Perioperative mucosal pH and splanchic endotoxin concentration in orthotopic liver transplantation†

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Summary

Although impairment of splanchic perfusion may induce mucosal hypoxia and endotoxaemia during orthotopic liver transplantation (OLT), little is known about the changes in mucosal oxygenation during and after the procedure. To study the effects of liver surgery itself on mucosal pH (pHi) and the response of pHi to acute changes in portal flow, we measured gastric pHi during six liver resections using tonometry: in two patients, after clamping of the hepatoduodenal ligament, pHi decreased within 30 min and recovered promptly after reperfusion. We then investigated gastric and sigmoid pHi (pHiG, pHiS) during the perioperative phase in 18 OLT. Median pHi values were low before surgery (pHiG = 7.28, pHiS = 7.27), although global oxygen delivery and haemodynamic variables remained constant and veno-venous bypass (VVB) was used to maintain portal flow, pHi declined during the anhepatic phase (pHiG = 7.19, pHiS = 7.13). Although global oxygen delivery and haemodynamic variables remained constant and VVB preserved mucosal oxygenation.

Endotoxaemia has been reported to occur during OLT. The highest endotoxin concentrations were measured at the end of the anhepatic phase before reperfusion of the graft, and endotoxaemia was found to correlate with postoperative patient outcome [8, 9]. To avoid the deleterious effects of portal clamping on intestinal perfusion and to limit the progression of tissue hypoxia, veno-venous bypass (VVB), which drains blood from the portal to the superior caval vein, has been suggested [2, 10]. Mucosal oxygenation, however, has not been assessed adequately during liver transplantation. It is not known if mucosal ischaemia occurs during OLT, if it is associated with endotoxaemia or if the use of VVB preserves mucosal oxygenation.

To assess mucosal oxygenation, we measured gastrointestinal mucosal pH (pHi) using tonometry [11]. In experimental studies, pH was found to be a sensitive marker of impaired intestinal blood flow [12–14] and adequacy of mucosal oxygen delivery [15]. In clinical trials, a low pH has been shown to be regional perfusion and oxygenation, particularly of the splanchic organs, although intestinal hypoxia may be a source of postoperative morbidity and graft dysfunction [3–5]. In patients with liver failure secondary to cirrhosis and presenting with a hyperdynamic circulatory state, impaired tissue oxygenation has been observed during operation, although global oxygen delivery and perfusion pressure were adequately maintained [2]. It may be postulated that inadequate tissue oxygenation occurs during transplantation in the intestinal mucosa, which is highly susceptible to a reduction in blood flow. This might be most relevant during the anhepatic phase, when clamping of the portal vein is required for the recipient hepatectomy. Impaired intestinal perfusion may induce mucosal barrier dysfunction and translocation of bacteria and endotoxin into the systemic and lymph circulations [4, 6, 7].

Key words


Perioperative changes in haemodynamic and metabolic variables and in tissue oxygenation are well established during orthotopic liver transplantation (OLT) [1, 2]. However, little is known about
an indicator of intestinal ischaemia after aortic surgery [16] and cardiopulmonary bypass [17], and a prognostic factor in critically ill patients [18, 19]. More recently, gastric pH measured 30 min after graft reperfusion has been reported to be an independent indicator of early graft viability in OLT [5].

The purpose of this study was to assess gastric and sigmoid mucosal pH during the perioperative phase of OLT. We hypothesized that preservation of splanchnic blood flow using VVB would prevent a reduction in pH during the anhepatic phase, a low pH would be related to the occurrence of endotoxaemia and low pH, values persisting after graft reperfusion would be an indicator of poor graft function.

Because at the time this study was performed VVB was used routinely for haemodynamic support during OLT in our institution, we could not include a control group without VVB. To assess the ability of pH to detect acute intraoperative changes of mucosal perfusion in humans and to determine the effects of laparotomy and hepatic surgery on mucosal oxygenation, we measured gastric pH in six patients undergoing hepatic resection before the study in OLT patients. However, it was not our intention to compare the results obtained in liver resection patients with those obtained in the different patient populations undergoing OLT.

Patients and methods

After obtaining approval from the local Ethics Committee and informed consent, we studied six patients undergoing liver resection and 18 consecutive OLT in 16 adult patients. Patient characteristics and indications for hepatic resection or transplantation are summarized in tables 1 and 2.

