Manuscript title:

Caval subtraction 2D phase-contrast MRI to measure total liver and hepatic arterial blood flow: Proof-of-principle, correlation with portal hypertension severity and validation in patients with chronic liver disease.

Short title:
Caval subtraction 2D PCMRI in cirrhosis

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Abstract:

Objectives

Caval subtraction phase-contrast MRI (PCMRI) non-invasive measurements of total liver blood flow (TLBF) and hepatic arterial (HA) flow have been validated in animal models and translated into normal volunteers, but not patients. This study aims to demonstrate its use in patients with liver cirrhosis, evaluate measurement consistency, correlate measurements with portal hypertension severity and invasively validate TLBF measurements.

Materials and methods

Local Research Ethics Committee approval was obtained. Twelve patients (mean 50.8±3.1 years, 10 male) with histologically confirmed cirrhosis were recruited prospectively, undergoing 2D PCMRI of the portal vein (PV), infra-hepatic and supra-hepatic inferior vena cava (IVC). TLBF and HA flow were estimated by subtracting infra-hepatic from supra-hepatic IVC flow, and PV flow from estimated TLBF respectively. Invasive hepatic venous pressure gradient (HVPG) and indocyanine green (ICG) clearance TLBF were measured within 7 days of PCMRI. Bland-Altman (BA) analysis of agreement,

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coefficients of variation and Pearson's correlation coefficients were calculated for comparisons with direct inflow PCMRI, HVPG and ICG clearance.

Results

The mean difference between caval subtraction TLBF and direct inflow PCMRI was (6.3±4.2 ml/min/100g, BA 95% Limits-of-Agreement (LoA) ±28.7 ml/min/100g). Significant positive correlations were observed between HVPG and caval subtraction HA fraction (r=0.780, p=0.014), but not for HA flow (r=0.625, p=0.053), PV flow (r=0.244, p=0.469) or caval subtraction TLBF (r=0.473, p=0.141). Caval subtraction and ICG TLBF agreement was modest (mean difference -32.6±16.6 ml/min/100g, BA 95% LoA ±79.7 ml/min/100g), but coefficients of variation were not different (65.7% vs 48.1%, p=0.28).

Conclusions

In this proof-of-principle study, caval subtraction PCMRI measurements are consistent with direct inflow PCMRI, correlate with portal hypertension severity and demonstrate modest agreement with invasive TLBF measurements. Larger studies investigating the clinical role of TLBF and HA flow measurement in patients with liver disease are justified.

Key words:

phase-contrast MRI; chronic liver disease; portal hypertension; liver blood flow; liver haemodynamics; hepatic arterial flow

Introduction

Quantifying the profound hepatic haemodynamic changes observed in chronic liver disease is complicated by the dual portal venous (PV) and hepatic arterial (HA) blood supply to the liver[1]. Phenomena such as portal hypertension are poorly understood partly because accurate assessment relies upon invasive reference standards[2, 3].

Caval subtraction 2D phase-contrast MRI (PCMRI) is a completely non-invasive method that has been recently validated for measurement of total liver and hepatic arterial blood flow in rat models of liver disease and successfully translated into normal human volunteers[4]. Total liver blood flow (TLBF) is estimated using the difference between 2D PCMRI flow measured in the supra-hepatic, sub-cardiac inferior vena cava (IVC) and the infra-hepatic, supra-renal IVC. HA flow can then be calculated by subtraction from directly measured 2D PCMRI PV flow measurements[4]. Caval subtraction PCMRI therefore addresses the difficulties posed by direct measurement of HA flow such as variable anatomy, small vessel size and tortuosity[5], in addition to challenges specific to PCMRI such as low signal-to-noise ratio (SNR), partial voluming errors, intra-voxel phase dispersion and spatial misregistration.

However, application of the technique is potentially challenging in patients with chronic liver disease, given the frequent presence of large extra-hepatic porto-systemic shunts and/or retrograde/obstructed PV flow. Furthermore, such patients are often unable to comply with demanding MR protocols that necessitate long breath holds and lying still, thereby increasing imaging artefacts and measurement errors. Beyond this, the clinical utility of absolute flow parameters in clinical practice remains unclear.

Hepatic venous pressure gradient (HVPG) and portal venous pressure are proven invasive biomarkers currently used clinically to guide patient management and for prognostication[6]. Formal indocyanine-green (ICG) clearance is an accepted reference standard for hepatic blood flow, but relies on invasive hepatic venous sampling and is therefore rarely used in routine clinical practice[7]. Existing data using PCMRI measurements of PV flow have been inconclusive, with very limited published HA flow data in patients[8].

The purpose of this study was to test the feasibility of applying caval subtraction 2D PCMRI to measure TLBF and HA flow in patients with chronic liver disease, evaluate the consistency of these measurements with direct inflow PCMRI, and correlate and validate these measurements with portal hypertension severity using invasive HVPG and ICG clearance.

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Materials and methods

Subjects and preparation

Regional ethics committee approval (reference08/H0724/35, Health Research Authority, United Kingdom) was obtained and all participants were recruited prospectively after providing informed written consent. Histologically confirmed cirrhotic patients undergoing elective invasive transjugular studies as part of usual clinical care were identified from the hepatology outpatient clinic (n = 10) and elective transjugular intra-hepatic portosystemic shunt (TIPSS) lists for refractory ascites (n = 5) between March 2012 and June 2014 at the Royal Free Hospital. Subjects were excluded if they (a) had any contraindication to MR imaging (n = 3), (b) were unable to consent (n = 0), (c) were allergic to ICG (n = 0) or (d) were on specific treatment for portal hypertension (e.g. beta-blockers)(n = 0). The final cohort consisted of 10 males (aged 49.5±3.5 years) and 2 females (mean age 58 years). Participants fasted for six hours prior to MRI and avoided caffeinated fluids.

