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REVIEW

Clinical Applications of 4D Flow MRI in the Portal Venous System

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Evaluation of the hemodynamics in the portal venous system plays an essential role in many hepatic pathologies. Changes in portal flow and vessel morphology are often indicative of disease. Routinely used imaging modalities, such as CT, ultrasound, invasive angiography, and MRI, often focus on either hemodynamics or anatomical imaging. In contrast, 4D flow MRI facilitiates a more comprehensive understanding of pathophysiological mechanisms by simultaneously and noninvasively acquiring time-resolved flow and anatomical information in a 3D imaging volume.

Though promising, 4D flow MRI in the portal venous system is especially challenging due to small vessel calibers, slow flow velocities, and breathing motion. In this review article, we will discuss how to account for these challenges when planning and conducting 4D flow MRI acquisitions in the upper abdomen. We will address patient preparation, sequence acquisition, postprocessing, quality control, and analysis of 4D flow data.

In the second part of this article, we will review potential clinical applications of 4D flow MRI in the portal venous system. The most promising area for clinical utilization is the diagnosis and grading of liver cirrhosis and its complications. Relevant parameters acquired by 4D flow MRI include the detection of reduced or reversed flow in the portal venous system, characterization of portosystemic collaterals, and impaired response to a meal challenge. In patients with cirrhosis, 4D flow MRI has the potential to address the major unmet need of noninvasive detection of gastroesophageal varices at high risk for bleeding. This could replace many unnecessary, purely diagnostic, and invasive esophagogastroduodenoscopy procedures, thereby improving patient compliance with follow-up. Moreover, 4D flow MRI offers unique insights and added value for surgical planning and follow-up of multiple hepatic interventions, including transjugular intrahepatic portosystemic shunts, liver transplantation, and hepatic disease in children. Lastly, we will discuss the path to clinical implementation and remaining challenges.

Keywords: *cirrhosis, 4D flow magnetic resonance imaging, hemodynamics, portal hypertension, portal vein*

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Hemodynamic Characteristics and Clinical Relevance of the Portal Venous System

Flow in the portal vein and associated pathologies

The portal vein delivers approximately 80% of the liver's blood supply by draining blood from the gastrointestinal tract, spleen, pancreas, and gallbladder to the liver for metabolization of nutrients and removal of potentially toxic substances. In contrast, the hepatic artery only contributes about 20% to the total blood flow to the liver. The normal flow waveform in the portal vein is constant, nonpulsatile, and hepatopetal, i.e., unidirectional blood flow toward the liver.[1]

Changes in portal flow are characteristic for a number of pathologies:[1] Decreased flow or even hepatofugal flow (i.e., flow reversal away from the liver) are typical features of end-stage liver disease (cirrhosis). Pulsatile flow can occur occasionally in patients with right-sided congestive heart failure

and tricuspid regurgitation.[1] While the precise mechanism is not fully understood, it is generally presumed that increased hepatic congestion from elevated central venous pressure due to heart failure increases through-liver transmission of cardiac pulsatility, leading to portal vein pulsatility. The absence of flow associated with portal vein thrombosis can occur in the setting of infiltrative malignancies or in cirrhosis due to stagnation of portal blood flow.[2,3] Physiologically, flow in the portal venous system significantly increases after a meal (postprandial hyperemia). An impaired ability to increase the portal venous flow in response to a meal has been described in patients with advanced cirrhosis.[4–7]

There are a variety of surgical and interventional procedures involving the portal vein and altering its hemodynamics. They can be aimed at decreasing the flow to one liver lobe as it is the case for embolization before hemihepatectomy to induce hypertrophy of the remnant liver segment.[8] Others are associated with a flow increase, e.g., in procedures aimed at treating portal hypertension by establishing portosystemic venous shunts that bypass flow around the liver.[9] Portal venous complications after surgery or transplantation or congenital anomalies can include stenosis or aneurysms.[3] Moreover, medical treatment can alter hemodynamics in the portal vein: Nonselective beta-blockers are used to treat portal hypertension by reducing splanchnic blood flow and thus by reducing portal pressure.[10]

Imaging of the portal venous system

In all these examples and pathologies, noninvasive anatomical and functional imaging of the portal venous system is of great interest.[3] In many imaging centers, contrast-enhanced CT angiography is the modality of choice for rapid anatomical evaluation with high resolution.[11,12] However, the associated hemodynamic and functional parameters cannot be assessed with CT, and the use of iodinated contrast agents may be contraindicated in patients with renal dysfunction, which is often present in patients with liver disease.

Ultrasound can provide both anatomic and functional evaluations of the large veins in the portal venous system. However, it is highly operator-dependent and can only measure velocity, but not flow volume. Furthermore, ultrasound is very limited in its ability to provide accurate depiction of variceal pathways often present in patients with advanced portal hypertension.[13,14] Moreover, there is often a limited acoustic window in patients with liver disease.[11]

MRI offers both anatomical and functional assessments of the portal venous system. For example, it plays an important role in the detection of portal vein thrombosis and characterizing its etiology.[2] 2D phase-contrast MRI (2D flow MRI) has been well validated for both velocity and flow volume measurements in the main portal vein[15–17] and showed lower variability and higher reproducibility than ultrasound.[18] Moreover, results correlated better with the degree of cirrhosis and portal hypertension than Doppler ultrasound parameters.[19] However, for comprehensive assessment of liver flow, numerous double-oblique 2D planes are required. This presents a prohibitively burdensome practical challenge as the prescription of such planes is complex, and variable anatomy requires a high degree of operator expertise. Fortunately, these challenges can be overcome by time-resolved 3D phase-contrast MRI with 3D flow encoding, i.e., 4D flow MRI. 4D flow MRI allows the easy prescription of a large imaging volume covering the upper abdomen and the retrospective analysis of flow and morphology within the volume of interest. Velocity measurements made using abdominal 4D flow MRI have been well validated against ultrasound measurements[20–22] and 2D flow MRI.[23,24] Mean velocity and flow volume at the splenomesenteric confluence of volunteers correlated moderately ($r = 0.644$ and $r = 0.515$, respectively) between MRI and ultrasound with an underestimation by MRI.[22] They showed strong repeatability and reproducibility,[25] as well as internal consistency.[26–29] Two acquisitions that were at least five months apart yielded average differences of 5% for mean velocities and of 6% for flow volume for the portal venous system.[25]

4D Flow MRI in the Portal Venous System – Technical Aspects

Imaging of the portal venous system in general and specifically with 4D flow MRI is challenging. Not only is the anatomy complex and highly variable (Fig. 1b and 1c) but also the vessels of interest are relatively small with slow flow, resulting in imprecise measurements. Moreover, it is necessary to cover a large area of the upper abdomen, which may be complicated by artifacts related to breathing motion.

