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3D Dynamic Contrast Enhanced Imaging of the Carotid Artery with Direct Arterial Input Function Measurement

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Abstract

Purpose—Kinetic analysis using dynamic contrast enhanced MRI to assess neovascularization of carotid plaque requires images with high spatial and temporal resolution. This work demonstrates a new 3D dynamic contrast enhanced imaging sequence, which directly measures the arterial input function with high temporal resolution yet maintains the high spatial resolution required to identify areas of increased adventitial neovascularity.

Theory and Methods—The sequence consists of multiple rapid acquisitions of a saturation prepared dynamic 3D gradient recalled echo (GRE) sequence temporally interleaved with multiple acquisitions of a 2D slice. The saturation recovery time was adjusted to maintain signal linearity with the very different contrast agent concentrations in the 2D slice and 3D volume. The K^{trans} maps were obtained from the 3D dynamic contrast measurements while the 2D slice was used to obtain the arterial input function. Calibration and dynamic studies are presented

Results—For contrast agent concentrations up to 5mM, a saturation recovery time for the 2D slice of 20ms resulted in less than a 10% deviation from the desired linear response of signal intensity with contrast agent concentration. The corresponding saturation recovery time of 83 ms for the 3D volume maintained less than a 10% deviation from the linear response up to contrast agent concentrations of 2mM while a contrast agent concentration of 5mM had almost a 30% deviation. There was a significant improvement in signal attenuation ($9 \pm 3\%$ vs $23 \pm 5\%$ at 40cm/s) when flow compensation was added to the slice select gradients. For patient studies, volume transfer and plasma fraction maps were calculated with data from the proposed sequence.

Conclusions—This work demonstrated a novel sequence for 3D dynamic contrast enhanced imaging with a simultaneously acquired 2D slice that directly measures the arterial input function with high temporal resolution. Acquisition parameters can be adjusted to accommodate the full

range of contrast agent concentration values to be encountered and the kinetic parameters obtained were consistent with expected values.

Keywords

Carotid Plaque; Dynamic Contrast Enhanced; Carotid Inflammation; Plaque Progression

INTRODUCTION

Neovascularization of adventitial vasa vasorum has been shown to play a significant role in both progression and instability of carotid plaque (1–10). There is evidence that adventitial neovascularity correlates with histological measures of plaque inflammation (macrophages and vascular density) and can be identified from kinetic analysis of dynamic contrast enhanced (DCE) spoiled gradient echo images (11–16). The DCE methods either estimate the area under the enhancement curve (17) or K^{trans} and v_p (12, 13, 16) which reflect permeability and vascularity.

One current problem is that the trade-off between spatial and temporal resolution limits assessment to a small number of 2D slices and ~15 seconds per time frame (12). Although an arterial input function (AIF) can be estimated by fitting an appropriate function to low temporal resolution data (18, 19), the use of an individually measured AIF is important for accurate kinetic parameter calculation (20, 21). Henderson et al. suggest that the AIF may need to be sampled every 1 second to ensure less than a 10% error in K^{trans} (22) and other studies suggest the tissue signal should have a maximum sampling time of about 12 seconds (23, 24).

Since the primary application of this work is to characterize plaque stability and predict future cerebral ischemic events, better spatial resolution would be valuable in detecting small changes in plaque vascularity. While previous studies have achieved an in-plane resolution of less than 1mm, 2D slice thickness has been limited to 3mm with a 1mm gap between slices. A 3D volume resolves these through plane issues, benefits from increased SNR and adds the ability to apply interpolation or undersampling techniques in the slice direction.

Another problem is that when the same data is used to determine blood and tissue contrast agent concentrations, only one saturation recovery time (SRT) is used. The higher contrast agent concentration expected in the blood requires a short SRT to prevent saturation of the signal, however, the lower contrast agent concentration in tissue would benefit from a longer SRT. Dual slice techniques have been used in cardiac applications (25–27) to address this issue but compound the previously mentioned tradeoff between spatial and temporal resolution. This can be partially overcome by acquiring a low spatial/high temporal resolution slice to determine the AIF while using a high spatial/low temporal resolution slice to determine the tissue enhancement (28). However, the small diameter of the common carotid artery (~6.5mm in men) make it difficult to reduce in-plane resolution without encountering errors due to partial volume effects of the vessel lumen and wall (29).

