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Endoluminal laser-Doppler measurements of jejunal perfusion in patients undergoing liver transplantation

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Abstract Patients undergoing liver transplantation are at risk of developing the multiple organ dysfunction syndrome, and attention has been focused on the pathogenic role of decreased gastro-intestinal mucosal perfusion. The aim of this study was to investigate the use of laser-Doppler flowmetry for determination of jejunal perfusion. In 10 patients an endoluminal laser-Doppler catheter was positioned with the tip in the jejunum for continuous measurements of jejunal perfusion. The anhepatic phase was associated with a progressive decrease in jejunal perfusion to 49 (40/65)% ($P < 0.01$) of dissection phase value. At the end of surgery the jejunal perfusion had increased to 134 (103/158)% ($P < 0.01$) of dissection phase jejunal perfusion. The endoluminal laser-Doppler technique was found to be easily applicable for continuous monitoring of jejunal perfusion, and the technique could prove valuable in detecting gastro-intestinal hypoperfusion in patients undergoing liver transplantation.

Keywords Liver transplantation · Laser-Doppler flowmetry · Splanchnic blood flow · Intestinal mucosa

Abbreviations *MODS* Multiple organ dysfunction syndrome · *KIU* Kallikrein inactivating units · *PU* Perfusion units · *LDF* Laser-Doppler flowmetry

Introduction

Patients undergoing liver transplantation are at risk of developing a systemic inflammatory response syndrome, which is usually transient and well-tolerated, but may eventually proceed to the development of the multiple organ dysfunction syndrome (MODS) [33]. This is a serious complication as MODS development after liver transplantation is associated with a prolonged hospital stay and a high mortality [33]. Since Marshall and Meakins in 1986 suggested the gastro-intestinal tract to be the "motor of multiple organ failure", extensive research has been focused on the role of the gastro-intestinal tract in the pathogenesis of MODS [9, 19, 21]. Attention has been directed to the unique vascular structure of the intestinal villi and the impact of the countercurrent exchange mechanism, which predisposes to villi hypoxia and epithelial damage, when gastro-intestinal mucosal perfusion is decreased [19].

Gastro-intestinal perfusion can be expected to be compromised during the liver transplantation procedure. During the anhepatic phase, clamping of the portal vein and the inferior caval vein interrupts venous return from the abdomen and the lower extremities, decreasing cardiac output and increasing systemic vascular resistance [16]. The use of a veno-venous bypass technique during the anhepatic phase has been suggested for venous decompression, improved haemodynamic stability, improved renal function, and decreased intraoperative blood loss [32], but does probably not result in normal perfusion of the abdomen and lower extremities, as indicated by increased infrahepatic caval vein pressure, decreased cardiac output, and continuous haemoconcentration during the bypass period [22, 27].

Table 1 Characteristics of patients and liver transplantation procedure. *APACHE* Acute physiology and chronic health evaluation, *UNOS* united network of organ sharing, *RBC* red blood cell, *VVB* veno-venous bypass, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

	Age	Indication for transplantation	Preoperative APACHE II score	UNOS score	Duration donor liver cold ischemia (h:min)	Duration anhepatic phase (h:min)	Duration surgery (h:min)	Intraoperative RBC transfusion (ml)	VVB	VVB flow (l/min)
1	45	Crytogenic cirrhosis	2	3	8:24	0:65	6:18	3000	Caval	1.6
2	47	Polycystic liver	4	3	12:30	2:08	5:48	900	Caval	1.3
3	36	Cholangiocarcinoma	0	3	11:36	0:37	10:18	1500	Caval	1.6
4	51	Alcoholic cirrhosis	8	2	7:30	1:00	6:06	2700	Caval	2.0
5	45	Crytogenic cirrhosis	4	3	9:30	0:48	5:48	600	Caval	1.8
6	54	Polycystic liver	8	3	11:06	2:53	11:12	3900	Caval + Portal	2.2
7	61	Chronic active hepatitis	6	2	7:00	0:54	6:48	8100	Caval	1.2
8	52	Crytogenic cirrhosis	4	3	12:24	0:37	4:24	2400	Caval	2.2
9	48	PBC	10	2	11:48	1:00	7:06	3600	Caval	2.6
10	36	PSC	1	3	11:42	0:55	5:18	1800	Caval	2.2

Laser-Doppler flowmetry represents an alternative method for estimation of gastro-intestinal perfusion [1, 5]. In man, laser-Doppler flowmetry has been used to measure gastro-intestinal perfusion in healthy volunteers [10, 14, 18, 20, 29], patients with liver cirrhosis [23, 25, 26], patients undergoing abdominal surgery [2, 3, 5] and patients undergoing cardiac surgery [17, 24, 34].