4D flow MRI provides a unique and comprehensive set of information within a single acquisition by establishing volumetric 3D velocity encoding in three directions together with anatomical information, making it a powerful technique for comprehensive noninvasive portal venous imaging. It gathers anatomical and functional flow information that can be quantified and visualized (Fig. 2). All these aspects can help understand and diagnose portal venous pathologies.[30,31]

Patient preparation

Prior to 4D flow MRI, the subject should be instructed to fast (typically 3–5 hours[26,27,32]) since there is a significant increase in flow volume and velocity after a meal, which can introduce considerable variability into quantitative results,[27,28] and thus may impede comparisons to reference values and long-term follow-up studies.

To examine the hemodynamic response to a meal, which can be reduced in advanced cirrhosis,[4–7] the postprandial MRI examination should be scheduled during the maximum hemodynamic response to a controlled meal stimulus. Depending on energy content and composition of the meal, time of maximum blood flow increase in the superior mesenteric artery measured by ultrasound has been reported between 15 and 60 mins with an increase in blood flow

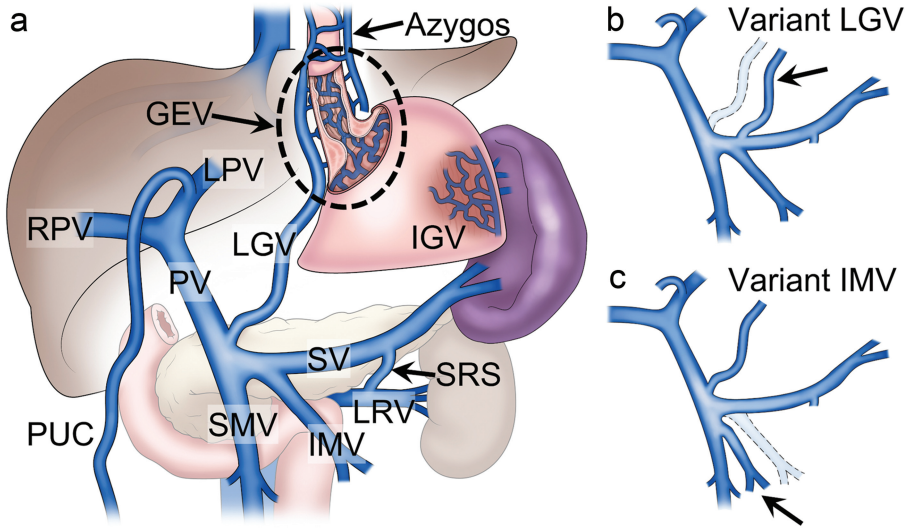

Fig. 1 Anatomical schematics of the portal venous circulation. (**a**) illustrates multiple forms of porto-systemic collaterals in portal hypertension. Shown are GEV fed by reversed flow in the LGV, PUC from the LPV, IGV from the splenic circulation, and SRS with flow from the SV into the LRV. The portal venous circulation is highly variable. Common variants include (**b**) the LGV confluent with the SV instead of the PV and (**c**) the IMV confluent with the SMV instead of the SV. GEV, gastroesophageal varices; IGV, isolated gastric varices; IMV, inferior mesenteric vein; LGV, left gastric vein; LPV, left portal vein; LRV, left renal vein; PUC, paraumbilical collaterals; PV, portal vein; RPV, right portal vein; SMV, superior mesenteric vein; SRS, spontaneous splenorenal shunt; SV, splenic vein.

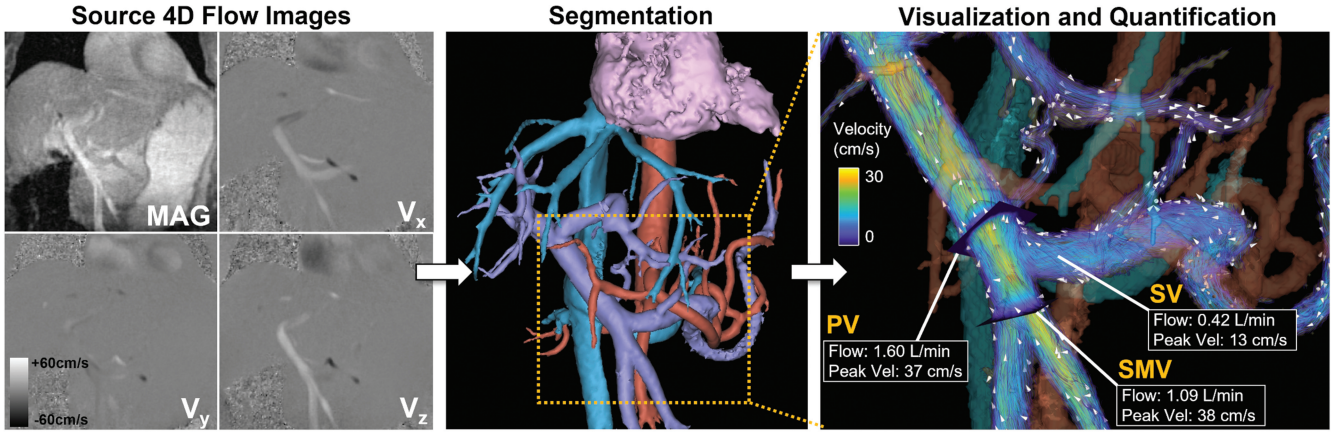

Fig. 2 Visualization and quantification of abdominal hemodynamics using 4D flow MRI: (Left) Time-averaged velocity images (Vx, Vy, and Vz) and MAG images from a 4D flow MRI acquisition in a healthy volunteer shown for a single coronal slice. These source images are used to semi-automatically create a vessel segmentation of venous (blue), arterial (red), and portal (purple) vasculature (middle). Within the boundaries given by the segmentation, velocity information can be portrayed via color-coded velocity streamlines and quantified. White arrows depict the direction of blood flow in portal vasculature. Volumetric flow rates of the SMV and the SV add up (0.42 mL/min + 1.09 mL/min = 1.51 mL/min) to the flow volume of the PV (1.6 mL/min) resulting in an error of 5.6% and confirming good data quality. MAG, magnitude; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein.

volume between 60% and 250% in healthy subjects.[33] Fat-rich meals typically induce a more intense and longer increase in blood flow and velocity compared with carbohydrate meals.[33,34] Hyperemia after fat-rich meals can remain at 79% above baseline 180 mins after the meal, whereas blood flow typically returns to baseline values 150 mins after a carbohydrate-rich meal.[34] In our experience, a delay of 20 mins after ingestion of a standardized meal (e.g., a readily available nutrition shake) is sufficient to induce a strong hyperemic response.[27,28] Other authors prefer delays of up to 60 mins.[35]

Data acquisition

4D flow MRI can be acquired at 1.5T or 3T. Most MRI vendors offer 4D flow MRI as a product sequence. Several sequences using either the traditional Cartesian[21,22,24] or non-Cartesian spatial encoding techniques have been validated for abdominal flow measurements. Non-Cartesian

Table 1 Typical acquisition parameters for Cartesian, radial, and spiral spatial encoding techniques found in the literature

