Published in final edited form as:

NMR Biomed. 2015 October ; 28(10): 1304–1314. doi:10.1002/nbm.3369.

Three dimensional (3D) dynamic contrast enhanced (DCE)MRI for the accurate, extensive quantification of microvascular permeability in atherosclerotic plaques

Claudia Calcagno,

Icahn School of Medicine at Mount Sinai, Department of Radiology

Mark E Lobatto,

Academisch Medisch Centrum, Department of Radiology

Hadrien Dyvorne,

Icahn School of Medicine at Mount Sinai, Department of Radiology

Philip M Robson,

Icahn School of Medicine at Mount Sinai, Department of Radiology

Antoine Millon,

University Hospital of Lyon, Department of Vascular Surgery

Max L. Senders,

Icahn School of Medicine at Mount Sinai, Department of Radiology

Olivier Lairez,

Icahn School of Medicine at Mount Sinai, Department of Radiology

Sarayu Ramachandran,

Icahn School of Medicine at Mount Sinai, Department of Radiology

Bram F. Coolen,

Academisch Medisch Centrum, Department of Radiology Black

Alexandra Black,

Icahn School of Medicine at Mount Sinai, Department of Radiology

Willem J.M. Mulder, and

Academisch Medisch Centrum, Department of Radiology

Zahi A. Fayad

Icahn School of Medicine at Mount Sinai, Department of Radiology

Abstract

Atherosclerotic plaques that cause stroke and myocardial infarction are characterized by increased microvascular permeability and inflammation. Dynamic contrast enhanced (DCE) MRI has been proposed as a method to quantify vessel wall microvascular permeability in vivo. Until now, most DCE-MRI studies have been limited to 2 dimensional (2D), multi-slice imaging. While providing

the high-spatial resolution required to image the arterial vessel wall, these approaches do not allow quantifying plaque permeability with extensive anatomical coverage, an essential feature when imaging heterogeneous diseases, such as atherosclerosis. To our knowledge, we present the first systematic evaluation of 3 dimensional (3D), high-resolution, DCE-MRI for the extensive quantification of plaque permeability along an entire vascular bed, with validation in atherosclerotic rabbits. We compare two acquisitions: 3D turbo field echo (TFE) with MSDE preparation (motion sensitized driven equilibrium), and 3D TSE (turbo spin echo). We find 3D TFE DCE-MRI to be superior to 3D TSE DCE-MRI in terms of temporal stability metrics. Both sequences showed good intra and inter-observer reliability, and significant correlation with ex vivo permeability measurements by Evans Blue near infra-red fluorescence (NIRF). Additionally, we explore the feasibility of using compressed sensing to accelerate 3D DCE-MRI of atherosclerosis, to improve its temporal resolution and therefore the accuracy of permeability quantification. Using retrospective under-sampling and reconstructions we show that compressed sensing alone may allow accelerating 3D DCE-MRI up to 4 folds. We anticipate that the development of high spatial resolution 3D DCE-MRI with prospective compressed sensing acceleration may allow for the more accurate and extensive quantification of atherosclerotic plaque permeability along an entire vascular bed. We foresee that this approach may allow for the comprehensive and accurate evaluation of plaque permeability in patients, and may be a useful tool to assess therapeutic response to approved and novel drugs for cardiovascular disease.

Abstract

We describe the validation of 3D DCE-MRI to quantify microvascular permeability in the aortic vessel wall of atherosclerotic rabbits. Based on our metrics of temporal stability, we find 3D TFE DCE-MRI superior to 3D TSE DCE-MRI, while both sequences were found to significantly correlate with ex vivo permeability by NIRF (near infra read fluorescence). Using retrospective reconstructions we also demonstrate that is it feasible to accelerate 3D DCE-MRI up to 4 folds using compressed sensing.

Introduction

Atherosclerotic plaques at high risk of causing severe clinical events, such as stroke or myocardial infarction, are characterized by increased microvascularization and endothelial permeability, associated with active vessel wall inflammation(1,2). In the past 10 years,

efforts to develop and validate non-invasive imaging techniques to quantify plaques microvascular permeability in both humans(3) and animal models(4) have intensified. Being able to quantify plaque permeability may not only help identifying high-risk lesions and/or patients, but may also allow us to 1) follow plaque progression in longitudinal studies(5,6), 2) evaluate the efficacy of approved and novel treatments (7-11), and 3) identify candidate patients that may benefit from specific treatments(12).

Dynamic contrast enhanced (DCE) MRI is a non-invasive imaging method originally developed to quantify tumors' vascularity and permeability(13,14). This technique involves the rapid acquisition of T1-weighted MR images before and during the injection of a gadolinium (Gd) based contrast agent. Signal enhancement curves in the tissue of interest are extracted from the MR acquisition and processed using kinetic models to derive quantitative estimates of fractional microvascular volume (v_p) and permeability (K^{trans}) (15,16). Moreover, non-model based parameters such as area under the curve (AUC), upslope, time to peak, or peak concentration can also be calculated as surrogates of microvascular volume or permeability (17). DCE-MRI has been employed in a variety of studies to quantify microvasculature and permeability in atherosclerotic plaques (18-20). A correlation between the fractional microvascular volume, v_p , by DCE-MRI and plaque neovessels in human carotid specimens has been demonstrated (3). Moreover, a relationship between v_p , K^{trans} (permeability) and plaque macrophages, neovessels and loose matrix, as well as risk factors for atherosclerosis (such as smoking, and elevated C reactive protein) (21,22) was found. In atherosclerotic rabbits, the non-model based parameter AUC was found to correlate with aortic plaque neovascularization(4,23). In the same animal model, AUC was able to capture therapeutically induced changes in plaque microvasculature/permeability(8-10).

Despite these successful results, current DCE-MRI protocols do not allow for the accurate and extensive quantification of microvascular permeability in vulnerable plaques. Imaging the arterial vessel wall requires high in-plane spatial resolution ($0.5\text{-}0.7\text{ mm}^2$) to capture the complex structure of plaques (24-26), to minimize partial volume artifacts and to provide good vessel wall/lumen delineation(4,5,27). Adequate anatomical coverage is also necessary, to map this heterogeneous disease along a whole vessel(28,29). Both these requirements make it difficult to acquire DCE-MRI with fast time resolution, which is necessary to capture contrast agent kinetics in the blood plasma (the so called arterial input function, AIF), and its extravasation in atherosclerotic plaques(30-33). Since it is challenging to satisfy all these requirements simultaneously, almost all vascular DCE-MRI studies have focused on the use of high spatial resolution, 2D, single or multi-slice acquisitions, thereby sacrificing temporal resolution and anatomical coverage (3-10,20-23,27,34).