Caval subtraction 2D PCMRI

PCMRI was performed with a 3.0T scanner (Achieva, Philips Healthcare, Best, Netherlands) and 16 channel body coil (SENSE XL-Torso, Philips Healthcare). Sequence parameters are given in Table 1.

Coronal (upper abdomen), sagittal (through the abdominal great vessels) and oblique (along the portal vein) breath hold balanced steady-state free precession (SSFP) images were acquired. Two-dimensional PCMRI with expiratory breath-hold and retrospective cardiac gating was planned in two planes by the study coordinator (MC, 4 years' experience of abdominal imaging) to ensure orthogonality to the target vessel.

PCMRI was then performed through the PV (velocity encoding setting (V_{enc})=40 cm/s), proper HA (V_{enc}=60 cm/s), infra-hepatic IVC (above the renal veins, below the hepatic IVC) (V_{enc}=60 cm/s) and supra-hepatic IVC (above the hepatic venous inflow, below the right atrial junction) (V_{enc}=80 cm/s). Initial V_{enc} settings were based on previous work[4]. Where HA anatomy varied (n=3), measurements were made as close as possible to the HA origin. At the time of acquisition, images were reviewed for aliasing and V_{enc} settings increased by 20 cm/s when appropriate.

Data were acquired using Philips' clinical flow quantification implementation. Phase maps were acquired at each V_{enc} setting with opposite flow encoding directions. Correction for background phase errors was undertaken by subtracting phase maps with opposing flow encoding directions, with the assumption that the phase of stationary spins was identical in each image. A local phase correction filter was also applied to correct for phase errors induced by eddy currents. Acquisition time for each measurement was less than 20 seconds. Each PCMRI measurement was repeated three times.

Flow quantification was performed using freely available software (Segment, Medviso, Lund, Sweden) by a single reader (MC, 4 years' experience of abdominal imaging) and the mean of triplicate measurements used for analysis. Caval subtraction TLBF, PV flow, HA flow and HA fraction were calculated as described previously [4] and compared with direct PCMRI of PV and HA inflow for assessment of consistency. For patients with hepatofugal PV flow, 'Q_{PV}' adopts a negative value (representing an outflow). In line with the principle of conservation of mass, HA flow (Q_{HA}) was estimated using caval subtraction and PV flow PCMRI measurements (Equation 1):

$$Q_{in} = Q_{out}$$
$$Q_{HA} = Q_{supra-hepatic\ IVC} - Q_{infra-hepatic\ IVC} - Q_{PV}$$

(Equation 1)

Liver volume was estimated using 5 mm slice thickness SSFP coronal images. Segmentation was performed manually by the study coordinator using Amira (Amira Resolve RT, Visage Imaging, Berlin, Germany). Tissue density of 1.0 g/ml was assumed[9]. PCMRI bulk flow measurements were normalised to liver weight/volume.

Invasive validation reference standards

Invasive reference measurements were obtained within 7 days of the MRI scan (mean 2.9±0.6 days, n=2 scanned before validation studies). Invasive validation studies were performed independently of the MRI scan so that researchers were blinded to the measurements obtained from either method. For patients undergoing TIPSS procedure (n=2), reference measurements (HVPG, ICG clearance) were obtained at the time of the TIPSS procedure but before creation of the shunt. All MRI scans in patients undergoing TIPSS procedure were performed prior to invasive validation. Child-Pugh scores were also recorded at the time of reference measurements.

HVPG measurement

After ultrasound guided cervical puncture of the right internal jugular vein (Sonosite Titan, SonoSite Inc, Washington, USA), the right hepatic vein was cannulated under fluoroscopic guidance (Axiom Artis Zee, Siemens Healthcare, Munich, Germany) using a balloon-tipped catheter (Cordis, Roden, Netherlands). The catheter was advanced into a wedged position, with no collateral run-off, confirmed using digital subtraction angiography (Omnipaque, Amersham Health, Little Chalfont, UK). Wedged and free hepatic venous pressure measurements were made with the balloon inflated and deflated respectively. Pressure traces were monitored continuously to confirm recording stability and paired pressure readings were performed in triplicate in succession. HVPG was calculated from the difference between free and wedge hepatic venous pressure. Mean measurements were used for final analysis.

ICG clearance validation of TLBF

Total liver blood flow was measured invasively using a weight-based primed and subsequent continuous infusion of ICG (Pulsion Medical Systems, Munich, Germany). Simultaneous paired samples, following radial artery puncture at the wrist and from the hepatic vein (following cannulation for HVPG measurement) were collected after 45 minutes (assumed steady-state concentration at this time, based on previous experience). ICG extraction was then calculated in accordance with the Fick principle[10, 11]. ICG TLBF measurements were normalised to anatomical MRI derived liver volumes for comparison with PCMRI measurements.

Statistical analysis

Data normality was confirmed using Kolmogorov-Smirnov testing. Agreement between measurements derived from caval subtraction PCMRI, direct inflow PCMRI and reference standard ICG clearance TLBF were assessed using Bland-Altman (BA) agreement analysis, and 95% Limits of

Agreement (LoA). Coefficients of variation were calculated and compared using methods described by Forkman[12]. The relationship between measurements derived from caval subtraction PCMRI and HVPG were tested using Pearson's correlation coefficient. To prevent skewing of small data sets, a patient with retrograde PV flow was excluded from HA fraction comparisons with HVPG (as HA fraction would have been 100%) and HVPG data from the patient with PV thrombus was not used (as HVPG in this context is not representative of sinusoidal pressure(11)).Data were expressed as mean±standard error and statistical significance assigned at $p<0.05$.

