Studies on predictability of early graft function after liver transplantation
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2005

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 13-12-2018
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Gastric mucosal pH is associated with initial graft function, but is not a predictor of major morbidity after liver transplantation

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Abstract

Background  Gastric mucosal pH reflects splanchnic perfusion. Monitoring gastric mucosal pH might be useful in predicting outcome after liver transplantation.

Methods  Forty patients were included. Gastric mucosal pH and gastric mucosal pH, corrected for systemic pH were compared with regard to initial liver function and morbidity.

Results  Eighty percent of the patients had at least one episode with a gastric mucosal pH < 7.32, and 84% of these had a concomitant arterial pH lower than 7.32. No differences in morbidity were found between patients with a gastric mucosal pH < 7.32 and those with a gastric mucosal pH > 7.32.
If gastric mucosal pH was corrected for arterial pH, only 49% of the patients had an episode during transplantation with a corrected gastric mucosal pH < 7.32.
Comparing these patients with the group that did not have such an episode we found that flow in the venovenous bypass system was significantly lower (2.9 versus 3.4 L/min., p < 0.02) in the first group. Also alanine aminotransferase and aspartate aminotransferase levels were higher and antithrombin III levels and lidocaine clearance rates were lower and protrombin times were longer in the group with corrected gastric mucosal pH < 7.32. No differences with regard to major morbidity and mortality were noted.

Conclusion  Gastric mucosal pH during liver transplantation should be corrected for arterial pH. Patients with a corrected gastric mucosal pH < 7.32, are more likely to develop initial liver function tests disturbances, but morbidity is not different from patients with gastric mucosal pH > 7.32.

Introduction

Measuring gastric mucosal pH (pH_i) with a tonometer is a relatively noninvasive technique for monitoring splanchnic perfusion. It has been proposed as the ideal monitor of aerobic metabolism in intestinal mucosa which is particularly vulnerable to alterations in perfusion and oxygenation. Low pH_i has been shown to be a
sensitive predictor of poor outcome in cardiac and aortic surgery. In the field of liver transplantation, claims in this direction have been published as well. On the other hand, impaired splanchnic tissue oxygenation has been observed during liver transplantation, even with the use of venovenous bypass, while no deleterious effect on outcome could be detected. During liver transplantation, shifts in arterial pH are well known. So far, it has remained unclear whether the measured pH should be corrected for arterial pH, but in case of a systemic disturbance in acid-base balance the use of a corrected pH (standard pH) is recommended. The aim of this study was to assess the influence of splanchnic perfusion, as measured by pH, on postoperative graft function, on morbidity and on comparing pH and standard pH.