The aim of the present study was to measure jejunal perfusion in patients undergoing liver transplantation, using an endoluminal laser-Doppler catheter. The general aims were to evaluate whether the method was applicable during clinical liver transplantation, whether it was possible to obtain continuous measurements of jejunal perfusion, and whether monitoring jejunal mucosal perfusion gave additional haemodynamic information, compared with the routine haemodynamic measurements.

Patients and methods

The study was approved by the Human Ethics Committee of the Göteborg University. After informed consent, 10 adult patients undergoing primary OLT were studied. Patient characteristics are shown in Table 1. None of the patients developed postoperative MODS according to the criteria proposed by Spanier and co-workers [33]. Anaesthesia was performed with thiopental sodium, fentanyl citrate and isoflurane in oxygen/air. Suxamethonium chloride and vecuronium bromide were used for muscle relaxation. Two radial artery catheters, a triple-lumen central venous catheter and a pulmonary artery catheter were inserted for continuous monitoring of systemic and pulmonary arterial pressures, blood sampling, and administration of drugs. Aprotinin infusion was started at the beginning of surgery with 1,000,000 KIU (kallikrein inactivating units) during the first 60 min followed by 500,000 KIU every 60 min. A continuous infusion of 3 μg/kg per min dopamine was started at the beginning of surgery and increased as needed to maintain mean arterial pressure. Liver transplantation was performed as an orthotopic liver transplantation using standard technique and veno-venous bypass.

Veno-venous bypass

In nine patients the veno-venous bypass was performed with caval bypass only, and in one patient a combined caval and portal vein bypass was used (Table 1). The veno-venous bypass was performed with the use of a non-occlusive centrifugal pump (model 540 Bio-Medicus®, Medtronic, Kerkrade-West, Holland), heparin-coated 3/4 inch diameter shunt tubing (Medtronic, Kerkrade-West, Holland), a 15 Fr. heparin-coated catheter inserted percutaneously into the right internal jugular vein and a 17 Fr. catheter inserted percutaneously into the right or left femoral vein (Medtronic, Anaheim, California, USA). A 16 Fr. heparin-coated insert probe (Carmeda AB, Täby, Sweden) was used for portal vein bypass. Blood drained from the femoral and portal vein catheters was returned to the patient through the catheter in the right internal jugular vein.

Haemodynamic measurements

Mean arterial pressure, mean pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac index and systemic vascular resistance index were registered at the end of dissection phase, at the end of anhepatic phase (5 min before reperfusion), during reperfusion, (after completion of the hepatic artery anastomosis) and at the end of surgery.

Laser-Doppler catheter

A commercially available, flexible, multichannel, polyethylene catheter (Ch 14, 160 cm, Model 6C, Synectics AB, Stockholm, Sweden) was used in all patients. Two or three of the wall channels were used to pass optical fibres to the distal end of the catheter. The distal end of the catheter was fitted with a plastic knob in which metal guiding tubes were moulded to direct the distal end of the optical fibres perpendicular to the axial line of the catheter. The optical fibres were used for transmitting and receiving laser light using a fibre separation of 0.25 mm. The endoluminal laser-

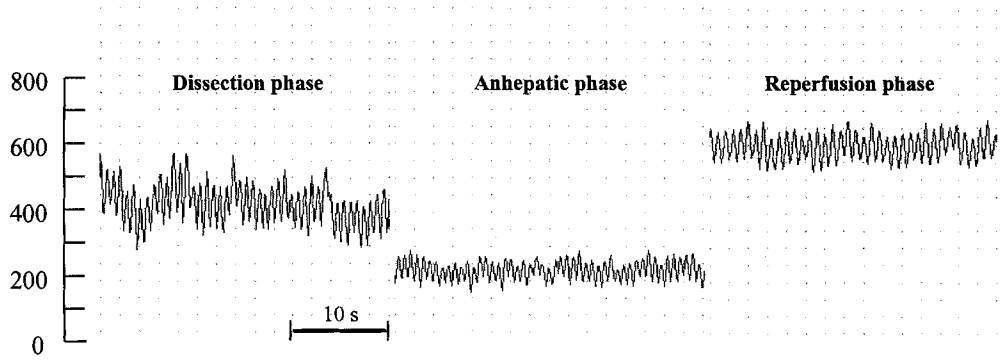

Fig. 1 A typical laser-Doppler registration (patient 1) showing pulse-synchronous variations in jejunal perfusion during the liver transplantation procedure