One hour before surgery flunitrazepam 1–2 mg orally was given for premedication. Anaesthesia was induced with either thiopentone 3–5 mg kg\(^{-1}\) or etomidate 0.1–0.3 mg kg\(^{-1}\), fentanyl 3–7 \(\mu\)g kg\(^{-1}\) and pancuronium 0.1 mg kg\(^{-1}\) and maintained with 0.4–1.0 vol % isoflurane, a continuous infusion of fentanyl 3.5–7.0 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) and incremental doses of pancuronium. The trachea was intubated and the lungs ventilated throughout OLT with 50 % oxygen in air. Tidal volume and ventilatory frequency were adjusted to maintain \(\text{Pa}_{\text{O}_2}\) at 4.8–5.3 kPa.

Standard monitoring included a 20-gauge radial artery catheter, a 12-French gauge triple-lumen central venous catheter and a 7-French gauge triple-lumen thermodilution fibroptic pulmonary artery catheter (Abbott Critical Care, Mountain View, CA, USA). For perioperative antibiotic prophylaxis, imipenem 0.5–1 g was given before operation. Selective digestive decontamination (SDD) was started 1 h before operation and repeated every 6 h by oral administration of polymyxin 50 mg, gentamicin 80 mg, vancomycin 125 mg and amphotericin B 5 ml [20]. Five patients had received systemic antibiotics for several days before operation. Gastric acid secretion was blocked before induction of anaesthesia with omeprazole 40 mg i.v. [21].

After induction of anaesthesia, tonometry catheters (Tonomonitor, Tonometrics, Worcester, MA, USA) were positioned in the stomach and the sigmoid colon. The correct position of the balloon was confirmed by intraoperative palpation. The colon had been emptied before operation by enema. The gastric catheter was left in place until the second postoperative day while the sigmoid catheter was removed at the end of surgery to avoid anal pressure necrosis.

The surgical procedure was standardized and all transplantations were performed by the same two surgeons (K.-W.J., E.F.) Orthotopic transplantation was performed in all patients. After percutaneous insertion of jugular (15- or 17-French gauge) and femoral (17-French gauge) cannulae and cannulation of the portal vein (24-French gauge wire-reinforced cannula) a heparin coated porto-femoro-jugular bypass (centrifugal pump, Biomedicus Medtronic, MN, USA) was used during the anhepatic phase. Bypass flow was adjusted initially to maximal values by increasing the pump speed near to the level where the portal or femoral vein collapsed. Flow rates ranged between 30 and 50 % of actually measured cardiac output.

Red blood cells (RBC) were transfused to maintain packed cell volume (PCV) above 25 %. Fresh frozen plasma (FFP) was substituted to increase partial thrombin time to 50 % of normal reference values. Platelet concentrates were given when the platelet count was less than 30 \(\times\) 10\(^{9}\) litre\(^{-1}\), depending on platelet function, determined from \(ex vivo\) bleeding time and volume [22].

Haemodynamic measurements were made, including: heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (PAP), central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP). Cardiac output (CO) was obtained from triplicate thermodilution measurements varying by less than 10 %, performed randomly throughout the respiratory cycle. Core body temperature was recorded from the thermistor of the pulmonary artery catheter.

Central venous blood samples were obtained for serial analyses of haemoglobin, PCV, platelet count, coagulation profile (PT, aPTT, antithrombin III, fibrinogen), electrolyte (sodium, potassium, ionized calcium) and glucose concentrations. In addition, alanine–leucine transferase (ALT; optical standard method of DGKC, Boehringer Mannheim, Germany), coagulation factor V (optical method, CA 5000) and creatinine clearance (serum creatinine, Jaffe method, Boehringer Mannheim, Germany) were determined after operation. Arterial and pulmonary arterial blood samples were obtained for blood-gas analyses and measurement of oxygen saturation (ABL 520 Radiometer, Copenhagen, Denmark). Global oxygen delivery (DO\(_2\)) and consumption indices (VO\(_2\)) in addition to oxygen extraction ratio were calculated from arterial and mixed venous oxygen contents and thermodilution derived CO. For measurement of plasma lactate concentration, blood samples from the pulmonary artery and portal vein were stored immediately on ice, centrifuged and analysed within 15 min (Kodak Ektachem Clinical Chemistry slide for lactate).
Plasma endotoxin concentration was measured using the limulus amoebocyte lysate test (Coatest Endotoxin, Chromogenix, Mölndal, Sweden). Blood samples from a separate lumen of the central venous catheter, the portal vein and the portal bypass catheter (during VVB) were obtained in pyrogen-free disposable syringes, anticoagulated with heparin, centrifuged immediately on ice for 5 min at 1200 rpm, and stored at −80 °C for later analysis. Standards were obtained from E. coli endotoxin (0111 : B4 standard endotoxin) in sterile water. The sensitivity of the test in our laboratory is 1.0 pg ml⁻¹.

