NMR studies of the human donor liver
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Chapter 8

Metabolic Assessment of Human Donor Livers with Non-Invasive$^{31}$P-MRS.

Prognostic Value of Liver Adenine Nucleotides for Early Graft Function. $^{1}$

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INTRODUCTION

The intrinsic capacity of a donor liver to regain its original function after transplantation is largely determined by the integrity of the adenine nucleotide metabolism of the organ[1-2]. The adenine nucleotide composition can be assessed for viability testing with high performance liquid chromatography (HPLC) [1-4]. HPLC is very sensitive but the results are not readily available to the clinician because the technique is time consuming. Another important drawback of HPLC for routine clinical use, is the necessity to take a liver biopsy which carries the risks of liver damage and bacterial contamination. It would be helpful, when a method was available for rapid, non-invasive assessment of the adenine nucleotide composition of the donor liver.

With $^{31}$P-magnetic resonance spectroscopy ($^{31}$P-MRS), the adenine nucleotide composition can be assessed non-invasively in living cells. A potential role for $^{31}$P-MRS in viability research for transplantation has already been demonstrated in several studies on isolated animal livers [5-12] as well as in human kidneys[13]. Preliminary experience on isolated human donor livers also suggested potential clinical value as a rapid viability test [14]. However, so far $^{31}$P-MRS findings from isolated human donor livers have not been correlated with posttransplant organ function and therefore, the clinical value of $^{31}$P-MRS as a viability test has not been validated.

The objective of this study was to investigate whether the adenine nucleotide composition of the isolated donor liver as assessed with $^{31}$P-MRS can serve as a viability indicator with prognostic value for transplantation outcome. Specifically, we have tested whether the respective spectral peak areas of the isolated donor liver correlated with the amount of hepatocellular
graft damage and liver metabolic function shortly after implantation.

MATERIALS AND METHODS

Donor livers: Forty human livers were harvested according to standardized procedures [15]. During in-situ cold flush approximately 4 L of UW (University of Wisconsin, DuPont Critical Care, Waukegan, IL) was flushed through the organ, 1.5 L through the portal vein, 2.5 L through the aorta. At the same time, the abdominal cavity was filled with cold saline to provide adequate surface cooling of the liver. On the backtable an additional amount of UW was flushed through the hepatic artery and portal vein until the outflow from the caval vein was clear. The biliary system was additionally flushed with UW. Subsequently, the graft was packed in sterile plastic bags and stored in UW solution on melting ice in styrofoam containers.

Spectroscopy: A standard spectroscopic measurement was performed one hour before the start of the recipient operation and took about 30 minutes. $^3$P-MRS was performed as described previously [14,16]. To determine time dependent alterations in the adenine nucleotide composition, sequential measurements of the same liver were performed when allowed by the logistics of the transplantation procedure. This was the case in 2 cases of a local liver donation and in 3 cases of a reduced size liver transplantation in which the remaining part of the liver was repeatedly examined.

Liver transplantation: Orthotopic liver transplantation was performed following standardized procedures [15].

Spectral analysis: As was known from our previous experiments [14], if PCr and βATP resonances were present, they were only very small which made them unsuitable for quantification by means of a peak area ratio. For that reason we determined whether the presence of PCr and/or βATP was correlated with the amount of hepatocellular damage or liver metabolic function. The significance of the presence of these peaks was tested with the Wilcoxon test. The remaining spectral resonances of PME, Pi, and PDE were quantitated relative to the area of the NADH peak. This peak is present in the spectra of all livers and its position on the horizontal scale is pH independent [9,12,17]. Peak areas were calculated in a time domain fitting procedure in which a sum of exponentially damped sinusoids is fitted to the time signal. Peak areas were corrected for saturation effects by determining $T_1$ values of the respective metabolites [18].

Data analysis: To determine the relation between the adenine nucleotide composition of the isolated liver and the amount of hepatocellular graft damage after transplantation, simple regression analysis of the peak area ratios was used versus the following biochemical markers: serum concentrations of aspartate-aminotransferase (AST), alanine-aminotransferase (ALT) and γ-glutamyl-transpeptidase (γ-GT) at days 1, 2, 3, and 7 after transplantation. To
determine the relation between the adenine nucleotide status of the isolated liver and post-transplant liver metabolic function, regression analysis of the calculated peak area ratios was used versus serum bilirubin, daily bile production, plasma fibrinogen, prothrombin-time (PTT) and antithrombin 3 (ATIII) levels at days 1, 2, 3, and 7 after transplantation. To determine the effect of the cold ischaemia time (CIT) on the adenine nucleotide composition, CIT was also included in the regression analysis. The significance of the presence of PCr and βATP was assessed non-parametrically. P values lower than 0.05 were considered significant. In all analyses, missing clinical or spectroscopical data led to exclusion of the specific case from that specific data analysis.

