LIVER AND BILIARY DISEASE

Biliary drainage for obstructive jaundice enhances hepatic energy status in humans: a ^{31}P -phosphorus magnetic resonance spectroscopy study

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Background: Biliary obstruction impairs liver function although the pathophysiological mechanism is incompletely understood.

Aims: The aim of this study was to examine serial changes in liver metabolism in patients with obstructive jaundice using image guided in vivo ^{31}P -phosphorus magnetic resonance spectroscopy (^{31}P MRS). This technique allows repeated and non-invasive assay of organ energy metabolism and phospholipid biochemistry.

Patients: We studied 10 patients presenting with obstructive jaundice secondary to extrahepatic localised malignancy. There were eight men and two women, median age 72 years (range 54–94), six with cholangiocarcinoma (all Bismuth type 1) and four with carcinoma of the head of the pancreas. Ten healthy volunteers (median age 24 years (range 21–26)) were studied for comparison.

Methods: Hepatic metabolism in jaundiced patients was measured by ^{31}P MRS at presentation and again after a one week period of biliary drainage. Conventional liver function tests were also recorded.

Results: Compared with controls, liver spectra from jaundiced patients contained an excess of phosphomonoester (PME) metabolites (PME/total phosphate median 10.3% (interquartile range 8.7–11.5) in controls, 15.4% (13.1–17.7) in jaundiced cases; $p < 0.01$). Biliary decompression was achieved in all patients (five with internal stents and five by external drainage catheters), and plasma biochemistry improved predictably (bilirubin 176 $\mu\text{mol/l}$ (158–351) at presentation, 110 $\mu\text{mol/l}$ (42–241) after drainage for one week; $p < 0.01$). Enhancement of hepatic energy status, measured by the ratio of adenosine triphosphate (ATP) to inorganic phosphate (Pi), was observed in all cases after relief of biliary obstruction (ATP/Pi 1.4 (1.17–1.69) at presentation, 1.97 (1.4–2.48) after drainage; $p < 0.01$) and was independent of the route of bile drainage. Hepatic phosphodiester (PDE) content was decreased after relief of obstruction (PDE/total phosphate 25.2% (20.5–27.4) at presentation, 19.8% (16.6–24.5) after drainage; $p < 0.01$). This change was probably due to a reduction in the contribution from bile contents to this resonance as a strong PDE signal was also detectable in spectra obtained from separate bile specimens.

Conclusions: Obstructive jaundice produces alterations in liver phosphoester biochemistry, most likely reflecting disturbances in phospholipid metabolism. Relief of biliary obstruction is associated with a measurable increase in hepatic energy status. Bile may contribute to the phosphodiester signal of the ^{31}P -phosphorus liver spectrum and changes in these resonances must therefore be interpreted with caution and in relation to the clinical situation. Monitoring of liver metabolism by ^{31}P MRS may allow clinicians to refine the selection and timing of therapeutic options in jaundiced patients.

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Biliary obstruction produces well recognised disturbances in liver physiology, including intermediary metabolism, protein turnover, and reticuloendothelial function.^{1,2} The mechanism of these derangements is incompletely understood although defects in mitochondrial performance,³ microsomal activity,⁴ and canalicular function⁵ have been variously implicated.

Liver dysfunction secondary to obstructive jaundice has rarely been examined from the viewpoint of intracellular energy metabolism. Animal experiments indicate that hepatic energy charge is reduced following bile duct occlusion⁶ with recovery of mitochondrial function after relief of obstruction.⁷ Our knowledge of the pattern and time frame of analogous changes occurring in the human liver is incomplete, largely due to the unfeasibility of repeated biopsy.⁸ The technique of ^{31}P -phosphorus magnetic resonance spectroscopy (^{31}P MRS) allows non-invasive assay of cellular metabolism because the naturally abundant ^{31}P isotope is central to biological energy transformation and ubiquitous in cell membrane

phospholipids.⁹ We have used image guided in vivo ^{31}P MRS to study serial changes in liver metabolism in patients presenting with obstructive jaundice and after biliary drainage.

PATIENTS AND METHODS

Patients

The study protocol was approved by the ethics committee of the Chinese University of Hong Kong, and written informed consent was obtained in each instance.

