Liver DCE-MR imaging with a blood pool contrast agent and distributed computing on the European Grid Infrastructure: An innovative method for whole liver perfusion quantification.

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INTRODUCTION

Liver fibrosis is an important cause of mortality and morbidity and contributes substantially to increase health care costs in patient with chronic liver diseases (1). While histological analysis after liver biopsy is the gold standard for the diagnosis, inherent risk make this method not suitable for clinical monitoring (2,3). Furthermore liver biopsies have additional limitations such as interobserver variability and sampling errors (4). Several studies, using Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) to quantify liver perfusion, have shown that some perfusion parameters were relevant indicators for liver fibrosis assessment (5,6). Nevertheless, these evaluations were restricted to ROI and regional variations, often met in diffuse liver diseases, could not be observed. ROI-based perfusion quantification required already heavy processing for image registration and data fitting. Processing time drastically increases and becomes prohibitive for potential clinical application for full 2D or 3D mapping. In this context, parallel computing on distributed infrastructures such as clusters, grids or clouds proven to be an attractive solution. Such approach have been already used for medical imaging (7,8) but never applied to 3D-liver perfusion mapping. This study presents a MR acquisition protocol and a processing method using distributed computing on the European Grid Infrastructure (EGI) to allow 3D liver perfusion parametric mapping after DCE-MR imaging with the MS-325 blood pool agent. In this preliminary study, processing speed, reproducibility and accuracy were assessed.

MATERIAL AND METHODS

Subjects: Seven patients (4 women, 3 men; mean age, 40 ± 12 years; mean weight 75 ± 8 kg) were enrolled. Six patients with biopsy-confirmed chronic liver diseases were prospectively enrolled. Liver fibrosis was staged according to METAVIR classification. One healthy patient was used as control.

MR acquisitions were performed using a 1.5T Magnetom Symphony system (*Siemens Medical Solutions, Erlangen, Germany*). A 3D VIBE sequence with parallel imaging technique was used (GRAPPA, R-factor = 2). Sequence parameters were as follows: TE/TR/α, 1.22/2.87 ms/12°; K-space partial filling, 6/8th; 256 × 192 matrix; 400 × 300 mm^2 FOV and 650 Hz.pixel^{-1} receiver bandwidth. A 6.4 cm slab thickness (16 coronal oblique slices of 4 mm) volume was acquired with a 1-sec temporal resolution. Acquisition simultaneously started with MS-325 *(Epix Pharmaceutical Inc, Lexington, Massachusetts, USA)* injection (1 mL.s^{-1} rate and 0.03 mM.kg^{-1} posology) and was performed in free breathing during 2 min.

Image pre-processing: First, images were imported on a personal computer running an in-house application written in Matlab r2010a (*The MathWorks, Natick, Massachusetts, USA*). Each volume was automatically registered with an algorithm based on a rigid affine transformation method. Secondly, native 3D + t volumes were converted in 3D+ t MS-325 mass concentration maps using the relationship between signal intensity and MS-325 concentration established in a previous calibration study (9). Finally, native arterial and portal input functions were measured using a 5x5 pixels squared ROIs respectively placed on abdominal aorta and main portal vein.