Our goal is to improve the quantification of plaque microvasculature and permeability by using 3 dimensional (3D) DCE-MRI with high spatial resolution and extensive anatomical coverage. In this study we compare two different approaches (3D TFE, turbo field echo, and TSE, turbo spin echo) for 3D DCE-MRI. To allow for accurate validation we use a pre-clinical rabbit model of aortic atherosclerosis, where in vivo permeability imaging with 3D DCE-MRI is compared with ex vivo Evans Blue (EB) near infra red fluorescence (NIRF)

measurements of endothelial permeability, used as gold standard (35,36). Moreover, we investigate the feasibility of using compressed sensing to accelerate 3D DCE-MRI of atherosclerosis, with the aim to improve the time resolution of 3D DCE-MRI and the quantification of microvascular permeability in atherosclerotic plaques.

Methods

Animal model

Atherosclerosis was induced in 4 New Zealand White (NZW) rabbits by a combination of a high cholesterol diet (4.7% palm oil and 0.3%, weeks 1 through 8, and 0.15%, weeks 8 through 16, cholesterol; Research Diet Inc., New Brunswick, NJ) and double balloon injury of the abdominal aorta (4,8-11,23). Three additional NZW rabbits were kept on chow diet and used as non-atherosclerotic controls. Experiments were conducted 6 months after diet initiation. All animal experiments were approved by the Icahn School of Medicine Institutional Animal Care and Use Committee (IACUC).

MR acquisition

Animals were imaged 3 times with DCE-MRI on a 3T clinical MR scanner (Philips Achieva), using a commercial knee coil (Philips 3T 8 channel) for signal reception. The average time in between sessions was 4.8 days (standard deviation 3.2 days). The order of the 3 imaging sessions was randomized for each rabbit. In all sessions, localizers and time-of-flight (TOF) non-contrast enhanced angiography were performed, to identify anatomical landmarks, such as the renal arteries and the iliac bifurcation. DCE-MRI was performed following these sequences. After the acquisition of three pre-contrast DCE-MRI frames, 0.2 mmol/kg of Gd-DTPA (gadopentatedimeglumine, Magnevist, Bayer Schering Pharma) was injected with a power injector, at the rate of 1 ml/s, followed by a 15 ml saline chase. During each imaging session either one of the following sequences was used for DCE-MRI: 1) 3D T1W turbo field echo (TFE) with motion sensitized driven equilibrium (MSDE) for blood suppression(28,37); 2) 3D T1W turbo spin echo (TSE)(29); 3) previously validated 2D double inversion recovery (DIR) T1W TSE, used as a gold standard(4,9-11,18). 3D sequences consisted of a sagittal volume covering the aorta from the renal arteries to the iliac bifurcation, while 2D DCE-MRI consisted of 5 axial slices, spaced to cover the identical anatomical region (slice spacing 10mm). Relevant imaging parameters can be found in Table 1. Figure 1 shows curved multi-planar reconstructions of the rabbits' aorta, from both 3D TFE and TSE (panels A and B). Orange lines indicate the left renal artery and the iliac bifurcation, respectively. Panels C-E show corresponding axial slices (right below the left renal artery) for 3D TFE (panel C), 3D TSE (panel D) and 2D TSE DIR (panel E), averaged in the time dimension of the dynamic series. Figure 1S in the Supplemental Materials shows dynamic imaging frames for all DCE-MRI sequences from one atherosclerotic and one control rabbit.

Ex vivo near infra read fluorescence (NIRF)

After the last MR imaging session, rabbits were injected with Evans Blue (EB), an albumin binding dye commonly used to quantify vascular permeability ex vivo(12,35,36,38). Thirty minutes after injection, rabbits were euthanized and the abdominal aortas were excised and

imaged with a Xenogen IVIS-200 optical imaging system with excitation and emission filters set at 605 and 680 nm, respectively. Ex vivo permeability was quantified as EB fluorescent radiant efficiency by NIRF imaging by dividing the rabbits' abdominal aorta in segments of equal length (1cm) from the left renal artery, down to the iliac bifurcation.

Image analysis

Assuming no significant motion artifacts during the dynamic acquisition in the anesthetized animals, temporal averages in the time dimension were used to trace the inner and outer vessel wall contours (Figure 1, panels C-E). Regions-of-interest (ROIs) encompassing the aortic vessel wall were drawn on all 5 axial slices for 2D DIR TSE DCE-MRI. For 3D sequences, ROIs were drawn on reformatted axial slices in the abdominal aorta, from the left renal artery to the iliac bifurcation. ROIs tracings were performed in OsiriX (www.osirix-viewer.com). ROI time curves were then extracted and analyzed using a custom made Matlab (The MathWorks, Inc., Natick, MA) program.

Temporal stability—To compare the quality of enhancement curves among different sequences, we calculated the temporal signal to noise ratio (tSNR) and vessel wall/lumen temporal contrast to noise ratio (tCNR), as follows(39):

$$tSNR = \frac{\overline{SI_{t=6:f}}}{\sigma(SI_{t=6:f})} \quad [1]$$

$$tCNR = tSNR^{VW} - tSNR^{Lumen} \quad [2]$$

$\overline{SI_{t=6:f}}$ and $\sigma(SI_{t=6:f})$ are the average and standard deviation of signal intensity between frame 6 and frame f , at the end of the dynamic acquisition. Given the difference in time resolution among the sequences, f was taken to be 20 for 3D TFE, 18 for 3D TSE, and 23 for 2D DIR TSE. These frames were chosen to calculate temporal stability (tSNR) and contrast between vessel wall and lumen (tCNR) of frames acquired after contrast agent extravasation in the plaque, for the same amount of time across different sequences during acquisition. Figure 1 (panel F) shows signal intensity curves derived from ROIs traced in the same axial slices showed in panels C-E, from all acquisitions, as a representative example of the signal and noise expected in the uptake curves. For each curve, the gray vertical bar indicates frames 6 and f , between which tSNR and tCNR were calculated. To facilitate comparisons between different sequences, tSNR and tCNR were normalized by slice thickness and by the square root of the acquisition time per frame of each sequence (Table 1), as previously validated(37).