Results

Patients

Mean liver volume was 1544±129.5 ml. Cirrhotic aetiologies included alcohol (n=10), hepatitis C (n=1) and non-alcoholic steatohepatitis (n=1), with a range of disease severity (Child-Pugh A n=5, B n=6 and C n=1). Clinically significant portal hypertension (HVPG>10 mmHg) was present in eight patients, mean 12.3±1.62 mmHg. HVPG measurements in one subject and ICG clearance measurements in 6 subjects were not performed due to hepatic extraction being too low for interpretation. The highest recorded bilirubin in patients undergoing ICG clearance measurements was 2.63 mg/dl.

Caval subtraction PCMRI technical feasibility

ECG and respiratory gated cine PCMRI flow studies through the cardiac cycle demonstrated physiological flow profiles through the PV, infra-hepatic IVC and supra-hepatic IVC (figure 1).

Retrograde PV flow and PV thrombus, both recognised phenomena in chronic liver disease, were observed in two subjects (figures 2 and 3). Retrograde PV flow was quantifiable, but yielded a negative measurement for PV flow. PV thrombus, whether partial or complete had the effect of reducing quantifiable PV flow. Severe motion artefact due to inability to breath-hold was observed (n=2, figure 4), but quantification of blood flow using PCMRI was possible in all 12 patients.

Mean patient PCMRI measurements across the cohort are listed in Table 2.

Caval subtraction PCMRI vs direct PCMRI measurement

The mean difference between caval subtraction PCMRI measurements of TLBF (mean 101.4±17.8 ml/min/100g) and direct PCMRI measured TLBF (sum of PV and common HA flow, mean 95.2±14.1 ml/min/100g) and between caval subtraction HA flow (mean 31.0±6.8 ml/min/100g) and direct PCMRI measured HA flow (mean 24.7±4.7 ml/min/100g) was 6.3±4.2 ml/min/100g. The BA 95% LoA for caval subtraction vs direct inflow PCMRI was ±28.7 ml/min/100g for both TLBF and HA flow (range 27.5-242.4 ml/min/100g and 3.3-84.4 ml/min/100g, respectively) (figures 5a and 5c). The coefficient of variation for caval subtraction PCMRI TLBF (61.0%) was not significantly larger than direct inflow TLBF (51.1%; $F_{(12,12)}=0.77$; $p=0.677$). Caval subtraction PCMRI HA flow (76.1%) was also higher than with direct PCMRI HA flow (66.4%) but this difference was also non-significant; $F_{(12,12)}=0.83$; $p=0.624$.

Validation reference standards

Caval subtraction PCMRI vs HVPG

Caval subtraction HA fraction was significantly correlated with HVPG (r=0.780, p=0.014)(figure 6b). The correlation between caval subtraction PCMRI HA flow and HVPG though positive was non-significant (r=0.625, p=0.053)(figure 6a).   Both PCMRI PV flow and caval subtraction PCMRI TLBF demonstrated no association with HVPG (r=0.244, p=0.469; and r=0.473, p=0.141 respectively)(figures 6c and 6d).

Caval subtraction PCMRI TLBF vs ICG clearance TLBF

The mean difference between caval subtraction PCMRI measurements of TLBF (mean 83.2±22.4 ml/min/100g) and ICG TLBF (mean 50.6±9.9 ml/min/100g) was -32.6±16.6 ml/min/100g. The BA 95% LoA for caval subtraction PCMRI TLBF vs ICG TLBF was ±79.7 ml/min/100g (range 27.5-181.8 ml/min/100g and 22.9-79.3 ml/min/100g, respectively), with a positive bias for the PCMRI measurement (32.6 ml/min/100g)(figure 7a). The coefficient of variation for caval subtraction PCMRI TLBF (65.7%) was not significantly larger than ICG TLBF (48.1%; F(6,6)=1.64; p=0.281).

Discussion

Caval subtraction PCMRI has been previously proposed and validated in animals and normal volunteers. The present study demonstrates that this technique is feasible in patients with established cirrhosis and provides a practical alternative to the challenges of measuring proper HA flow and TLBF using direct PCMRI. As a proof-of-principle in two subjects, it has been demonstrated that the equation underpinning caval subtraction PCMRI (equation 1) is likely to remain valid both in the context of partial/complete PV obstruction (e.g. secondary to thrombus) and in the presence of retrograde PV flow, where TLBF equates to HA flow alone (and not the sum of PV and HA contributions).

Compliance with long breath-hold can be challenging in cirrhotic patients. In two subjects with substantial motion artefact, it was demonstrated that caval subtraction PCMRI was still possible. This is likely to be due to the technique relying on measurements from large, high-flow volume vessels and the use of triplicate-averaged measurements. Such data is encouraging as the technique now moves to testing in larger cohorts.

Using direct PCMRI measurements of PV and HA flow, good consistency with caval subtraction PCMRI measurements of TLBF and HA flow was demonstrated, similar to that achieved in normal volunteers (±23.1 ml/min/100g)[4] but reassuringly over a wider range of flow measurements. The level of disagreement was also not contingent on the actual flow quantity (i.e. there was no systematic bias). As in healthy volunteers, patient HA flow estimates suffer from error propagation from the multi vessel flow measurements used to derive them. However, they are likely less prone to non-physiological results (such as negative HA flow) as HA flows tend to be higher in liver disease. This could also account for the superior caval subtraction HA flow coefficient of variation in patients (66.4%) compared with those from volunteers (123.2%)[4].

