Original Article

Intraoperative reperfusion assessment of human pancreas allografts using hyperspectral imaging (HSI)

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Background: The most common causes of early graft loss in pancreas transplantation are insufficient blood supply and leakage of the intestinal anastomosis. Therefore, it is critical to monitor graft perfusion and oxygenation during the early post-transplant period. The goal of our pilot study was to evaluate the utility of hyperspectral imaging (HSI) in monitoring the microcirculation of the graft and adequate perfusion of the intestinal anastomosis during pancreatic allotransplantation.

Methods: We imaged pancreatic grafts and intestinal anastomosis in real-time in three consecutive, simultaneous pancreas-kidney transplantations using the TIVITA® HSI system. Further, the intraoperative oxygen saturation (StO_2), tissue perfusion (near-infrared perfusion index, NIR), organ hemoglobin index (OHI), and tissue water index (TWI) were measured 15 minutes after reperfusion by HSI.

Results: All pancreas grafts showed a high and homogeneous StO_2 (92.6%±10.45%). Intraoperative HSI analysis of the intestinal anastomosis displayed significant differences of StO_2 (graft duodenum 67.46%±5.60% *vs.* recipient jejunum: 75.93%±4.71%, P<0.001) and TWI {graft duodenum: 0.63±0.09 [I (Index)] *vs.* recipient jejunum: 0.72±0.09 [I], P<0.001}. NIR and OHI did not display remarkable differences {NIR duodenum: 0.68±0.06 [I] *vs.* NIR jejunum: 0.69±0.04 [I], P=0.747; OHI duodenum: 0.70±0.12 [I] *vs.* OHI jejunum: 0.68±0.13 [I], P=0.449}. All 3 patients had an uneventful postoperative course with one displaying a Banff 1a rejection which was responsive to steroid treatment.

Conclusions: Our study shows that contact-free HSI has potential utility as a novel tool for real-time monitoring of human pancreatic grafts after reperfusion, which could improve the outcome of pancreas transplantation. Further investigations are required to determine the predictive value of intraoperative HSI imaging.

Keywords: Hyperspectral imaging (HSI); pancreas transplantation; intraoperative imaging

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Introduction

While outcomes have continued to improve, pancreas transplantation is still associated with significant potential morbidity and mortality (1). The incidence of anastomosis site leakage after pancreatic transplantation ranges from 5% to 8% and is related to technical problems, such as impaired blood supply and ischemia of the graft (2,3). Adequate oxygen delivery at the tissue level is critical for maintaining graft viability and promoting aerobic metabolism. At present, there are no established techniques to measure tissue oxygenation of pancreas allografts. Routine monitoring of vascular flow and tissue oxygenation is challenging to perform in the clinical setting; however, it may facilitate early detection of events that jeopardize graft perfusion.

Hyperspectral imaging (HSI) has emerged as a novel technology for the measurement of tissue physiology, morphology, and composition (4). HSI provides an enhanced visualization of objects by capturing ultraviolet and infrared wavelength spectra located at either side of visible light of the electromagnetic spectrum. Based on the absorption and reflectance of the analyzed tissue, HSI acquires bidimensional spatial images across the electromagnetic spectrum, which are ultimately formed into a tridimensional data set called the hypercube (5). Computerized imaging procedures subsequently provide pictures of the chemical tissue composition indicating the oxygen saturation (StO_2), tissue perfusion (near-infrared perfusion index, NIR), organ hemoglobin index (OHI), and tissue water index (TWI) of the tissue investigated (6).

Several clinical and experimental studies have shown that HSI may have the potential to enhance the surgeon's visualization beyond gross macroscopic assessment and may have a crucial impact on surgical guidance through tissue characterization (7). A number of studies have recently explored the utility of HSI in assessing tissue perfusion during reconstructive surgery (8), neurosurgery (9), hepatic surgery (10), and gastrointestinal surgery (11).