RESULTS

spectra: In all cases spectra with excellent signal to noise ratios could be obtained. A representative spectrum is shown in figure 1.

In five livers the Pi peak area could not be determined due to major overlap with the Pi signal from the UW inorganic phosphate. Similarly, in 6 cases the PDE peak area could not be determined. The distribution of the peak area ratios PME/NADH, Pi/NADH and PDE/NADH is given in table 1. PCr could be
detected in 34 of the 40 livers. β-ATP was detectable in 11 of the 40 livers. Sequential spectra were obtained in 5 livers, a representative case is shown in figure 2. It is clearly visible that with lengthening of the CIT, ATP disappeared, PME decreased and Pi levels increased. The NADH peak was consistently present in all livers and its peak area hardly changed over time (Fig 2).

![Sequential spectra of the remaining part of a reduced size donor liver.](image)

**Fig 2** Sequential spectra of the remaining part of a reduced size donor liver.

post-transplant liver tests: The liver tests from the first post-operative week in the 40 recipients are listed in table 2. The transaminases were highest at day 2. Bilirubin was still rising at day 7; however protein synthesis as measured by ATIII and prothrombin time was improving at the end of the first week.

correlations: Simple regression analysis showed a positive correlation between PME/NADH and fibrinogen concentrations on day 1, 2 and 3 (p<0.001, p<0.01 and p<0.01 respectively). AST, ALT, γ-GT, bilirubin, ATIII concentrations, daily bile production and prothrombin time were not correlated with any of the peak area ratios. Livers exhibiting the PCr peak showed significantly (p<0.02) elevated ALT on day 7 (median value 349.5, 95% confidence interval 208-439)
Metabolic Assessment with $^{31}$P-MRS

cmpared to livers without detectable PCr (median value 132, 95% confidence interval 125-196). The presence of the βATP resonance was significantly and positively correlated with several indicators of the extent of hepatocellular graft damage and liver metabolic function, the most striking of which was the persistent correlation with postoperative bilirubin levels and prothrombin time (Table 3). A short CIT was associated with the presence of the βATP resonance but not with the presence of the PCr resonance.

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>mean</th>
<th>S.D.</th>
<th>min.</th>
<th>max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PME/NADH (n=40)</td>
<td>3.0</td>
<td>1.2</td>
<td>0.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Pi/NADH (n=35)</td>
<td>3.6</td>
<td>2.0</td>
<td>0.8</td>
<td>8.0</td>
</tr>
<tr>
<td>PDE/NADH (n=34)</td>
<td>0.9</td>
<td>0.9</td>
<td>0.2</td>
<td>4.5</td>
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</table>
Table 1 Distribution of the peak area ratios.