Measurement of HVPG though invasive, is essential for diagnosis and management of portal hypertension. Relationships between flow parameters and HVPG help understand the pathophysiology of portal hypertension and can facilitate the development of non-invasive haemodynamic parameters to predict HVPG independently[13]. Consistent with previously published PCMRI studies [9, 14-17], there was no correlation between HVPG and PV flow. While in individuals with normal liver function, a relationship between HVPG and splanchnic flow is likely, in portal hypertension, significant quantities of efferent splanchnic blood bypasses the PV, and is diverted via extra-hepatic shunts into the systemic circulation at sites of porto-systemic anastomoses[3]. As TLBF is primarily composed of PV flow, this could also explain the poor correlation observed between TLBF and HVPG. Conversely, the positive correlations between HVPG and HA flow/fraction suggest that larger scale studies investigating the relationship between caval subtraction HA flow and portal hypertension would be valuable.

Invasive ICG clearance derived total liver blood flow was also used as a reference standard in some of the cohort – measurements in 6 subjects were not valid as the hepatic extraction was too low for interpretation. ICG clearance is dependent not just on blood flow, but also the capacity of hepatocytes to take up ICG dye (and therefore hepatocyte function). The use of caval subtraction PCMRI to yield meaningful measurements in patients with severe liver disease in whom hepatic extraction is poor could also be an important application of the method.

ICG TLBF was consistently lower than caval subtraction TLBF and this was reflected in modest agreement between the methods, with a positive bias for the PCMRI measurement. Impaired hepatocyte uptake of ICG in patients with chronic liver disease would thus expectably lead to lower TLBF estimations than caval subtraction TLBF, which purely measures bulk efferent hepatic blood flow. It should also be noted that although the current reference standard, ICG derived TLBF is imperfect and the modest correlation with the caval subtraction technique could also reflect deficiencies in the standard of reference. The positive relationship between the flow data derived from the two techniques is encouraging, although of course preliminary given the small study sample size and will need to be confirmed in larger cohorts.