We studied 10 patients presenting with obstructive jaundice secondary to extrahepatic localised malignancy. There were

Abbreviations: ATP, adenosine triphosphate; FID, free induction decay; NTP, nucleotide triphosphates; PDE, phosphodiester; Pi, inorganic phosphate; PME, phosphomonoester; PCr, phosphocreatine; ^{31}P MRS, ^{31}P -phosphorus magnetic resonance spectroscopy; ppm, parts per million; VOI, volume of interest.

Figure 1 Representative serial magnetic resonance images. (A) At presentation with jaundice, demonstrating grossly dilated intrahepatic bile ducts. (B) Same patient after biliary drainage, the ductal system now being decompressed.

eight men and two women, median age 72 years (range 54–94), six with cholangiocarcinoma (all Bismuth type 1 with communicating right and left hepatic ductal systems) and four with carcinoma of the head of the pancreas. Obstructive jaundice was established on the basis of liver function tests and ultrasound scanning. Patients then underwent magnetic resonance imaging and spectroscopy (^{31}P MRS) of the liver, as described below. Depending on the clinical and radiological features, biliary drainage was established in each patient either endoscopically (internal stent or external nasobiliary drain) or by the percutaneous route (external transhepatic drain). Initial bile specimens were collected for microbiological culture. Hepatic recovery was monitored by serial liver function tests, and clinical signs were recorded to identify episodes of overt biliary sepsis. After a drainage period of one week, a second magnetic resonance evaluation was performed. When accessible, bile was again collected for culture at this time. All 10 patients subsequently underwent surgical exploration with definitive resectional surgery or palliative internal surgical bypass, at which time histological confirmation of malignancy was established and bile recultured.

In selected patients with external drainage, bile was collected for separate spectroscopic analysis, to clarify the contribution of this fluid to the overall liver spectrum (as detailed below).

Liver function tests (bilirubin, alanine aminotransferase, alkaline phosphatase, albumin, and prothrombin time) were measured by standard laboratory techniques.

Ten healthy volunteers (seven males and three females, median age 24 years (range 21–26)) were studied for comparison. All had normal liver function tests, negative hepatitis serology, and unremarkable hepatic parenchyma on ultrasound examination.

Magnetic resonance studies

All studies were performed on a 1.5 T whole body magnetic resonance system (Gyrosan ACS-NT; Philips Medical Systems, Best, the Netherlands). Patients and volunteers were fasted for four hours prior to magnetic resonance scanning.

Figure 2 ^{31}P -Phosphorus magnetic resonance spectrum from the liver of a healthy volunteer. The peak area is proportional to the amount of metabolite. Peaks labelled on scan: PME, phosphomonoesters (mainly phospholipid precursors, phospho compounds of choline and ethanolamine, with some contribution from sugar phosphates); Pi, inorganic phosphate (product of adenosine triphosphate (ATP) hydrolysis); PDE, phosphodiester (phospholipid catabolites, glycerophospho compounds of choline and ethanolamine, with some contribution from cell membranes); and γ , α , and β phosphates of nucleotide triphosphates (NTP, high energy phosphate compounds). By convention, the $[\beta\text{-P}]$ NTP peak is taken to represent ATP. Phosphocreatine peak (not labelled) at zero ppm (assumed from muscle contamination). Data are conventionally presented as ratios of peak areas, comprising phosphoester metabolites (PME/PDE) and energy status (ATP/Pi), respectively. Alternatively, individual peaks may be expressed as a proportion of the total phosphate signal. Liver intracellular pH was derived from the chemical shift difference between $[\alpha\text{-P}]$ NTP (assigned -7.5 ppm) and Pi, according to the supplied calibration data. ppm, resonance chemical shift in parts per million.

Magnetic resonance imaging

Axial and coronal images were obtained with the body coil and used for localisation of the voxel for spectroscopic acquisition, ensuring that malignant tissues were excluded. Representative images obtained before and after biliary drainage are shown in fig 1.