Gastric and sigmoid tonometer balloons were filled with 5 ml of room temperature normal saline. For measurement of pH, the first 1 ml of saline aspirated from the balloon was discarded (dead-space), and the remaining fluid was collected and immediately analysed for $P_{CO_2}$ ($P_{CO_2}$tono; ABL 520, Radiometer, Copenhagen, Denmark). Immediately after each collection, the tonometer was refilled. Simultaneously, an arterial blood-gas sample was obtained. Blood-gas analysis was performed at 37 °C without correction for temperature. pH, was calculated from arterial $HCO_3^−$ and $P_{CO_2}$tono using a modified Henderson–Hasselbalch equation [11]. Because equilibration of carbon dioxide between saline in the balloon and mucosa is time and temperature dependent, $P_{CO_2}$tono was corrected for dwell time and core temperature by multiplying the measured value by a correction factor (Tonometrics product insert 002-TGS) [16]. To avoid over extrapolation, the dwell time was extended as long as possible between consecutive intraoperative measurements (mean 48 (SD 21) min).

Intraoperative measurements were performed before bypass (I), 30 min after the start of VVB (II), 5 min before reperfusion of the graft (III), 30 min into the neohepatic phase (IV) and at the end of surgery when the peritoneum was closed (V). After operation, haemodynamic and oxygenation variables and gastric pH, were assessed 6 h after admission to the intensive care unit (ICU; VI) and 12 (VII) and 24 h (VIII) later.

Before the study in OLT patients, we measured gastric pH, in six patients undergoing liver resection (table 1). The perioperative regimen was the same as in the OLT patients except that SDD was not administered. The same haemodynamic, oxygenation and laboratory variables were assessed except for sigmoid pH, and endotoxin concentration. In two patients the hepatic artery and portal vein were clamped for 41 and 63 min, respectively, to reduce bleeding from the hepatic resection surface.

Measurements were obtained after induction of anaesthesia, before surgery, 30 min after skin incision, during liver resection and at skin closure. In patients with clamping of the hepatoduodenal liga-ment, additional measurements were performed during clamping.

**STATISTICAL ANALYSIS**

The Kolmogorov–Smirnov test revealed non-normal distribution of data; therefore, non-parametric tests were used. Friedman’s test was performed to examine the effect of time (SPSS for Windows, SPSS Software, Munich, Germany). For significant $F$ values the following measurements were compared by Wilcoxon signed ranks test: before VVB (I) vs VVB (III), before bypass (I) vs end of surgery (V), and before bypass (I) vs 24 h after ICU admission (VIII). Bonferroni correction was applied as appropriate and differences were considered significant if $P < 0.05$. Bivariate correlations between pH, and blood-gas variables and between pH, and duration of VVB, duration of surgery and blood loss were determined by Spearman’s rank correlation test. Data are reported as median (first/third quartiles).

**Results**

Patient data, indications for surgery and transfusion requirements of patients undergoing hepatic resection are presented in table 1.

Haemodynamic and oxygenation variables remained unchanged throughout surgery (data not shown). Although pH, decreased slightly in all patients after laparotomy, no significant overall effects of time were observed for arterial pH and gastric pH, (Friedman test: $P = 0.22$ for arterial pH, $P = 0.1$ for pH,) (fig. 1). In the two patients, in whom portal blood flow was interrupted transiently by clamping of the hepatoduodenal ligament, pH, decreased instantaneously. The lowest pH, value (6.95) was encountered in the patient with the longest clamping time (63 min). After release of the portal clamp, pH, returned to the range of baseline values and did not differ from pH, in patients without portal clamping by the end of surgery.

