Validation of radially undersampled 4D-Flow-MRI in an animal model of portal hypertension

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TARGET AUDIENCE: Physicians (Gastroenterologists, Hepatologists, Radiologists, Abdominal Surgeons), MR physicists, Biomedical engineers, Veterinarians

PURPOSE: The liver is unique in that it has (1) a dual vascular supply (hepatic artery, portal vein) with a wide range of blood flow velocities and waveforms and (2) singular hepatic venous drainage. The portal venous system is often affected in chronic liver disease when liver tissue stiffening leads to increased vascular resistance, resulting in portal hypertension (PHTN). PHTN is associated with potentially life-threatening complications. Recent advances in 4D Flow MRI have motivated several studies of splanchic and portal venous flow. However, *in-vivo* validation studies of 4D Flow MRI have so far been limited to comparisons with 2D PC MRI and consistency checks. Therefore, the ***purpose of this study*** was twofold: A) to create an animal model of PHTN and B) to validate 4D-Flow-MRI *in-vivo* using a radially undersampled, time-resolved three-dimensional phase contrast sequence sensitive towards motion in all three spatial directions[1] in comparison to perivascular ultrasound.

METHODS: Studies were performed in 7 pigs of approx. 60kg body weight after approval of the local Research Animal Resources Center (RARC). Studies consisted of i) a pre-operative MR session, ii) an operative session that consisted of baseline ultrasound (US) measurements, the procedure to induce portal hypertension, and a final US session, and iii) a post-operative MR-session. During the procedure, pigs were kept on a respirator in deep anesthesia following an RARC-approved protocol and were constantly monitored for depth of anesthesia, heart rate and temperature. After completion of experiments, animals were euthanized per RARC protocol.

Induction of portal hypertension. Portal hypertension was induced by partially ligating the extrahepatic portal vein. The ligature was put around the portal vein and an adjacent 8mm (5/16") Allen wrench which was removed shortly after the ligature was secured.

MR sessions (i/iii) on a 3T scanner (Discovery MR 750, GE Healthcare, WI) with a 32-chanel body coil (NeoCoil) consisted of localizer sequences, bi-phasic (arterial and portal venous) contrast-enhanced MR-angiography (CE-MRA) using 0.03mmol/kg of gadofosveset trisodium (Ablavar, Lantheus) to facilitate planning of flow acquisitions and to improve SNR of 4D-Flow-MRI[2]. Scan details included: 5-point PCVIPR cine phase contrast sequence[3 4] covering the vasculature of the entire upper abdomen with spherical FOV 26x26x26cm, readout = 256, TR/TE = 6.6-7.7 / 2.4-2.5ms; FA = 14-16° reconstructed to an isotropic spatial resolution of 1.0x1.0x1.0mm^3 and 12 cardiac frames. Offline vessel segmentation using MIMICS (Materialize, Leuven) preceded data visualization using EnSight (CEI) to position cut-planes orthogonal to each vessel-of-interest. Cut-planes were exported into FlowTool, a Matlab-based in-house software[5], for flow quantification. During quantification, two independent readers (MR1, MR2) were blinded to the exam number and status pre / post induction of portal hypertension. An interobserver comparison (MR1, MR2) was performed; data from intraobserver variability is pending to guarantee a sufficiently large interval between evaluations.

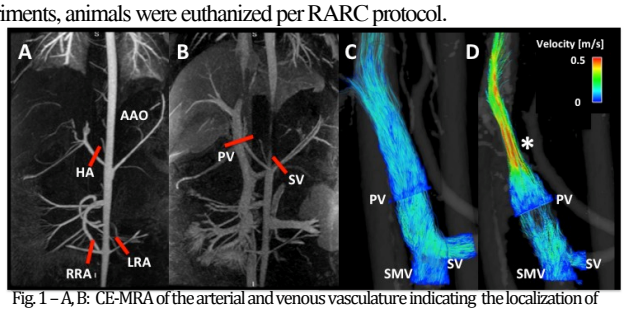

Fig. 1 – A, B: CE-MRA of the arterial and venous vasculature indicating the localization of ultrasound and MR measurements. C, D: Color-coded streamline visualization of flow before (C) and after (D) induction of protal hypertension by partial ligature of the portal vein. * indicates increased blood due to stenosis. For abbreviations please see Methods.

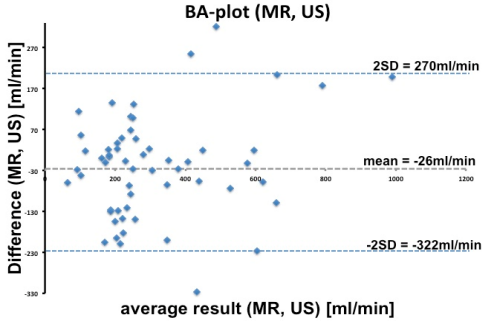

Fig. 2 – Bland-Altman plot of differences between perivascular ultrasound (US) and MR-acquisitions flow of all tested vessels by reader 1 (MR1) reveals a small underestimation by ultrasound.

Ultrasound (ii) was performed using a pre-calibrated ultrasound flowmeter (Transonic Perivascular Ultrasound TS 420) with perivascular flow probes adapted to each vessel's diameter. Vessels of interest were portal vein (PV), splenic vein (SV), hepatic artery (HA), left and right renal artery (LRA, RRA), see Fig. 1. During the procedure, each vessel was carefully assessed by an experienced hepatobiliary surgeon. Vessel loops were installed after each ultrasound measurement to guarantee matching locations for the postprocedural measurement.

Statistical analysis. Data were digitally stored and analyzed offline. Data were compared using paired t-tests ($p<0,05$ indicating significant differences), Bland-Altman-plots (BA, mean difference ± 2SD considered clinically acceptable)

RESULTS AND DISCUSSION: Experiments were successfully performed in all animals before partial portal vein ligature and 6/7 animals post procedure. One animal had to be euthanized during surgery due to procedural complications. Overall, 60 out of 65 vessel measurements were successfully acquired (33 pre procedure, 27 post procedure), dropouts were due to vessel inaccessibility during surgery or vasospasms. Agreement between US and MR was good for both readers with a mean flow of all tested vessels of 312 ± 225ml/min (US) vs. 338 ± 197ml/min (MR1a), 321 ± 200 (MR1b) and 292 ± 188ml/min (MR2) (p = n.s. for all). BA for comparison of US and MR1 showed a small underestimation by MR of (mean ± 2SD) -26 ± 298ml/min (see Fig. 2), the interobserver comparison showed a good mean ± 2SD of 16 ± 67ml/min (MR1, MR2). Both US and MR detected decreased portal venous flow (PV, SV) comparing pre- and post-procedural flows indicating successful induction of portal hypertension: US pre: 443ml/min, US post: 320ml/min, MR pre 520ml/min, MR post 336ml/min while differences did not reach statistical significance. Flows in the arteries decreased as well: US pre 287ml/min, US post 224ml/min, MR pre 318ml, MR post 208ml/min albeit to a lesser extent not depicting the expected hyperemic arterial response. Differences did not reach statistical difference. However, due to inaccessibility and vasospasms the hepatic artery was assessed in 4 cases only.

CONCLUSION: Our data demonstrate the successful induction of portal hypertension in a pig model by ligature of the extrahepatic portal vein. The lack of a hyperemic arterial response is attributed to technical issues including vasospasms and inaccessibility of the vessels of interest such as superior mesenteric artery and celiac trunk but will be assessed in future MR-based evaluations. Successful validation of flow measurements in-vivo is unprecedented and is reassuring for future use of PCVIPR as a comprehensive tool for hemodynamic research of the liver.

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