3D MRA Visualization and Artery-Vein Separation Using Blood-Pool Contrast Agent MS-325

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RATIONALE AND OBJECTIVES

Magnetic resonance angiography (MRA) is established as an important complementary technique to conventional angiography, and contrast-enhanced MRA (CE-MRA) offers even higher contrast between the vascular lumen and surrounding structures. MS-325 is a gadolinium-based MR contrast agent designed specifically for blood-pool imaging, or MRA, and is the only gadolinium-based intra-vascular contrast agent undergoing trials in humans. MS-325 provides excellent vascular and selective arterial enhancement during dynamic MRA. The long blood residence time also allows acquisition of steady-state images of the arteries and veins with excellent spatial resolution (1,2).

With the increasing use of CE-MRA, venous contamination of arterial images becomes a common concern (ie, venous enhancement may confound the visualization of arteries). Currently available viewing techniques, such as targeted maximum intensity projection, multiplanar reformation, and “fly through” used in virtual endoscopy, can be used only to minimize this problem but not to solve it (3,4). These techniques are also time intensive and require more operators. Although the ability to acquire dynamic images may facilitate artery-vein separation by providing an artery mask that can be applied to steady-state images, this approach requires motion correction and image registration between dynamic and steady-state images.

The separation of artery and vein is of significant importance to correctly diagnose and treat peripheral vascular diseases. The strategies for artery-vein separation include both acquisition methods and postprocessing techniques. Among the current developments, acquisition methods include phase-contrast and time-resolved acquisition approaches (5–7), and postprocessing techniques cover correlation analysis and graph searching methods (8–10). The shortcomings of these approaches are the limitations of their applications and the costs. For instance, phase-contrast acquisition approaches (5) are limited to cases in which the blood flow directions in artery and vein are opposite to each other. In the time-resolved acquisition approaches (6,7), the image must be acquired during the first pass of a contrast agent or accomplished with cardiac gating. Correlation analysis (8) requires seven or eight MRA data sets in a single breath hold for a three-dimensional (3D) angiogram of the lung. In graph searching approaches (9), the node costs require 3D edge strength and a model of preferred branch direction. The enhanced artery visualization method (10) is limited to the segmentation of a small number of the main overlapping veins in the peripheral vasculature. Clearly, a more general approach for artery-vein separation is desirable.

MATERIALS AND METHODS

Principle

We have developed a segmentation approach for separating artery and vein and a shell-rendering method for visualizing vascular structures (11,12). The anatomic separation uses fuzzy connected object delineation principles and algorithms (13,14). In fuzzy connected object definition, the notion of an “object” is captured by how the image elements “hang together” relative to each other in
the image. “Hanging-togetherness” is described formally through the fuzzy topologic notion of fuzzy connectedness. To every possible pair \( (v_1, v_2) \) of image elements, a “strength of connectedness,” which is a number between 0 and 1, is assigned. This strength is determined to be the largest of the strengths of all possible connecting paths (a “path” is simply a sequence of nearby image elements) between \( v_1 \) and \( v_2 \). The strength of a particular path is defined as the smallest “affinity” along the path between pairwise nearby image elements. Affinity between two image elements is expressed as a function of the distance between the elements and the degree of similarity of a number of image intensity properties (such as actual intensity, its rate of change) estimated at the two elements.

In short, a fuzzy connected object is defined based on both intensity criteria and topologic criteria, both of which are handled in a fuzzy setting. Practical algorithms based on dynamic programming have been developed for extracting fuzzy connected objects in 2-, 3-, and higher-dimensional images. Their effectiveness has been proved in several medical applications, such as routine quantification of multiple sclerosis lesions via multiprotocol MR imagery (15–20), MRA (14), independent clutter-free display of hard- and soft-tissue structures (including detailed neurovascular structures) from computed tomography (CT) data for craniomaxillofacial surgery (21), and, recently, in mammographic density quantification (22).

Method

The first step of this separation process is the segmentation of the entire vessel structure from the background and other clutter of the CE-MRA image via absolute fuzzy connectedness (22). The object of interest here is the entire vessel, and one set of “seed” image elements is required. In the earlier stage of this research, we used several simple intensity-based features (original intensity, gradient magnitude) locally computed at every image element. Given the feature vector associated with each of a pair of image elements, their affinity is determined as a function of these two vector variables. Multivariate Gaussian and ramp functions were used. It is clear that this formulation is defined on fixed neighborhood structure to capture affinity between two image elements. Therefore, the affinity is really independent of local structure size and can become sensitive to noise. We use a simple but effective method that formulates fuzzy affinity based on the local structure size—“scale.” By using scale-based affinity (23), local hanging-togetherness is defined over a neighborhood the size of which varies with the size of the local structure.