<table>
<thead>
<tr>
<th>parameter (units)</th>
<th>n=40</th>
<th>mean</th>
<th>S.D.</th>
<th>min.</th>
<th>max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/l)</td>
<td>day 1</td>
<td>1065</td>
<td>1314</td>
<td>105</td>
<td>6843</td>
</tr>
<tr>
<td></td>
<td>day 2</td>
<td>1314</td>
<td>1619</td>
<td>110</td>
<td>6851</td>
</tr>
<tr>
<td></td>
<td>day 3</td>
<td>569</td>
<td>650</td>
<td>36</td>
<td>3110</td>
</tr>
<tr>
<td></td>
<td>day 7</td>
<td>171</td>
<td>306</td>
<td>25</td>
<td>1675</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>day 1</td>
<td>989</td>
<td>1246</td>
<td>86</td>
<td>6629</td>
</tr>
<tr>
<td></td>
<td>day 2</td>
<td>1504</td>
<td>1793</td>
<td>130</td>
<td>7582</td>
</tr>
<tr>
<td></td>
<td>day 3</td>
<td>1287</td>
<td>1580</td>
<td>22</td>
<td>7008</td>
</tr>
<tr>
<td></td>
<td>day 7</td>
<td>489</td>
<td>584</td>
<td>91</td>
<td>3094</td>
</tr>
<tr>
<td>γ-GT (U/l)</td>
<td>day 1</td>
<td>77</td>
<td>64</td>
<td>14</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>day 2</td>
<td>94</td>
<td>71</td>
<td>18</td>
<td>284</td>
</tr>
<tr>
<td></td>
<td>day 3</td>
<td>154</td>
<td>125</td>
<td>21</td>
<td>465</td>
</tr>
<tr>
<td></td>
<td>day 7</td>
<td>284</td>
<td>170</td>
<td>49</td>
<td>671</td>
</tr>
<tr>
<td>bilirubin (umol/l)</td>
<td>day 1</td>
<td>146</td>
<td>90</td>
<td>21</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td>day 2</td>
<td>115</td>
<td>104</td>
<td>16</td>
<td>467</td>
</tr>
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<td></td>
<td>day 3</td>
<td>117</td>
<td>99</td>
<td>7</td>
<td>417</td>
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<td></td>
<td>day 7</td>
<td>182</td>
<td>132</td>
<td>26</td>
<td>481</td>
</tr>
<tr>
<td>fibrinogen (g/l)</td>
<td>day 1</td>
<td>2.87</td>
<td>0.78</td>
<td>0.34</td>
<td>4.75</td>
</tr>
<tr>
<td></td>
<td>day 2</td>
<td>3.03</td>
<td>0.86</td>
<td>1.18</td>
<td>5.54</td>
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<tr>
<td></td>
<td>day 3</td>
<td>3.03</td>
<td>1.20</td>
<td>1.05</td>
<td>7.29</td>
</tr>
<tr>
<td></td>
<td>day 7</td>
<td>2.70</td>
<td>1.17</td>
<td>0.61</td>
<td>5.33</td>
</tr>
<tr>
<td>antithrombin III</td>
<td>day 1</td>
<td>59</td>
<td>16</td>
<td>18</td>
<td>105</td>
</tr>
<tr>
<td>(as % of reference)</td>
<td>day 2</td>
<td>58</td>
<td>14</td>
<td>37</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>day 3</td>
<td>59</td>
<td>14</td>
<td>33</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>day 7</td>
<td>77</td>
<td>41</td>
<td>41</td>
<td>129</td>
</tr>
<tr>
<td>bile (ml)*</td>
<td>day 1</td>
<td>98</td>
<td>108</td>
<td>0</td>
<td>327</td>
</tr>
<tr>
<td></td>
<td>day 2</td>
<td>138</td>
<td>152</td>
<td>0</td>
<td>590</td>
</tr>
<tr>
<td></td>
<td>day 7</td>
<td>296</td>
<td>243</td>
<td>0</td>
<td>925</td>
</tr>
<tr>
<td>prothrombin time</td>
<td>day 1</td>
<td>23</td>
<td>9</td>
<td>13</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>day 2</td>
<td>24</td>
<td>12</td>
<td>14</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>day 3</td>
<td>21</td>
<td>9</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>day 7</td>
<td>17</td>
<td>4</td>
<td>12</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2 Clinical data of the recipient group. *bile production on day 2 was not accurately recorded for all cases.
Metabolic Assessment with $^{31}$P-MRS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\beta$ATP present median value (*)</th>
<th>$\beta$ATP absent median value (*)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIT</td>
<td>4.3 (3.5-7.5)</td>
<td>6.5 (6-8)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>AST day 3</td>
<td>162 (102-838)</td>
<td>544 (260-668)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Bilirubin day 1</td>
<td>71 (24-139)</td>
<td>170 (89-257)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilirubin day 2</td>
<td>50 (24-128)</td>
<td>108 (84-161)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilirubin day 3</td>
<td>34 (13-86)</td>
<td>111 (69-196)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilirubin day 7</td>
<td>65 (29-137)</td>
<td>189 (99-343)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fibrinogen day 2</td>
<td>3.72 (2.98-4.47)</td>
<td>2.67 (2.34-2.91)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fibrinogen day 3</td>
<td>3.65 (2.48-4.61)</td>
<td>2.58 (2.26-2.87)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AT III day 3</td>
<td>69 (45-78)</td>
<td>55 (42-58)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>PTT day 2</td>
<td>16.4 (15.3-18.9)</td>
<td>22.6 (20.7-28.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PTT day 3</td>
<td>14.7 (14.2-18.6)</td>
<td>21.9 (19.9-28.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PTT day 7</td>
<td>14.2 (13.0-18.1)</td>
<td>17.6 (16.3-19.1)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

*values in parentheses represent 95% confidence interval

Table 3. Relation of the $\beta$-ATP resonance with recipient parameters.