**Patients and methods**

After approval from the local Ethics Committee and after informed consent was obtained, 40 liver transplant patients were included in the study. In 1 patient introduction of the tonometer was difficult and attempts were stopped because of serious nasal blood loss, therefore, the total study group consisted of 39 patients. Patient characteristics are shown in Table 1. Indications for liver transplantation were end stage cirrhosis in all but 2 patients who were transplanted because of acute liver failure. Only donor livers that fulfilled the following criteria were accepted. Donors should not be older than 65 years and did not have a history of liver disease, alcoholism or drug abuse. They had not experienced hypotensive periods or had recovered from a hypotensive period for more than 24 hours with normal or near normal liver function tests afterwards. They had not been treated consistently with > 10 μg/kg/min. of dopamine, and liver function tests were less than triple normal values. All livers were preserved in University of Wisconsin solution. Anesthesia was induced with midazolam 0.1 mg/kg, vecuronium 0.1 mg/kg, sufentanyl 1 mg/kg and maintained with continuous infusions of midazolam, vecuronium, and sufentanyl. The trachea was intubated and the lungs ventilated throughout the procedure with 40% of oxygen in air. Tidal volume and ventilatory frequency were adjusted to maintain PaCO₂ at 4.5 kPa. Patients were monitored using two 20-gauge radial artery catheters and a
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pulmonary artery catheter inserted through a sheath in a jugular vein. After induction of anesthesia a tonometer was positioned in the lumen of the stomach. The correct position was confirmed by intraoperative palpation. All patients were treated preoperatively with ranitidine or omeprazole. During transplantation, no bicarbonate was infused except when systemic pH decreased to < 7.15; then 100 ml. sodium bicarbonate 8.4% was given. To also equilibrate also areas with low perfusion, no bicarbonate was infused at least 1 hour before and during sampling of pH_i was performed. Unless systemic pH was < 7.05, this was to prevent a possible pseudonormalization, as was reported in literature 11. In all patients, orthotopic liver transplantation was performed by using a standard surgical procedure 12. Venovenous bypass was performed using a centrifugal pump and heparinized tubing in 35 patients. In 2 patients only the femoral and axillary vein were cannulated, while in 18 patients the portal vein was also cannulated. In 15 patients, the superior mesenteric vein was cannulated. In the remaining 4 patients, the liver was transplanted using the so-called piggy-back technique during which the inferior caval vein is left in situ. Flow through the inferior caval vein was possible during the transplantation because a side clamp was used to insert the suprahepatic inferior caval vein end to side. In these patients, no temporary portocaval shunt was performed. Flow was maximized to levels in which the inflow was obstructed because of collapse of the involved veins or tubing. Hemodynamic measurements included heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, pulmonary artery occlusion pressure, and cardiac output. Cardiac output was calculated from triplicate measurements by thermodilution method. Gastric mucosal pH_i was assessed by filling the balloon with 3 ml of saline and aspirating 1 ml. after 30 minutes. With the other 2 ml the pCO_2_ was measured with a Radiometer type 330 blood gas analyzer (Radiometer, Copenhagen, Denmark) within 10 min. of sampling. Parallel to this assessment, an arterial blood sample was taken to evaluate arterial blood gasses. By using the Henderson-Hasselbalch formula, the pH, was calculated. For correction of low arterial pH (pH_a) the corrected pH_i was calculated as follows 10: standard pH_i = 7.4 - (pH_a - pH_i). In the first analysis, patients were grouped using a cutoff point of 7.32 for the uncorrected pH_i which is 2 SDs less than normal 13, as was done in many studies previously 14-16. In the second analysis, patients were
grouped using the standard pH, with the same cutoff point. An arterial blood sample and a saline sample were taken after induction; 30 and 60 min after start of bypass; 30 min before end of bypass; 30, 60 and 120 min after reperfusion of the graft; and also 12 and 36 hours after admission to the intensive care unit. **End points** of the study were graft function on 7 consecutive days after transplantation, the occurrence of infection and rejection, duration of ventilation and length of intensive care unit stay.

**Graft function** was assessed by alanine aminotransferase, aspartate aminotransferase, prothrombin time, activated partial thromboplastin time (APTT), fibrinogen, antithrombin III and total bilirubin. Also, a monoethylglycinexylidide (MEGX) test was performed 12 and 36 hours after reperfusion.

**Primary non function** was considered present if regrafting was necessary within 1 week after transplantation. The indication for regrafting was based on the combination of parameters such as transaminase and bilirubin levels, coagulation profile, hypoglycemia, bile production and quality, circulatory and mental status and, if applicable, histological findings.

**Infection** was scored if there was cholangitis, abdominal infection, pneumonia, or bacteremia. Cholangitis was diagnosed if there was fever, chills, contaminated bile and obstruction of the biliary system. Abdominal infection was present when there was fever > 38°C and a positive ascites culture or when an abdominal abscess was surgically drained. Pneumonia was diagnosed if the clinical pulmonary infection score (CPIS) was ≥ 7. In ventilated patients, a bronchoalveolar lavage was performed in case the CPIS score was ≥ 7. Bacteremia was present if there were positive blood cultures taken on clinical grounds.

**Rejection** was considered present if rejection was noticed by the pathologist in the routine 1-week biopsy specimen using the classification described by Snover et al. In a second evaluation, rejection was considered present if a biopsy specimen taken on clinical indication showed rejection or when rejection was treated on the basis of clinical data without histological confirmation during admission.

**Statistical analysis** was performed using SPSS for Windows (SPSS, Chicago, IL). Comparisons between groups were performed using the Student-t-test for normally distributed variables and the Wilcoxon signed rank-sum test for nonparametrically distributed variables. Pearson Chi-square test was used to compare dichotomous variables between groups. Analysis of variance for repeated measures and Scheffe’s method for significance of comparisons between groups were applied.
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for multiple comparisons between the groups. Differences were considered significant if p values were <0.05.

Results

Only 8 of 39 patients (20%) had a normal pH$_i$ throughout the transplantation procedure, whereas 31 patients had a pH$_i$ <7.32 at least once. Gastromucosal pH was closely related to pH$_a$ (Fig. 1).