Modeling and distributed computing: Hepatic capillary system was modeled by a 3-parameters dual input one-compartment pharmacokinetic model. The equation describing this model is as follow: $C(t) = \rho\left[C_A(t-\tau_A)\times\phi_A + C_p(t-\tau_P)\times\phi_P\right] \otimes e^{-\frac{t}{MTT}}$ [1] where $\otimes$ designates the convolution product, ρ the volemic mass assumed to be equal to 1 g.ml^{-1}. The parameters ϕ_A and ϕ_P are the arterial and portal perfusion respectively expressed as mL.100g^{-1}.min^{-1}. C_A and C_P are respectively the arterial and portal input functions. The two delays, τ_A and τ_P, take into account the temporal offset between central compartment input and measured input from arterial and portal ROIs. While ϕ_A, ϕ_P and MTT are model parameters, delays are independent from the fit procedure. The Hepatic Perfusion Index, defined as the arterial perfusion to total perfusion (arterial + portal perfusion) ratio, was also calculated. A pixel-by-pixel tissular time activity curves was obtained and a non-linear least-square fit was performed according to the model described previously [1]. Data fitting was realized with Levenberg-Marquardt algorithm associated to multi-start technique to improve fit robustness. For each fit procedure, delays were determined as the time between the beginning of tissular enhancement and the beginning of arterial enhancement in abdominal aorta. These starting points are chosen as the maximum of second order derivative of tissue time activity curve and arterial input function. This step was parallelized and executed on EGI within the biomed Virtual Organization. The parallelization was handled at the input data level, by splitting each volume into several pieces. Each piece was processed with independent jobs running in parallel on multiple grid resources and eventually merged. The whole processing operations were modeled and implemented as a grid workflow using the Gwendia language (10) and the MOTEUR workflow engine (11). The splitting and merging algorithms were developed in C++, while the processing algorithm was developed in Matlab. All three programs were compiled on a grid compliant operating system (CentOS) and deployed on the fly on the grid nodes. For the Matlab code we used the Matlab Compiler and the Matlab Compiler Runtime. From this step, three perfusion parametric-maps were obtained, one for each parameter of the model used.

RESULTS

Among the 6 biopsied patients, histological results were as follows: 2 patients were scored F0, 3 patients scored F2, and 1 patient scored F4. A significant correlation was observed between ROI-based and distributed method for each parameter. Spearman's rho coefficients were 0.86, 0.92 and 0.80 ($p<0.05$) for arterial perfusion, portal perfusion and MTT respectively. Regarding the t-test and Bland-Altman plot, no significant difference was shown between compared methods. Reproducibility was assessed based on a test and re-test. All computed relative standard variation maps were null or very close to zero. A total of 2.9 CPU years (corresponding to twenty-one 3D mapping procedures) were computed in only 9.5 days. The speed-up ratio varied among the 21 workflows from 71 to 242 with an average value of 126. The average error ratio for the experiments presented here was of 18%, with a maximum of 43% for one of the workflows. The late completion of the last jobs significantly increases the makespan. Indeed, the current makespan is almost tripled (from roughly five to fifteen hours) because of poor scheduling of late tasks.

DISCUSSION

Results showed that this method was reproducible and that estimated parameters were correlated with ROI-based reference method ran locally on a personal computer. Quantified parameters values were found to be in the same range as those obtained with the ROI-based reference method and those related in the literature (5,6). Nevertheless, taken patients by patients, quantified values were slightly but not significantly modified. Indeed, compared to the ROI-based method, blood flow quantified with the presented 3D method is overestimated whereas, on the contrary, MTTs are underestimated. With the ROI-based method, arterial and portal delays are optimally set by the user. However, these delays depend on spatial location and take into account the time shift between the measured input functions and the position where modeling take place in parenchyma. Hence, manual setting was prohibited with 3D method and an automatic estimation of both delays was mandatory. Nevertheless this estimation was noise-sensitive and probably explains the slight difference observed between ROI-based and 3D method. The parallelization of the method brings significant speed-up and appears feasible in a reasonable computing time. Nevertheless, performance can be still significantly improved with better scheduling. Indeed, the scheduling of the last tasks was poor due to platform heterogeneity and multiple task resubmissions caused by high error ratios. Data transfers account for most of the errors, while the rest are mostly application failures due to improper grid node configuration. To conclude, the presented method allows 3D liver perfusion quantification in a reasonable processing time which is now suitable for clinical use in a research context. While the distributed processing method was validated compared to the ROI-based quantification, such fully automatic processing requires higher image quality which are achievable on the latest 3T MRI systems available. Further work will have to demonstrate the interest of parametric 3D perfusion-maps for fibrosis assessment on a larger number of subjects with chronic liver disease.

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