Holmer *et al.* (12) have recently described the potential clinical utility of HSI for an experimental study of tissue oxygenation in porcine renal grafts during normothermic machine perfusion. First human data in kidney transplant recipients investigated after organ reperfusion indicate a potential for early prediction of delayed graft function based on parenchymal tissue oxygenation and perfusion parameters (13). However, to date, no studies have investigated the utility of HSI in evaluating the quality of perfusion of pancreatic tissue and transplant anastomosis. Therefore, the objective of the present study was to test intraoperative HSI measurement for real-time monitoring of pancreas grafts, which might help to identify early onset of tissue malperfusion and hypoxia. We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-744/rc).

Methods

Patients

For proof of concept, three consecutive simultaneous pancreas kidney allograft recipients were included into this study. All methods were performed in accordance with relevant guidelines and regulations. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all patients. The study was approved by the institutional review board of the Medical University of Leipzig (AZ 111-16-14032016). Donor and recipient demographics and transplant relevant data were collected.

Surgical technique

The pancreas and kidney grafts were procured according to the guidelines provided by Eurotransplant (ET). As described earlier, the pancreas was explanted in a no-touch technique *en bloc* with the spleen and duodenum. The spleen and perihepatic fat were removed back-table. An illiac y-graft was used for reconstruction of the superior mesenteric and the splenic artery. The pancreas was transplanted transabdominally using a standard technique with an intraperitoneal location in the right iliac fossa. Arterial anastomosis was performed between the y-graft and the recipient´s common iliac artery using 6-0 Prolene running sutures. The portal vein was anastomosed to the inferior vena cava of the recipient. Exocrine drainage was carried out with a hand-sutured side-to-side duodenojejunostomy 40 cm beyond the flexure of Treitz, as described earlier by our group (14,15).

Kidneys were positioned transabdominally into the left iliacal fossa. Anastomoses of the renal artery and vein were performed to the corresponding external iliac vessels and the ureter was implanted into the bladder according to the Lich-Gregoir technique using a double-J intra-ureteral splint.