![Figure 1](image.png)

*Figure 1* Relation between arterial pH and pH$_i$. Values represent means and SDs of pH$_a$ (dotted line) and pH$_i$ (straight line) (all patients). The black box signifies time on venovenous bypass.

In the normal pH$_i$ group only 3 of 8 patients (38%) had a pH$_a$ <7.32 at some point during the operation, whereas in the low pH$_i$ group a total of 26 of 31 patients (84%) showed a pH$_a$ <7.32 simultaneously with the low pH$_i$.

There were no statistically significant differences between the two groups in total rate of infection (50% in the normal pH$_i$ group versus 65% in the low pH$_i$ group), abdominal infection (13% versus 39% respectively) and clinically relevant rejection (13% versus 23% respectively). Length of intensive care unit stay and duration of ventilator dependency were similar. In the first postoperative week, no differences between the groups were identified in the liver function tests. Primary non function did not occur in these 39 patients.
If gastric pH was corrected for pHₐ according to the formula: standard pHᵢ = 7.40 - (pHₐ - pHᵢ) 19 of 39 patients (49%) had a value ≥ 7.32 (group 1). The remaining twenty patients (51%) had a standard pHᵢ < 7.32 at least once during the procedure (group 2). The mean values and SDs of the standard pHᵢ for both groups are shown in Fig 2.

Sixteen of these twenty patients (80%) had at least two consecutive standard pHᵢs of <7.32. Seventeen of the twenty patients with a standard pHᵢ <7.32 (85%) experienced this during bypass (8 of 17) or during and after venovenous bypass (9 of 17). One patient only had a standard pHᵢ < 7.32 at the start of the operation (immediate resampling showed a standard pHᵢ <7.32 again). Two patients of the twenty with a standard pHᵢ <7.32 (10%) had a standard pHᵢ <7.32 only 1 hour after reperfusion.

Recipient and donor characteristics and ischemia times of both groups are shown in Table 1, and hemodynamic measurements are shown in Figure 3. No differences were identified between the groups with regard to systemic hemodynamic monitoring. Also, the frequency of bicarbonate infusion in the
Figure 3  Hemodynamics during transplantation. Values represent means and SDs of Cardiac output (straight line) and mean arterial pressure (dotted line) (all patients).

The black box signifies time on venovenous bypass.

<table>
<thead>
<tr>
<th>Donor variables</th>
<th>standard pH&lt;sub&gt;i&lt;/sub&gt; &gt; 7.32</th>
<th>standard pH&lt;sub&gt;i&lt;/sub&gt; &lt; 7.32</th>
<th>NS</th>
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<tr>
<td>Age</td>
<td>34(13)</td>
<td>41(12)</td>
<td></td>
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<td>Sodium (mmol/L)</td>
<td>142(9)</td>
<td>149(9)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>78(16)</td>
<td>82(20)</td>
<td>NS</td>
</tr>
<tr>
<td>ALAT (U/L)</td>
<td>31(18)</td>
<td>33(16)</td>
<td>NS</td>
</tr>
<tr>
<td>ASAT (U/L)</td>
<td>57(42)</td>
<td>53(34)</td>
<td>NS</td>
</tr>
<tr>
<td>bilirubin (μmol/L)</td>
<td>18(18)</td>
<td>11(7)</td>
<td>NS</td>
</tr>
<tr>
<td>ICU stay</td>
<td>1.9(1.5)</td>
<td>2.6(2.7)</td>
<td>NS</td>
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<table>
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<th>Recipient variables</th>
<th>standard pH&lt;sub&gt;i&lt;/sub&gt; &gt; 7.32</th>
<th>standard pH&lt;sub&gt;i&lt;/sub&gt; &lt; 7.32</th>
<th>NS</th>
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</thead>
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<tr>
<td>Age</td>
<td>41(11)</td>
<td>43(13)</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh score(A/B/C)</td>
<td>24/18/59</td>
<td>26/32/42</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>45/55</td>
<td>50/50</td>
<td>NS</td>
</tr>
<tr>
<td>Cold ischemia time (min.)</td>
<td>62(18)</td>
<td>73(18)</td>
<td>NS</td>
</tr>
<tr>
<td>Warm ischemia time (min.)</td>
<td>58(11)</td>
<td>63(18)</td>
<td>NS</td>
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<td>Bypass duration (min.)</td>
<td>159(52)</td>
<td>168(43)</td>
<td>NS</td>
</tr>
<tr>
<td>Anhepatic phase (min.)</td>
<td>162(52)</td>
<td>161(42)</td>
<td>NS</td>
</tr>
<tr>
<td>Bypass flow (L/min.)</td>
<td>3.4(0.6)</td>
<td>2.9(0.4)</td>
<td>p=0.034</td>
</tr>
</tbody>
</table>

Values are expressed as means and SDs in the two groups.