Quantification of in vivo permeability—ROI curves were converted to contrast agent concentration assuming linearity with MR signal as previously validated (40,41):

$$C^{VW}(T) \propto \frac{SI^{VW}(T) - SI_{pre}^{VW}}{SI_{pre}^M} \bigg/ (T1_{pre}^{VW} \cdot r1) \quad [3]$$

where $C^{VW}(T)$ and $SI^{VW}(T)$ are respectively the contrast agent concentration and signal intensity in the vessel wall at time T , $\overline{SI_{pre}^{VW}}$ and $\overline{SI_{pre}^M}$ are respectively the average signal intensity in the vessel wall and in muscle in the first 3 frames (pre-contrast); $T1_{pre}^{VW}$ is the pre-contrast T1 relaxation time of the vessel wall, and rI is the longitudinal relaxivity of the contrast agent. Pre-contrast T1 was taken to be 1.5s(42), while rI was taken to be 4.3 (mM*s)⁻¹(43). Additional details about the method used to convert MR signal to contrast agent concentration can be found in the Supplemental Materials section. Normalization to skeletal muscle as a reference tissue was chosen based on its similar pre-contrast T1 to the vessel wall (42). After conversion to concentration, the area under the concentration versus time curve (AUC) was calculated to quantify the extravasation of contrast agent in the vessel wall, in the first 2 minutes after injection(9-12). AUC is a non-model based parameter and a validated measure of plaque microvasculature/permeability in rabbits(4,8-10,23). Furthermore, ROI curves were analyzed to calculate kinetic parameters according to the following modified Tofts-Kermode model(15), under Patlak assumption(3,44), as previously validated(3,21,22):

$$C^{VW}(T) = v_p C_p(T) + K^{trans} \int_0^T C_p(t) dt \quad [4]$$

where $C^{VW}(T)$ and $C_p(T)$ are respectively the contrast agent concentration in the vessel wall and in the blood plasma compartment at time T , v_p is the fractional microvascular volume and K^{trans} is a measure of the extravasation of contrast agent from the plasma to the tissue compartment (in this case indicating endothelial permeability). Fitting to the kinetic model was implemented using the function *lsqnonneg* (linear least squares with non-negativity constraints) in Matlab. The use of a black blood acquisition for DCE-MRI, precludes sampling $C_p(T)$ from the MR images themselves(4,5). Therefore, a population input curve derived from the literature was used(45). Figure 2S in the Supplemental Materials shows examples of ROI concentration curves from corresponding axial slices from all acquisitions. Dashed lines indicate experimental data, while continuous lines indicate data fitting to the kinetic model.

Compressed sensing acceleration

Based on its better performance in regards to temporal stability metrics, 3D TFE DCE-MRI data were used for this analysis. Retrospective reconstructions were performed by Fourier transforming magnitude images back into k-space data, which were under-sampled using a pseudo-random k_{xy-t} pattern, in order to generate incoherent aliasing artifacts (Figure 3S, Supplemental Materials). This approach does not take into account information deriving from phase, different elements of the receiving coils, as well as previous under-sampling during acquisition, but simply relies on the anatomical characteristics of the images and of the temporal enhancement to evaluate the application of compressed sensing. A sixth-order polynomial distribution function, defined as $(1 - k)^6 + d$ (with $-1 < k < 1$, while d is a constant parameter), was used to generate a different variable-density random under-sampling pattern along k_{xy} for each DCE-MRI frame. This pattern ensures a higher density at the center of k-space than the edges, and provides a better starting point for the iterative reconstruction algorithm than uniform random sampling, as previously described.(46-48). Retrospectively

under-sampled data were reconstructed using a previously validated k_f -SPARSE-SENSE algorithm, using temporal principal component analysis (PCA) as the sparsifying transform(46-48):

$$\hat{m} = \underset{m}{\operatorname{argmin}} \{ \|F_s m - y\|_2 + \lambda \|p_t m\|_1 \} \quad [5]$$

where F_s is the under-sampled 3-dimensional spatial Fourier transform, m is the reconstructed image, y is the acquired k-space data from the scanner, P_t is the temporal principal component analysis (PCA). $\|\cdot\|_1$ is the l_1 -norm, used to enforce sparsity, while $\|\cdot\|_2$ is the l_2 -norm used to enforce data consistency. λ (in this case taken to be 0.075) is a weighting parameter that controls the balance between sparsity in the temporal PCA domain (right hand term) and data consistency (left-hand term). Six different under-sampling rates ($R = 2, 4, 6, 8, 10$ and 15) were used for off-line reconstructions (Figure 3S, Supplemental Materials). Compressed sensing reconstructions were evaluated using 2 metrics: 1) image quality, in terms of vessel wall/lumen delineation; 2) root mean square error between ROI signal curves derived from under-sampled and fully sampled reconstructions, normalized by the average signal intensity of the fully-sampled curve (N_RMSE). Vessel wall/lumen delineation was quantified as:

$$D = \frac{\overline{SI_{t=6:20}^{VW}} - \overline{SI_{t=6:20}^L}}{\overline{SI_{t=6:20}^{VW}}} \quad [6]$$

where $SI_{t=6:20}^{VW}$ and $SI_{t=6:20}^L$ are respectively the average signal of the vessel wall and lumen after contrast agent injection. This metric is expected to decrease with increasing acceleration, due to blurring of the vessel wall/lumen contours in the under-sampled reconstructions. N_RMSE for each curve was calculated as

$$\sqrt{\sum_1^N (SI_{FS} - SI_{US})^2 / N} / \operatorname{mean}(SI_{FS}) \quad [7]$$

where SI_{FS} and SI_{US} are respectively the signal intensity of the fully sampled and under-sampled curves, and N is the number of data points in each curve. N_RMSE is expected to increase with increasing acceleration.

Statistical analysis

For fully sampled data, tSNR and tCNR were compared among sequences using paired t-tests. For each rabbit, slice-by-slice AUC, v_p , and K^{trans} were averaged in segments from the left renal to the aortic bifurcation, corresponding to the number of segments used for EB analysis. Parameters derived from DCE-MRI acquisitions and EB fluorescent radiant efficiency were correlated using Pearson's correlation. A p value less than 0.05 was considered significant. Intra- and inter-observer reliability (see Supplemental Materials section) was evaluated using intra-class correlation coefficients (ICCs) and Bland Altman analysis of DCE-MRI parameters in each segment. For under-sampled data, only analysis by observer 1 was taken into account. The highest under-sampled rate yielding both vessel

wall/lumen delineation and average signal curves N_RMSE within 10% of the fully sampled scanner reconstruction was considered suitable for further investigation.

Results

Comparison between 3D TFE, 3D TSE and 2D DIR TSE DCE-MRI

tSNR and tCNR normalized by slice thickness and temporal resolution were significantly higher in both 3D DCE-MRI sequences compared to 2D DIR TSE ($p < 0.05$), with 3D TFE being significantly higher than 3D TSE ($p < 0.05$, Figure 2). This indicates an average higher temporal stability, and vessel wall enhancement (compared to the signal in the lumen) in ROI curves derived from 3D TFE DCE-MRI compared to 3D TSE and 2D DIR TSE DCE-MRI. Figure 2 shows temporal stability results derived from the tracings by observer 1. Tracings from the two observers and repeated tracings from observer 2 did not yield significantly different results from the ones described here ($p \geq 0.4$).