	Cartesian	Radial	Spiral
References	21, 22, 24, 29, 47	26-28, 32, 44, 45	36, 37
FOV (cm^3)	22 × 32 × 8.6 *[21]	32 × 32 × 22–32	40 × 40 × 6
Spatial resolution (mm^3)	1.3–2.8 × 1.7–3.2 × 1.3–4.0 (not specified if acquired or interpolated)	1.25–1.4 isotropic (acquired)	2.5 × 2.5 × 5 (acquired); (1.3 × 1.3 × 2.5, interpolated)
Mean number of time frames in cardiac cycle	9–20	14	8–15**
Temporal resolution (ms)	29–64	43–71 **	66–71
Mean scan duration (min)	7–23	10–12	0.3–0.4 (1 breath hold)

*FOV mentioned only in 1 study. ** calculated for 60-100 bpm

spatial encoding techniques, such as radial[20,26] or spiral[36,37] undersampling, accelerate data acquisition, which can be used to increase the FOV and improve spatial or temporal resolution. Moreover, they are more robust to motion.[38,39]

Acquisition time is a critical factor for 4D flow sequences, which tend to be long due to the encodes needed to provide cine data over a large imaging volume and 3D velocity encoding. Therefore, novel acceleration methods, such as radial undersampling[40], k-t acceleration,[41,42] and compressed sensing,[36] have been introduced instead of the traditional parallel imaging. Acceleration factors typically start at 2 and can have clinically feasible acquisition times for the portal venous system range in the order of 10–15 mins, which can be further accelerated by advanced acceleration methods. An overview of typical acquisition parameters and acquisitions times can be found in Table 1.

The preferred orientation of the imaging slab depends on the specific task. Axial slabs are well suited for non-Cartesian acquisitions because the slab excitation effectively limits the spatial extend of the imaging volume, minimizes artifact from signal outside the imaging volume, and takes advantage of signal gains from the inflow effect. For Cartesian encoding, coronal acquisitions may be advantageous with superior robustness to respiratory motion and larger volumetric coverage of the abdomen and pelvis. Axial oblique[25,43] or paracoronal[44] orientations angled along the portal vein also allow the coverage of the portal vein in a smaller FOV to minimize the acquisition time for Cartesian 4D flow acquisitions.

To reduce motion artifacts, respiratory gating should be applied. Using an adaptive window, the acceptance rate is typically set to 50% during expiration.[27,28,32,45,46] Using a gating navigator at the liver–lung interface, an acceptance window of 6–8 mm[21,24,47] typically corresponds to 50%–60% acceptance. If needed, the navigator can be placed on the spleen–lung interface to avoid interference with the main ROI. Recently, a free-breathing self-navigated, Cartesian 4D flow sequence[29] has been proposed for hepatic flow analysis that uses scan time more efficiently.

To account for the pulsatile blood flow during the cardiac cycle, cardiac synchronization must be used, typically accomplished with electrocardiogram (ECG) triggering. Retrospective cardiac gating is superior to prospective gating as it covers the entire cardiac cycle.[48] Studies using prospective gating need to adjust the quantitative flow measurements to represent the full cardiac cycle based on the percent captured and the heart rate[49] – this is more important when measuring nonpulsatile flow (e.g., in the portal vein) compared with pulsatile flow (e.g., in large arteries), where late diastole contributes very little to the flow volume.

While high temporal resolution is required to resolve pulsatile flow with large velocity changes during the cardiac cycle, e.g., in the aorta, high temporal resolution is not necessary in the portal vein, which has largely steady flow. Landgraf et al.[46] proposed to use time-averaged reconstructions for the portal venous system to save imaging time. They showed that time-averaged reconstructions outperform time-resolved reconstructions regarding flow quantification, average streamline length, and visualization quality. However, to date, most studies use time-resolved reconstructions, allowing not only the assessment of flow volumes and mean velocity but also the assessment of dynamic parameters such as peak velocities.

4D flow can be acquired with or without an exogeneous contrast agent used in MR angiography, such as gadolinium chelates or iron nanoparticles. The use of a contrast agent provides better image quality and velocity measurements through improved SNR and noise reduction in the velocity data.[50] Many sites acquire the 4D flow sequence after contrast administration for a clinical contrast-enhanced angiography. The flip angle should be increased for contrast-enhanced acquisitions compared to exams without contrast in order to maximize SNR and optimize T1 weighting.[48]

To acquire flow velocities accurately, an optimal choice of the velocity encoding setting (venc) is of vital importance. The venc is set during scan prescription and adjusts the velocity encoding gradients such that the maximum velocity

that can be measured with phase-contrast MRI without velocity aliasing. If it is chosen too low, the velocities higher than the venc cannot be encoded properly, and aliasing occurs. If the venc is chosen too high, the velocity-to-noise ratio (VNR) decreases. Ideally, the venc should be chosen approximately 10% above the peak velocity.[48] 50–60 cm/s is a typical venc used for portal venous imaging.[21,24,32,46,49] However, this choice of venc may be too low for the arterial system[22,27,28] or postinterventional imaging in patients after transjugular intrahepatic portosystemic shunt (TIPS)[32], where a venc of 100 cm/s (80–120 cm/s) may be helpful. In contrast to other studies, one group[47] stated that a very high venc of 225 cm/s helped them to better evaluate TIPS performance, although further evaluation of this venc recommendation is needed. Since even a venc of 100 cm/s inevitably compromises the quality of portal venous flow measurements, contrast administration is recommended to improve SNR performance when attempting to evaluate both portal venous and hepatic arterial flows in a single acquisition.

Postprocessing and quality assurance

Postprocessing of 4D flow MRI should include correction for concomitant gradient field effects (Maxwell terms) and phase background effects due to eddy currents.[48] In order to analyze flow information in vessels that may be corrupted by velocity aliasing (phase wraps), phase-unwrapping algorithms should be used. Simple phase wraps can be detected visually in the areas of high-flow velocities where the flow direction of some voxels apparently changes without any physiological explanation.[51]

For quality assurance of 4D flow data, visual inspection of not only the magnitude data but also the velocity images in all three directions is recommended to evaluate for artifacts, such as wrap-around artifacts and velocity aliasing. Moreover, conservation of mass[25–29,45] analysis in the portal venous system is an important component of quality assurance. For example, flow volume of superior mesenteric vein and splenic vein should add up to match that of the proximal portal vein (Fig. 2). Similarly, the distal portal vein should distribute its flow volume into its branching veins. Often, there will remain a small error since many small veins contribute to and originate from the portal vein, or from inherent imprecision in flow measurements. Typical mean errors of the conservation of mass analysis for the portal vein for radial acquisitions range from 5% to 7% (standard deviation [SD], between 3% and 5%) with excellent correlation (r^2 = 0.98-0.99 and R^2 = 0.89).[26,27,46] For Cartesian acquisitions, which frequently have a lower spatial resolution, reported errors range between 3% and 9% (SD, 5%–16%).[25,49]

Analysis

There are several software tools available for analyzing 4D flow MRI data, ranging from in-house developed solutions to regulatory approved software packages for purchase. However, most focus on thoracic and arterial analyses and offer no dedicated workflow for the portal venous circulation. For this article, image preprocessing and background phase correction were performed using a customized MATLAB toolbox (Mathworks, Natick, MA, USA). Time-averaged complex difference datasets were exported to Mimics (Materialize, Leuven, Belgium) for semi-automatic vessel segmentation. Segmented angiograms and time-resolved velocity data were then exported to Ensight (ANSYS, Canonsburg, PA, USA) for blood flow visualization and cut-plane flow quantification. Depending on the complexity of the case and the number of measurement planes, an individual analysis typically takes between 20 and 50 mins.