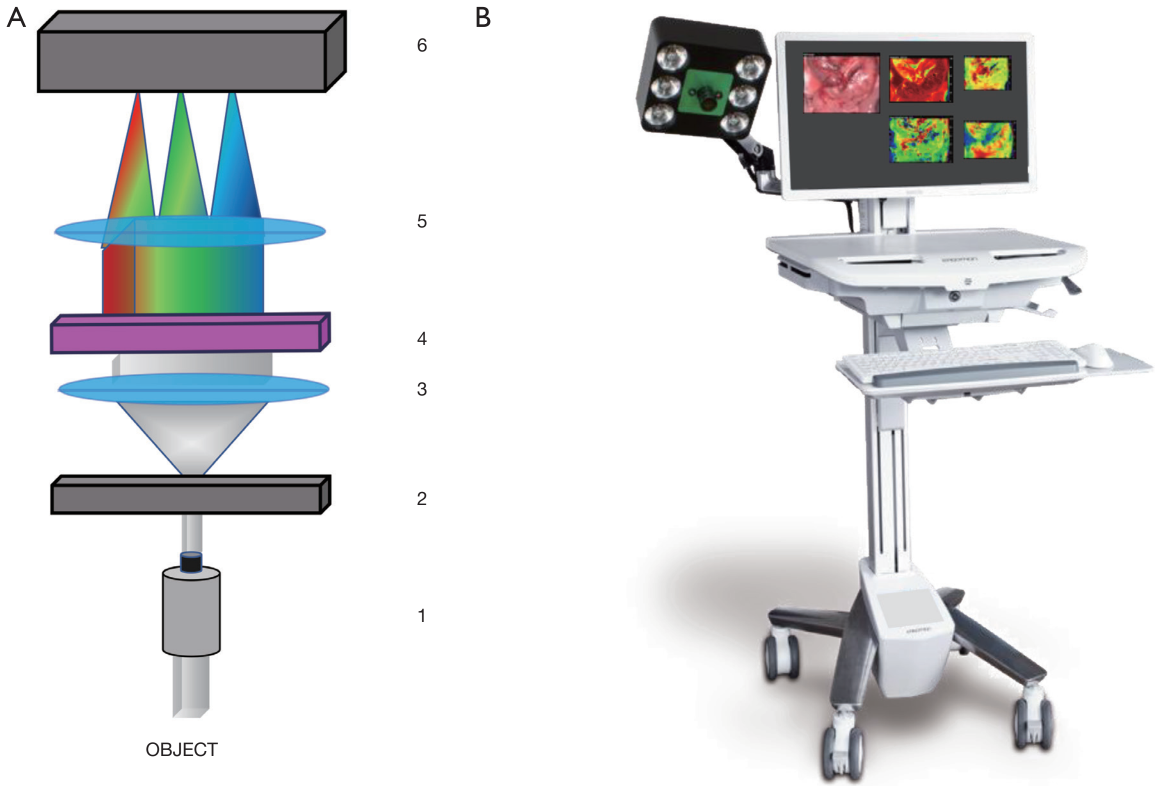

Figure 1 Hyperspectral imaging (HSI) with the TIVITA® hyperspectral camera system. (A) Schematic drawing of hyperspectral image acquisition. The tissue under investigation (object) gets illuminated by a light source. The reflected light from the tissue is captured by the objective lens [1] and focused to the entrance slit [2] of the spectrograph. A disperse device [3-5] inside the spectrograph, consisting of special lenses [3 and 5] and a transmission grating [4] splits the light into several beams depending on the wavelength. Finally, an image sensor [6] for digital processing captures these beams. (B) TIVITA® (Diaspective Vision) device that is mounted on a mobile cart with light source and hyperspectral camera system attached to a holding arm. During HSI the spectrograph inside the camera is moved over the image plane by an integrated motor to scan the whole object. The false-color imaging procedure is calculated with the attached computer and visualized on a monitor.

Optical remission spectroscopy

Principles of optical remission spectroscopy consist of a physical measurement, in which tissue is irradiated by white light. The incoming light is scattered by different inhomogeneities of the tissue structure and absorbed by different tissue components like hemoglobin and water. This process is influenced by the perfusion state of the organ. Depending on the wavelength, scattering and absorption leads to a different remission spectrum, which is detected by an optical lens mounted on a HSI camera device (*Figure 1*). The HSI camera system subsequently generates a hyperspectral data-cube, whose information can subsequently be processed with camera specific software.

Intraoperative reperfusion assessment of pancreas allografts using HSI

Intraoperative images were acquired using the TIVITA® Tissue Hyperspectral imaging system (Diaspective Vision, Am Salzhaff, Germany). A supplemental video demonstrates how the device is used intraoperatively to take pictures of a reperfused pancreas allograft. For undisturbed image acquisition and data generation the ambient light in the operating room had to be dimmed. The camera system incorporates a high number of spectrally differentiated channels which acquires pictures with a high spectral resolution (5 nm) in the visible and near-infrared range (500–1,000 nm). This scanner is

Table 1 Donor demographics

Variable	Donor		
	A	B	C
Age, years	35	22	18
Gender	Female	Male	Male
Size, cm	175	170	176
Weight, kg	75	60	70
BMI, kg/m^2	24.5	20.8	22.6
Cause of death	Cerebrovascular event	Intracranial injury	Cerebral oedema
Laboratory tests			
Sodium, mmol/L	147	143	160
Potassium, mmol/L	4.0	3.9	3.6
Serum creatinine, µmol/L	44.0	88.4	62
Lipase, U/L	23	15	31
Anti-CMV-IgG	Positive	Negative	Negative
Secondary disease	Hypothyroidism	None	None

BMI, body mass index; CMV, cytomegalovirus.