The second step is to separate artery from vein within this entire vessel structure by relative fuzzy connectedness (24). Let artery and vein be the object of interest and the co-object in the image, respectively. Two sets of “seed” image elements are specified inside each of these objects. The strength of connectedness of every image element with respect to each of these “seed” image elements is then determined using a different affinity relation for each of the objects. An image element is considered to belong to that object (or co-object) for which the strength of connectedness with respect to its “seed” image elements is the highest. The image domain is thus partitioned into two regions, each representing an object (or a co-object). In the fuzzy description of each object, outside the respective region, the image elements are assigned a zero value, and inside, either the original image intensity or the winning strength of connectedness is assigned. Scale-based affinity is also used in this relative connectedness analysis.

The separation of artery-vein structures is performed in an iterative fashion. The small regions of the bigger aspects of artery and vein are separated in the initial stage. Some of the image elements in these already separated regions are then used as “seeds” in a second stage for separation of finer aspects of the vessels, and so on. Further regions are added in subsequent stages so that a fairly complete separation up to the level of fine vessels is achieved.

Procedure

The implementation of the previously described two-step process is based on 3DVIEWNIX—an open, transportable, multidimensional, multimodality, multiparametric imaging software system—and its library of 3D imaging functions, designed, developed, and maintained by the Medical Image Processing Group, University of Pennsylvania (25).

In the step of vessel segmentation, “seed” image elements are specified on some typical segments of the vessels in the CE-MRA images. Then a map of absolute fuzzy connectedness that indicates how the image elements in the image hang together to form vessels is formed. By thresholding this connectedness map, a binary image is generated. By using this binary image to mask the original CE-MRA images, an object (vessel-only) image is created.
In the step of artery-vein separation, after a set of “seed” image elements is created inside each artery and vein, respectively, two individual maps of relative fuzzy connectedness that are the binary images for artery and vein are formed. The iteration is stopped once there is no further change of image elements in these two maps. Then, by using these two binary images to mask the vessel-only image, the object and co-object (artery and vein) images are generated.

“Seed” selection in vessel segmentation and artery-vein separation is the only human interaction procedure required by this entire approach. In vessel segmentation, a human operator “paints” a few “seed” image elements. In artery-vein separation, a pair of “seed” image elements (the start and the end) for each branch to be included is specified by the 3D shell-rendered image (Fig 1). Then a central line algorithm is applied on a distance image, which is created by applying a 3D distance transformation to the binary image of the entire vessel structure to obtain “central” paths inside the vessels (Fig 2). All image elements on these paths will serve as “seed” image elements in the separation. The central line algorithm chooses the local maximum as a cost function for creating best paths.

Fuzzy objects (vessel, artery, and vein) are represented by a data structure called a “shell,” and shell rendering is used for 3D visualization of vascular information (26). For distinguishing arteries and veins, the shell renditions can be colored differently for the two objects in a composite display, or the objects can be turned on and off selectively. Shell rendering retains object heterogeneity, and, therefore, object composition can be more accurately depicted. Two-dimensional object images (artery and vein) in the slice can also be colored differently and superimposed in one display by using the 3DVIEWNIX library.

**RESULTS**

This approach has been applied to EPIX Medical’s CE-MRA data (MS-325 [AngioMARK; EPIX Medical, Cambridge, Mass]). A total of 109 original CE-MRA data sets (from 28 patients) from three university hospitals have been processed. In our study, CE-MRA data were acquired during the precontrast, dynamic (arterial phase), and early and late postcontrast steady state, with various resolutions and orientations, stored in DICOM (Digital Imaging and Communications in Medicine) format. In all of our case studies, unified parameter settings were adopted without requiring per-study adjustments. 3D images and movies of objects (vessels, arteries, and veins) have been created for each study. Shell renditions are colored differently for the two objects in a composite dis-
play, or the objects can be turned on and off selectively. All of our case studies were performed on a personal computer (PC) (Gateway 2000 [300-MHz/256-MB memory]; Pentium) under the Linux operating system. The whole procedure, which includes vessel segmentation, artery-vein separation, and shell rendering, is completed in a few minutes per study.