For quantitative analysis in the portal venous system, the vessel contour should be segmented at the position of interest. There exist two main approaches that will depend on the software used. First, a 2D ROI can be placed to delineate the cross section of a vessel. Alternatively, a 3D mask of the vasculature of interest can be created. Cut planes are then placed with no need to delineate the vessel again. We recommend using the time-averaged complex difference angiogram or a contrast-enhanced angiogram for delineating 3D contours in the portal venous system. In our experience, movement of the portal vein during the cardiac cycle is negligible and can be ignored. Moreover, one does not need to account for pulsatility. This allows the delineation of vessels in the time-averaged data, which have higher SNR than the time-resolved dataset.

Most relevant quantitative parameters in the assessment of portal venous flow are the direction (hepatofugal or hepatopetal), maximum and mean velocity (m/s), as well as flow. There are two different flow measurements: “Instantaneous flow” (mL/s) quantifies the flow in a ROI, e.g., a vessel cross section, at a specific time point. If the vessel cross section is contoured not only at one time point but throughout the cardiac cycle, “flow volume” can be calculated by integrating the instantaneous flow measurements over time. Flow volume can be expressed as L/min or L/cardiac cycle – since portal venous flow is not pulsatile but constant, most often L/min is given. Published quantitative results for healthy subjects and patients with liver cirrhosis are summarized in Table 2. Vessel area can also be assessed and can be used to detect dilatation of the portal vein in portal hypertension, or in response to a meal.[52] Advanced quantitative flow parameters, such as wall shear stress or energy loss, have not been tested in the portal venous system, and the clinical relevance of such parameters is not clear. Secondary quantitative flow parameters are often vulnerable to acquisition parameters such as spatial resolution and to low SNR. This can lead to poor reproducibility due to a large impact from anticipated small-scale changes in the venous system, particularly in the setting of steady flow.

Qualitative analysis of portal venous flow patterns is not well established. Typically, qualitative description of flow patterns includes helices and vortices. A helix is defined as a spiral, antegrade movement of blood in main flow direction. In contrast, a vortex describes recirculating blood deviating

Table 2 Reference values for the portal vein for healthy subjects and patients with liver cirrhosis

Publication	Subjects (number)	Subjects (age, y)	Fasting prior to MR exam	Maximum velocity (m/sec)	Mean velocity (m/sec)	Flow volume (L/min)
Healthy volunteers						
Brunsing et al. 2021[29]	21 (14♀)	50.4 (26–77)	Not specified	–	–	0.97 ± 0.32
Roberts et al. 2021[28]	20 (8♀)	44.4 (19–73)	5 hrs fasting	–	–	1.1 ± 0.35 Response to meal challenge: + 57 ± 48%
Roldán-Alzate et al. 2015[27]	6 (2♀)	32±10 (20–45)	5 hrs fasting	–	–	1.13 ± 0.46 Response to meal challenge: + 142%
Landgraf et al. 2014[46]	15	–	Not specified	–	–	0.93 ± 0.27
Roldán-Alzate et al. 2013[26]	7 (3♀)	32.2 ± 10.1	3 hrs fasting	–	–	1.1 ± 0.4 (0.9-2.1)
Stankovic et al. 2013[22]	10 (4♀)	56 ± 6.1	Not specified	0.21 ± 0.04	0.09 ± 0.03	0.72 ± 0.14
Stankovic et al. 2012[21]	21 (14♀)	27.5 ± 3.3 (22–37)	Not specified	0.26 ± 0.09	0.11 ± 0.04	0.67 ± 0.54
	20 (10♀)	58.5 ± 5.9 (50-69)	Not specified	0.22 ± 0.04	0.10 ± 0.02	0.64 ± 0.19
Stankovic et al. 2010[24]	18 (10♀)	28.6 ± 3.1	Not specified	0.27 ± 0.07	0.12 ± 0.03	–
Patients with liver cirrhosis with and without portal hypertension (different stages of cirrhosis, no TIPS)						
Brunsing et al. 2021[29]	19 (8♀)	57.3 (20–79)	Not specified	–	–	0.84 ± 0.28
Motosugi et al. 2019[45]	23 (9♀)	52.3 (25–75)	5 hrs fasting	-	-	High risk varices: 0.82 (0.05–1.70) Low risk varices: 0.78 (0.65–1.06) No varices: 0.94 (0.52–1.35)
Bannas et al. 2016[32]	7 (1♀)	52 ± 10	3 hrs fasting	0.40 ± 0.16	–	0.76 ± 0.62
Roldán-Alzate et al. 2015[27]	12 (5♀)	54 ± 12 (26–73)	5 hrs fasting	–	–	1.04 ± 0.37 Response to meal challenge: + 22%
Stankovic et al. 2015[74]	11 (2♀)	62.5 ± 9.0	Not specified	0.19 ± 0.05	–	0.56 ± 0.37
Landgraf et al. 2014[46]	29	-	Not specified	–	–	1.34 ± 0.61
Roldán-Alzate et al. 2013[26]	17 (4♀)	58.6 ± 6.7	3 hrs fasting	–	–	1.09 ± 0.8 (–0.4 to 3.2)
Stankovic et al. 2013[22]	5 (1♀)	66.4 ± 7.0	Not specified	0.17 ± 0.06	0.07 ± 0.02	0.45 ± 0.28
Stankovic et al. 2012[21]	20 (8♀)	57.7 ± 11.6 (27–73)	Not specified	0.20 ± 0.06	0.08 ± 0.03	0.79 ± 0.32
Stankovic et al. 2010[24]	5 (3♀)	62.5 ± 13.7	Not specified	0.17 ± 0.06	0.09 ± 0.03	
Patients with liver cirrhosis and portosystemic shunt (TIPS)						
Brunsing et al. 2021[29] *	7 (5♀)	59.9 (33–76)	Not specified	–	–	1.51 ± 0.81
Bannas et al. 2016[32]	7 (1♀)	52 ± 10	3hrs fasting	0.60 ± 0.18	-	1.64 ± 0.98
Stankovic et al. 2015[74]	11 (2♀)	62.5 ± 9.0	Not specified	0.28 ± 0.07	–	1.83 ± 0.97

Values are given as mean ± standard deviation and (range), where available. *Included patients with portosystemic shunt (either TIPS or large collaterals). Measurement planes were placed in the proximal portal vein near the confluence or in the middle segment of the portal vein. ♀, female; hrs, hours; SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt; y, years of age.

from main flow direction and therefore is characterized by areas with antegrade as well as retrograde flow.[53–55] Stankovic et al.[24] found homogenous filling of the portal vein with laminar flow and clearly separated flow channels from splenic vein and superior mesenteric vein contributions in 17 volunteers in contrast to 1 volunteer who presented with helical mixing of both inflow streams. With increasing experience over the years, it is now known that a small helical flow structure often develops distal to the splenic–mesenteric confluence in the portal vein. In fact, Rutkowski et al.[56] showed, using computational fluid dynamic (CFD) simulations and phantom studies, that vessel geometry and a meal challenge influence both the flow distribution and helical flow development.