This work demonstrates the use of a 3D dynamic contrast enhanced imaging sequence which directly measures the arterial input function. A high temporal resolution 2D slice was temporally interleaved with the acquisition of a high spatial resolution 3D volume. The 2D slice was acquired in close spatial proximity to the 3D volume which allowed blood contrast agent concentration to be determined from the 2D images while tissue contrast agent concentrations were determined from the 3D images. The main objectives considered in this work were to estimate the range of blood and tissue contrast agent concentrations that could be accurately measured by the proposed sequence, demonstrate the ability of the proposed sequence to capture the contrast agent concentration dynamics and apply the sequence to a patient with known carotid disease.

THEORY

A fast low angle shot (FLASH or spoiled gradient recalled echo) sequence was modified to acquire temporally interleaved 2D and 3D data. To allow comparison of the AIF from the 2D slice and 3D volume, the 2D data were acquired from a slice downstream (towards the patient's head) from the 3D imaging volume (Figure 1a). This prevented previously excited blood from the 2D slice from entering the 3D volume. For clinical applications it is not necessary to compare the input function from the 2D slice and 3D volume and the AIF slice may be placed either upstream or downstream from the tissue of interest.

The total number of lines in the 2D slice was kept the same as the total number of lines in a 3D partition. Thus during the acquisition of a full 3D volume with N_p partitions, the 2D slice was acquired N_p times. Data were acquired in a segmented fashion such that each sequence block consisted of a nonselective saturation pulse followed by N_l 2D lines and N_l 3D lines (Figure 1b).

Buckley et al. demonstrated the importance of model selection in minimizing uncertainty with tracer kinetics (30). Although Chen et al. showed that the extended graphical model exhibits better performance for some combinations of kinetic parameters, they described the modified Kety/Tofts as the most biologically accurate when data acquisitions are long in duration (16). A linear version of the modified Kety/Tofts is (31):

$$C_t(t) = v_p C_p(t) + K^{trans} \left(1 + \frac{v_p}{v_e} \right) \int_0^t C_p(\tau) d\tau - \frac{K^{trans}}{v_e} \int_0^t C_t(\tau) d\tau \quad [1]$$

where $C_t(t)$ is the total tissue contrast agent concentration, $C_p(t)$ is the blood plasma contrast agent concentration, K^{trans} is the volume transfer constant and v_p and v_e are the fractional volumes of blood and extravascular-extracellular space respectively. A centric encoding scheme was used as suggested by Kim et al. (32). While in this work a constant flip angle was used for both the 2D slice and 3D volume, there is evidence that two different flip angles should be used (33).

METHOD

All studies were performed on a MAGNETOM TIM Trio 3T MRI scanner (Siemens Healthcare, Erlangen, DE) with all human studies approved by the institutional review

board. Phantom experiment data were acquired with a 12 channel head coil while patient data were acquired with a 16 element phased array surface coil (34). Patients were required to have a minimum Glomerular Filtration Rate of 45 mL/min/1.73m² and to provide informed consent. The contrast agent used in this work was Gd-BOPTA (Gadobenate dimeglumine or MULTIHANCE, Bracco Diagnostics, Princeton, NJ) (35).

For the first objective, a phantom with a set of vials (50ml, 2.7cm diameter) containing various contrast agent concentrations (mixed with saline) was constructed. The contrast agent concentrations were calculated from T_1 relaxation times measured with an inversion recovery GRE sequence. Data were segmented with 3 centrically encoded lines acquired each TR interval (TR=10s). Other relevant parameters were TE=4.21ms, 192 × 162 voxels (123 lines with partial Fourier), 1mm × 1mm × 5mm resolution, 15° flip angle, 6 minutes 50 seconds acquisition time per image with 11 total images (TI=30ms, 40ms, 50ms, 60ms, 80ms, 100ms, 200ms, 300ms, 500ms, 1000ms and 2000ms). Contrast agent concentration was calculated with the following equation:

$$\frac{1}{T_1} = \frac{1}{T_{1(0)}} + r \cdot C \quad [2]$$

where a vial of pure saline was included to determine $T_{1(0)}$ and relaxivity of the contrast agent was taken as 4.0 s⁻¹ as shown by Rohrer et al. (36). Signal intensity was measured as the average signal in a 2cm circular region of interest centered on each vial. The calculated agent concentrations ranged from 0 mM (pure saline) to 5 mM.