DISCUSSION

The role of adenine-nucleotides in liver viability has been extensively studied with $^{31}$P-MRS in isolated perfused animal livers, either with or without subsequent transplantation [5-12,19,20]. From these experiments it appeared that assessment of the adenine nucleotide status with $^{31}$P-MRS could offer a viability test with prognostic capacity for transplantation outcome.

In this clinical study using a commercial whole body 1.5 Tesla magnet, a number of peak resonances could be evaluated for their capacity to predict postoperative metabolic function and hepatocellular damage. The significances and the relationships with transplantation outcome of the spectral peaks is discussed next.

The PME peak is a multicomponent peak which is considered to represent glycolytic intermediates and precursors of membrane biosynthesis [21,22]. The lower PME signal which was observed with longer CIT is due to a decrease in the AMP fraction of the PME peak as cold ischemia induces dephosphorylation of AMP. This effect is well known and has also been observed in human donor kidneys [13]. In the individual donor liver the PME resonance may therefore be an indicator for the length of the CIT. The clinical importance of such a single parameter however appears to be limited. Although a significant positive correlation between PME and postoperative fibrinogen was found, it appears that PME in human livers is not the prognostic indicator for postoperative organ function like it has been shown in human kidneys [13]. We
could not confirm a significant relation between PME and CIT among different livers. This also suggests that CIT is not the only factor influencing the PME resonance which is in agreement with evidence that PME may also be dependent on the donor nutritional status [23].

The increase of the free inorganic phosphate fraction during CIT can be attributed to cold ischemia induced dephosphorylation of ATP, ADP and AMP and is clearly visible in the sequential spectral plots (Fig 2). An explanation for the absence of a correlation between hepatic inorganic phosphate and postoperative hepatocellular damage and metabolic function may be that experiments at 1.5 Tesla do not discriminate between cytosolic Pi and intramitochondrial Pi. Since the action of Pi in these two cellular compartments on the enzymes they contain (the glycolytic enzymes in the cytosol and the terminal respiratory chain in the mitochondria) may be completely different [19,20], the Pi peak with its heterogeneous contents observed in our measurements is not suited for clinical viability research.

The PDE peak has been reported to be elevated in membrane breakdown processes [21,22]. Furthermore, the PDE peak has been reported to be dependent on liver glycogen content and nutritional status of the donor [6,23]. Thus the PDE peak appeared to be a useful tool for viability testing. Moreover, previous experiments on isolated human donor livers indeed indicated a potential role for the PDE peak as an indicator for cumulated organ damage [14]. However, as the present study did not show any correlation with liver metabolic function or hepatocellular damage, the role of PDE for viability testing appears to be limited and its significance as an indicator for cumulated organ damage remains unclear. As with PME, the PDE peak area may also be dependent on non-viability related factors, yet unknown.

Phosphocreatine (PCr) has been reported not to be spectroscopically detectable in the human liver [8,21]. It was therefore surprising to find that in the majority of cases of our study, a small but distinct resonance at the PCr site was present (Fig 1). To our knowledge, this may be the first MR spectroscopic demonstration of PCr in the human liver, although its possible detection with MR spectroscopy has been speculated upon [24]. The PCr resonance is most likely originating from the sinusoidal endothelium since these cells contain creatine-kinase-BB, the enzyme that catalyses the reaction: creatine + ATP \rightarrow \text{PCr} + \text{ADP} + \text{H}^+. A small part of the PCr resonance might be originating from the \( \text{CK}_{\text{m}} \) fraction in the hepatocyte mitochondria [25]. As damaged sinusoidal cells release the enzyme into the perfusate, creatine-kinase has gained particular attention as a marker of damage to the sinusoidal epithelium for liver transplantation [24,26-27]. Others have questioned the value of such a test for clinical liver transplantation [28-29]. Although we could not demonstrate creatine-kinase itself spectroscopically, the presence of its reaction product PCr correlated with a significant lower ALT on day 7. However, in the absence of similar changes of other markers for parenchymal damage, this finding is of doubtful clinical significance. The true meaning of the presence of a PCr resonance is not yet known. Further studies may provide more insight in the
metabolic role of PCr during cold ischemia and its potential to act as an ATP buffer during ischemia [11].