More pronounced helical or even vortical flow was described in children after surgery (e.g., after correction of a portal shunt) or with portal hypertension.[43] Abnormal flow characteristics in patients with liver cirrhosis include vortical flow in the splenic–mesenteric confluence, retrograde flow in any veins of the portal venous system, and detection of flow in portosystemic collaterals.[21,24,45]

The time-averaged complex difference angiogram allows for anatomical assessment of the portal venous vasculature, mainly detection of anatomical variants and varices. However, this requires excellent image quality and high spatial resolution.

Clinical Applications of 4D Flow MRI in the Portal Venous System

Liver cirrhosis and portal hypertension: Diagnosis and risk stratification

Cirrhosis is characterized by advanced liver fibrosis, liver failure, and portal hypertension. Its incidence is expected to increase dramatically due to the rapidly rising prevalence of nonalcoholic fatty liver disease (NAFLD),[57] which is emerging as a leading cause of cirrhosis,[58] Sinusoidal fibrosis results in increased liver stiffness, which elevates the resistance to blood flow and therefore portal blood pressure. Decreased flow to the liver leads to circulating endogenous vasodilators that further exacerbate portal pressure by paradoxically increasing splanchnic blood flow.

Direct pressure measurements in the portal vein are highly invasive and no longer conducted.[59] An indirect method to assess portal pressure is the invasive measurement of the hepatic venous pressure gradient (HVPG). The HVPG is the pressure difference between the portal vein and the inferior vena cava. It is invasively determined by measuring pressure in the hepatic veins with a balloon catheter with the balloon inflated and thus occluding the hepatic veins (wedge pressure) and with the deflated balloon in the patent hepatic veins, respectively.[60]

Portal hypertension is characterized by an elevated HVPG over 5 mmHg.[61] When the HVPG exceeds 10 mmHg, patients can develop portosystemic collaterals that shunt blood away from the liver[62] (Fig. 1a). The most clinically relevant collaterals are gastroesophageal varices (GEV) that are fragile and can rupture if the HVPG exceeds 12 mmHg.[62] Rupture can lead to catastrophic exsanguination being the direct cause of death in about 30% of cirrhotic patients and frequently the precipitating factor leading to liver failure and death.[63] Early detection of GEV at risk for bleeding is of paramount importance to initiate primary prophylaxis,[61] which reduces mortality by 50%–70%.[64–66] Currently, the American Society for the Study of Liver Diseases (AASLD) and Baveno guidelines recommend initial esophagogastroduodenoscopy (EGD) screening in patients with newly diagnosed cirrhosis.[61,67,68] Depending on the severity of cirrhosis, indefinite surveillance for GEV with EGD is recommended every 1–3 years.[61,67,68] However, EGD is invasive, expensive, and requires sedation, and compliance with surveillance is very poor. For these reasons, the AASLD has identified the development of noninvasive markers that predict the presence of high-risk varices as a major unmet need in the management of cirrhosis.[68]

Early studies have shown very promising results, indicating that 4D flow MRI may be a suitable approach for the noninvasive identification of high-risk GEV with a single MRI examination. Previous studies[22,26,69] have confirmed feasibility and excellent internal consistency of flow measurements in patients with liver cirrhosis. Under normal conditions, the left gastric vein drains blood from the stomach into the portal vein. A flow reversal with hepatofugal flow develops in the left gastric vein in the presence of increased portal venous pressure. It becomes the main contributor to GEV by shunting blood away from the liver. GEV drain into the systemic circulation, mainly the azygos vein. To detect high-risk varices, Motosugi et al.[45] focused on these two characteristic hemodynamic changes: flow reversal in the left gastric vein and increased flow in the azygos vein. Since the left gastric vein was often too small to be directly analyzed by 4D flow MRI, they developed an indirect metric of hepatofugal blood flow. They calculated the fractional flow change in the portal vein by measuring flow volume in the portal vein in the liver hilum (PV_{dist}) compared to the portal vein at the mesosplenic confluence (PV_{prox}). In order to capture the left gastric vein between both measurement planes, it is recommended to measure flow volumes from superior mesenteric vein (SMV) and splenic vein (SV) as a proxy for the most proximal part of the portal vein (Fig. 3):

$$\textit{Fractional flow change in portal vein} = \frac{PV_{dist} - PV_{prox}}{PV_{prox}} = \frac{PV_{dist} - (SMV + SV)}{SMV + SV} \quad [1]$$

If the fractional flow change in the portal vein was less than 0, i.e., less blood arrived in the portal vein in the liver hilum than initially flowed into the portal vein, the presence of hepatofugal flow in tributary vessels to the portal vein is indirectly demonstrated. Importantly, a negative fractional