The proposed DCE sequence was then applied to the same phantom with four different saturation recovery times (SRT_{2D} =20ms, 40ms, 60ms and 80ms corresponding to SRT_{3D} =83ms, 103ms, 123ms and 143ms respectively). Other parameters of the DCE sequence were 256 × 216 voxels (170 lines with partial Fourier), 17 segments per TR, 0.75mm × 0.75mm × 7mm resolution for the 2D slice, 8 partitions (6 partitions with partial Fourier) with 0.75mm × 0.75mm × 1mm resolution for the 3D volume, 20mm distance between the center of the 2D slice and 3D volume, 15° flip angle, TE=1.76ms and TR=171.56ms, 191.56ms, 211.56ms and 231.56ms corresponding to the different saturation recovery times (corresponding 2D/3D temporal resolutions were 1.7s/10.3s, 1.9s/11.5s, 2.1s/12.7s and 2.3s/13.9s).

To test the second objective a flow phantom with 20m of 0.5cm diameter tubing with a total system capacity of about 1100ml was used. Velocities inside the tube were measured with a 2D phase contrast GRE sequence with 256 × 128 voxels, 0.75mm × 0.75mm × 5mm resolution, 15° flip angle, TE=10ms and TR=150ms. Peak velocity available from the selected pump was about 60 cm/s.

The proposed DCE sequence was applied with and without flow compensating gradients in the slice direction and signal intensity was measured at different velocities and contrast agent concentrations (1.3mM, 1.9mM and 2.5mM). Imaging parameters of the DCE sequence were 256 × 216 voxels (170 lines with partial Fourier), 17 segments per TR, 0.75mm × 0.75mm × 7mm resolution for the 2D slice, 8 partitions (6 partitions with partial Fourier) with 0.75mm × 0.75mm × 1mm resolution for the 3D volume, 20mm distance

between the center of the 2D slice and 3D volume, 15° flip angle and $SRT_{2D}=20\text{ms}$. In addition, TE increased to 2.41ms (from 1.76ms) and TR increased to 185.84ms (from 171.56ms) to accommodate the flow compensating gradients. Signal intensity was taken as the average signal within a 0.3cm diameter circular region (centered on a 0.5cm diameter tube). Attenuation values were determined by comparing signal intensity at a selected velocity with the signal intensity with no flow.

Two dynamic experiments were also performed with the flow phantom. Data were acquired with the proposed DCE sequence for both a low and high dose of injected contrast agent (with peak contrast agent concentrations of 0.2mM and 1.6mM respectively). Imaging parameters of the DCE sequence were 128×128 voxels (108 lines with partial Fourier), 27 segments per TR, $1.0\text{mm} \times 1.0\text{mm} \times 7\text{mm}$ resolution for the 2D slice, 8 partitions (6 partitions with partial Fourier) with 1.0mm isotropic resolution for the 3D volume, 20mm distance between the center of the 2D slice and 3D volume, 15° flip angle, $SRT_{2D}=50\text{ms}$, $SRT_{3D}=139\text{ms}$, TE=1.55ms and TR=264ms. A total of 60 data sets were acquired over 5 minutes 56 seconds (corresponding temporal resolution of the 2D/3D data sets were 1.0s/ 5.9s). The input functions from the 2D slice and 3D volumes were calculated from the average signal over a 0.3cm diameter circular region (centered on a 0.5cm diameter tube). Input functions were converted to contrast agent concentrations using the relaxation time of saline measured during the first objective of this work ($T_1=2.2\text{s}$).

