. Although this is a limitation of our study, understanding of techniques and parameters are important for the evaluation and set-up of further studies. Variability of parameters makes it hard to evaluate different techniques. We need studies with the same outcome variables and a gold standard to test diagnostic accuracy in perfusion monitoring. Techniques are in an initial phase; 1-3 stage of IDEAL. Moreover, validation of techniques is needed, by using a reference test or a standard laboratory setting (phantom study), to evaluate measured parameters before we can implement new modalities in the clinic. This systematic review shows a lack in validation of optical techniques and parameters.

Advice for perfusion monitoring

A quantitative parameter is needed to objectify perfusion during surgery. The ideal perfusion parameter would be mL/min/gram. Future prospective studies need to validate quantitative parameters using a gold standard or a standard setting (phantom study). Furthermore, techniques have to be tested at the same time point during surgery to compare modalities and their parameters.

CONCLUSION

Optical techniques are valuable for perfusion evaluation in gastric tube surgery, giving their real-time, high-resolution and high-contrast measurements.

LSCI and FI give a real-time wide field overview of perfusion, unfortunately they both lack in terms of quantitative parameters. LDF and LSCI use arbitrary Perfusion Units, and are therefore difficult in interpretation. Moreover, point measurements (LDF) should not be the first choice in perfusion evaluation, taking vascular heterogeneity into account. SDF and OCT have great potential in perfusion diagnostics, but patient studies are needed.

Future prospective studies need to determine a threshold value for quantitative parameters to predict anastomotic failure.

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