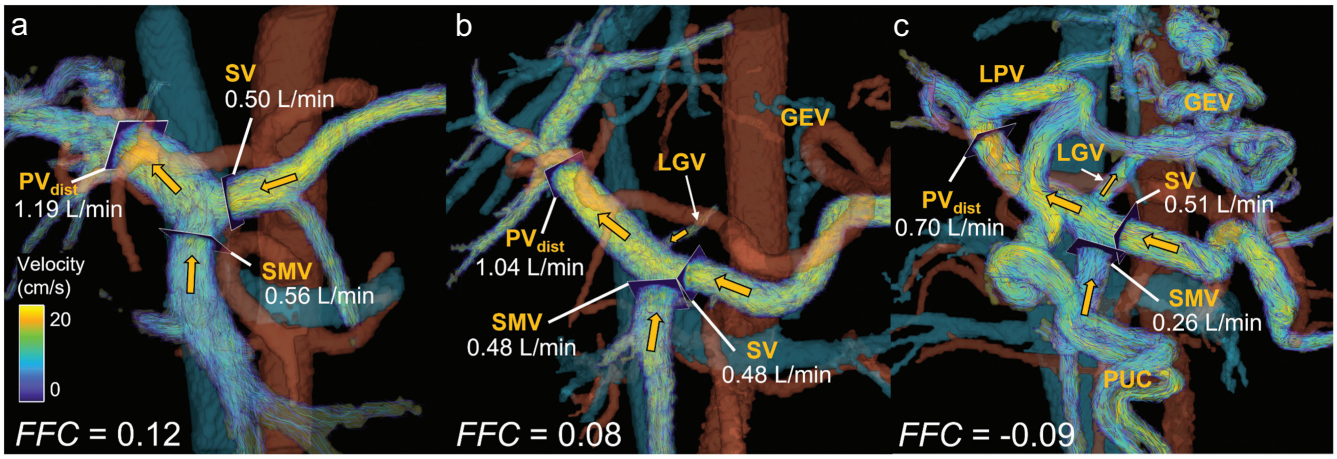

Fig. 3 Risk assessment of GEV. Velocity color-coded streamlines of portal vasculature and semi-transparent segmentation masks of arteries (red) and veins (blue) in the upper abdomen. Direction of flow is demarcated by orange arrows. (**a**) Healthy 46-year-old woman with no varices and hepatopetal flow in the SMV, SV, and portal vein. A FFC above 0 confirms the absence of portosystemic shunts between the measurement planes in SV, SMV and PV_{dist}. (**b**) A 64-year-old man with varices at an endoscopically assessed low risk of bleeding. Note the hepatopetal flow in the LGV. (**c**) A 54-year-old man with high-risk varices. Hepatofugal flow is observed in the LGV and in gastroesophageal varices. FFC is below 0, reflecting increased shunting. This patient also has PUC supplied by the LPV. FFC, fractional flow change; GEV, gastroesophageal varices; LGV, left gastric vein; LPV, left portal vein; PUC, paraumbilical collaterals; PV_{dist}, distal portal vein; SMV, superior mesenteric vein; SV, splenic vein.

flow change in the portal vein was highly predictive of high-risk varices as seen on endoscopy. Using this new noninvasive quantitative biomarker, the authors identified at-risk varices with 4D flow MRI with high sensitivity (100%) and specificity (94%) in 7 out of 23 patients with cirrhosis. Similarly, azygos flow greater than 0.1 L/min was an independent indicator for high-risk varices with high sensitivity (100%), but lower specificity (62%).

Importantly, the calculation of the fractional flow change in the portal vein as proposed in this study did not account for anatomical variants, e.g., when the left gastric vein drains into the splenic vein (Fig. 1b) and will therefore need to be adapted to the individual's anatomy. These promising results need to be confirmed in a larger patient cohort, along with correction methods for anatomical variants. If confirmed, 4D flow MRI could reduce unnecessary EGD procedures and increase compliance of GEV surveillance through access to a noninvasive method.

Roldán-Alzate et al.[27] proposed another promising approach to diagnose and grade liver cirrhosis. They analyzed portal venous hemodynamics after 5 hours of fasting, as well as 20 mins after a standardized meal challenge. They did not observe significant differences in portal flow between healthy volunteers and patients with cirrhosis in the fasting state. However, they found a significant increase in azygos vein blood flow in patients with cirrhosis after a meal, indicating increased portosystemic shunting volume. After a meal challenge, flow volumes in portal vein and superior mesenteric vein increased to a lesser extent in patients as compared with volunteers (Fig. 4). The same was true for the fraction of portal vein flow volume (PV) compared to the total blood supply of the liver (flow volume in portal vein and hepatic artery, PV + HA):

$$Portal\ vein\ fraction = \frac{PV}{PV + HA} \quad [2]$$

Patients with liver cirrhosis showed a lower increase in portal vein fraction after the meal challenge compared with healthy volunteers. However, these differences between patients and volunteers were not statistically significant with patients presenting higher variability in their results – presumably due to a heterogenous patient cohort with mostly mild cirrhosis stage. This underlines the importance of accounting for different grades of cirrhosis when assessing the value of 4D flow MRI. Similar to a stress test in cardiac MRI, the combination of a resting state examination and a meal challenge has the potential to detect early stages of portal hypertension that might not have been detected with the analysis of fasting hemodynamics alone.

In multiple studies, the authors reported flow reversal in the portal vein, superior mesenteric vein, or splenic vein, as well as direct visualization and measurement of collateral flow, e.g., in the umbilical vein, in a small subset of examined patients with cirrhosis[21,24,26,27,30,45] (Fig. 5). Both observations are highly specific to portal hypertension. However, given the relatively low percentage of cirrhotic patients that presented with these findings, they do not seem very sensitive, especially in less severe cases.

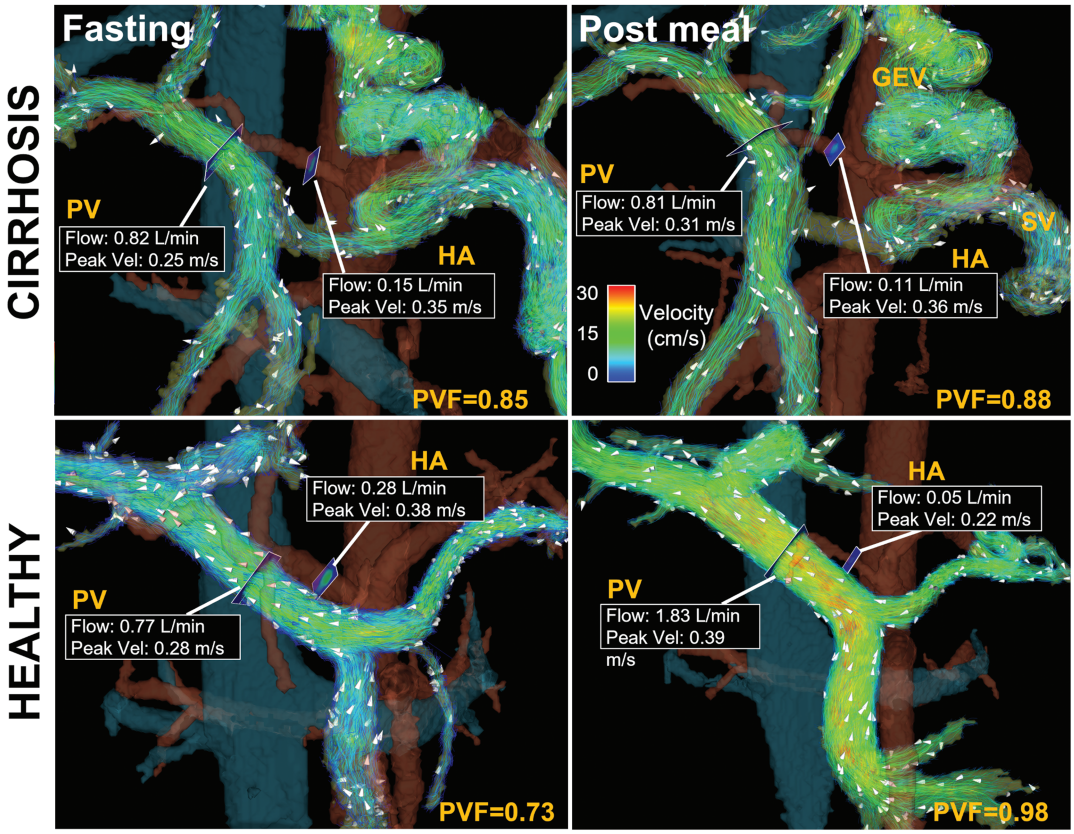

Fig. 4 Velocity streamlines in the portal venous system before and after a meal challenge in a cirrhotic patient with large GEV and a healthy subject. Note the absence of relevant flow changes in the PV and the HA of the cirrhotic patient after the meal challenge. This is reflected by the relatively constant PVF. In contrast, there is a relevant increase in flow and velocity in the portal vein after the meal and a reduction in these parameters in the hepatic artery. This results in a substantial increase in the PVF after the meal, which is characteristic for healthy subjects. GEV, gastroesophageal varices; HA, hepatic artery; PV, portal vein; PVF, portal vein fraction

A recent case report by Hyodo et al.[44] presents two patients with liver cirrhosis having large portosystemic collaterals, which shunt the blood from the superior mesenteric vein directly into the systemic circulation and lead to hepatic encephalopathy. With 4D flow MRI, they were able to identify the varices that were then treated interventionally, highlighting the clinical relevance of this diagnostic method.