For the last objective, a patient with known carotid disease was imaged. Relevant parameters of the DCE sequence were 192×192 voxels (170 lines with partial Fourier), 17 segments per TR, $0.82\text{mm} \times 0.82\text{mm} \times 7\text{mm}$ resolution for the 2D slice, 8 partitions (6 partitions with partial Fourier) with $0.82\text{mm} \times 0.82\text{mm} \times 1\text{mm}$ resolution for the 3D volume, 20mm distance between the center of the 2D slice and 3D volume, 15° flip angle, TE=2.42ms and TR=184.14. The temporal resolution of the each 3D measurement was 11s with 30 measurements acquired over a period of 5 minutes 31 seconds. The temporal resolution of each fully sampled 2D slice was 1.8s. A full dose of contrast agent (13.7ml) followed by 20ml of saline flush were injected at a rate of 2ml/s. The sequence ran for about 50s before the injection was started. The input function from the 2D slice and 3D volume were calculated from the average signal over a 0.3cm diameter circular region centered on the carotid artery being investigated. Signal intensities from the 2D slice and 3D volume AIF were converted to contrast agent concentrations assuming a T_1 relaxation time of blood of 1.65s (37), $SRT_{2D}=20\text{ms}$ and $SRT_{3D}=139\text{ms}$.

RESULTS

The signal intensity of selected contrast agent concentrations in saline are plotted in Figure 2. For contrast agent concentrations up to 5mM, a saturation recovery time for the 2D slice of 20ms resulted in less than a 10% deviation from the desired linear response of signal intensity with contrast agent concentration (solid black line in Fig. 2c). The corresponding saturation recovery time of 83 ms for the 3D volume maintained less than a 10% deviation from the linear response up to contrast agent concentrations of 2mM (dashed black line in Fig. 2c) while a contrast agent concentration of 5mM had almost a 30% deviation. Low signal to noise at low concentrations ($<0.5\text{mM}$) resulted in a false increase in deviation.

Signal attenuation was measured for three different contrast agent concentrations (1.3mM, 1.9mM and 2.5mM) over a range of flow velocities (Figure 3). There was a significant improvement in signal attenuation ($9\pm3\%$ vs $23\pm5\%$ at 40cm/s) when flow compensation was added to the slice select gradients.

In Figure 4, the input function calculated from the 2D slice is compared to the input function calculated from the 3D volume. For the lower dose phantom study (Fig. 4a) the standard deviation of the difference between the input function from the 3D volume and the input function from the 2D slice was 0.02mM with a maximum difference during the first pass peak of 0.04mM. However, for the higher dose phantom study, the standard deviation of the difference between the 2D and 3D derived input functions was 0.08mM with a maximum difference during the first pass peak of 0.35mM (Fig. 4b).

The AIF and kinetic parameter maps for a patient with known carotid disease are shown in Figure 4c and Figure 5 respectively. The input function from the 3D volume was saturated during the first pass peak (red line in Fig. 4c) differing by 2.28mM from the input function derived from the 2D slice. The black arrow indicates an area of the internal carotid artery wall with increased K^{trans} (Figure 5).

DISCUSSION

This work has presented a temporally interleaved dual imaging DCE sequence suitable for measuring adventitial neovascularity in the carotid artery. If the signal intensities scale linearly with contrast agent concentration then calculation of dynamic model parameters (v_p and K^{trans}) can be done with appropriately scaled signal intensities. The difference in saturation recovery times for the 2D slice and 3D volume require the arterial input function (derived from the 2D slice) to be appropriately scaled (to match the 3D volume). To calculate the scale factor only the tail end of the input functions should be matched since the AIF signal intensity in the 3D volume is expected to saturate during the first pass peak. If the range of contrast agent concentration is too large, then signal intensities will not scale linearly with contrast agent concentration and signal intensities must be first converted to contrast agent concentrations. To avoid this conversion step, the saturation recovery times should be calibrated so that signal intensities scale linearly within the expected range of contrast agent concentrations.