The NADH peak, is a broad multicomponent peak consisting of NAD+/NAD(H) and NADP+/NADP(H) as well as contributions from α-ADP and α-ATP. The NADH peak was consistently present in all livers and its peak area hardly changed over time (Figs 2). The NADH peak indicates the presence of intact mitochondria. In the time span of safe clinical preservation (less than 20 hours) this peak remains stable, probably because the terminal respiratory chain is blocked by the absence of oxygen to act as H⁺ acceptor. After more prolonged cold ischemia NAD(H) decreases which may reflect decomposition of mitochondria [10]. Both effects are visible in the sequential spectra (Fig 2). The stability of the peak during preservation makes it useful as a reference peak against which to measure other signal intensities [9,12,17]. At the same time, because of its stability, it is not suited as an indicator of viability. In contrast to human donor kidneys where the presence of NAD(H) correlated with good post-transplant organ function [13], this correlation was not found in human donor livers.

ATP when present, could be demonstrated in the spectra in only very small amounts as compared with in-vivo spectra [30]. This is not surprising since (both warm and cold) ischaemia during organ procurement is known to cause a rapid decrease of ATP due to dephosphorylation[2,6]. During cold storage the remaining portion of the ATP is also decreasing, albeit in a much slower way. In one of the sequential measurements on the remaining part of a reduced size liver ATP could no longer be detected after 17 hours of cold ischemia (Fig 2). In livers examined after a very short CIT, a fair amount of ATP could be detected (Fig 1). The ATP presence was of prognostic significance for the prothrombin time, bilirubin, fibrinogen and ATIII levels after transplantation (table 3). It therefore appears that ATP presence during cold storage predicts a better liver metabolic capacity after transplantation. This is in agreement with the findings in human donor kidneys [13]. However, ATP absence can not be regarded as a specific predictor of early graft dysfunction since none of the 29 livers without detectable ATP demonstrated primary non-function.

The presence of ATP was faintly linked to the degree of hepatocellular damage as indicated by the AST levels at day 3. However, this was not paralleled by ALT levels which makes this correlation of minor clinical significance. So, the degree of hepatocellular damage is not determined by pretransplant ATP presence which suggests that hepatocellular damage is determined by other, probably reperfusion related, factors.

The importance of ATP for liver viability has been addressed by HPLC studies on biopsied human donor livers at the end of cold ischemia. Kamiike and others found that transplantation outcome was independent of the ATP level itself [1,4] whereas Lanir et al. demonstrated a positive correlation between high ATP content and good posttransplant outcome [3]. Our non-invasive NMR study on whole organs demonstrates that it was the presence of ATP that appeared to be important. If the presence of ATP signifies intact mitochondria capable of
maintaining low ATP levels, it may mean that the presence of ATP also indicates
the regeneration capacity for ATP after transplantation. Since it has been well
established that the regeneration capacity for ATP determines liver viability
[1,3,31], this could be an explanation for the prognostic significance of ATP for
liver metabolic function found in this study.

Potential sources of error in this study are inevitably caused by its clinical
setting which is essentially different from in-vitro animal experiments under fully
controlled laboratory conditions. Recipient conditions were not taken into
account. Furthermore, the recipient data not only reflect the degree of (pre-)
preservation injury but they also include additional effects of reperfusion injury
as described by Clavien et al [32]. Such variables cannot be graded exactly, yet
they may have interfered with the outcome of our study. Also, although our
recipient population contained several cases with initial poor graft function, there
was no proven case of primary non-function. Therefore, this study was unable to
identify a spectrum which was prognostic for PNF. Other potential sources of
error could be resulting from the curve fitting procedures used for spectral
quantification. Finally, the non-detectability of PCr and ATP may be due to a
certain threshold detection level of these compounds with the equipment we
used.

In conclusion, the results of the study indicate that the individual PME, Pi,
PDE and NADH peaks are not prognostic for postoperative hepatocellular
damage or liver metabolic capacity. The presence of ATP however, predicts a
significant better metabolic capacity to eliminate bilirubin, to synthesize
fibrinogen and ATIII and to maintain a better prothrombin time after
transplantation. Furthermore, this study may be the first 31P-MRS demonstration
in the human liver of phosphocreatin, which presumably originates from the
sinusoidal lining cells. Although PCr presence was not significantly associated
with liver viability, its role in liver
metabolism during cold storage is worth being determined. In the clinical setting
described, metabolic assessment using 31P-MRS did not result in a reliable non-
invasive test to predict primary graft dysfunction.

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