Correlation between in vivo and ex vivo permeability

AUC and K^{trans} (permeability) from 3D TFE and TSE, and 2D DIR TSE DCE-MRI were significantly different between atherosclerotic and control animals ($p < 0.05$, Figure 3, panels A and B). This difference was corroborated by ex vivo results, where microvascular permeability was quantified using Evans Blue NIRF. This measure was also significantly different between atherosclerotic and control rabbits ($p < 0.05$, see Figure 4S in the Supplemental Materials). The parameter v_p (microvascular volume) was not significantly different between atherosclerotic and control rabbits for all acquisitions. Figure 4 shows representative AUC pixel-by-pixel maps for one representative atherosclerotic and one control rabbit. For 2D DIR, one axial slice is shown, while for 3D acquisitions 3D curved MPRs are represented. In addition, ex vivo EB NIRF for both rabbits is shown. Yellow lines in the 3D curved MPRs and EB NIRF indicate the left renal artery and the iliac bifurcation. In both AUC maps and EB images, hotter colors indicate higher permeability. The higher permeability in the EB NIRF of the atherosclerotic rabbit is mirrored in the “hotter” AUC maps for all acquisitions. On the contrary the control animal shows modest Evans Blue extravasation and very low AUC maps indicating low endothelial permeability. In atherosclerotic animals, AUC from 3D TFE ($R^2 = 0.204$), TSE ($R^2 = 0.150$) and 2D DIR ($R^2 = 0.286$) was significantly correlated with ex vivo permeability by EB NIRF ($p < 0.05$, Figure 5). For 3D TFE, K^{trans} was also significantly correlated with EB uptake ($R^2 = 0.144$, $p < 0.05$). No significant correlation was found between v_p and EB uptake for all acquisitions.

Compressed sensing acceleration

Vessel wall/lumen delineation (quantified as difference in vessel wall and lumen signal, normalized by the vessel wall signal itself) was found to decrease with increasing acceleration, from 35.1% for the scanner reconstruction, to 28.3% for an under-sampling rate of 15. Figure 6, panel A shows a reduction in this parameter with increasing acceleration rate. Correspondingly, increased blurring in the images can be found with increased under-sampling (panel B). The highest under-sampling rate with vessel wall/lumen delineation within 10% of the scanner reconstruction was $R=8$ (gray dashed line, Figure 6, panel A). The N_RMSE between fully sampled and under-sampled signal curves

was instead found to increase with increasing acceleration, ranging from 9.2% for $R=2$, to 14.3% for $R=15$ (Figure 7). Representative signal intensity curves reconstructed with increasing degrees of under-sampling show increasing difference with curves derived from the reference images (panel B). The higher acceleration rate with N_{RMSE} within 10% of the scanner reconstruction signal intensity curves was $R=4$ (gray dashed line, Figure 7, panel A). Based on these results we foresee that compressed sensing alone may allow accelerating 3D DCE-MRI up to 4 folds.

Discussion

To our knowledge this study describes the first validation of 3D black blood DCE-MRI to quantify microvascular permeability in the abdominal aorta of atherosclerotic rabbits. Microvascular permeability, together with plaque inflammation, is one of the recognized hallmarks of vulnerable atherosclerotic plaques at high-risk for causing severe cardiovascular events(1,2).

Previous studies have employed 2 dimensional (2D), multi-slice DCE-MRI to quantify microvascular permeability in the vessel wall (3-6,8-10,20-22,27,34). These approaches have yielded high, in-plane spatial resolution, to accurately delineate the atherosclerotic wall. However, these strategies provided limited anatomical coverage (necessary to evaluate this heterogeneous disease along a whole vessel), and relatively slow time resolution (thereby potentially compromising the accuracy of permeability quantification). To extend anatomical coverage, several groups have already proposed the use of 3D, high-resolution, isotropic, black blood acquisitions to characterize atherosclerotic plaque burden and composition in humans. To our knowledge these techniques have never been applied compared in atherosclerotic rabbits for DCE-MRI of the arterial vessel wall. These previous studies have focused on two types of acquisitions: 1) gradient echo based, with Motion Sensitized Driven Equilibrium (MSDE) for black blood imaging, so called 3D MERGE (MSDE prepared rapid gradient echo)(28,37); 2) spin echo based, using 3D SPACE (Sampling Perfection with Application optimized Contrast using different flip angle Evolutions)(29).

In this manuscript, we built upon these approaches and compared 3D turbo field echo (TFE) with MSDE preparation (equivalent to 3D MERGE) and 3D turbo spin echo (TSE, equivalent to 3D SPACE) between each other and with gold standard multi-slice, 2D double inversion recovery (DIR) turbo spin echo (TSE)(4) for DCE-MRI of aortic atherosclerosis in rabbits. We find a positive, significant correlation between in vivo microvascular permeability calculated from both 3D and 2D DCE-MRI and permeability calculated from ex vivo NIRF with Evans Blue. For both 3D and 2D sequences, we evaluated temporal stability metrics(39), intra and inter-observer reproducibility(49) (see Supplemental Materials) and correlation with ex vivo permeability. Among 3D sequences, 3D TFE DCE-MRI showed superior tSNR and tCNR, while both 3D TFE and TSE DCE-MRI showed significant correlation with ex vivo NIRF and good intra and inter-observer reliability.

Despite the higher steady state signal with a flip angle of 90° and $TR = 500$ ms enjoyed by 3D TSE compared to values of 20° and 6.2 ms of 3D TFE, the signal for 3D TSE can be

degraded by many factors. Predominantly, contamination of the T1 weighted signal by residual T2 weighting is more significant compared to that of the MSDE preparation and TFE readout. Furthermore, the variable refocusing flip angles train used in 3D TSE results in a lower flip angle at the center of k-space, which reduces the signal amplitude. Receiver bandwidth was also higher for 3D TSE (777 Hz/pixel) with respect to 3D TFE (360 Hz/pixel), therefore affecting the noise levels in the acquisition. Last but not least, the 3D TFE acquisition was acquired with 3 signal averages, while 3D TSE was averaged only once in the same frame duration. Take together, all these factors may have contributed to a lower signal enhancement and higher noise levels in the 3D TSE acquisition with respect to 3D TFE, thereby explaining our finding of lower temporal SNR and CNR for this sequence.