Our study has important limitations: this is a proof-of-principle study and approaches to dealing with retrograde/obstructed PV flow, motion artefact and general application to patients with chronic liver disease needs testing on larger numbers of patients where such abnormalities would be relatively frequent. Measurement of PV flow is likely to be inaccurate when there are large extra-hepatic shunts between the PV flow measurement site and the hilum or in the setting of cavernous transformation, where measuring inflow from multiple small collaterals is impractical using PCMRI. Caval subtraction PCMRI is also likely to be less successful in patients with abnormal hepatic venous outflow, such as in the setting of venous outflow obstruction (Budd-Chiari syndrome). Caval blood flow may be influenced variably at different levels by respiration phase, a phenomenon not investigated in this study. Finally, agreement with invasive ICG TLBF was modest – this is likely to reflect inherent differences between the methods, but also underlines the need for new studies in larger patient cohorts to determine if caval subtraction PCMRI can be used a clinically practicable alternative.

In conclusion, it has been demonstrated that caval subtraction PCMRI is feasible in patients with chronic liver disease and portal hypertension and that caval subtraction and direct PCMRI measurements obtained in patients are consistent. The positive correlation between HVPG and caval subtraction HA flow and fraction warrant further investigation and underscores the potential of this method as an investigative tool and biomarker for portal hypertension. Technical advances such as improving the speed of PCMRI acquisitions (thereby shortening required patient breath-holds)[18], and systems to aid with planning PCMRI studies will be important in facilitating translation of this method into routine clinical practice. Caval subtraction is in summary a practical and technically feasible method that can be used to derive consistent and clinically viable measurements of TLBF and HA flow in patients with liver disease.
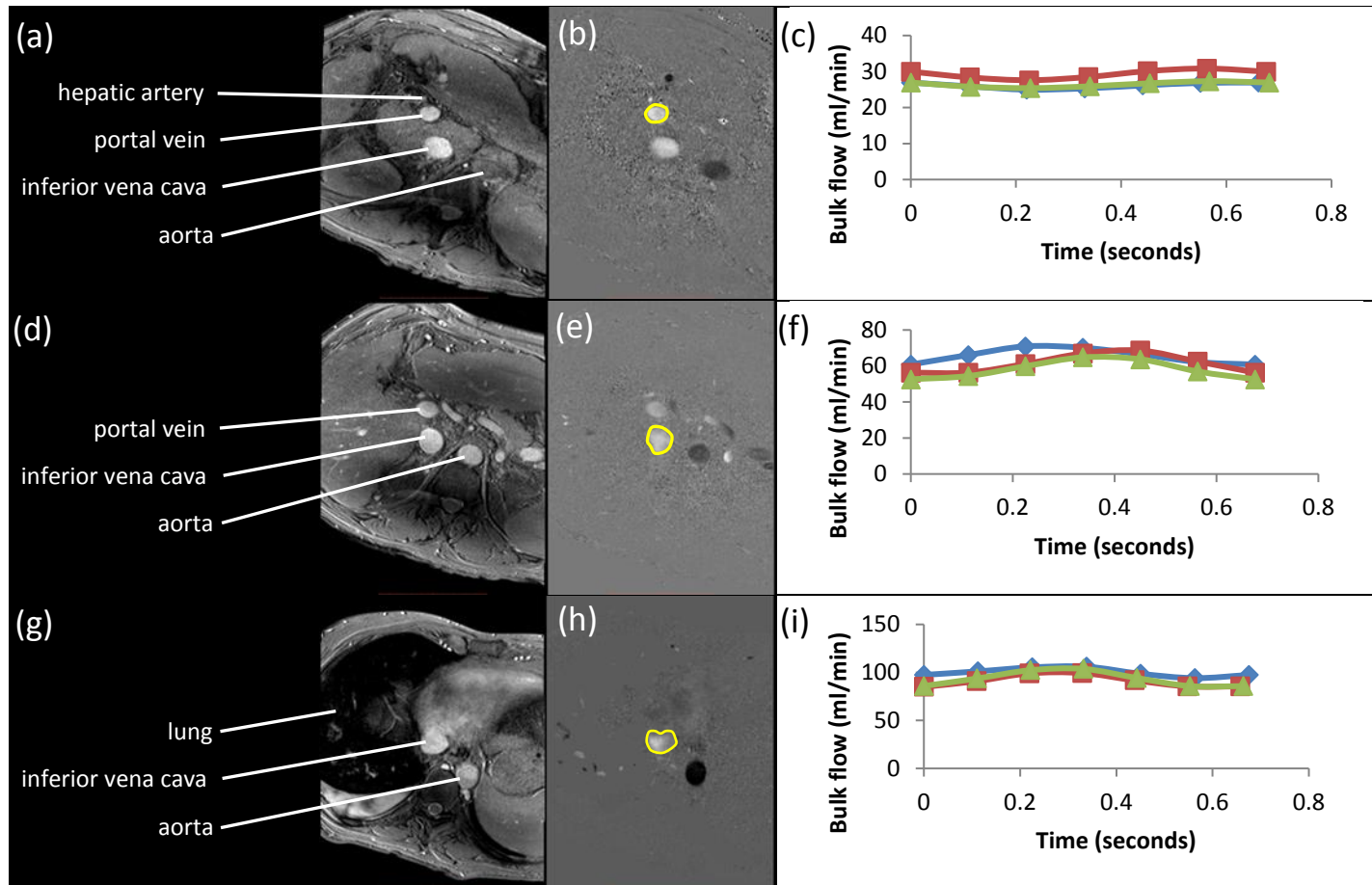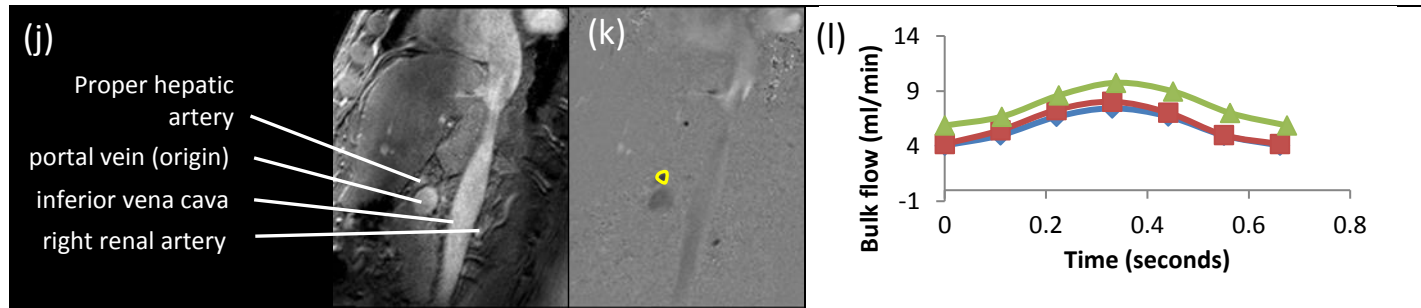
Figures