Doppler equipped catheters were custom manufactured by Perimed AB, Järfälla, Sweden. A Teflon-coated guidewire was passed through the central lumen of the catheter to facilitate positioning. Prior to the beginning of surgery the endoluminal laser-Doppler catheter was passed through the nose and into the stomach. Following laparotomy, the tip of the endoluminal laser-Doppler catheter was manipulated by the surgeon to a position distal to the Treitz ligament in the proximal jejunum, and the endoluminal laser-Doppler catheter was then left for the duration of surgery.

Data acquisition and analysis

The endoluminal laser-Doppler catheter was connected to a dual channel Periflux 4001 base unit (Perimed AB, Järfälla, Sweden). The laser-Doppler signal was registered from the RS232 interface of the Periflux 4001 base unit using Perisoft software (Perimed AB, Järfälla, Sweden) running on an IBM 80386 PC. Measurements are given as arbitrary perfusion units (PU). For all laser-Doppler flow measurements a time constant of 0.2 s and a band with of 12 kHz was used. Calibration was performed as recommended by the manufacturer. The mean laser-Doppler signal during a period of 10–30 s without artefacts was defined as one measurement. Data are reported as medians and 25th to 75th percentiles. The significance of changes were studied using the Friedman test and the Wilcoxon signed rank test. Simple regression analysis was used for correlation studies of haemodynamic parameters. Results were considered significant when $P < 0.05$ [6].

Results

A typical recording of the jejunal perfusion during liver transplantation is demonstrated in Fig. 1. The first registration period represents the jejunal perfusion during the end of the dissection phase, with a mean perfusion of 418 PU. The second registration period represents the jejunal perfusion during the end of the anhepatic phase, with a mean perfusion of 240 PU. The third registration period represents the jejunal perfusion during the reperfusion period, after completion of the portal vein, inferior caval vein, and hepatic artery anastomoses, with a mean perfusion of 591 PU. All three registration periods exhibit pulse-synchronous changes in jejunal perfusion. Characteristically, the jejunal perfusion pulse amplitude was reduced during the anhepatic phase, compared with the dissection phase and the reperfusion phase.

The relative changes in jejunal perfusion are given in Fig. 2. The anhepatic phase was associated with a progressive decrease in median jejunal perfusion. At 1 min and 5 min after portal vein clamping, the jejunal perfusion was decreased to 74 (60/103)% (ns), and 72 (42/80)% ($P < 0.01$) of the dissection phase jejunal perfusion, respectively. The decrease in jejunal perfusion continued until the end of the anhepatic phase, when the jejunal perfusion was reduced to 49 (40/65)% ($P < 0.01$) of the dissection phase value. Reperfusion of the transplanted liver was associated with an increase in jejunal perfusion to 77 (64/96)% (ns) and 84 (52/107)% ($P < 0.01$) of the dissection phase value, at 1 min and 5 min after portal vein declamping, respectively. This initial jejunal hyperaemia was followed by a successive further increase in jejunal perfusion. At the end of surgery, the jejunal perfusion had increased to 134 (103/158)% ($P < 0.01$) of the dissection phase jejunal perfusion.

In terms of perfusion units (PU), the median dissection phase jejunal perfusion was 418 (352/515) PU, de-

Table 2 Measurements of jejunal perfusion (perfusion units)

Patient	Dissection phase	Anhepatic phase[a]	Reperfusion	End surgery
1	400	161	465	581
2	429	115	493	442
3	507	284	307	722
4	792	548	403	561
5	392	256	610	720
6	623	250	406	480
7	408	181	328	665
8	373	278	287	469
9	515	284	465	535
10	280	100	210	441
Median (25th/75th percentile)	418 (352/515)	253 (161/284)[b]	405 (307/465)	548 (469/665)