Surgical planning and follow-up: TIPS

Patients with portal hypertension that cannot be controlled by medical therapy can be treated by the creation of portosystemic venous shunts that divert flow from the portal system directly into the systemic circulation and bypassing the liver. This intervention reduces the HVPG and thus ascites, the accumulation of fluid in the peritoneal cavity, and risk for variceal hemorrhage.[70,71] Historically, a variety of surgical procedures were used to create portosystemic shunts.[72] Today, the interventional placement of a TIPS is the most commonly used approach to create portosystemic shunting without the need for laparotomy. The two major long-term complications of TIPS are a shunting volume that is either too high, leading to increased levels of circulating ammonia inducing hepatic encephalopathy, or too low, failing to decrease the pressure gradient adequately to reduce bleeding risk.[9] Reasons for these complications are either miss-sizing of the stent, in-stent stenosis, or thrombosis.

The feasibility of TIPS flow measurements using 4D flow MRI has been demonstrated by Stankovic at al.,[73] as well as Bannas et al.,[32] who proposed 4D flow MRI for pre- and postinterventional follow-up imaging for TIPS in a pilot study with seven patients. As expected and confirmed by other studies,[47,74] both groups found a significant increase in flow volume and peak velocity in the portal venous system after the procedure (Fig. 6). They also calculated the shunt fraction, defined as the ratio between flow volumes in the TIPS in relation to the portal vein, and compared peak velocity in the TIPS to the portal vein. Interestingly, in the Bannas study,[32] a single patient with recurrent postprocedural ascites presented with an increased shunt fraction and peak velocity in the TIPS. This was explained by the presence of an arterio-portal-venous shunt from a peripheral branch of the left hepatic artery into a branch of the left portal vein, which was only detected by 4D flow MRI. This

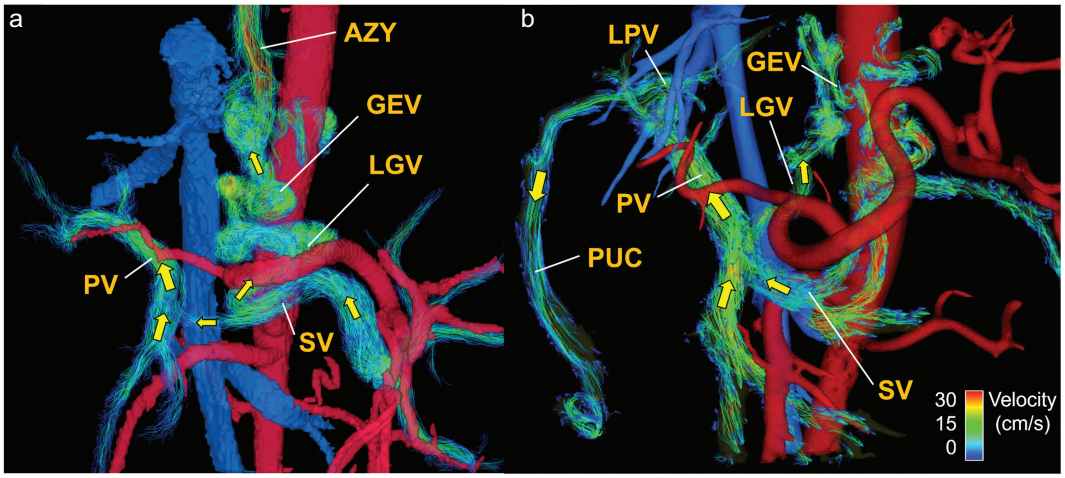

Fig. 5 Portosystemic shunts: (**a**) Patient with a large LGV with streamlines visualizing hepatofugal flow draining blood into GEV from where it drains into the AZY. Flow in the azygos vein measured 0.24 L/min, an independent risk factor for indicator for GEV at high risk for bleeding. Note the anatomical variant of the LGV that is confluent with the SV. (**b**) Patient with paraumbilical collaterals originating from the LPV as well as GEV that are supplied by the LGV. Again, flow reversal can be seen in the LGV that is confluent with the PV. Direction of flow is demarcated by yellow arrows. AZY, azygos vein; GEV, gastroesophageal varices; LGV, left gastric vein; LPV, left portal vein; PV, portal vein; SV, splenic vein.

example underscores the importance of analyzing all available data comprehensively.

Owen et al.[47] performed 4D flow MRI in 16 patients after TIPS to evaluate possible shunt dysfunction, namely, stenosis or occlusion compared to Doppler ultrasound, venogram, and 6-month clinical follow-up. In three patients with venogram confirmed stenosis, they found focal turbulence and abnormal peak velocities (for ultrasound defined as > 190 cm/s or < 90 cm/s[1]), in contrast to seven patients without evidence of stenosis, who presented without turbulence and normal flow velocities. However, they found either turbulence or abnormal velocities in six patients without evidence of shunt dysfunction. They concluded that both parameters must be abnormal to detect stenosis with high specificity and sensitivity. Unfortunately, they did not define the term "turbulence" in this context and did not provide image examples.

Shunt fraction, peak velocity (ratio), and abnormal flow patterns are promising parameters to assess TIPS function comprehensively using 4D flow MRI. Further evaluations of these parameters in larger studies with long-term follow-up are needed to determine their diagnostic performance and clinical utility.

Surgical planning and follow-up: Liver transplantation

Pre-operative 4D flow MRI of the portal venous system can be used for surgical planning and prediction of postsurgical outcome. Assessment of the portal hemodynamics in living liver donors and recipients is crucial as a pre- and postoperatively constant blood volume must flow through fewer central portal venous vessels postoperatively, inevitably leading to higher resistance. Potentially, this may lead to presinusoidal portal hypertension, early graft dysfunction, and tissue damage in recipients.[75]

Importantly, the hemodynamic outcomes of healthy liver donors that underwent partial liver resection for living donor liver transplantation must also be considered. Rutkowski et al.[52] proposed a workflow that includes pre-operative 4D flow MRI, virtual surgery, CFD simulations, and *in vitro* models. They were able to predict postoperative hemodynamics in three living liver donors considering the ability of the portal venous system in healthy volunteers to dilate after a meal.[27] It is known that the individual's capacity of portal venous dilation varies significantly.[27] The proposed method could be optimized by performing an MRI examination in preparation for surgery. The individual capacity of a liver donor to increase portal venous flow and adapt the vascular anatomy to those flow changes could be determined by 4D flow MRI before and after a meal challenge. If the results correlate with the dilation of the portal vein after partial liver resection, this could become a valuable marker to predict the risk of postoperative portal hypertension.