Contrarily to other studies(3) we have not found a positive correlation between the DCE-MRI parameter v_p (microvascular volume) and ex vivo permeability. This may be attributed to difference in the subjects examined (human carotid plaques(3,21,22) versus aorta of atherosclerotic rabbits(4,5,9,10)), MR acquisition parameters and sequences (bright(3,21,22) versus black(4,5,9,10) blood, 2D versus 3D), different time resolutions (~15s(3,21,22) versus ~30s) and direct AIF sampling(3,21,22) versus use of a population AIF, or non model based analysis methods^{4,5,9}. While they do not allow for direct AIF sampling, two dimensional black blood acquisitions, have been successfully employed in the past to quantify vessel wall microvasculature and permeability in atherosclerotic rabbits, either using non model-based approaches, or kinetic modeling (4,5,8-11,20,23,50). Our group has recently corroborated these previous findings using AUC calculated from 3D black blood DCE-MRI in two additional independent studies(12,50). While these results are encouraging, to mitigate possible inaccuracies in the quantification of vessel wall permeability when using a population AIF, our group and others are investigating either hybrid acquisition approaches(51) or relative modeling methods(52), to directly derive the AIF from the DCE-MRI data. Last but not least, the ex vivo validation method used in our study (ex vivo Evans Blue NIRF), is different than immunohistochemistry based methods used conventionally in other studies, a factor that may also have impacted the strength of the correlation between in vivo and ex vivo metrics. Evans Blue (EB) is a dye that binds to albumin and extravasates in tissues with increased microvascular permeability. EB has been previously validated as a measure of endothelial permeability in atherosclerotic mice(38) and rabbits(12,50). Better than immunohistochemistry, which is limited to few representative tissue samples, EB NIRF allows quantifying permeability along the whole rabbit abdominal aorta, thus closely matching the in vivo quantification of permeability by 3D DCE-MRI. However, EB has significantly higher molecular weight (66.5 kDa) than Gd-DTPA (0.547 kDa(53)), the contrast agent used for 3D DCE-MRI. This property affects the extravasation rates of the two molecules, with EB-albumin being slower with respect to Gd-DTPA, and requiring a highly permeable endothelium to extravasate, and may explain the fairly low correlation between ex vivo NIRF and 3D DCE-MRI. Ex vivo validation methods that more closely mimic the uptake of Gd-DTPA in the vessel wall, while maintaining the extensive anatomical coverage provided by NIRF are the subject of future investigations.

The second goal of our study was to explore the feasibility of using compressed sensing(54) to accelerate and improve the time resolution of 3D DCE-MRI, for a more accurate quantification of plaque microvasculature and permeability in atherosclerotic plaques.

Compressed sensing is a novel acceleration technique, that can be used alone or in combination with parallel imaging, to accelerate the acquisition of images that are “sparse” in a given transform domain(54). Using a previously validated compressed sensing algorithm, with temporal principal component analysis (PCA) as the sparsifying transform(46,47,55), we performed retrospective reconstructions using different acceleration rates (different levels of under-sampling)(48). Other studies have investigated the feasibility of using compressed sensing to accelerate the acquisition of 3D black blood vessel wall imaging(28,56,57), although none of these studies involved DCE-MRI. These studies employed spatial sparsifying transforms, different from the temporal PCA used in this study. We foresee that a combination of spatial and temporal sparsifying transforms may help accelerating 3D DCE-MRI acquisitions even further. A limitation of the compressed sensing feasibility analysis in this work is the retrospective nature of the reconstructions and the lack of validation with prospective acquisitions. As mentioned in the methods section, retrospective reconstructions were performed by Fourier transforming magnitude data therefore not taking into account information deriving from phase and different elements of the receiving coils, as well as previous under-sampling with SENSE parallel imaging. Using this approach alone we find that acceleration rates up to 4 fold can be achieved without significantly compromising vessel wall/lumen contrast or the quality of the tissue enhancement curves (within 10% of the scanner reconstructions). We anticipate that developing a prospective under-sampled acquisition and reconstruction including information from multiple receiving channels, and employing a combination of compressed sensing and parallel imaging (44) may yield even higher acceleration rates.

In conclusion, in this study we present the first systematic validation of 3D DCE-MRI to quantify microvascular permeability in the entire abdominal aorta of atherosclerotic rabbits. We compare two three dimensional sequences (3D TFE and 3D TSE DCE-MRI) among themselves and against 2D DIR TSE DCE-MRI, a previously validated acquisition. We find 3D TFE DCE-MRI to be superior to 3D TSE DCE-MRI in terms of temporal stability metrics. Both sequences showed good intra and inter-observer reliability, and significant correlation with ex vivo permeability measurements by Evans Blue NIRF. Furthermore, we perform retrospective reconstructions to explore the feasibility of improving 3D DCE-MRI of atherosclerosis by using compressed sensing acceleration. Our retrospective reconstructions suggest that compressed sensing alone may yield up to 4 fold acceleration rates. We anticipate that combining 3D DCE-MRI with prospective compressed acceleration, may allow for the improved quantification of both plaque microvascular volume (v_p) and permeability (K^{trans}) along an extensive anatomical region. This approach may allow for the improved evaluation of heterogeneous diseases (such as atherosclerosis) along an entire vessel. Furthermore, it may be useful as a tool for development of new anti-atherosclerotic compounds, whose impact on plaque permeability could be evaluated extensively and accurately in longitudinal in vivo studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH grants NIH/NHLBI R01 HL071021, R01 HL078667; NIH/NIBIB R01 EB009638 (Z.A.F.). C.C. is supported by a Post-Doctoral Fellowship from the American Heart Association (13POST16340006). O.L. is supported by a grant from the Fédération Française de Cardiologie. H.D. is supported by NIH/NINDS R00 NS070821-03. M.E.L. is supported by the Dutch network for Nanotechnology NanoNext NL in the subprogram Drug Delivery, as well as by the International Atherosclerosis Society and the Foundation “De Drie Lichten” in the Netherlands.