Figure 1: Patient caval subtraction PCMRI dataset
Data from a patient with chronic liver disease demonstrating magnitude images for a single slice at a single phase of the cardiac cycle planned orthogonally through the (a) portal vein, (d) infra-hepatic IVC, (g) supra-hepatic IVC and (j) proper HA, with the corresponding phase contrast velocity map and vessel segmentation (yellow ROIs) for the (b) portal vein, (e) infra-hepatic IVC, (h) supra-hepatic IVC and (k) common HA. Flow profiles through the cardiac cycle for the (c) PV (overall flow 1634 ml/min), (f) infra-hepatic IVC (overall flow 3750 ml/min), (i) supra-hepatic IVC (overall flow 5722 ml/min) and (l) proper HA. Caval subtraction methods (based on data from all the vessels except the common HA), yielded estimates of TLBF (1972 ml/min), HA flow (338 ml/min) and %HA flow (17.1%). Note comparability with directly measured absolute HA flow (397 ml/min) and %HA flow (19.5%). Multiple flow profiles are shown for each vessel as three measurements were performed in succession.
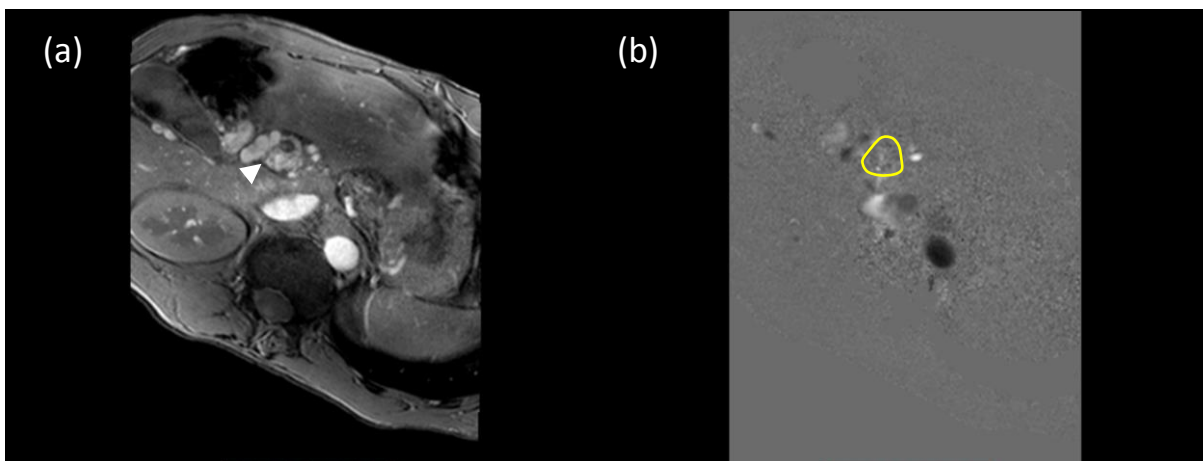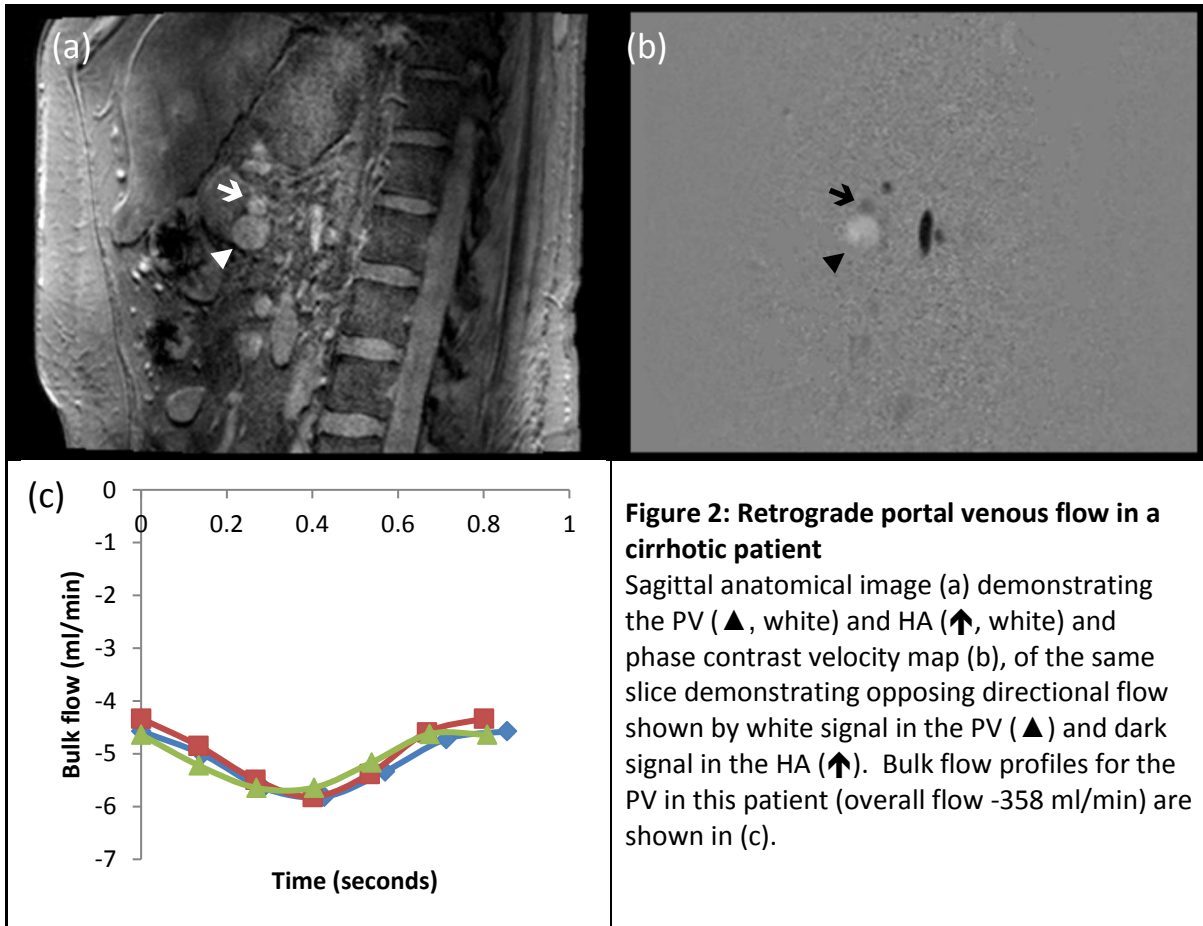
Figure 2: Retrograde portal venous flow in a cirrhotic patient