Magnetic resonance spectroscopy

A 14 cm transmit/receive surface coil was used for spectroscopic measurements. ^{31}P spectra were obtained from the liver and skeletal muscle (for later correction of muscle contamination during liver spectroscopy). Using image guidance, the coil was positioned over the thigh quadriceps muscle and subsequently over the liver with the centre of the coil as close as possible to the region of interest. The precise spatial location and size of the volume of interest (VOI) were reproduced for individual patients at each time point using the same three dimensional anatomical coordinates. Magnetic field shimming was performed automatically at the proton (water) resonance frequency of 63.9 MHz. Typically, the VOI used was $60 \times 60 \times 100$ mm (360 ml) for both muscle and liver. Volume selection was performed using a modified image selected in vivo spectroscopy protocol (ISIS). The surface coil was manually matched and tuned to the operating frequency for phosphorus (25.9 MHz). Both proton decoupling and nuclear Overhauser effect spectral enhancement techniques were used for signal acquisition. Data were acquired at 512 points with a spectral bandwidth of 1500 Hz and a repetition time of two seconds. For liver, 256 free induction decay (FID) signals were averaged to produce each in vivo spectrum (128 signal averages were used for muscle). The acquisition time for the imaging and spectroscopy protocol was about 45 minutes.

In three patients, bile was collected for the first 24 hours following external drainage. Spectra were obtained from 500 ml aliquots of these samples using the same acquisition parameters outlined above for the liver. We also performed semiquantitative analyses using double volume acquisition techniques for bile and liver together and for each of these individually against a reference solution of known concentration.

Table 1 Liver function tests

Blood test	Healthy controls (n=10)	Jaundice group (n=10)	
		At presentation	After drainage
Bilirubin (μmol/l)	11 (8–12)††	176 (158–351)	110 (42–241)**
Alk P (IU/l)	64 (53–83)††	535 (390–1028)	416 (227–521)**
ALT (IU/l)	23 (22–28)††	143 (75–187)	79 (48–109)**
Albumin (g/l)	42 (41–44)††	29 (26–31)	26 (20–30)
Prothrombin time (s)	10 (9.9–10.2)	10.6 (10–11.1)	10.4 (10.3–11.3)

Data are median (interquartile range).

††*p*<0.01 healthy controls versus jaundice group at presentation.

***p*<0.01 jaundice group after drainage versus value at presentation.

Alk P, alkaline phosphatase; ALT, alanine aminotransferase.

Spectral processing

The averaged FIDs from the liver were initially filtered using a convolution difference procedure (50 Hz) and apodisation (6 Hz) using the manufacturer's software to reduce noise and remove broad signals from less mobile phospholipids (no prior processing was required for muscle or bile signals). The filtered FID was processed in the time domain using the MRUI software package (Magnetic Resonance User Interface, kindly provided by A van den Boogaart, Katholieke Universiteit, Leuven, Belgium) and a variable projection (VARPRO) subroutine, running on an offline UNIX workstation.

The resonance frequencies and line widths were selected manually in the frequency domain as the initial values in the fitting process (fig 2).

Minor contamination of liver spectra from the body wall musculature (liver phosphocreatine (PCr)/total visible phosphate typically less than 5%) was corrected by subtraction of the relative phosphate compound (P_c peak) contribution derived from the muscle spectra using the formula: (liver P_c peak_{corrected} = liver P_c peak_{actual} - ((liver PCr/muscle PCr) × muscle P_c peak)). No attempt was made to correct for longitudinal relaxation (T_1) related partial saturation effects as fully relaxed spectral acquisition was unfeasible in this group of patients due to the time constraints of scanning.

Statistical analysis

Statistical comparisons were made by non-parametric methods. Between group comparisons were carried out using the Mann-Whitney U test, and serial (paired) changes were analysed by the Wilcoxon matched pairs test. Probability values were accepted as significant at the 5% level. Data are presented as median (interquartile range), unless stated otherwise. Computations were made using Statistica 4.0 (Statsoft, Tulsa, Oklahoma, USA).

RESULTS

Plasma biochemistry was severely deranged in the jaundiced group at presentation (table 1). Decompression of the biliary system was achieved in all patients; five with internal stents and five by external drainage catheters. There was a predictable improvement in liver function tests after relief of obstruction, with the exception of albumin (long half life) and prothrombin time (not initially deranged) which changed little (table 1).

³¹P-Phosphorus liver spectra from jaundiced patients were visibly different from those of healthy controls (figs 2, 3A). The major disturbance at presentation was an elevation in the phosphomonoester (PME) resonance, whereas intracellular acid-base and energy balance appeared to be maintained (table 2).