References

1. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol.* 2006; 47(8 Suppl):C13–18. [PubMed: 16631505]
2. Virmani R, Ladich ER, Burke AP, Kolodgie FD. Histopathology of carotid atherosclerotic disease. *Neurosurgery.* 2006; 59(5 Suppl 3):S219–227. discussion S213–213. [PubMed: 17053606]
3. Kerwin W, Hooker A, Spilker M, Vicini P, Ferguson M, Hatsukami T, Yuan C. Quantitative magnetic resonance imaging analysis of neovasculature volume in carotid atherosclerotic plaque. *Circulation.* 2003; 107(6):851–856. [PubMed: 12591755]
4. Calcagno C, Cornily JC, Hyafil F, Rudd JH, Briley-Saebo KC, Mani V, Goldschlager G, Machac J, Fuster V, Fayad ZA. Detection of neovessels in atherosclerotic plaques of rabbits using dynamic contrast enhanced MRI and 18F-FDG PET. *Arteriosclerosis, thrombosis, and vascular biology.* 2008; 28(7):1311–1317.
5. Chen H, Ricks J, Rosenfeld M, Kerwin WS. Progression of experimental lesions of atherosclerosis: Assessment by kinetic modeling of black-blood dynamic contrast-enhanced MRI. *Magn Reson Med.* 2012
6. Mani V, Wong SK, Sawit ST, Calcagno C, Maceda C, Ramachandran S, Fayad ZA, Moline J, McLaughlin MA. Relationship between particulate matter exposure and atherogenic profile in “Ground Zero” workers as shown by dynamic contrast enhanced MR imaging. *Int J Cardiovasc Imaging.* 2013; 29(4):827–833. [PubMed: 23179748]
7. Dong L, Kerwin WS, Chen H, Chu B, Underhill HR, Neradilek MB, Hatsukami TS, Yuan C, Zhao XQ. Carotid artery atherosclerosis: effect of intensive lipid therapy on the vasa vasorum—evaluation by using dynamic contrast-enhanced MR imaging. *Radiology.* 2011; 260(1):224–231. [PubMed: 21493792]
8. Lobatto ME, Fayad ZA, Silvera S, Vucic E, Calcagno C, Mani V, Dickson SD, Nicolay K, Banciu M, Schiffelers RM, Metselaar JM, van Bloois L, Wu HS, Fallon JT, Rudd JH, Fuster V, Fisher EA, Storm G, Mulder WJ. Multimodal clinical imaging to longitudinally assess a nanomedical anti-inflammatory treatment in experimental atherosclerosis. *Mol Pharm.* 2010; 7(6):2020–2029. [PubMed: 21028895]
9. Vucic E, Dickson SD, Calcagno C, Rudd JH, Moshier E, Hayashi K, Mounessa JS, Roytman M, Moon MJ, Lin J, Tsimikas S, Fisher EA, Nicolay K, Fuster V, Fayad ZA. Pioglitazone modulates vascular inflammation in atherosclerotic rabbits noninvasive assessment with FDG-PET-CT and dynamic contrast-enhanced MR imaging. *JACC Cardiovasc Imaging.* 2011; 4(10):1100–1109. [PubMed: 21999870]
10. Vucic E, Calcagno C, Dickson SD, Rudd JH, Hayashi K, Bucarius J, Moshier E, Mounessa JS, Roytman M, Moon MJ, Lin J, Ramachandran S, Tanimoto T, Brown K, Kotsuma M, Tsimikas S, Fisher EA, Nicolay K, Fuster V, Fayad ZA. Regression of inflammation in atherosclerosis by the LXR agonist R211945: a noninvasive assessment and comparison with atorvastatin. *JACC Cardiovasc Imaging.* 2012; 5(8):819–828. [PubMed: 22897996]
11. Lobatto ME, Calcagno C, Metselaar JM, Storm G, Stroes ES, Fayad ZA, Mulder WJ. Imaging the efficacy of anti-inflammatory liposomes in a rabbit model of atherosclerosis by non-invasive imaging. *Methods Enzymol.* 2012; 508:211–228. [PubMed: 22449928]
12. Kim Y, Lobatto ME, Kawahara T, Lee Chung B, Mieszawska AJ, Sanchez-Gaytan BL, Fay F, Senders ML, Calcagno C, Becraft J, Tun Saung M, Gordon RE, Stroes ES, Ma M, Farokhzad OC, Fayad ZA, Mulder WJ, Langer R. Probing nanoparticle translocation across the permeable

- endothelium in experimental atherosclerosis. *Proc Natl Acad Sci U S A*. 2014; 111(3):1078–1083. [PubMed: 24395808]
13. Yang X, Knopp MV. Quantifying tumor vascular heterogeneity with dynamic contrast-enhanced magnetic resonance imaging: a review. *J Biomed Biotechnol*. 2011:732–848.
 14. Ferl GZ, Port RE. Quantification of antiangiogenic and antivascular drug activity by kinetic analysis of DCE-MRI data. *Clin Pharmacol Ther*. 92(1):118–124. [PubMed: 22588603]
 15. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging*. 1999; 10(3):223–232. [PubMed: 10508281]
 16. Sourbron SP, Buckley DL. Tracer kinetic modelling in MRI: estimating perfusion and capillary permeability. *Phys Med Biol*. 2012; 57(2):R1–33. [PubMed: 22173205]
 17. Padhani AR. Dynamic contrast-enhanced MRI in clinical oncology: current status and future directions. *J Magn Reson Imaging*. 2002; 16(4):407–422. [PubMed: 12353256]
 18. Calcagno C, Mani V, Ramachandran S, Fayad ZA. Dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) of atherosclerotic plaque angiogenesis. *Angiogenesis*. 2010; 13(2):87–99. [PubMed: 20526859]
 19. Calcagno C, Ramachandran S, Millon A, Robson PM, Mani V, Fayad Z. Gadolinium-Based Contrast Agents for Vessel Wall Magnetic Resonance Imaging (MRI) of Atherosclerosis. *Curr Cardiovasc Imaging Rep*. 2013; 6(1):11–24. [PubMed: 23539505]
 20. Chen H, Wu T, Kerwin WS, Yuan C. Atherosclerotic plaque inflammation quantification using dynamic contrast-enhanced (DCE) MRI. *Quant Imaging Med Surg*. 2013; 3(6):298–301. [PubMed: 24404443]
 21. Kerwin WS, Oikawa M, Yuan C, Jarvik GP, Hatsukami TS. MR imaging of adventitial vasa vasorum in carotid atherosclerosis. *Magn Reson Med*. 2008; 59(3):507–514. [PubMed: 18306402]
 22. Kerwin WS, O'Brien KD, Ferguson MS, Polissar N, Hatsukami TS, Yuan C. Inflammation in carotid atherosclerotic plaque: a dynamic contrast-enhanced MR imaging study. *Radiology*. 2006; 241(2):459–468. [PubMed: 16966482]
 23. Calcagno C, Vucic E, Mani V, Goldschlager G, Fayad ZA. Reproducibility of black blood dynamic contrast-enhanced magnetic resonance imaging in aortic plaques of atherosclerotic rabbits. *J Magn Reson Imaging*. 2010; 32(1):191–198. [PubMed: 20578026]
 24. Cai J, Hatsukami TS, Ferguson MS, Kerwin WS, Saam T, Chu B, Takaya N, Polissar NL, Yuan C. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation*. 2005; 112(22):3437–3444. [PubMed: 16301346]
 25. van Wijk DF, Strang AC, Duivenvoorden R, Enklaar DJ, van der Geest RJ, Kastelein JJ, de Groot E, Stroes ES, Nederveen AJ. Increasing spatial resolution of 3T MRI scanning improves reproducibility of carotid arterial wall dimension measurements. *MAGMA*. 2013
 26. Millon A, Mathevet JL, Boussel L, Faries PL, Fayad ZA, Douek PC, Feugier P. High-resolution magnetic resonance imaging of carotid atherosclerosis identifies vulnerable carotid plaques. *J Vasc Surg*. 2013; 57(4):1046–1051. e1042. [PubMed: 23375613]
 27. Calcagno C, Ramachandran S, Izquierdo-Garcia D, Mani V, Millon A, Rosenbaum D, Tawakol A, Woodward M, Bucerius J, Moshier E, Godbold J, Kallend D, Farkouh ME, Fuster V, Rudd JH, Fayad ZA. The complementary roles of dynamic contrast-enhanced MRI and 18F-fluorodeoxyglucose PET/CT for imaging of carotid atherosclerosis. *Eur J Nucl Med Mol Imaging*. 2014; 40(12):1884–1893. [PubMed: 23942908]
 28. Li B, Dong L, Chen B, Ji S, Cai W, Wang Y, Zhang J, Zhang Z, Wang X, Fang J. Turbo fast three-dimensional carotid artery black-blood MRI by combining three-dimensional MERGE sequence with compressed sensing. *Magn Reson Med*. 2013; 70(5):1347–1352. [PubMed: 23280949]
 29. Fan Z, Zhang Z, Chung YC, Weale P, Zuehlsdorff S, Carr J, Li D. Carotid arterial wall MRI at 3T using 3D variable-flip-angle turbo spin-echo (TSE) with flow-sensitive dephasing (FSD). *J Magn Reson Imaging*. 2010; 31(3):645–654. [PubMed: 20187208]