Sagittal anatomical image (a) demonstrating the PV (▲, white) and HA (↑, white) and phase contrast velocity map (b), of the same slice demonstrating opposing directional flow shown by white signal in the PV (▲) and dark signal in the HA (↑). Bulk flow profiles for the PV in this patient (overall flow -358 ml/min) are shown in (c).

Figure 3: Flow measurement in the context of partially occlusive PV thrombus in a cirrhotic patient

Oblique anatomical image (a) demonstrating the PV (▲, white) with central low signal in keeping with partially occlusive thrombus. The corresponding phase contrast velocity map (b), demonstrates some flow signal around the thrombus which was still quantifiable (yellow ROI). The triplicate measurement average PV flow for this patient was 271 ml/min.
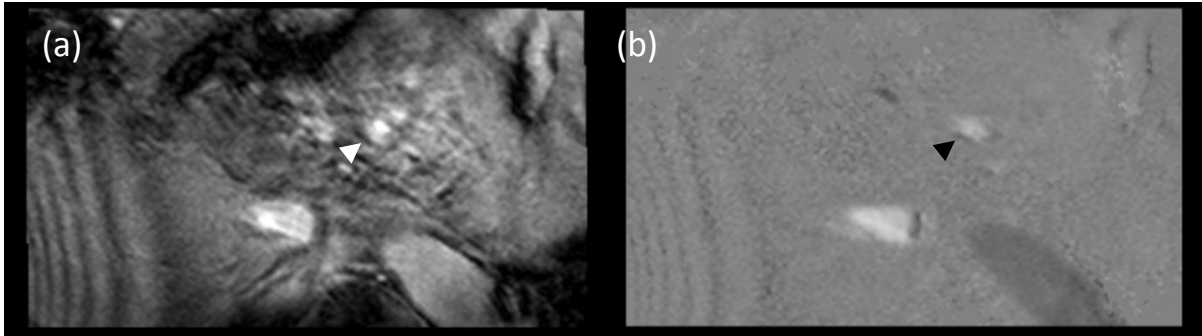
Figure 4: Motion artefact during measurement of portal venous flow in a cirrhotic patient
Oblique anatomical image (a) demonstrating the PV (▲, white) and phase contrast velocity map
(b), of the same slice demonstrating flow signal from the PV (▲). In spite of the corruption by
motion artefact best appreciated in (a), bulk PV flow was still quantifiable. The triplicate
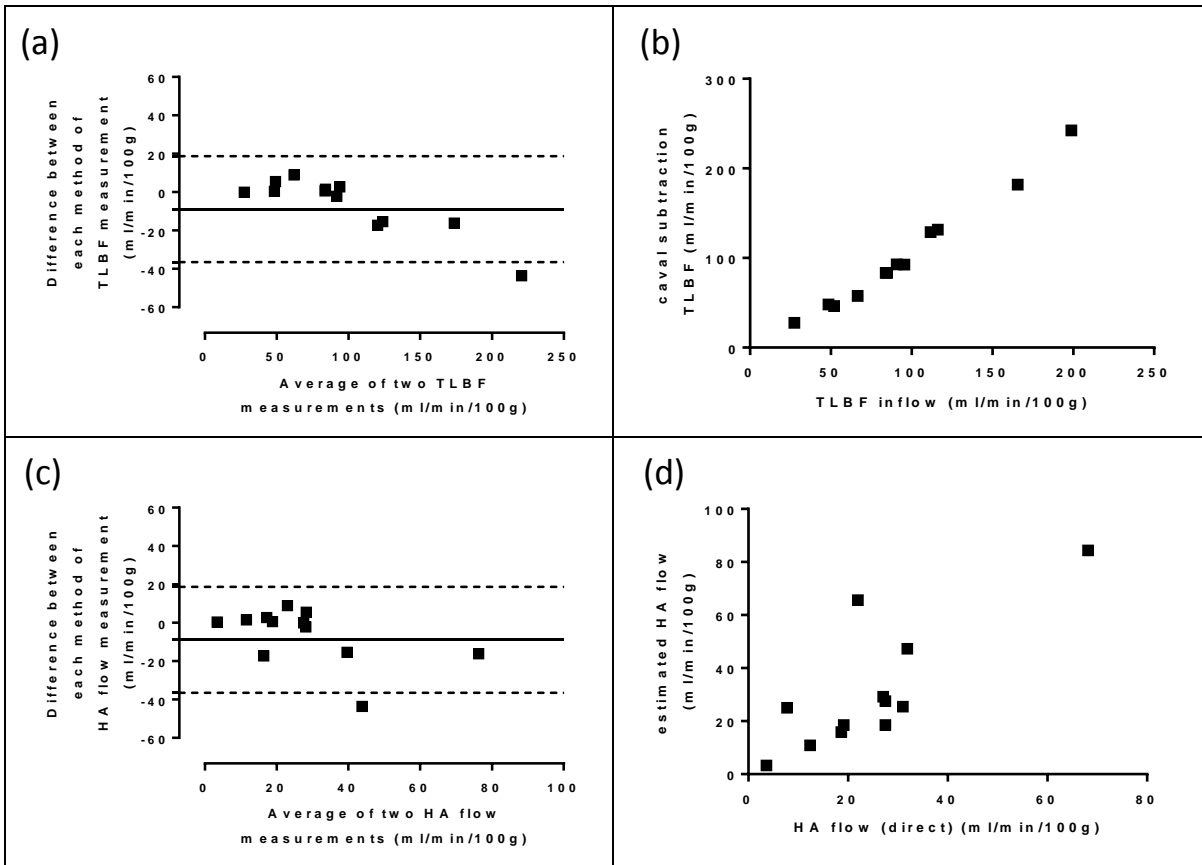measurement average for this patient was 551 ml/min.