mounted on a moving arm which is brought to the patient from the right side of the operating table. Using a 25-mm focal lens, a constant distance of 30 cm between the object and camera has to be retained during image acquisition. The HSI camera subsequently takes and RGB picture and in parallel computes a pseudo-color image, that represents physiologic parameters like tissue oxygen saturation (StO_2%), perfusion (NIR Perfusion index), organ hemoglobin (OHI) and TWI of the recorded tissue area. The maximum relative penetration depth of this HSI system is 6 mm. Quantitative StO_2% measurements can either be performed at a depth of up to 1 mm for superficial microcirculation evaluation as well as at a depth of 4–6 mm which corresponds to wavelengths recorded within the near-infrared (NIR) spectrum. HSI can be applied almost "real time" and the acquisition for the hyperspectral image takes less than 10 seconds. All images are stored and further analysis of the hyperspectral data can be performed on the system with the TIVITA® Suite software. In a retrospective analysis, markers representing the region of interest (ROI) were inserted into the pseudo-colored images and the index average from the values inside the ROI were calculated.

Statistical analysis

Statistical analyses were performed using Microsoft excel 2019 and Prism Graph Pad 8 software (Version 8.4.1; GraphPad Software Inc., La Jolla, CA, USA). Parameters are presented as mean/median ± SD/SEM and quartiles. An unpaired two tailed Student's *t*-test was used to determine statistical significance. P values <0.05 were considered significant.

Results

Pancreas transplants

Donor and recipient demographics and transplant relevant data are provided in *Tables 1,2*. In short, all patients had insulin dependent diabetes mellitus type 1 (IDDM1) with end stage renal disease (ESRD) requiring hemodialysis. All patients were listed by ET for simultaneous pancreas kidney transplantation. Reported organ quality was good for all, pancreas and kidney allografts. Immunosuppressive therapy comprised an induction therapy with the interleukin-2 receptor antagonist basiliximab followed by a triple maintenance immunosuppression of tacrolimus,

Table 2 Recipient demographics and transplant data

SPKT	1	2	3
Recipient			
Age, years	39	42	48
Gender	Female	Female	Female
Size, cm	163	165	160
Weight, kg	58	62	59
BMI, kg/m^2	21.8	22.8	23.0
Primary disease	IDDM I, diabetic nephropathy	IDDM I, diabetic nephropathy	IDDM I, diabetic nephropathy
Dialysis type	Hemodialysis	Hemodialysis	Hemodialysis
Dialysis duration, months	44	69	53
Time on the waiting list, months	51	63	35
Anti-CMV-IgG	Positive	Positive	Positive
Graft/transplant			
Duration of surgery, minutes	314	358	312
Pancreas			
Organ quality	Good	Good	Good
Implantation side	Right	Right	Right
Exocrine drainage	Duodenojejunostomy	Duodenojejunostomy	Duodenojejunostomy
CIT, minutes	462	797	313
Anastomosis, min	30	28	30,0
Kidney			
Organ quality	Good	Good	Good
Donated side	Left	Left	Left
Implantation side	Left	Left	Left
Artery			
Number	1	2	2
Patch	Yes	Yes	Yes
Vein			
Number	1	1	1
Patch	Yes	Yes	Yes
Ureteral anastomosis	Ureterocystostomy	Ureterocystostomy	Ureterocystostomy
CIT, minutes	583	904	426
Anastomosis, min	30	38	47
Immunosuppression			
Induction therapy	Basiliximab	Basiliximab	Basiliximab
CNI	Tacrolimus	Tacrolimus	Tacrolimus
AP drug	MMF	MMF	MMF

Table 2 (*continued*)

Table 2 (*continued*)

SPKT	1	2	3
Postoperative			
ICU, days	6	5	4
Complications	Secondary wound healing, lymphocele	None	None
Hospital stay, days	48	15	16
Rejection			
Grade	Banff-1a, kidney	None	None

1, recipient 1; 2, recipient 2; 3, recipient 3. BMI, body mass index; CMV, cytomegalovirus; IDDM 1, Insulin dependent diabetes mellitus type 1; ICU, intensive care unit; SPKT, simultaneous pancreas-kidney transplantation.

mycophenolate-mofetil and tapered steroids. One patient developed a Banff 1a rejection which was responsive to steroid treatment. Otherwise the postoperative course was uneventful. No anastomotic leaks were recorded.