Patient data, indications for transplantation, duration of surgery and VVB, respectively, units of RBC and FFP transfused, and duration of post-operative ventilatory support and ICU stay in OLT patients are summarized in table 2. Cirrhosis was the most common indication for transplantation (13 of 16 patients). In two patients, re-transplantation was performed 4 and 51 days after the first transplantation for primary graft non-function and

| Table 1 Patient characteristics, indications, duration of surgery, ventilatory support and ICU stay, and blood product requirements of patients undergoing liver resection (median (Q1/Q3)). RBC = red blood cells; FFP = fresh frozen plasma |
|---------------------------------|------------------|
| Liver resection (n = 6)         |                  |
| Age (yr)                       | 60.0 (53.4/74.3) |
| Weight (kg)                    | 66.5 (56.6/78.80) |
| Sex (F/M)                      | 2/4              |
| Indications                    |                  |
| hepatocellular carcinoma       | 6                |
| Duration of surgery (min)      | 198              |
| Duration of ventilatory support (days) | 0 |
| Duration of ICU stay (days)    | 0                |

| Blood product requirements     |                  |
| RBC (total units)              | 0                |
| FFP (total units)              | 0                |


Mucosal oxygenation during liver transplantation

chronic rejection, respectively. RBC and FFP requirements were highest during the anhepatic phase.

Central haemodynamic variables and $D_O^2$ index were essentially unchanged throughout the peri-operative period (table 3). MAP declined slightly during the anhepatic and neohepatic phases and was significantly lower at the end compared with the beginning of surgery ($P < 0.01$). CI remained high, which is typical for patients presenting with cirrhosis. $V_O^2$ index changed significantly over time (Friedman test: $P < 0.02$); $V_O^2$ index was low during OLT and increased after admission to the ICU (table 3).

The perioperative course of mixed venous lactate concentration, mixed venous oxygen saturation ($S_V^O_2$), arterial pH, gastric and sigmoid pH, and endotoxin concentrations in mixed venous and portal blood is shown in figure 2. Mixed venous lactate concentration increased continuously during transplantation, peaked after graft reperfusion (5.9 (3.5/7.15) mmol litre$^{-1}$; $P < 0.01$ vs baseline) and declined to baseline values 30 h after ICU admission. $S_V^O_2$ remained constant at a high level (> 87 %) during OLT, began to decline after operation and reached its lowest value 30 h after ICU admission (76 (70/79) %, $P < 0.01$ vs baseline). Arterial pH decreased significantly from 7.39 (7.35/7.43) at the beginning of OLT to 7.32 (7.24/7.34) during VVB ($P < 0.01$). To prevent further progression of metabolic acidosis, sodium bicarbonate (110 mmol) was given to 12 patients during the anhepatic or neohepatic phase. After reperfusion of the graft, arterial pH remained less than baseline values and recovered to normal values after ICU admission.

Gastric pH ($pH_i$) decreased significantly from baseline values of 7.28 (7.22/7.34) to 7.19 (7.13/7.23) during VVB ($P < 0.01$) and remained low during the anhepatic phase. After reperfusion of the graft, $pH_i$ increased within 30 min and did not differ from baseline values at the end of OLT (ns). After operation, gastric pH increased further, reaching the highest values 18 and 30 h after ICU admission (7.34 (7.28/7.38) and 7.34 (7.26/7.38), respectively). After adjusting for multiple comparisons, the difference in gastric pH between baseline and 30 h ICU did,
Table 3  Perioperative changes in haemodynamic and oxygenation variables (median (Q1/Q3)). MAP = Mean arterial pressure; PAP = mean pulmonary arterial pressure; PCWP = pulmonary artery wedge pressure; CI = cardiac index; Hb = haemoglobin concentration; \( Ca_\text{O}_2 \) = arterial oxygen content; \( CV_\text{O}_2 \) = mixed venous content; \( DO_2 \) index = global oxygen delivery index; \( VO_2 \) index = oxygen consumption index. I = Before veno-venous bypass, II = 30 min of veno-venous bypass, III = 5 min before reperfusion, IV = 30 min of neohepatic phase, V = end of surgery, VI = ICU admission, VII = 12 h in ICU, VIII = 24 h in ICU. ** \( P < 0.01 \): beginning vs end of surgery

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<tr>
<td>( VO_2 ) index (ml min(^{-1}) m(^{-2}))</td>
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however, not reach statistical significance ($P = 0.1$).