The saturation recovery time for the 2D slice should be as long as possible to maximize recovery but short enough to prevent saturation. Some studies suggest that when the error of the input function reaches ~25%, more accurate and robust parameter estimation can be achieved by fitting a biexponential function to more slowly but more accurately sampled data (24). Ishida et al. reported that for a standard dose and injection rate of 3ml/s, the average peak contrast agent concentration in the aorta was 4.9mM (38). For the 2D slice, with a saturation recovery time of 20ms (black line in Fig. 2a), the expected 10% error in AIF estimation at 5mM would still favor an individually sampled AIF over a model based method. For the 3D volume, the corresponding saturation recovery time ($SRT_{3D}=83ms$) resulted in a 10% error in tissue enhancement for contrast agent concentrations up to 2mM (black line in Fig. 2b). The contrast agent concentration in tissue is not expected to exceed

2mM. If it does, SRT_{3D} can be decreased by decreasing the number of lines acquired each TR interval. For our patient data, the contrast agent concentration in tissue is not expected to exceed 1mM and SRT_{3D} was increased to 139ms (total measurement time was 11 seconds). Schabel et al. report that a total measurement time of 12s showed minimal bias and uncertainty while the bias and uncertainty become abruptly larger for measurement times of 14s or longer (23).

For the application of DCE to the carotid artery our preferred slice orientation was in the transverse plane. As such, it was the slice direction that would most benefit from flow compensated gradients. Flow phantom results indicate that when no through plane flow compensating gradients were used, signal attenuation was $23 \pm 5\%$ at 40cm/s (solid lines in Fig. 3). This is significant since peak systolic velocity of blood in the carotid artery frequently exceeds 80cm/s (39).

For injections of low doses of contrast agent, the AIF from the 3D volume matched well with the AIF calculated from the 2D slice (Figure 4). In this case, the advantage of using the AIF derived from the 2D slice was increased temporal resolution. However, with higher doses of contrast agent, the AIF derived from the 3D volume was seen to saturate during the first pass peak (as evidenced by the mismatch with the AIF from the 2D slice in Fig. 4b). In this case, the AIF derived from the 2D slice offered increased temporal resolution and accuracy.

Although v_p and K^{trans} maps are shown for a patient with known carotid disease (Fig. 5), with reasonable values of K^{trans} (15), the authors acknowledge that the sequence has been applied to limited number of patients. However, the main purpose of this work was to show the feasibility of a temporally interleaved carotid DCE pulse sequence to directly measure the arterial input function.

CONCLUSION

This work demonstrated a novel sequence for 3D dynamic contrast enhanced imaging with a simultaneously acquired 2D slice that directly measures the arterial input function with high temporal resolution. The effective saturation delay times for 2D and 3D acquisitions were adjusted to accommodate different ranges of contrast agent concentrations in blood pool and tissue. The temporal resolution of the arterial input function and tissue enhancement signal were within the range suggested to obtain accurate kinetic parameter estimations. Kinetic parameter estimations obtained from a patient with known carotid disease were consistent with expected values.

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Figure 1.

Slice position and basic sequence block of the proposed DCE sequence. Spatial location of the temporally interleaved 2D slice and 3D imaging volume is shown in (a). A nonselective saturation pulse was followed by a small saturation recovery time (SRT_{2D}) and then the acquisition of N_I 2D and N_I 3D lines as shown in (b).

Figure 2.

Linearity of the measured signal with varying contrast agent concentrations. Data from the 2D slice is shown in (a) with corresponding data from the 3D volume shown in (b). The circles are measured data while the lines are the linear fit to the low contrast agent concentration data ($<1\text{mM}$) for each saturation recovery time. The deviation of the measured data from the desired linear response are shown in (c) for $SRT_{2D}=20\text{ms}$ and $SRT_{3D}=83\text{ms}$.

Figure 3.

Signal attenuation due to flow with the proposed DCE sequence at various contrast agent concentrations. The solid lines indicate signal attenuation of the sequence with no flow compensation. The dashed lines are the corresponding signal attenuation when slice select flow compensating gradients were added.

Figure 4.

Input functions of the proposed DCE sequence. The blue lines represent input functions from the 2D slice while the red lines correspond to the input function measured from the 3D volume. For flow phantom studies, the lower dose of contrast agent is shown in (a) while the results from a higher dose of contrast agent are shown in (b). Patient arterial input function with a standard dose of contrast agent is shown in (c).

Figure 5.

Volume transfer constant and plasma fraction maps from a patient with known carotid disease. The K^{trans} (min⁻¹) and v_p maps of the right internal/external carotid arteries are shown in (a) and (b) respectively. A corresponding dark blood TSE image is shown in (c) for reference. The arrow indicates an area of the carotid wall with increased K^{trans} .