30. Larsson C, Kleppeto M, Rasmussen I Jr, Salo R, Vardal J, Brandal P, Bjornerud A. Sampling requirements in DCE-MRI based analysis of high grade gliomas: simulations and clinical results. *J Magn Reson Imaging*. 2013; 37(4):818–829. [PubMed: 23086710]
31. Li X, Huang W, Rooney WD. Signal-to-noise ratio, contrast-to-noise ratio and pharmacokinetic modeling considerations in dynamic contrast-enhanced magnetic resonance imaging. *Magn Reson Imaging*. 2012; 30(9):1313–1322. [PubMed: 22795931]
32. Heisen M, Fan X, Buurman J, van Riel NA, Karczmar GS, ter Haar Romeny BM. The influence of temporal resolution in determining pharmacokinetic parameters from DCE-MRI data. *Magn Reson Med*. 2010; 63(3):811–816. [PubMed: 20187187]
33. Evelhoch JL. Key factors in the acquisition of contrast kinetic data for oncology. *J Magn Reson Imaging*. 1999; 10(3):254–259. [PubMed: 10508284]
34. Chen H, Cai J, Zhao X, Underhill H, Ota H, Oikawa M, Dong L, Yuan C, Kerwin WS. Localized measurement of atherosclerotic plaque inflammatory burden with dynamic contrast-enhanced MRI. *Magn Reson Med*. 2010; 64(2):567–573. [PubMed: 20665799]
35. Phinikaridou A, Andia ME, Protti A, Indermuehle A, Shah A, Smith A, Warley A, Botnar RM. Noninvasive magnetic resonance imaging evaluation of endothelial permeability in murine atherosclerosis using an albumin-binding contrast agent. *Circulation*. 2012; 126(6):707–719. [PubMed: 22753191]
36. Phinikaridou A, Andia ME, Passacquale G, Ferro A, Botnar RM. Noninvasive MRI monitoring of the effect of interventions on endothelial permeability in murine atherosclerosis using an albumin-binding contrast agent. *J Am Heart Assoc*. 2013; 2(5):e000402. [PubMed: 24072533]
37. Balu N, Yarnykh VL, Chu B, Wang J, Hatsukami T, Yuan C. Carotid plaque assessment using fast 3D isotropic resolution black-blood MRI. *Magn Reson Med*. 2011; 65(3):627–637. [PubMed: 20941742]
38. Lundeberg E, Van Der Does AM, Kenne E, Soehnlein O, Lindbom L. Assessing large-vessel endothelial permeability using near-infrared fluorescence imaging--brief report. *Arteriosclerosis, thrombosis, and vascular biology*. 2015; 35(4):783–786.
39. Murphy K, Bodurka J, Bandettini PA. How long to scan? The relationship between fMRI temporal signal to noise ratio and necessary scan duration. *Neuroimage*. 2007; 34(2):565–574. [PubMed: 17126038]
40. Schabel MC, Parker DL. Uncertainty and bias in contrast concentration measurements using spoiled gradient echo pulse sequences. *Phys Med Biol*. 2008; 53(9):2345–2373. [PubMed: 18421121]
41. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging*. 1997; 7(1):91–101. [PubMed: 9039598]
42. Yang Q, Liu J, Barnes SR, Wu Z, Li K, Neelavalli J, Hu J, Haacke EM. Imaging the vessel wall in major peripheral arteries using susceptibility-weighted imaging. *J Magn Reson Imaging*. 2009; 30(2):357–365. [PubMed: 19629989]
43. Johansson L, Kirchin MA, Ahlstrom H. Gadobenate dimeglumine (MultiHance) in MR angiography: an in-vitro phantom comparison with gadopentetate dimeglumine (Magnevist) at different concentrations. *Acta Radiol*. 2012; 53(10):1112–1117. [PubMed: 23081961]
44. Nguyen VL, Kooi ME, Backes WH, van Hoof RH, Saris AE, Wishaupt MC, Hellenthal FA, van der Geest RJ, Kessels AG, Schurink GW, Leiner T. Suitability of pharmacokinetic models for dynamic contrast-enhanced MRI of abdominal aortic aneurysm vessel wall: a comparison. *PLoS One*. 2013; 8(10):e75173. [PubMed: 24098370]
45. McGrath DM, Bradley DP, Tessier JL, Lacey T, Taylor CJ, Parker GJ. Comparison of model-based arterial input functions for dynamic contrast-enhanced MRI in tumor bearing rats. *Magn Reson Med*. 2009; 61(5):1173–1184. [PubMed: 19253360]
46. Otazo R, Kim D, Axel L, Sodickson DK. Combination of compressed sensing and parallel imaging for highly accelerated first-pass cardiac perfusion MRI. *Magn Reson Med*. 2010; 64(3):767–776. [PubMed: 20535813]
47. Kim D, Dyvorne HA, Otazo R, Feng L, Sodickson DK, Lee VS. Accelerated phase-contrast cine MRI using k-t SPARSE-SENSE. *Magn Reson Med*. 2012; 67(4):1054–1064. [PubMed: 22083998]