Three examples for vessel segmentation and artery-vein separation are reported here to demonstrate the performance of this approach. In these examples, the early postcontrast steady-state images were used. The segmented vessel images for each example (from the belly to the feet) are shown in Figures 3, 7, and 11; and the separated artery and vein images for each example are shown in Figures 4, 8, and 12 and Figures 5, 9, and 13, respectively. The composite displays of artery (in red) and vein (in blue) for each example are given in Figures 6, 10, and 14. Images shown are selected from 90-frame movies.

**Figures 3–6.** (3) Image of vessel of example 1. (4) Image of arteries of example 1. (5) Image of veins of example 1. (6) Images of arteries and veins of example 1.

**DISCUSSION**

CE-MRA has fundamentally changed angiography and is established as an important complementary technique to conventional angiography. However, this technique requires advanced vascular visualization as part of clinical protocols, and its utility can be significantly enhanced for evaluation and treatment of diseases when artery and vein structures are further separated. Our technique, by combining the strengths of fuzzy connected object definition, object separation, and shell rendering, provides a high-quality 3D display of vascular information in a single CE-MRA image. This technique seems to be the only image-processing approach available for artery and vein separation in a general scope (3–10, 27–29).

We have presented an image-processing approach for artery-vein separation and for their 3D visualization. The results show that this approach is quite automated, unsu-
pervised, and robust. We are in the process of refining this development. The following issues will be addressed in the near future.

Toward a fully automated and entirely unsupervised approach, the “seed” selection will be improved. Because the intensity of image elements in the vessels of MS-325 CE-MRA data is far above the 95th percentile of the volume histogram, it is possible to directly apply a higher threshold on the original CE-MRA images to obtain some vessel regions (instead of painting a few “seed” image elements) as the bank of “seed” image elements for vessel segmentation, thus eliminating one user interaction step.

Both vessel segmentation and artery-vein segmentation require the computation of connectedness. We have recently developed, independent of this research, a “queue” method in connectedness computation. After the affinity is computed, at the stage of tracking, the queue method arranges the strengths of connectedness in a descending order; then it removes the image elements that have the highest strength. This operation is repeated until the tracking is over. It has been shown that this method can shorten connectedness computation time by a factor of about 20 because it cuts off the process of revisiting the image elements with the highest strength of connectedness. For example, the segmentation of the brain parenchyma in a $256 \times 256 \times 60$ volume can be accomplished in about 5–10 seconds on a 300-MHz Pentium PC. The queue method will be included in the processes of computing connectedness in both vessel segmentation and artery-vein separation, making all processes interactive.
The accuracy of separation and the level of the vessel tree up to which meaningful separation can be achieved will be determined through manual segmentation of a subset of MS-325 CE-MRA data and comparison with the computer-produced results. A more general subjective accuracy evaluation procedure will be developed and tested for both vessel segmentation and artery-vein separation.

REFERENCES

Improvement of Vascular Signal Intensity in Contrast-enhanced MRA with Gd-BOPTA:
Comparison with Gd-DTPA

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RATIONALE AND OBJECTIVES
The need to reduce the acquisition time in contrast material–enhanced magnetic resonance angiography (MRA) requires a reduction of the signal-to-noise ratio (SNR). The SNR can be raised by administering double doses of gadopentetate dimeglumine (Gd-DTPA). Our purpose was to evaluate the possibility of performing contrast-enhanced MRA with a high-relaxivity paramagnetic contrast agent, that is, gadobenate dimeglumine (Gd-BOPTA).

MATERIALS AND METHODS
Twelve patients with suspected carotid artery stenosis were examined on a 1.5-T magnet (Vision Plus; Siemens, Erlangen, Germany) using a time-resolved MRA sequence. In all patients, MRA was performed twice within 24 hours by using the same sequence parameters, injecting (at the same flow rate of 2 mL/s) 15 mL of Gd-DTPA (Magnevist; Berlex Laboratories, Wayne, NJ, USA) in the first study and 10 mL of Gd-BOPTA (MultiHance; Bracco, Milano, Italy) in the second study.