Hyperspectral assessment of pancreas parenchyma after transplantation

Hyperspectral images of pancreatic allografts were acquired 15 minutes after reperfusion (*Figure 2*). There were no remarkably differences of pancreas tissue parameters between the three patients/cases. Pancreas grafts showed a high and homogeneous oxygen saturation (StO_2: 92.6%±10.45%) On average, mean/median NIR was 0.54±0.07 [I (Index)], OHI 0.84±0.12 [I] and TWI 0.63±0.11 [I], respectively. Perfusion deficits within the organ were not detected. Furthermore, no differences in head corpus and tale perfusion were detected (data not shown).

HSI of intestinal anastomoses after transplantation

Intraoperative HSI of the intestinal anastomosis displayed significant differences of oxygen saturation (StO_2 duodenum 67.46%±5.60% *vs.* jejunum: 75.93%±4.71% P<0.001), and TWI {TWI duodenum: 0.63±0.09 [I] *vs.* TWI jejunum: 0.72±0.09 [I], P<0.001} between donor duodenum and recipients' jejunum. The other two-color coded images (NIR and OHI) did not display remarkably differences {NIR duodenum: 0.68±0.06 [I] *vs.* NIR jejunum: 0.69±0.04 [I], P=0.747; OHI duodenum: 0.70±0.12 [I] *vs.* OHI jejunum: 0.68±0.13 [I], P=0.449}. Representative images and distribution of the four calculated tissue parameters are illustrated in *Figure 3*.

Discussion

In this study, we describe for the first time the use of HSI in patients receiving a simultaneous kidney-pancreas transplantation to evaluate the perfusion quality of the pancreatic tissue and the intestinal graft anastomosis. Using this novel technology, our main purpose was to augment the surgeon's visual armamentarium for the assessment of the pancreas allograft and the duodenojejunal anastomosis after reperfusion, before wound closure is performed. In addition, we aimed to quantify the oxygenation and perfusion status of the different components of the pancreas graft as well as the intestinal anastomosis and lay the foundation for further larger cohort studies.

During solid organ transplantation, adequate delivery of oxygen at the tissue level is critical for maintaining graft viability and promoting aerobic metabolism (16-19). Real-time monitoring of vascular flow and tissue oxygenation indicates viable tissue and facilitates early detection of malperfusion. Currently, available technology is inconvenient for routine clinical use. The simplicity of HSI makes it attractive for clinical use, but the lack of a "gold standard" technique for measuring tissue oxygen saturation makes validation challenging.

Previous studies have applied polarographic electrodes for monitoring of pancreatic tissue oxygenation in patients undergoing pancreaticoduodenectomy (20). However, these invasive sensors do only provide localized tissue information and increase the risk of tissue damage. In contrast, HSI is non-invasive and provides the surgeon with no-touch advanced visualization, extended into the infrared and near-infrared wavelength regions, creating a specific "oxygenation map" of the whole organ. HSI oxygenation