The intraoperative course of sigmoid pH$_i$ (pH$_{si}$) showed essentially the same pattern as gastric pH$_i$; the lowest values were measured during VVB (7.13, 7.06/7.24), and sigmoid pH$_i$ at the end of surgery did not differ significantly from baseline.

The maximal intraoperative decrease in gastric or sigmoid pH$_i$ did not correlate either with the duration of VVB (pH$_{gr}$, $r = 0.17$; pH$_{si}$, $r = 0.34$; ns) or with the number of RBC units transfused (pH$_{gr}$, $r = -0.19$; pH$_{si}$, $r = 0.04$; ns). pH$_i$ values obtained after graft reperfusion did not correlate with duration of postoperative ventilatory support (pH$_{gr}$, $r = 0.41$; pH$_{si}$, $r = 0.29$; ns) (table 2), duration of ICU stay (pH$_{gr}$, $r = 0.39$; pH$_{si}$, $r = 0.29$; ns) (table 2) or with creatinine clearance on the second postoperative day (pH$_{gr}$, $r = 0.34$; pH$_{si}$, $r = -0.18$; ns) (table 4).

Postoperative hepatic function, as assessed by plasma activity of factor V and prothrombin time (table 4), and the degree of hepatocellular damage, as assessed by serum ALT (table 4), did not correlate with pH$_i$ after reperfusion of the graft (pH$_{gr}$, $r = 0.28$; pH$_{si}$, $r = 0.34$; ns) or at the end of surgery (pH$_{gr}$, $r = 0.31$; pH$_{si}$, $r = -0.15$; ns). In the one patient requiring re-transplantation for primary graft non-function, pH$_i$ values after graft reperfusion (pH$_{gr}$, 7.28, pH$_{si}$, 7.23) and at the end of OLT (pH$_{gr}$ 7.27, pH$_{si}$ 7.28) were in the range obtained from patients with adequate primary graft function.

Plasma endotoxin concentrations were determined during the course of 12 OLT. Endotoxin concentrations in plasma from mixed venous or portal venous blood did not increase significantly during OLT (fig. 2). Correlation analysis revealed no statistically significant relationship between either portal or mixed venous endotoxin concentrations and the lowest values of gastric or sigmoid pH$_i$ measured during the surgical procedure ($r = 0.45$, $r = 0.41$, respectively). One patient presented with high endotoxin concentrations during the anhepatic phase in both mixed venous (58 pg ml$^{-1}$) and portal blood (71 pg ml$^{-1}$); at the corresponding time, pH$_i$ values were 7.09 and 7.14 in the stomach and sigmoid colon, respectively.

**Discussion**

A decrease in mucosal pH$_i$ is considered to reflect inadequate oxygen delivery to the gut to meet metabolic demands. Accordingly, a close relationship between acute changes in splanchnic perfusion and mucosal pH$_i$ has been demonstrated [13]. In pigs, pH$_i$ measured using tonometry decreased as early as 20 min after partial occlusion of the superior mesenteric artery and returned to baseline values within 60 min after release of the occlusion [13]. Although tonometrically measured pH$_i$ slightly underestimated the pH$_i$ changes measured directly with a pH microelectrode, there was a close correlation between values obtained with both methods and the direction of pH$_i$ changes was always reflected.
accurately by tonometry [13]. Thus the accuracy and response time of tonometry appears adequate to assess acute intraoperative alterations of intestinal perfusion in humans.

Indeed, our study in a limited number of patients undergoing liver resections confirmed that acute interruption of intestinal blood flow was reflected closely by a decrease in tonometrically measured gastric pH. In two of six patients in whomportal blood flow was interrupted intentionally by clamping of the hepatoduodenal ligament, gastric pH decreased within 30 min after portal occlusion and, after release of the portal clamp, returned to baseline values towards the end of surgery. In patients without portal clamping, pH remained essentially unchanged (fig. 1). An increase in gastric pH has also been reported after release of chronic intestinal ischaemia caused by portal thrombosis [23]. In contrast, a recent study on the effects of dopexamine on splanchnic oxygenation in cardiac surgical patients revealed that gastric pH did not adequately reflect changes in splanchnic blood flow, as measured by the indocyanine green dilution technique [24].