RESULTS
With Gd-BOPTA, signal intensity showed a mean increase of 1.5 times the intensity with Gd-DTPA, and the SNR increased 1.4 times compared with Gd-DTPA. The differences between the two groups were significant (P < .05) regarding both signal intensity and SNR.

CONCLUSION
Gd-BOPTA–enhanced MRA can provide superior vascular signal intensity and SNR, as compared with Gd-DTPA, due to its higher relaxivity, even at lower doses. Therefore, Gd-BOPTA can be used to reduce costs and improve vascular enhancement.
Comparative Studies on the Efficacy of MRI Contrast Agents in MRA

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RATIONALE AND OBJECTIVES

The objective was to analyze the potential of various para- and superparamagnetic agents as contrast agents for magnetic resonance angiography (MRA).

MATERIALS AND METHODS

Values for the signal intensity (SI) of plasma samples spiked with different concentrations (0.005–25 mmol/L) of various paramagnetic agents (gadopentetate dimeglumine [Magnevist; Schering AG, Berlin, Germany]; gadoxetic acid [Eovist; Schering AG]; Gadomer-17 [Schering AG]; gadobenate dimeglumine [MultiHance; Bracco, Milan, Italy]; MS-325 [EPIX Medical, Cambridge, Mass]; and the ultrasmall superparamagnetic iron oxide [USPIO], SH U 555C [Schering AG]) were measured at 1.5 T (Allegra; Siemens AG, Erlangen, Germany). A three-dimensional (3D) MRA sequence (4.7/1.89 [repetition time msec/echo time msec], 25° flip angle) was used. The SI values of the maximum intensity projections (MIP) were measured, and the apparent T1 and T2* relaxivities were calculated from the SI-versus-concentration curves using the known dependence of the SI from sequence parameters and relaxation times (1).

MRA studies using a superconducting MR imager (Allegra; Siemens AG) were performed in rabbits after intravenous injection of two dose regimens. The contrast agents were injected after starting the imaging sequence to achieve optimum bolus concentrations during the k space of the sequence. Additional images were taken at 3, 10, and 30 minutes after dosing. A dose of 0.2 mmol/kg was used for all agents to allow a comparison of the various agents with the currently performed practice with extracellular gadolinium chelates (eg, Magnevist). A second dose was adjusted to the calculated T1 relaxivity of Magnevist in plasma.

RESULTS

All para- and superparamagnetic agents elicited similar SI-versus-concentration profiles. After reaching maximum SI, the values dropped with increasing concentrations (Figure). Maximum SI was reached at concentrations between 3 and 10 mmol/L, depending on the contrast agent used (Table). The gadolinium compounds produced comparable maximum SI values. The USPIO displayed a somewhat different profile. Maximum SI was about 60% of the values measured for gadolinium compounds. The highest SI of this USPIO was obtained at about 3 mmol/L.

The low-molecular-weight gadolinium compounds elicited a T1 relaxivity of 3.5–5.2 L mmol^-1 sec^-1; the compounds with a larger molecular weight or strong plasma protein binding exhibited T1 relaxivities of about 12 L mmol^-1 sec^-1. The T2* relaxivities of all gadolinium compounds were similar and significantly larger than the T1 relaxivities. The T2* relaxivity of the iron agent displayed a much larger value of about 70 L mmol^-1 sec^-1.

The high dose of 0.2 mmol/kg yielded excellent angiograms. The arterial phase occurred during the first 12 seconds of imaging; later images displayed both arterial and venous enhancement. The bolus MRA images immediately after the injection of the gadolinium agents were superior to the USPIO images. The strong susceptibility effect of the USPIO diminished the image quality during the very first imaging after bolus injection.

MultiHance and Eovist exhibit similar enhancement characteristics to Magnevist. The blood enhancement declined...
rapidly due to extravasation and excretion. A longer lasting venous and arterial enhancement was seen with Gadomer-17 and MS-325, due to the particular pharmacokinetics of these agents.

The USPIO demonstrated good enhancement even at 30 minutes after injection. However, the arterial MRA images do not display significant differences if the dose is adjusted to the T1 relaxivity of Magnevist.