Table 1  Recipient, donor and peroperative variables
two groups was not different (40% of group 2 and 28% of group 1). In only 2 patients (1 per group), bicarbonate was infused within 1 hour of measuring pH1. If the six patients in whom no splanchnic bypass was performed were excluded, mean bypass flow was 2.9 L/min. in group 1 versus 3.4 L/min. in group 2 (p<0.02).

Figure 4 Alanine aminotransferase (ALAT) levels. Values represent means and SDs of postoperative alanine aminotransferase levels in group 1 (straight line) and group 2 (dotted line).

Figure 5 Prothrombin time (PTT). Values represent means and SDs of postoperative alanine aminotransferase levels in group 1 (straight line) and group 2 (dotted line).
This difference was not caused by the type of portal decompression because flow in the portal decompression versus inferior mesenteric vein decompression was 3.28 ± 0.67 versus 3.1 ± 0.49 (p = 0.39). Postoperative liver function tests were significantly different: group 2 had higher alanine aminotransferase (Fig 4) and aspartate aminotransferase levels in the first 5 days after transplantation (MANOVA for repeated measures).

Also, prothrombin time was significantly higher (Fig 5) and antithrombin III levels were significantly lower (Fig 6) in group 2 during the first 5 days after transplantation.

Finally, in group 2, the clearance of lidocaine as assessed by the MEGX test was significantly lower on the second postoperative day (48 ±43 ng/ml in group 1 versus 93 ±42 ng/ml in group 2, p<0.015).

No differences in morbidity were identified between the 2 groups (Table 2).

Figure 6 Antithrombin III (AT III) levels. Values represent means and SDs of postoperative alanine aminotransferase levels in group 1 (straight line) and group 2 (dotted line).
If we correct pH\textsubscript{i} for arterial pH as suggested by Fiddian-Green in case of severe metabolic acidosis\textsuperscript{10} we find a clear-cut difference between the group with a low standard pH\textsubscript{i} with regard to postoperative liver function parameters. All measured parameters showed that the group with a standard pH\textsubscript{i} < 7.32 had more cell death in the newly implanted liver as assessed by the alanine aminotransferase and aspartate aminotransferase concentrations. Also, protein synthesis was reduced in the first 5 postoperative days in this group as shown by the decreased levels of antithrombin III and by the longer prothrombin times. Finally, the clearance of lidocaine was less in this group as compared to those that showed no standard pH\textsubscript{i} < 7.32, as assessed by the MEGX test on the first 2 postoperative days. Interestingly, our data add some evidence to the hypothesis that gastric mucosal pH reflects splanchnic flow because we found that bypass flow in the group with standard pH\textsubscript{i} < 7.32 was significantly lower than the flow in the group with a standard pH\textsubscript{i} > 7.32. Only patients operated with a venovenous bypass were included in this comparison. Unfortunately, in this study, only a few patients underwent transplantation without the use of a venovenous bypass so we could not prove the beneficial effect of venovenous bypass on postoperative liver function. It is important to realize that none of the donor parameters or the systemic hemodynamic parameters

### Table 2: Postoperative morbidity

| Incidence in percentage of the total number of patients in each group is shown |

<table>
<thead>
<tr>
<th></th>
<th>group 1</th>
<th>group 2</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Infection (%)</td>
<td>53</td>
<td>70</td>
<td>NS</td>
</tr>
<tr>
<td>Cholangitis (%)</td>
<td>16</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal (%)</td>
<td>22</td>
<td>47</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>16</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Bacteremia (%)</td>
<td>37</td>
<td>45</td>
<td>NS</td>
</tr>
<tr>
<td>Rejection (% grade 1 or more in one week biopsy)</td>
<td>39</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Rejection (in hospital)</td>
<td>16</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Intensive care unit stay (days)</td>
<td>6(±8)</td>
<td>14(±20)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Discussion