Lenz et al.[76] presented a patient who had received a liver transplant with renoportal anastomosis due to thrombosis of the native portal vein, superior mesenteric vein, and splenic vein. Postoperatively, she developed bleeding from GEV. After EGD-assisted hemostasis, further surgical procedures were discussed. At this point, 4D flow MRI was considered crucial as it showed hepatopetal flow in both varices and relevant veins, indicating reversal of portal hypertension after transplantation and thus substantial risk reduction in bleeding. Informed by this finding, further surgery could be avoided.

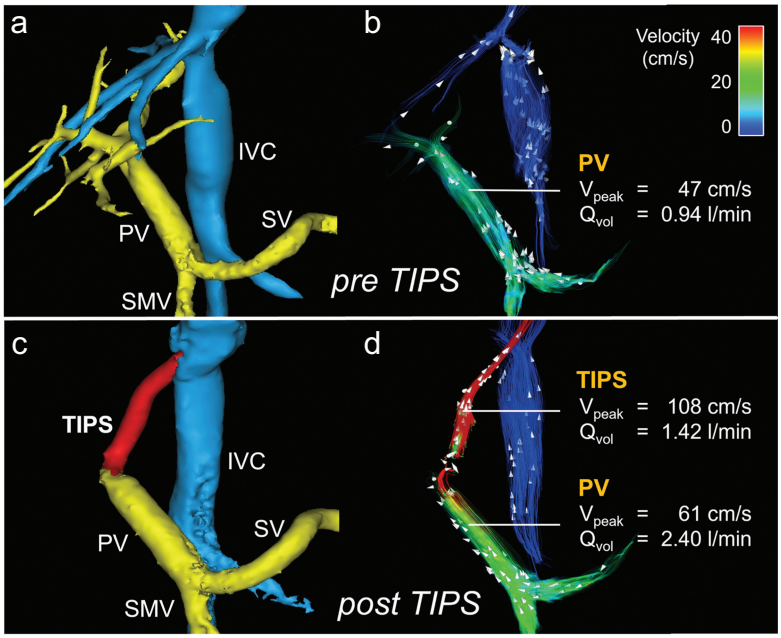

Fig. 6 Assessment of TIPS placement in a 54-year-old man with nonalcoholic steatohepatitis, portal hypertension, and resultant refractory ascites. (**a** and **c**) Colored 3D segmentation masks of the complex difference angiogram and (**b** and **d**) velocity streamlines with arrowheads depict anatomy and hemodynamics, respectively. (**a** and **b**) before and (**c** and **d**) 2 weeks after TIPS procedure. Note the increase in blood flow in the portal vasculature after the procedure and the high velocities within the shunt. Disordered flow explains the signal dropout at the proximal end of the shunt. Ascites resolved after TIPS placement. IVC, Inferior vena cava; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein; TIPS, transjugular intrahepepatic portosystemic shunt.

Hyodo et al.[77] reported the case of a 33-year-old woman who had a portal vein stenosis after living-liver transplantation. Preprocedural 4D flow MRI offered viable information on the flow direction and the impact of the stenosis in the whole portal venous vasculature. They found a poststenotic dilatation with vortex formation in the anterior branch of the portal vein. Moreover, they were able to quantify flow volume within the segmental branches of the portal vein and proved an inhomogeneous flow distribution throughout the liver transplant. The stenosis was successfully treated interventionally by the placement of a stent. Treatment success could be confirmed by postinterventional 4D flow MRI. It showed a reduction in vortical flow and more homogenous flow throughout the segmental branches of the portal vein.

Surgical planning and follow-up in children

Noninvasive, radiation-free surgical planning and follow-up is of paramount importance, particularly in children. Parekh et al.[43] demonstrated the feasibility of portal flow evaluation with 4D flow MRI in children between 5 and 17 years. They included children with a non-operated portal system, as well as children with surgically palliated extrahepatic portal vein thrombosis that was bypassed either by a meso-portal or portosystemic shunt. They found flow acceleration and atypical helical and/or vortical flow patterns in patients with stenosis of the shunt or portal vein and in one patient with new onset of portal hypertension. There are several other clinical scenarios in children, who could benefit from 4D flow MRI of the portal venous system. These include follow-up of children after liver transplantation, who have an increased risk of developing portal vein thrombosis and portal hypertension.[78]

Unmet Needs for Implementation in Clinical Routine

The clinical relevance of the method and the quantitative parameters that 4D flow MRI can measure must be established for different indications prior to its widespread implementation into clinical routine for evaluation of the portal venous system. Therefore, studies with large cohorts and long-term follow-up must be performed. The added diagnostic value of a meal challenge should also be assessed. This may be important in the setting of mild-to-moderate disease, where a meal challenge may play a helpful role to unmask more subtle hemodynamic abnormalities.

Several technical improvements could also facilitate the integration of 4D flow MRI into daily practice. Sequences that acquire two or more venc settings during one acquisition without increasing scan time could considerably improve data quality, improving the dynamic range of interrogated blood flow velocities. With such a multi-venc sequence, a comprehensive, simultaneous assessment of portal, arterial, and venous flow in the upper abdomen should be possible, and promising approaches are emerging.[79–82] However,

these methods all require longer acquisition times compared to a single venc sequence. Moreover, a reduction in acquisition and postprocessing time could improve acceptance in daily routine. Deep learning-based solutions could significantly reduce the burden of postprocessing as it has been recently proposed for the thoracic aorta.[83] Other potential areas of improvement for 4D flow MRI generally include test–retest repeatability, as well as reproducibility and standardization between sites, MRI system vendors, sequences, and postprocessing software.

Conclusion

4D flow MRI offers unique advantages over clinically established imaging modalities by providing temporally resolved information on both hemodynamics and morphology, in a 3D volume. These characteristics can be utilized to address clinically relevant pathologies of the portal venous system. The most relevant clinical applications are the diagnosis and risk stratification of cirrhotic liver disease. Most notably is the potential to provide noninvasive bleeding risk stratification of GEV in portal hypertension. Initial studies confirmed that 4D flow MRI meets all requirements laid out by the AASLD for a noninvasive marker to identify high-risk varices in patients with liver cirrhosis. Moreover, 4D flow MRI offers unique insights and added value for surgical planning and follow-up of multiple hepatic interventions.

On the path to clinical implementation, large multicenter and multivendor follow-up studies are needed to confirm the diagnostic value of 4D flow MRI in the portal venous system. Furthermore, improvements to the workflow, including standardized and faster acquisition and postprocessing, will facilitate its widespread clinical implementation.

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Conflicts of Interest

None of the authors have any relevant conflicts. Unrelated to this work, Dr. Reeder has ownership interests in Calimetrix, Reveal Pharmaceuticals, Cellectar Biosciences, Elucent Medical, and HeartVista. The University of Wisconsin receives research support from GE Healthcare and Bracco Diagnostics.

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