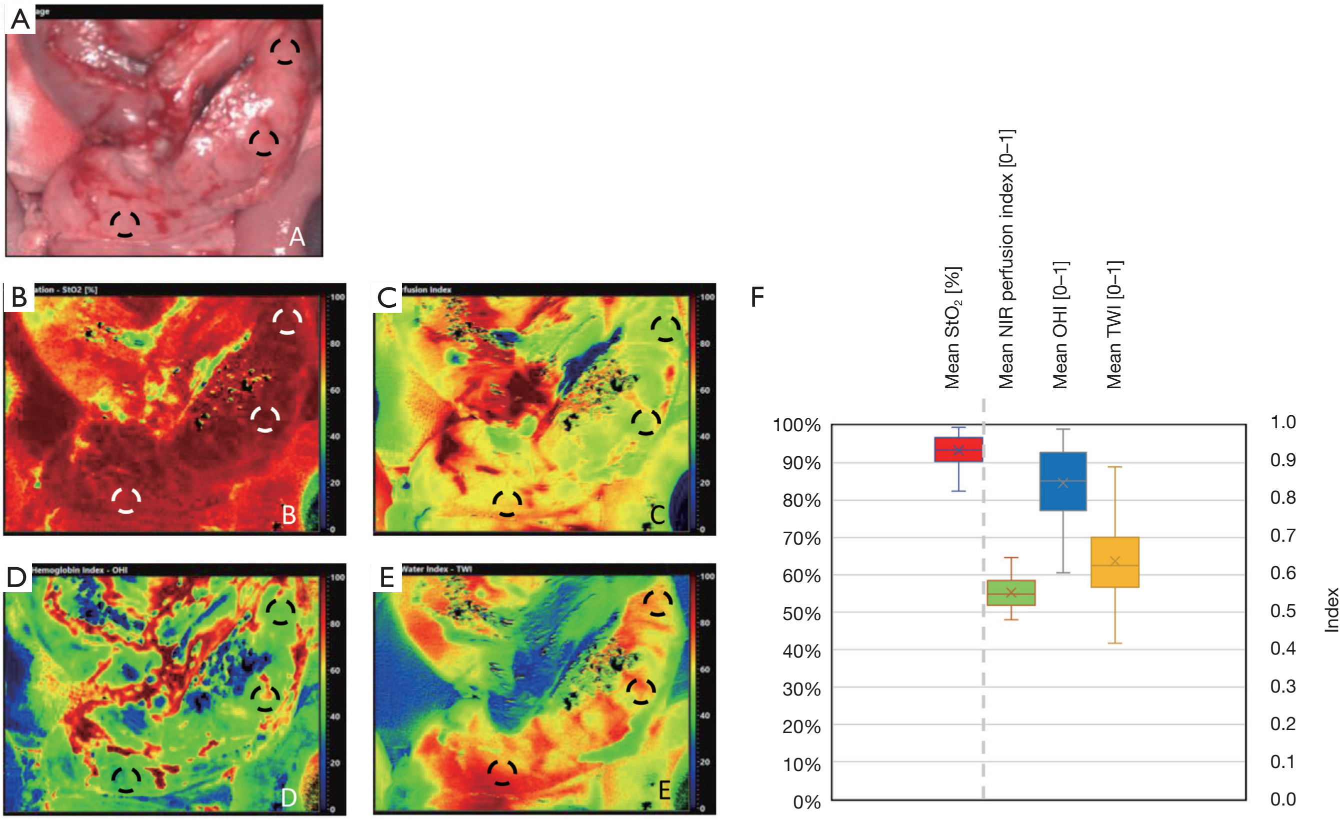

Figure 2 Hyperspectral images and tissue parameters of the pancreas graft after reperfusion. Representative intraoperative (A) RBG image, and corresponding hyperspectral imaging (HSI) generated (B) color coded oxygen saturation (StO_2), (C) near-infrared perfusion (NIR), (D) organ hemoglobin index (OHI), and (E) tissue water index (TWI) 15 minutes after reperfusion of the pancreas graft. Three standardized markers, were placed on pancreas head, body and tail to evaluate the tissue perfusion. (F) Mean absorbance spectra/distribution of pancreatic tissue parameters. All data are presented as the mean ± SD (n=3).

mapping allows for assessment of critical and/or jeopardized areas after reperfusion and provides information about the heterogeneity of oxygen supply in the tissue. Our preclinical studies in porcine kidney grafts subject to machine perfusion showed that the oxygenation map provided by HSI detected arterial occlusions and differentiated between perfused and non-perfused tissue regions (12). In our recent study on human kidney allografts, we were able to proof that intraoperative HSI of the kidney parenchyma early after reperfusion allowed for identification of grafts which subsequently developed a delayed graft function. Our conclusions were built on characteristic differences in tissue oxygenation and near infrared perfusion indices, measured in the parenchyma of the transplanted organs. Our technique furthermore allowed for the assessment of ureter tissue viability which facilitated a better estimation at which distance from the renal pelvis a save uretreo-cystostomy of a sufficiently perfused ureter segment could be performed (13).