[a] 5 min before reperfusion
[b] $P < 0.01$, compared to dissection phase

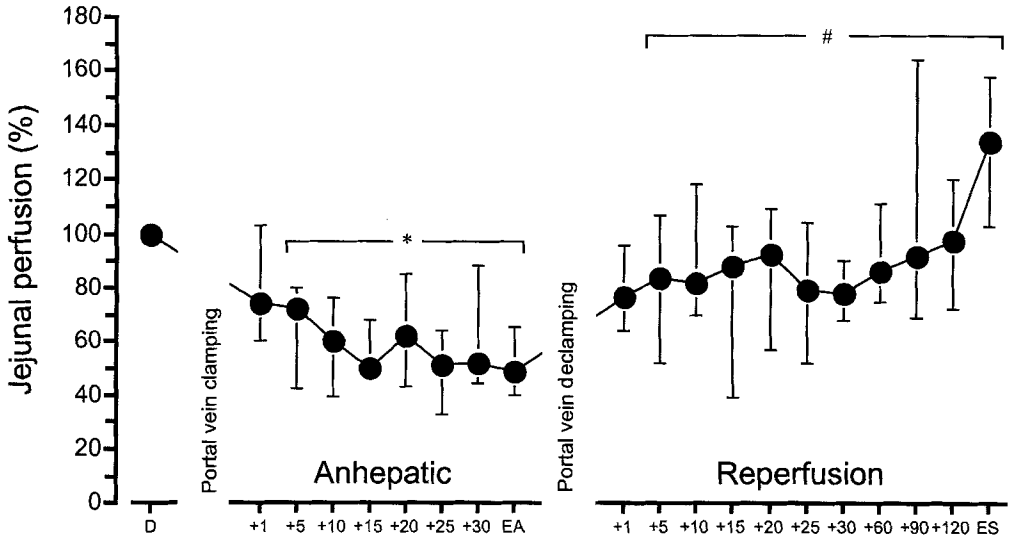

Fig. 2 Relative changes in jejunal perfusion during the liver transplantation procedure. *D* end of dissection phase, *EA* end of anhepatic phase, immediately before reperfusion, *ES* end of surgery. * $P < 0.05$, compared to end of dissection phase; # $P < 0.05$, compared to end of anhepatic phase

creasing to 253 (161/284) PU at the of the anhepatic phase ($P < 0.01$, compared with dissection phase) and increasing to 403 (307/465) PU after reperfusion (ns, compared with dissection phase). The decrease in jejunal perfusion during the anhepatic phase was observed in all patients, including patient 6, who underwent OLT with the use of a combined caval vein and portal vein bypass technique (Table 2). In all patients but two, (patient 4 and 6) the jejunal perfusion at the end of surgery was higher than during the dissection phase.

Haemodynamic data are shown in Table 3. The changes in jejunal perfusion during the liver transplantation procedure were accompanied by smaller changes in cardiac index, which, during the anhepatic phase, decreased to 85 (81/94)% of the dissection phase value ($P < 0.01$). Reperfusion was associated with an increase in cardiac index to 119 (106/133)% of the dissection phase value ($P < 0.01$). The changes in jejunal perfusion and cardiac index were paralleled by inverse changes in systemic vascular resistance index, which during the anhepatic phase increased to 126 (112/149)% of the dissection phase value ($P < 0.05$) and decreased to 64 (53/72)% of the dissection phase value during the reperfusion phase ($P < 0.05$). Regression analysis showed a significant correlation between jejunal perfusion and cardiac index ($r = 0.540$, $P < 0.001$); systemic vascular resistance index ($r = 0.420$, $P < 0.01$) and mean arterial pressure ($r = 0.373$, $P < 0.05$). There was no significant correlation between jejunal perfusion and central venous pressure or pulmonary capillary wedge pressure.

Discussion

Intestinal blood flow is regulated by sympathetic innervation, circulating vasoactive substances, systemic

Table 3 Hemodynamic data ($n = 10$). *MAP* Mean arterial pressure, *CI* cardiac index, *CVP* central venous pressure, *PCWP* pulmonary capillary wedge pressure, *SVRI* systemic vascular resistance index. Data are given as median (25th/75th percentiles)