If we correct pH\textsubscript{i} for arterial pH as suggested by Fiddian-Green in case of severe metabolic acidosis\textsuperscript{10} we find a clear-cut difference between the group with a low standard pH\textsubscript{i} with regard to postoperative liver function parameters. All measured parameters showed that the group with a standard pH\textsubscript{i} < 7.32 had more cell death in the newly implanted liver as assessed by the alanine aminotransferase and aspartate aminotransferase concentrations. Also, protein synthesis was reduced in the first 5 postoperative days in this group as shown by the decreased levels of antithrombin III and by the longer prothrombin times. Finally, the clearance of lidocaine was less in this group as compared to those that showed no standard pH\textsubscript{i} < 7.32, as assessed by the MEGX test on the first 2 postoperative days. Interestingly, our data add some evidence to the hypothesis that gastric mucosal pH reflects splanchnic flow because we found that bypass flow in the group with standard pH\textsubscript{i} < 7.32 was significantly lower than the flow in the group with a standard pH\textsubscript{i} > 7.32. Only patients operated with a venovenous bypass were included in this comparison. Unfortunately, in this study, only a few patients underwent transplantation without the use of a venovenous bypass so we could not prove the beneficial effect of venovenous bypass on postoperative liver function. It is important to realize that none of the donor parameters or the systemic hemodynamic parameters
differed between the two groups. This makes it more likely that standard pH$_i$ is associated with postoperative liver function.

Our study did not focus on the mechanism through which gastric mucosal pH and liver function are related. Although it is important to realize that gastric mucosal pH was low, the liver graft was not yet reperfused at the time. In 19 of 20 patients standard pH$_i$ was < 7.32 at 30 min. before reperfusion. After reperfusion, standard pH$_i$ normalized within 1 hour in 15 of the total 20 patients. This makes it unlikely that initial liver function is related to splanchnic perfusion after reperfusion. It is therefore more likely that some sort of messengers are produced in the gut at the time the gastric mucosal pH is low. This might lead to increased levels of endotoxin, cytokines, prostaglandins or any other activator, which leads to decreased liver function tests.

The results of our study clearly show that gastric mucosal pH as such is not related to postoperative complications such as infection or rejection. Moreover, none of the 6 patients who had a pH$_i$ of <7.32 at the end of the operation (±3 hrs after reperfusion) developed primary non function. These findings are in contrast to the report by Frenette et al. In our opinion, their conclusions were not supported by the data presented in the study. Other explanations for this difference are that our endpoints were more rigid, thus leading to a more precise group description; secondly, that arterial blood gasses were not routinely corrected by giving bicarbonates; and thirdly, since pH$_i$ is highly correlated with pH$_a$ and pH$_a$ is known to decrease during transplantation because of factors other than ischemia, the pH$_i$ as such is likely to shift.

Our data confirm other reports that pH$_a$ drops during the anhepatic phase and returns to normal after reperfusion. Because gastromucosal pH is calculated using the systemic bicarbonate concentration, it is easily understood that gastromucosal pH reflects, at least partly, systemic pH in cases of metabolic acidosis. Therefore, in our view, it is not surprising to find that gastromucosal pH is low in almost all patients with a pH$_a$ <7.32. This makes it easier to understand that, in our series in contrast to reports from the literature, a low pH$_i$ was not associated with any endpoint, like infection, rejection or liver function.

In this study, we could not demonstrate any difference in outcome between the groups with a low standard pH$_i$ compared with normal standard pH$_i$. In our view, this is not an unexpected finding because these complications, especially in patients who have undergone liver transplantations, are multicausal and not
solely dependent on hemodynamic interventions like patients in septic shock. In conclusion, in liver transplantation, gastric mucosal pH needs to be corrected for pH$_4$ to investigate the influence of splanchnic perfusion on postoperative liver function. In the group with a standard pH$_4$ of <7.32, initial liver function is not as good compared to the group with normal standard pH$_4$. The difference disappears within one week after liver transplantation. In our study no relation was found between gastric mucosal pH, corrected or uncorrected, and complications after liver transplantation. Further research is needed in order to clarify the influence of splanchnic perfusion on post operative liver function.
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References

Schotvrij wij zitten stil
Vergelijken de wil met de wens
De wellust met de helderheid