**CONCLUSION**

Gadolinium complexes with plasma protein binding or increased molecular weight elicit higher T1 relaxivities than Magnevist. The highest values are obtained with Gadomer-17 and MS-325, the agent with the strongest protein binding. The T1 relaxivities of the latter agents are lower than previously reported for 0.47 T (2). The suboptimal correlation times of these gadolinium complexes at 1.5 T weaken their T1 relaxivities (3) in such a way that differences seen at 0.47 T between Gadomer-17 and MS-325 disappear. Complexes with weak protein binding, such as MultiHance and Eovist, exhibit a somewhat stronger T1 relaxivity than Magnevist. Strong T2* relaxivities influence the SI even at that extremely short echo time. These effects cause a strong SI reduction at high concentrations, most prominent with USPIO. The T2* relaxivities of the gadolinium complexes do not differ significantly because of the identical magnetic moments of the compounds.

The T2*/T1 ratio determines the maximum achievable SI to some extent. Practically no maximum SI (SI\text{max}) differences are observed among the various gadolinium compounds. In other words, similar maximal contrast enhancement is achievable independent of the gadolinium chelate used. Because of the disadvantageous large T2*/T1 ratio, USPIO compounds are less suitable for arterial bolus contrast-enhanced MRA than gadolinium complexes. To avoid dominating T2* effects, lower concentrations of such agents are beneficial. Consequently, delayed images with USPIO do not display large susceptibility effects because the concentrations are about five times lower than in the bolus peak phase.

The imaging experiments demonstrate the favorable characteristics of gadolinium agents in the early bolus phase, whereas the advantages of large complexes (MS-325 and Gadomer-17) and USPIO compounds are most evident in the distribution phase.

**REFERENCES**

Arterial Concentration Profiles of Two Blood Pool Agents and Gd-DOTA after Intravenous Injection in Rabbits

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RATIONALE AND OBJECTIVES

Gadolinium-enhanced magnetic resonance angiography (MRA) is a technique influenced by the injection parameters of the contrast agent and the acquisition parameters. Different techniques have been proposed to standardize MRA protocols (1).

Because there is no linear relationship between the contrast and the gadolinium blood concentrations (2), it is difficult with imaging modalities to analyze the contribution of each injection parameter and also to compare contrast agents. An experimental model in rabbits was developed to mimic an MRA protocol to determine the gadolinium blood concentrations during the time immediately following injection. The influences of the injection parameters (injection rate, duration of injection, volume of injection, dose) were tested, and two blood pool agents (P760, P717) were compared to the nonspecific agent gadodate meglumine (Gd-DOTA) in similar conditions. P717, a Gd-DOTA–dextran derivative, is a slow-clearance blood pool agent (SC-BPA); and P760, a macromolecular Gd-DOTA derivative, is a low-diffusion agent (LDA), as defined previously (3).

MATERIALS AND METHODS

Products

Gd-DOTA (0.5 M Dotarem; Guerbet, Roissy, France) was used as an example of a nonspecific agent. To test the influence of the injection rate, Gd-DOTA at a dose of 300 μmol/kg was injected in the same volume using injection rates of 0.08, 0.13, 0.25, 0.5, and 1 mL/sec. Under these conditions, the total duration of the injection was 25, 14, 8, 4, and 1.25 seconds, respectively.

To allow the same injection parameters as with P760, Gd-DOTA was diluted to 0.033 M and injected at a dose of 30 μmol/kg (duration of injection, 4.2 seconds; injection rate, 0.5 mL/sec).

P760 (0.033 M, LDA) and P717 (0.1 M, SC-BPA, CMD-A2-Gd-DOTA), both research products from Guerbet, were tested at the dose of 30 μmol/kg at an injection rate of 0.5 mL/sec. The duration of injection was 4.2 seconds for P760 (4) and 1.6 seconds for P717 (5).

Pharmacokinetic Experiment

All animal experiments were performed in compliance with the European Economic Community directive (86/609/EEC) on animal welfare. Male New Zealand rabbits (2.5–3.5 kg) were anesthetized by intramuscular injection of ketamine at 50 mg/kg and xylazine at 0.5 mL/kg. The femoral artery was catheterized with a 1–1.5-mm catheter (Vygon, East Rutherford, NJ). The ear marginal vein was catheterized (Insyte Vialon 22G; Becton Dickinson, Pont de Clairx, France) and maintained with sticking plaster. The products were injected through an automatic injector (Perfuseur Sage M362; Orion Europe, Cambridge, England) using 5-mL syringes (Becton Dickinson, Madrid, Spain) connected to the ear marginal vein catheter.