In recent years indocyanine green fluorescence staining has gained popularity in various surgical disciplines including liver surgery (21-23), biliopancreatic surgery (24), upper Gi surgery (25,26), colorectal surgery (27), thoracic surgery (28) and transplant surgery (29). As a matter of fact, the use of ICG fluorescence angiography, and near-infrared spectroscopy showed promising results in duodenum-preserving pancreatic head resection providing intraoperative demarcation of pancreatic tumors (30) as well as anatomic liver resections performed with vascular inflow control (31). A first case report of duodenal perfusion assessment in pancreas transplantation by means of ICG fluorescence was published in 2014 (32). A recent study described the application of ICG

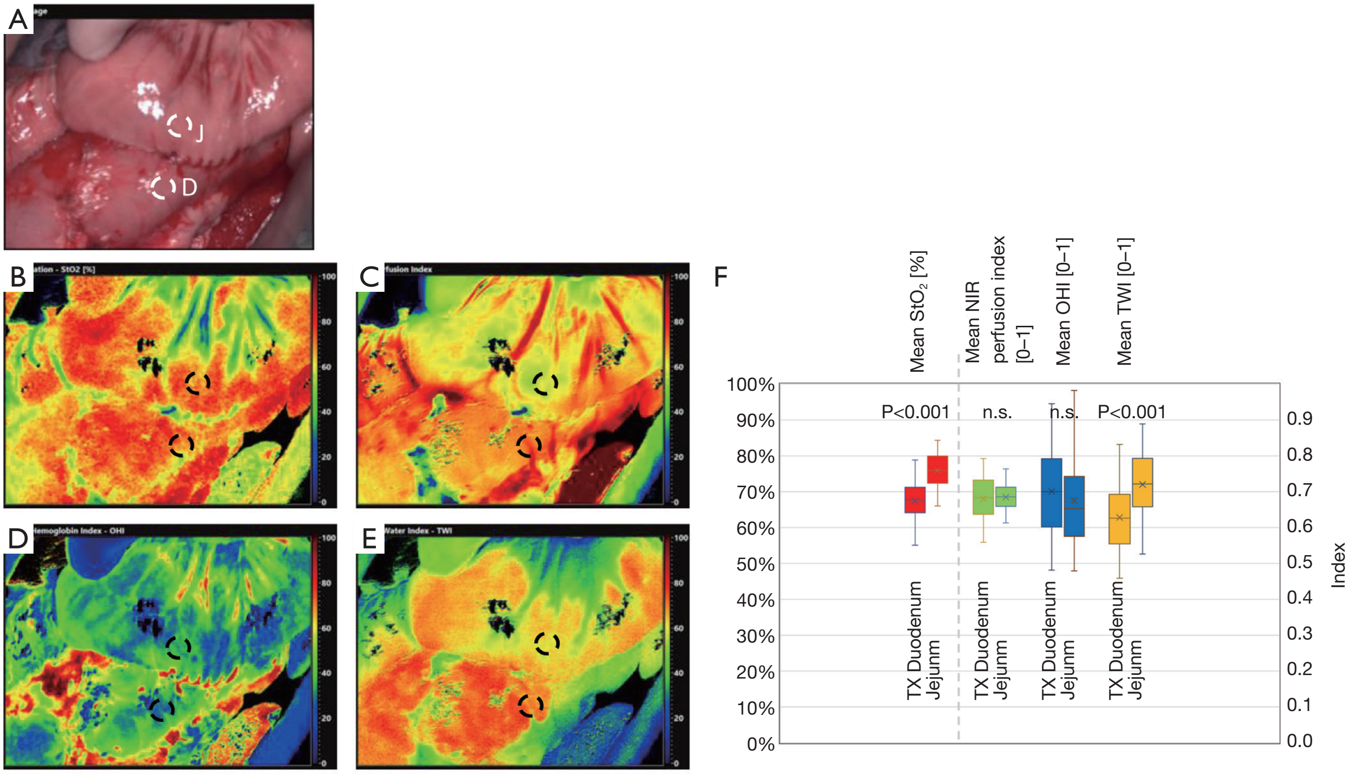

Figure 3 Hyperspectral images and tissue parameters of the intestinal anastomosis during pancreas transplantation. Representative intraoperative (A, J = jejunum; D = duodenum) RBG image and corresponding hyperspectral imaging (HSI) generated (B) color coded oxygen saturation (StO_2), (C) near-infrared perfusion (NIR), (D) organ hemoglobin index (OHI), and (E) tissue water index (TWI) of the intestinal anastomosis. Two markers, standardized in site, were placed on the duodenum of the graft and the recipients' jejunum to evaluate the tissue perfusion. (F) Comparison of tissue parameters of the intestinal anastomosis. All data are presented as the mean ± SD (n=3).

fluorescence angiography during liver and pancreas transplantation in a larger series of patients (33). The detection of intraoperative perfusion defects allowed for real time modification of technical strategies. In fact, the detection of an ischemic area of a duodenal stump in a pancreas allograft could promptly be addressed and a consecutive synchronous second resection of the ischemic area led to an uneventful healing of the duodenal-enteric anastomosis. ICG is a fluorescent dye, which following intravenous injection binds to albumin and gets removed from the blood stream by the liver. In this context it has been traditionally used for liver function assessments prior major liver resections, since the removal rate of ICG provided a quantitative estimate of liver mass (34). Although very rare, severe adverse anaphylactic reactions to intravenous ICG application have been reported in the literature (35).

When compared to ICG angiography, the near infrared perfusion index gained by HSI is capable to provide all the visual and quantitative information on organ perfusion. On top, our novel technology is capable to provide a visual measurement of tissue oxygenation, tissue hemoglobin concentration and tissue water concentration. In this regard it does not require the introduction of a fluorescent agent and hence qualifies to be designated as a true non-invasive, no-touch examination method.