	Dissection phase	Anhepatic phase[a]	Reperfusion phase	End surgery
MAP (mmHg)	77 (73/81)	77 (73/89)	66 (62/66)[c]	70 (74/80)[b]
Relative change (%)		104 (101/110)	84 (80/88)	88 (81/99)
CI (l/min/m2)	4.0 (3.3/5.3)	3.4 (2.8/4.4)[c]	5.2 (3.9/6.3)[c]	4.8 (3.8/6.0)[b]
Relative change (%)		85 (81/94)	119 (106/133)	118 (109/131)
CVP (mmHg)	13 (10/17)	12 (10/13)	21 (17/22)[b]	17 (16/18)
Relative change (%)		83 (65/109)	143 (105/191)	118 (98/152)
PCWP (mmHg)	17 (14/23)	15 (12/19)	23 (18/30)	24 (19/25)
Relative change (%)		101 (78/112)	142 (117/164)	119 (76/155)
SVRI (dyn · sec · cm^{-5} · m^2)	1111 (868/1324)	1586 (1134/1890)[c]	638 (560/859)[c]	819 (685/1063)[b]
Relative change (%)		126 (112/149)	65 (53/72)	88 (62/94)

[a] 5 min before reperfusion
[b] $P < 0.05$ compared to dissection phase
[c] $P < 0.01$ compared to dissection phase

haemodynamic changes, myogenic control and local metabolic control [12]. An increase in venous outflow pressure results in a myogenic-controlled mesenteric arteriolar vasoconstriction with reduced intestinal blood flow [12]. This arteriolar vasoconstriction is present in the mucosal arterioles, but is usually absent in the muscular layer, i.e. when portal vein pressure increases, intestinal blood flow is diverted from the mucosa to the muscular layer [8]. In this study, all patients but one underwent liver transplantation with the use of an isolated caval vein bypass technique. As expected, the jejunal perfusion decreased considerably upon portal vein clamping. However, in none of the patients did the jejunal perfusion or the jejunal perfusion pulse amplitude approach zero, and pulse-synchronous changes in laser-Doppler signal were still present during the anhepatic phase, indicating pulsatile flow. This indicates that when the main gastro-intestinal venous outflow route is completely obstructed, alternative venous outflow routes can be used. Considering the patients with end-stage liver cirrhosis, characterised by portal vein hypertension and collateral venous gastro-intestinal outflow, this would explain why jejunal perfusion is relatively well preserved during the anhepatic phase, although a portal veno-venous bypass technique was not used. Interestingly, even in patients without indications of portal vein hypertension (patients 3 and 10), the jejunal perfusion was relatively well preserved during the anhepatic phase. As these patients cannot be expected to have collateral gastro-intestinal venous outflow prior to clamping of the portal vein, this would indicate that collateral circulation may begin rapidly when portal vein pressure increases. It is unclear whether a similar response is present during portal vein clamping in other patients without previous portal hypertension (i.e. patients undergoing liver tumour resection). Although it can be hypothesised that the effect of acute portal hypertension in terms of jejunal perfusion in patients undergoing liver tumour resection would be comparable to the response in the present study patients without indications of previous portal vein hypertension, more studies are needed. It would therefore be of great interest to use laser-Doppler flowmetry to investigate the effect of portal vein clamping on jejunal perfusion in patients undergoing liver tumour resection.

The one patient undergoing OLT with the use of a combined caval and portal veno-venous bypass technique, had a significant decrease in jejunal perfusion during the anhepatic phase compared with the dissection phase. This finding agrees with previous studies demonstrating decreased cardiac output, increased infrahepatic caval vein pressure, vascular fluid extravasation to the interstitial space, and increased colloid osmotic pressure inversely correlated to veno-venous bypass flows during the anhepatic phase [22, 27, 35]. Although it is difficult to extrapolate the results from this one patient to a larger population, the results support the hypothesis that the use of a combined caval vein and portal vein bypass technique does not ensure gastro-intestinal and lower body perfusion [22, 27, 35].

It is well documented that the outcome for patients undergoing OLT is related to the severity of the preoperative illness [33]. The present study includes patients in relatively good preoperative condition, and although all patients experienced a substantial decrease in jejunal perfusion during the anhepatic phase, none of them developed postoperative MODS. Therefore, at least in this group of patients, a transient decrease in jejunal perfusion during the anhepatic phase was insufficient to trigger a systemic inflammatory reaction with MODS development. It can only be speculated, whether patients with more severe preoperative illness, according to the "second hit theory", would be more susceptible to the impact of a decreased gastro-intestinal perfusion [9].