These apparently conflicting results may be caused by different underlying pathophysiological mechanisms; sudden mechanical interruption of venous outflow induces complete stasis of intestinal microvascular blood flow whereas a pharmacologically outflow induces complete stasis of intestinal microvascular flow whereas a pharmacologically induced increase in arterial perfusion may redistribute microvascular flow.

Based on the results obtained during hepatic resection, the reversible reduction in both gastric and sigmoid pH during the anhepatic phase ofOLT implies that transient intramural hypoxia of the gastrointestinal mucosa had developed. Moreover, pH decreased although portal blood flow was maintained by VVB allowing total flow rates of up to 50 % of cardiac output. As intraoperative pH changes were essentially similar at both locations (stomach and sigmoid colon), the reduction in gastric pH also cannot be attributed to alterations in gastric mucosal perfusion as induced by surgical manipulations or falsely low pH values caused by reflux of alkaline duodenal fluid [25]. Although there are no data on microvascular mucosal perfusion during liver transplantation, the reduction in pH observed during the anhepatic phase suggests that preservation of overall portal blood flow by means of VVB did not achieve adequate distribution of intestinal blood flow. Inappropriate flow distribution has been suggested recently to explain the decrease in gastric pH, despite the increase in splanchnic oxygen delivery achieved in postoperative cardiac surgical patients by means of dopexamine [24].

In our study pH decreased as early as 30 min after the beginning of the anhepatic phase and this suggests that the short period of complete portal clamping necessary to allow insertion of the VVB cannula into the portal vein may be sufficiently long to induce prolonged impairment of microvascular mucosal perfusion. This is supported by the finding that the degree of mucosal acidosis was not related to the duration of VVB.

The increase in lactate concentration observed in our patients during OLT may be interpreted as an indicator of tissue hypoxia only with caution (fig. 2). Steib and colleagues found in a comparable group of hyperdynamic OLT patients that arterial lactate and $S_{\text{VO}_2}$ indices of tissue oxygenation conventionally used in critically ill patients, failed to accurately reflect tissue hypoxia, as evidenced by supply dependent oxygen consumption [2]. During OLT, lactic acidosis appears to reflect more the absence of metabolic liver function than tissue hypoxia. Moreover, considerable amounts of lactate are added to circulating blood with each unit of stored blood transfused. In fact, we measured lactate concentrations higher than 30 mmol litre$^{-1}$ in stored red cell concentrates (data not shown).

$D_{\text{O}_2}$ index remained unchanged throughout OLT. Consistent with the results of Steib and colleagues, we observed a tendency towards a decreased $D_{\text{O}_2}$ index during the anhepatic phase, a finding attributable to a combination of intraoperative hypothermia (temperature at the end of OLT 33.7 (32.8/36.1) °C) and absence of metabolic liver function [2]. During operation, $S_{\text{VO}_2}$ remained high, which is typical in cirrhotic patients (> 87 %), and tended to increase further during the anhepatic phase (93 (86/95) % before reperfusion). As a consequence, continuous intraoperative $S_{\text{VO}_2}$ monitoring appears to be an inappropriate method to detect tissue hypoxia in hyperdynamic cirrhotic patients. Although increased lactate and decreased $S_{\text{VO}_2}$ appear not to be reliable markers of tissue hypoxia in cirrhotic patients undergoing OLT, tissue hypoxia has been suggested to be present during OLT, as evidenced by oxygen supply dependency [2]. The decrease in pH, in the present study clearly demonstrated that the intestinal mucosa is one site of tissue hypoxia.

We are not aware of “normal values” for gastric or sigmoid pH, in patients with liver cirrhosis. Baseline values in our patients were, however, low compared with normal values reported in the literature for cardiac surgical patients [23] and those regarded as the lower limit for therapeutic interventions in critically ill patients [18]. Thus chronic mucosal hypoxia may be present in end-stage liver cirrhosis associated with portal hypertension and massive collateral circulation. “Normalization” of gastric pH, on the second postoperative day may indicate furthermore that elimination of portal hypertension and restoration of normal splanchnic perfusion after liver transplantation allow rapid improvement of mucosal blood flow and oxygenation.