Figure 3 Representative serial ³¹-phosphorus magnetic resonance spectra before and after relief of biliary obstruction (same patient as in fig 1). (A) Liver spectrum from jaundiced patient at presentation. (B) Subsequent liver spectrum one week after biliary drainage. Note change in phosphodiester (PDE) resonance. (C) Spectrum obtained from a bile sample from the same patient. Note the peak at 3.5 ppm in the PDE region. (Similar appearances were obtained in bile specimens from two other patients.) Further study using a double volume acquisition technique with known reference solution (methylphosphonic acid 300 mmol/l) indicated that the PDE concentration in bile was approximately 10 mmol/l; in comparison, the content of these compounds within the liver was approximately 20 mmol/l. These quantitative estimates are approximations, determination of absolute metabolite concentrations being admittedly inexact by this methodology. PME, phosphomonoester; Pi, inorganic phosphate; NTP, nucleotide triphosphates; ppm, parts per million.

Representative ³¹-phosphorus liver spectra obtained before and after biliary drainage are shown in fig 3. Hepatic energy status, measured by the adenosine triphosphate/inorganic phosphate (ATP/Pi) ratio, was enhanced after relief of biliary obstruction (table 2). This energetic improvement (more easily interpreted when expressed as per cent change) occurred in all cases, and was independent of the route of bile drainage (fig 4). Biliary decompression was associated with a reduction in the contribution of phosphodiester (PDE) to the total phosphorus signal (table 2).

The spectra obtained from pure bile (fig 3C) contained no high energy phosphate or inorganic phosphate signals but did contain a resonance in the region of PDE metabolites.

Table 2 Hepatic metabolism measured by ^{31}P phosphorus magnetic resonance spectroscopy (^{31}P MRS)

^{31}P MRS measurement	Healthy controls (n=10)	Jaundice group (n=10)	
		At presentation	After drainage
ATP/Pi	1.25 (1.01–1.6)	1.4 (1.17–1.69)	1.97 (1.4–2.48)**
PME/PDE	0.38 (0.36–0.5)††	0.71 (0.54–0.82)	0.93 (0.65–1.1)**
PME/TP %	10.3 (8.7–11.5)††	15.4 (13.1–17.7)	17.6 (14.2–18.9)
PDE/TP %	25 (22.1–26.7)	25.2 (20.5–27.4)	19.8 (16.6–24.5)**
pHic	7.32 (7.16–7.38)	7.44 (7.29–7.47)	7.37 (7.27–7.45)

Data are median (interquartile range).

†† $p < 0.01$ healthy controls versus jaundice group at presentation.

** $p < 0.01$ jaundice group after drainage versus value at presentation.

ATP, adenosine triphosphate; Pi, inorganic phosphate; PME, phosphomonoester; PDE, phosphodiester; TP, total visible phosphate; pHic, intracellular pH.

Figure 4 Changes in energy status. Data are presented as percentage change with respect to value at presentation. ATP, adenosine triphosphate; Pi, inorganic phosphate.

All initial bile specimens were sterile, and there were no recorded instances of clinical biliary sepsis during the one week period of drainage. Subsequent bile cultures were invariably positive, with coliforms, pseudomonas, or enterococcal organisms isolated (alone or in combination) in each instance.

DISCUSSION

We have evaluated hepatic metabolism in patients with obstructive jaundice using localised *in vivo* ^{31}P MRS. The major abnormality in spectra from jaundiced patients was an elevated amount of PME when compared with healthy controls. After a one week period of biliary drainage, the predominant finding was enhancement of liver energy status and a reduction in the content of phosphodiester.

Impedance to the normal flow of bile produces well recognised impairment in global liver functions. Although the exact mechanism of these disturbances is incompletely understood, the clinical relevance is that surgical risk is related to the degree of hepatic functional impairment.^{10–12} Relief of obstruction produces an improvement in circulating biochemical

parameters and also in objective measurements of liver function, such as indocyanine green handling.¹³ Nevertheless, randomised controlled trials have failed to demonstrate benefit when planned biliary decompression is undertaken prior to surgery.^{14–17} It is generally believed that this strategy fails because complications related to stent placement (principally sepsis) tend to nullify any advantage gained by improvement in the condition of the liver.

The pathophysiology of obstructive jaundice has seldom been studied from the perspective of hepatocyte energy balance.^{6, 18} Animal studies have confirmed that mitochondrial function is impaired when the biliary system is occluded, and restoration of oxygen handling by these organelles follows relief of obstruction.⁷ Changes in human liver are less well defined although the available data indicate a reversible defect in mitochondrial respiratory characteristics when jaundice is relieved.⁸ An obvious limitation of these earlier methods is the requirement for liver biopsy to obtain tissue for *in vitro* analysis. Herein lies the appeal of ^{31}P MRS as this technique allows repeated and non-invasive measurement of *in vivo* organ metabolism.