48. Calcagno, C.; Dyvorne, H.; Otazo, R.; Robson, P.; Lobatto, ME.; Ramachandran, S.; Mani, V.; Fayad, ZA. Compressed sensing (CS) for dynamic contrast enhanced (DCE) MRI of atherosclerosis: preliminary experience in a rabbit model of disease. International Society for Magnetic Resonance in Medicine; 20th Annual Meeting and Exhibition; Melbourne, Australia. 2012.
49. Hotker AM, Schmidtman I, Oberholzer K, Duber C. Dynamic contrast enhanced-MRI in rectal cancer: Inter- and intraobserver reproducibility and the effect of slice selection on pharmacokinetic analysis. *J Magn Reson Imaging*. 2013
50. Lobatto ME, Calcagno C, Millon A, Senders ML, Fay F, Robson PM, Ramachandran S, Binderup T, Paridaans MP, Sensarn S, Rogalla S, Gordon RE, Cardoso L, Storm G, Metselaar JM, Contag CH, Stroes ES, Fayad ZA, Mulder WJ. Atherosclerotic plaque targeting mechanism of long-circulating nanoparticles established by multimodal imaging. *ACS nano*. 2015; 9(2):1837–1847. [PubMed: 25619964]
51. Wu T, Wang J, Song Y, Deng X, Li A, Wei J, He L, Zhao X, Li R, Zhou Z, Wu W, Huang J, Jiao S, Yuan C, Chen H. Homologous black-bright-blood and flexible interleaved imaging sequence (HOBBI) for dynamic contrast-enhanced MRI of the vessel wall. *Magn Reson Med*. 2015; 73(5): 1754–1763. [PubMed: 24805922]
52. Yankeelov TE, Luci JJ, Lepage M, Li R, Debusk L, Lin PC, Price RR, Gore JC. Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model. *Magn Reson Imaging*. 2005; 23(4):519–529. [PubMed: 15919597]
53. Bock JC, Kaufmann F, Felix R. Comparison of gadolinium-DTPA and macromolecular gadolinium-DTPA-polylysine for contrast-enhanced pulmonary time-of-flight magnetic resonance angiography. *Invest Radiol*. 1996; 31(10):652–657. [PubMed: 8889654]
54. Lustig M, Donoho D, Pauly JM. Sparse MRI: The application of compressed sensing for rapid MR imaging. *Magn Reson Med*. 2007; 58(6):1182–1195. [PubMed: 17969013]
55. Calcagno C, Dyvorne HA, Otazo R, Robson PM, Lobatto ME, Ramachandran S, Mani V, Fayad ZA. Compressed Sensing (CS) for Dynamic Contrast Enhanced (DCE) MRI of Atherosclerosis: Preliminary Experience in a Rabbit Model of Disease. 2012
56. Prieto C, Andia ME, von Bary C, Onthank DC, Schaeffter T, Botnar RM. Accelerating three-dimensional molecular cardiovascular MR imaging using compressed sensing. *J Magn Reson Imaging*. 36(6):1362–1371. [PubMed: 22865680]
57. Makhijani MK, Balu N, Yamada K, Yuan C, Nayak KS. Accelerated 3D MERGE carotid imaging using compressed sensing with a hidden Markov tree model. *J Magn Reson Imaging*. 36(5):1194–1202. [PubMed: 22826159]

List of abbreviations

2D	2 dimensional
3D	3 dimensional
3D MERGE	3D MSDE prepared rapid gradient echo
3D SPACE	3D Sampling Perfection with Application optimized Contrast using different flip angle Evolutions
CNR	contrast to noise ratio
DCE-MRI	dynamic contrast enhanced magnetic resonance imaging
DIR	double inversion recovery
EB	Evans Blue
Gd-DTPA	gadopentatedimeglumine

Kt-SPARSE SENSE	Kt-SPARSE SENSitivity Encoding
IACUC	Institutional Animal Care and Use Committee
MPR	multi-planar reconstruction
MSDE	motion sensitized driven equilibrium
N_RMSE	normalized root mean squared error
NIRF	near infra red fluorescence
NZW	New Zealand White (rabbit)
PCA	principal component analysis
ROI	region of interest
SNR	signal to noise ratio
TFE	turbo field echo
TSE	turbo spin echo

Figure 1.

A and B, curved maximum intensity projection (MPR) of the abdominal aorta of one rabbit imaged using 3D TFE and TSE DCE-MRI, respectively. Orange lines indicate the left renal artery and the iliac bifurcation. C and D, one representative axial slice of the abdominal aorta of the same rabbit shown in A and B, imaged using 3D TFE and TSE DCE-MRI, respectively. E, one representative axial slice of the same rabbit, imaged using 2D TSE DIR. Red arrow indicates the abdominal aorta. F, time-intensity curves for an aortic ROI in the same axial slice showed in C-E for all 3 sequences. Blue line, 3D TFE DCE-MRI. Red line, 3D TSE DCE-MRI. Green line, 2D DIR TSE DCE-MRI. Gray bars indicate the data points from which temporal SNR and CNR were calculated. X axis, time (min). Y axis, signal intensity (a.u.).

Figure 2. Average temporal signal-to-noise ratio (tSNR, panel A) and temporal contrast-to-noise ratio (tCNR, panel B) for 3D TFE (blue bar), 3D TSE (red bar) and 2D DIR (green bar) DCE-MRI. Black lines represent the standard deviation of the mean. Black stars indicate significant difference ($p < 0.05$).

Figure 3. Difference between AUC (panel A) and K^{trans} (panel B) for atherosclerotic and control animals. For each sequence darker colors represent atherosclerotic animals, while lighter shades represent the control rabbits. Black lines, error bars (standard deviation of the mean). Asterisk indicates significant difference.

Figure 4. Difference between permeability in atherosclerotic (A) and control (B) animals. Hotter colors in AUC maps and EB images indicated higher permeability. Yellow lines indicate the left renal artery and the iliac bifurcation. The higher ex vivo permeability of the atherosclerotic rabbit (EB) is mirrored in the “hotter” AUC maps. On the contrary the control animal shows poor Evans Blue uptake and very low AUC maps.

Figure 5.

Correlations between in vivo permeability by DCE-MRI and ex vivo permeability by Evans Blue near infra red fluorescence. Panel A, 3D TFE DCE-MRI (blue). Panel B, 3D TSE DCE-MRI (red). Panel C, 2D DIR TSE DCE-MRI (green). Black dashed line, regression line.

Figure 6.

A, vessel wall/lumen contrast is shown to decrease with increasing acceleration rate, indicating blurring and poorer wall/lumen delineation with increasing under-sampling. Red dashed line, vessel wall/lumen contrast within 5% of the fully sampled acquisition. Gray dashed line, vessel wall/lumen contrast within 10% of the fully sampled acquisition. Vertical black lines, standard deviation. B, representative images of the dynamic series (averaged in the time dimension) reconstructed with compressed sensing after different degrees of under-sampling. Vessel wall is bright after contrast agent injection. Images show increased

blurring at high accelerations. S, fully sampled scanner reconstruction, used as the reference image. Based on data shown in panel A, reconstruction from data under-sampled 8 fold show vessel wall/lumen delineation within 10% of the reference images (S).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 7.

A, normalized root mean square error between curves derived from under-sampled and fully sampled (scanner) reconstructions. N_RMSE is shown to increase with increasing acceleration. Gray dashed line, N_RMSE within 10% of scanner reconstruction. Vertical black lines, standard deviation. B, representative signal intensity curves from acceleration 2,4,6 and 15. S, scanner reconstruction.

Table 1

Sequence Parameters	2D DIR TSE	3D MSDE TFE	3D TSE
Echo time (TE), ms	10	2.8	55.42
Repetition time (TR), ms	400	6.2	500
Excitation flip angle (FA)	90°	20°	90°
Refocusing FA	115°	NA	Variable
Fat Suppression (SPIR)	ON	ON	ON
In plane spatial resolution	0.6mm ²	0.6mm ²	0.6 mm ²
Slice Thickness	3mm	0.6mm	0.6mm
Number of slices	5	20	20
Acquisition plane	Axial	Sagittal	Sagittal
Number of averages	1	3	1
Echo Train Length	5	80	25
Pixel Bandwidth (Hz/pixel)	534	360	777
Parallel imaging (SENSE)	2	2	2
Half scan	0.6	NA	NA
Temporal resolution	26s	32s	36s
Number of frames	25	20	20