Our group recently demonstrated that HSI could help surgeons to visualize intestinal perfusion and help determine resection margins during colorectal resection (36). In this study, we did not experience any future anastomotic leakage, which is in line with the hyperspectral data of our pancreas transplant duodenojejunostomies which displayed comparable tissue perfusion indices and homogeneous oxygen saturation map. In case of abnormal hyperspectral tissue oxygenation and perfusion the transplant surgeon has the real time option to either control arterial inflow and venous outflow improve organ positioning and in case revise the anastomosis or worst case remove the graft to avoid devastating complications. The application of an exocrine bladder drainage might furthermore be an alternative to the entero-enteric drainage. However, if this method is superior in case of ischemia of the transplanted duodenum remains speculative. In case of exclusion of any surgical errors with regard to vascular inflow and outflow an adjustment of postoperative anticoagulation therapy might be considered as well.

Main limitations of HSI comprise the fact that this technique can only be applied intraoperatively and no hyperspectral organ assessment can be performed after wound closure. As a matter of fact, a second glance to the transplanted organ would require redo-surgery. Furthermore, in accordance with the current available technology, HSI is only feasible in open surgical procedures, however a laparoscopic device should be available soon.

At this point we can conclude that HSI offers a real-time examination of the pancreatic graft and anastomotic site. Intraoperative measurement of the perfusion of the parenchyma and intestinal anastomosis during pancreas transplantation might help evaluating regional tissue injury and microcirculation following pancreas reperfusion. Our results suggest that HSI may be a useful tool for optimizing pancreatic transplantation by guiding the surgeon with the help of an objective decision aid that may improve surgical accuracy and lower complications. Our present study confirmed feasibility of the intro-operative imaging of the pancreas/duodenal graft with optimal perfusion. The value of the detection of hypo perfused areas remains to be assessed in future applications.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-744/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-744/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-744/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of the University of Leipzig (No. AZ: Nr: 111–16 14,032,016) and informed consent was taken from all individual participants.

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