We have estimated hepatic energy state by the ratio ATP/Pi, which can be considered analogous to cellular energy charge.¹⁹ This key metabolic parameter regulates the balance between energy consuming and producing reactions, thereby maintaining the biochemical poise of the adenylate high energy phosphate system.²⁰ Although steady state energy balance appeared to be intact in jaundiced patients at presentation (compared with healthy controls), we found enhancement in energy status after relief of biliary obstruction, which coincided with improvement in liver function tests. This potentiation of energy condition was of similar magnitude in the internal and external drainage groups, suggesting that the underlying mechanism was related to relief of obstruction *per se* rather than reintroduction of bile into the gastrointestinal tract.

Conceptually, an increase in hepatic energy status would be expected to translate into an augmented ability to support endergonic reactions involving synthetic, secretory, and storage functions. This increased work capacity may be of clinical relevance. One such instance would be when definitive treatment of a biliary or intrahepatic malignancy necessitates liver resection in a jaundiced patient. The remnant liver after hepatectomy must support differentiated function (the average cellular metabolic load being increased in proportion to the lost cell mass), and also sustain widespread hepatocyte mitosis as the liver regenerates. These substantial increases in energy demands should be matched by compensatory changes in ATP availability if energy balance and organ performance are to be maintained.²¹ In animal models of obstructive jaundice and liver resection, recovery of liver mass is more efficient when biliary drainage is employed²² and death from liver failure can be averted.²³ Our observations may explain the mechanism for these findings, and we are currently investigating whether these outcome advantages can be reproduced in humans.

Changes in PME and PDE resonances are more difficult to interpret. These peaks are multicomponent, receiving contributions from several classes of molecules which cannot be resolved at the field strengths currently used in clinical magnetic resonance systems. The PME peak includes signals from compounds classically considered to be phospholipid anabolites (phosphoesters of choline and ethanolamine) together with varying contributions from phosphorylated glycolytic intermediates and nucleotide monophosphates.²⁴ The PDE peak comprises compounds on the phospholipid degradation pathway (glycerophospho conjugates of choline and ethanolamine) together with contributions from phospholipids and bilayers, including endoplasmic reticulum.^{25, 26} Although the specific biochemical events behind variation in these resonances remain uncertain, it is interesting that in many

instances recurring patterns of change have been found. For example, spectra from malignant hepatic tissues are typically associated with a relative increase in phospholipid precursors (PME) and depletion of phospholipid breakdown products (PDE), these alterations being assumed to reflect active neoplastic cell membrane synthesis.²⁷ Similar changes have been found in benign proliferative processes of the liver, including regeneration after partial hepatectomy.^{28, 29} In diffuse parenchymal liver disease, elevation of PME has been attributed to ongoing cellular renewal and repair, while hepatic fibrosis and loss of endoplasmic reticulum have been postulated to explain an associated decrease in PDE.³⁰ We have demonstrated that qualitatively similar alterations in these compounds also occur in obstructive jaundice. How can these changes be explained? Hepatocyte mitosis is a recognised consequence of biliary obstruction and some of the derangements we measured may reflect this response.⁶ However, we have shown that bile itself may contribute to the hepatic ³¹P MRS signal, a possibility which had also been suggested from studies on chronic rejection of the transplanted liver.³¹ A reduction in the contribution of soluble phosphodiester metabolites and/or phospholipids from bile is one explanation for the decreased PDE signal we observed after biliary drainage. Further study of bile at higher magnetic field strengths would be useful to determine not only which of the biliary constituents is contributing to the phosphorus spectrum³² but also how the (phospho)lipid composition of bile may vary over the course of biliary obstruction and decompression.³³ Whatever the underlying biochemical explanation, it is evident that caution is warranted when interpreting changes in hepatic phosphoester resonances, and that these should be evaluated in relation to the clinical context.

Notwithstanding these limitations, we have shown that organ specific monitoring techniques such as ³¹P MRS can provide new insights into the pathophysiology of biliary obstruction. In the future, in vivo measurements of liver metabolism may allow clinicians to refine the selection and timing of therapeutic options in jaundiced patients.

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