Figure 5: Caval subtraction PCMRI consistency
Caval subtraction PCMRI TLBF and HA in patients with liver disease were compared with
contemporaneous inflow PCMRI measurements. Bland-Altman analysis of agreement and
scatterplots between (a, b) caval subtraction estimated TLBF and inflow PCMRI TLBF and (c, d)
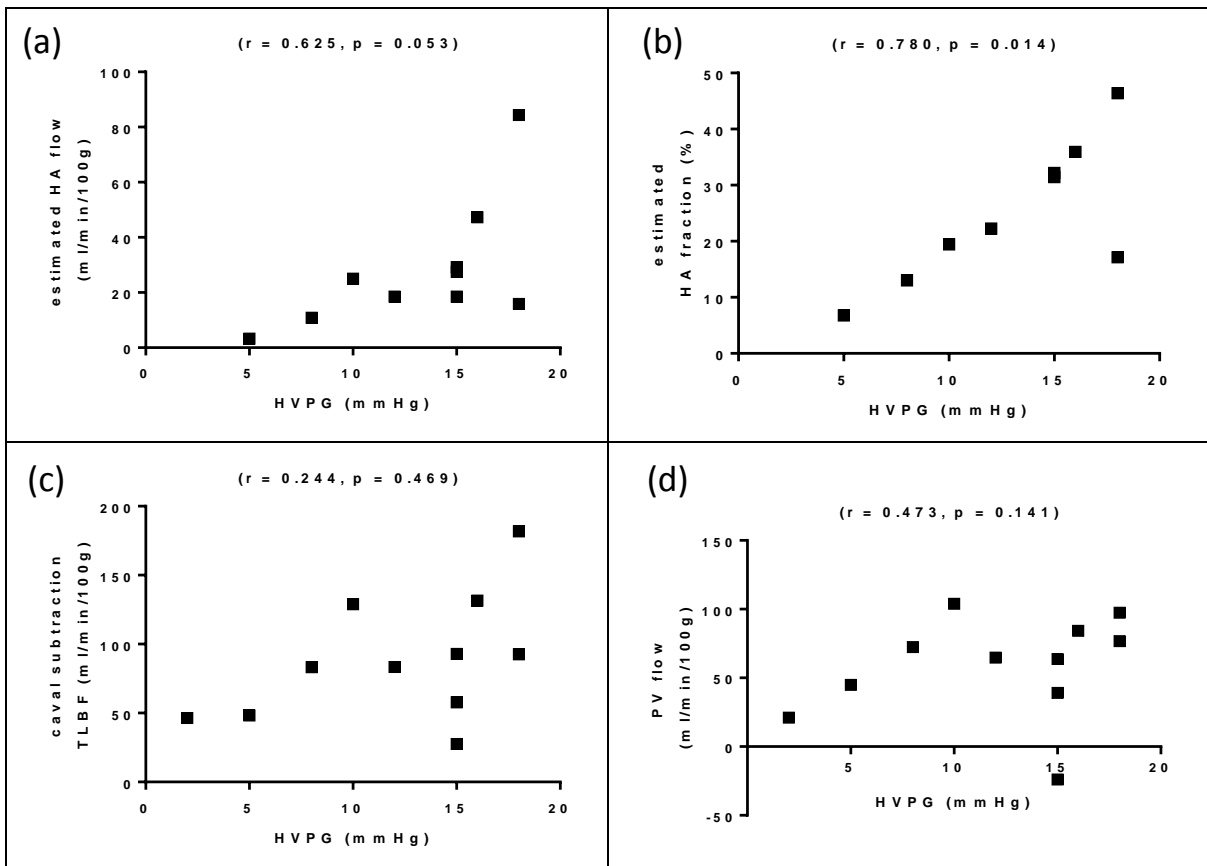caval subtraction estimated HA flow and inflow PCMRI proper HA flow.

Figure 6: Relationship between caval subtraction PCMRI derived HA flow and fraction, and HVPG

Caval subtraction PCMRI HA flow and fraction were compared with invasive HVPG measurements obtained within seven days of the MRI scan. Positive correlations, significant between HA fraction and HVPG were recorded but not for other caval subtraction PCMRI parameters.
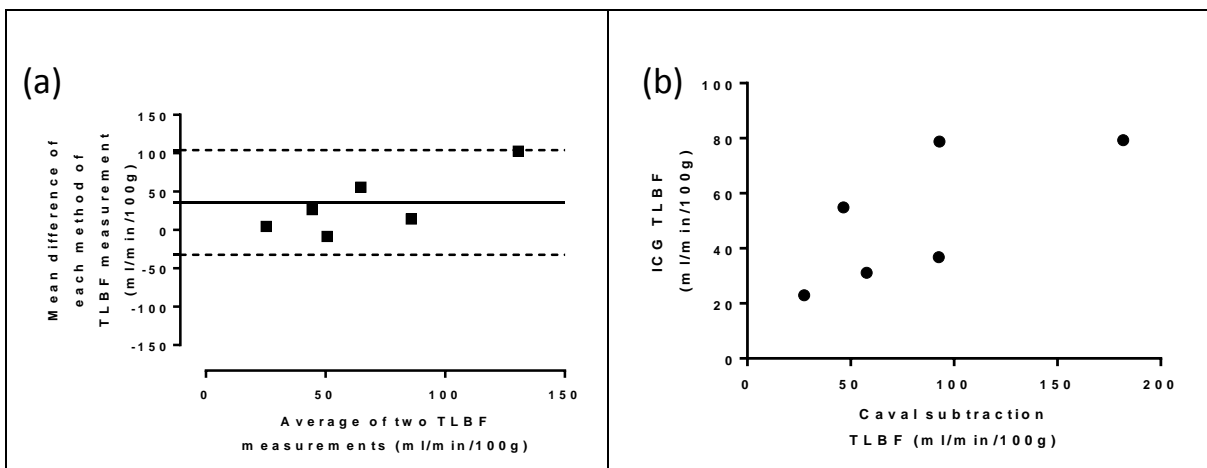

Figure 7: Agreement between ICG clearance and caval subtraction PCMRI total liver blood flow

Validation of caval subtraction TLBF was undertaken using invasive measurements of ICG clearance. Bland-Altman analysis of agreement (a) and scatter plot (b) are shown. Coefficients of variation for both methods were similar.

Tables

Table 1: Sequence parameters

	ANATOMICAL IMAGES (SSFP)	PCMRI (GE+PC)
TR/TE (milliseconds)	2.47/1.23	8.70/5.22
Flip angle (°)	45	10
Matrix size (pixels)	352 x 352	336 x 336
Field-of-view (mm)	350 x 350	271 x 210
Spatial resolution (mm^2)	0.994 x 0.994	0.808 x 0.625
Slice thickness (mm)	5	5
Slice gap (mm)	5.5	-
Cardiac cycle phases	-	7

(GE – gradient echo, GE+PC – gradient echo with additional bipolar phase contrast gradients, SSFP – steady-state free precession)

Table 2: Patient PCMRI measurements

	MEAN±SE	(UPPER LIMIT, LOWER LIMIT)
PV flow (ml/min/100g)	68.5±14.1	(-24.0, 176.8)
Caval subtraction TLBF (ml/min/100g)	101.4±17.8	(27.5, 242.4)
Caval subtraction HA flow (ml/min/100g)	31.0±6.8	(3.3, 84.4)
Caval subtraction HA fraction (%)	27.9±4.3	(6.8, 54.8)

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