A close relationship between acute changes in splanchnic perfusion and gastro-intestinal mucosal pH (pHi) has been demonstrated in animal studies, and a decrease in pHi is therefore considered to reflect inadequate regional oxygen delivery to meet metabolic needs [7]. Previous studies using indirect tonometric measurement and calculation of pHi have demonstrated gastro-intestinal mucosal acidosis in patients undergoing OLT [11, 36]. However, the use of pHi for monitoring gastro-intestinal perfusion has been criticised, due to several flaws in the tonometric technique for determination of pHi [30]. Instead the tonometric-arterial PCO_2 gradient has been proposed as an indicator of gastro-intestinal perfusion [31]. In a recent study of patients undergoing OLT, there were only slight changes in tonometric PCO_2 and PCO_2 gradient, suggesting reduced gastro-intestinal perfusion in the range of aerobic metabolism [28]. The present study reproduces the flow changes previously demonstrated, using determination of tonometric PCO_2 and PCO_2 gradient.

The jejunal perfusion correlated significantly with cardiac index, systemic vascular resistance index, and mean arterial pressure. However, the pronounced reduction in jejunal perfusion during the anhepatic phase was out of proportion to the considerably smaller changes in cardiac index and systemic vascular resistance index. This indicates that laser-Doppler measurements of gastro-intestinal perfusion may provide information about the regional gastro-intestinal perfusion, which could not be estimated from central haemodynamic parameters.

The gastro-intestinal blood flow is unevenly distributed throughout the intestinal wall with mean mucosal blood flow two to four times greater than the muscularis flow, expressed per unit weight of tissue [12]. Different physiological and pharmacological interventions may

further affect this uneven blood flow distribution [8, 12]. Therefore, knowledge of the tissue-penetrating depth of the laser-Doppler signal is important when interpreting data of gastro-intestinal blood flow [12]. In previous studies of gastro-intestinal blood flow laser-Doppler flowmetry (LDF) data have been used to calculate absolute blood flow values in the human jejunum, which correlated well with values simultaneously obtained using the total venous outflow technique [4]. The close correlation between total venous outflow and the LDF signal suggested that the LDF signal reflected blood flow throughout the entire thickness of the intestinal wall. This was confirmed by LDF recordings from corresponding sites at the mucosal and the serosal side of the intestinal wall, showing comparable LDF signals [4]. With the LDF equipment used in the present study, recordings from corresponding sites at the mucosal and the serosal side of the intestinal wall were not associated, indicating that the LDF signal reflected perfusion in the more superficial layers of the intestinal wall (Åneman and co-corkers, personal communication). The differences in laser-Doppler tissue-penetrating depth between the equipment used in previous studies [5] may be due to differences in optical fibre diameter, probe geometry or the wavelength used [13, 15].

In comparison with previous techniques for monitoring gastro-intestinal perfusion, the LDF technique offers the advantage of continuous monitoring. The technique is, on the other hand, limited by artefacts caused by tissue movements due to respiratory movements, intestinal peristalsis and surgeons' tissue manipulation [5]. Artefacts were distinguishable from ordinary flow recordings, as the former were characterised by an abnormal increase in the laser-Doppler signal, loss of pulse-synchronicity and a decrease in total backscatter. Total backscatter is the proportional amount of emitted laser light scattered from the tissue back to the registering optical fibres. A high total backscatter indicates adequate optical coupling, and thus a high quality laser-Doppler signal. In the present study, artefacts were mainly due to surgeons' tissue manipulation. During anaesthesia, artefacts due to respiratory movements and intestinal peristalsis were not seen. Periods without tissue manipulation were characterised by excellent data continuity with continuous pulse-synchronous variations in the laser-Doppler signal and a high total backscatter indicating a high quality laser-Doppler signal. These artefacts were distinguishable from the ordinary flow recordings, exhibiting typical pulse-synchronous changes in the laser-Doppler signal. Furthermore, artefacts were recognised by a decrease in total backscatter, i.e. the proportional amount of emitted laser-light backscattered from the tissue and received by the registering optical fibre. During anaesthesia artefacts due to respiratory movements and intestinal peristalsis were not seen.

In summary, the present study demonstrates the use of an endoluminal laser-Doppler catheter for measurements of jejunal perfusion in patients undergoing OLT. During the anhepatic phase there was a progressive decrease in jejunal perfusion followed by a recovery of jejunal perfusion after reperfusion of the transplanted liver. The reduction in jejunal perfusion was out of proportion to changes in other haemodynamic parameters. In general, the endoluminal laser-Doppler technique was found to be easily applicable for continuous monitoring of jejunal perfusion, and the technique could prove valuable for detecting gastro-intestinal hypoperfusion in patients undergoing OLT and in other clinical settings.

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