$D_{\text{O}_2}$ did not find a correlation between intraoperative gastric or sigmoid pH, measured after reperfusion of the graft and postoperative graft viability. This is in contrast with the results of a recent study that reported a predictive value for postoperative early graft dysfunction of a gastric pH value $< 7.32$ measured 30 min after graft reperfusion [5]. Although this study included a larger number of patients ($n = 35$), its conclusion was based on only one patient requiring re-transplantation for primary graft non-function. More importantly, gastric pH values were consistently higher than arterial pH values, a finding attributable to incomplete equilibration of carbon dioxide be-
tween the mucosa and the tonometer [11]. In contrast, pH in our study was always lower than arterial pH at the corresponding times. In the one patient requiring early re-transplantation, pH values did not differ from those of the other patients with an uneventful postoperative course. Furthermore, we could not demonstrate a relationship between intraoperative pH and postoperative function of other organ systems, as postoperative creatinine clearance, duration of ventilatory support and total duration of ICU stay were unrelated to intraoperative pH. It is noteworthy, however, that Downing and colleagues found an association between intraoperative pH, values < 7.32 and graft dysfunction, acute renal failure, sepsis and the need for ventilatory support after OLT [26]. Unfortunately, this report does not contain details on patient selection and use of tonometry. Moreover, despite the predictive value of pH, for postoperative complications, the mortality rate was not different between patients with pH values higher than 7.32 or lower than 7.32.

In previous studies, endotoxaemia has been demonstrated during liver transplantation, although venous stasis during the anhepatic phase, which could have accelerated the translocation of endotoxin from the gut into the portal blood [6], was avoided by the use of VVB [8, 9]. Moreover, a high systemic endotoxin concentration was a prognostic factor for primary graft non-function, postoperative pulmonary complications and mortality [8, 9]. In our patients significant endotoxaemia was absent in portal and mixed venous blood, although the reduction in pH, suggested the presence of intraoperative mucosal hypoxia, a situation promoting translocation of enteric micro-organisms (fig. 2). The one patient in whom intraoperative endotoxaemia in both portal and systemic blood was proved had a normal graft function and an uneventful postoperative course. Even though we did not observe endotoxaemia, we cannot exclude the occurrence of translocation completely. First, pre- or perioperative administration of antibiotics and the use of SDD may have reduced the viability and number of enteric micro-organisms; in addition, binding of polymyxin to the lipid A portion of endotoxin may have prevented absorption of endotoxin from the gut [27, 28]. Second, portal and systemic blood may have been inappropriate sources to detect endotoxin. In liver transplantation in rats, bacteria were translocated to mesenteric lymph nodes within 20 min of portal vein occlusion [29]. Similarly, translocation of bacteria to mesenteric lymph nodes has been found in humans after abdominal trauma, however, without being associated with postoperative complications [30].

When interpreting mucosal acidosis the effects of systemic disturbances in acid–base balance on pH have to be considered. It has been suggested that in the presence of systemic acidosis the difference between arterial and mucosal pH, the “pH gap”, would more accurately reflect changes in mucosal pH originating from regionally inadequate mucosal oxygenation [31]. In our study, we did not calculate the pH gap, because this index has never been validated as an independent measure for the adequacy of mucosal oxygenation. Although it is conceivable that pH decreases when systemic acidosis emerges, the fact that pH, in our patients increased rapidly after reperfusion of the graft while arterial pH remained low supports the concept that pH primarily reflects local hydrogen ion production caused by anaerobic metabolism (fig. 2). Moreover, theoretical considerations suggest that mucosal acidosis is caused by local generation of hydrogen ions from anaerobic metabolism rather than stagnation of carbon dioxide removal as mucosal blood flow decreases [25].

To avoid the confounding effects of different blood-gas analysers while interpreting pH values, we used the same blood-gas analyser, ABL 520 (Radiometer), in the OR and ICU [32]. This device has been shown to measure PCO2 accurately in saline [31].

The hypothesis that VVB would mitigate the reduction in pH, was not strictly tested in this study. To estimate accurately the effects of preserved portal blood flow on mucosal oxygenation, it would have been necessary to compare OLT performed with and without VVB in a randomized study. However, because at the time this study was performed VVB was used routinely at our institution, we could not implement a randomized study design. Although we cannot exclude the possibility that pH may have decreased to even lower values without the use of VVB, the finding of impaired mucosal oxygenation while portal blood flow was maintained suggests that additional mechanisms must account for the preservation of mucosal perfusion during OLT.

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References

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