Starting at the beginning of the injection, femoral artery blood samples were collected continuously over 30 seconds. Blood was directly transferred from the catheter into a series of tubes. Samples of approximately 300 μL each were taken every second. After this period, samples were obtained every 5 seconds for 1 minute and then at 2
and 5 minutes. All experiments were performed in triplicate, with the exception of the injection rate experiment ($n = 1$, injection rate condition).

**Gadolinium Measurements**

Blood gadolinium concentrations were measured using spectroscopic emission atomic inductively coupled plasma (SEA-ICP) equipment (Spectraspan VII; Perkin Elmer, Boston, Mass) after water dilution (1/20).

**Parameters**

The maximum concentration ($C_{\text{max}}$) and the time to $C_{\text{max}}$ ($T_{\text{max}}$) were estimated from the graph of the blood gadolinium concentrations versus time. These two parameters describe the bolus phase. The postbolus phase was described by the parameter $C_i/C_0$, which corresponds to the blood gadolinium concentration measured at time $i$ after the injection, divided by the theoretical initial concentration $C_0$ at time zero ($C_0 =$ theoretical concentration based on the injected dose in micromoles per kilogram, which is instantaneously homogenized in the blood volume of 60 mL/kg).

**RESULTS**

For the same injected dose of Gd-DOTA, 300 $\mu$mol/kg, the injection rate (and, consequently, the total injected volume) modifies the bolus peak profile (Fig 1). Increasing the injection rate produces a sharpening of the peak ($C_{\text{max}}$ increase, $T_{\text{max}}$ decrease, peak length decrease). At a low injection rate, the first pass presents a plateau form. The $C_{\text{max}}$ is 10.1, 10.3, 20.1, 22.8, and 25.3 mmol/L, and $T_{\text{max}}$ is 31, 20, 12, 11, and 6 seconds at respective injection rates of 0.08, 0.13, 0.25, 0.5, and 1 mL/sec. Concentrations at the postbolus phase are identical for all of the injection rates at 1 and 5 minutes after injection.

To evaluate the pharmacokinetic contribution of the blood pool properties in this model, P760, P717, and Gd-DOTA were injected at the same dose (0.03 mmol/kg). Under these conditions, the three products showed the same bolus phase (Fig 2). The earlier $T_{\text{max}}$ and slightly higher $C_{\text{max}}$ for P717 are attributed to the higher concentration of the injected solution (0.1 M) compared to Gd-DOTA and P760 (0.033 M solution for both in this experiment). At the postbolus phase, there is a clear differentiation in the gadolinium concentration as a function of the blood pool properties of each agent (Fig 3). Forty-five seconds after injection, 84% of the P717 molecules are still present in the blood compartment, whereas 65% of the P760 molecules and only 51% of the Gd-DOTA molecules remain.
CONCLUSION

The maximum concentration is very sensitive to the injection rate and, consequently, to the total duration of the injection. A decrease in the injection rate leads to a decrease in the $C_{max}$, the bolus having a plateau form. Thus, the duration of the plateau depends on the total duration of the injection. Conversely, an increase in the injection rate sharpens the bolus peak and increases the $C_{max}$. The changes in the bolus profile according to the injection parameters have to be taken into account for each MRA protocol (6). Substantial changes in the gadolinium concentrations during signal acquisition induce artifacts (7). Furthermore, the hemodynamic parameters (cardiac output, blood pressure) influence the bolus profile ($T_{max}$, $C_{max}$, length).

Injected under similar conditions, blood pool agents P760 and P717 have a comparable profile to Gd-DOTA during the bolus phase. The site of injection is in the ear marginal vein, and arterial blood samples are collected from the femoral artery. This means that no significant extravasation is observed, although the products traverse once through the lung, the heart, and large arteries. The short arrival time of the bolus peak (ie, $T_{max} < 7$ seconds) indicates that the product measured from this arterial site remains mainly in the macrocirculation. On the basis of these data, blood pool agent properties in this protocol have no significant advantage over nonspecific agents in the bolus phase, with the bolus phase being mainly used for breath-hold techniques (8).

Conversely, at the postbolus phase, the concentrations of the blood pool agents are higher than with Gd-DOTA. This is due to the absence of extravasation or to delayed extravasation and renal excretion compared to Gd-DOTA. Forty-five seconds after injection, approximately 50% of the Gd-DOTA has left the blood compartment, compared to only 35% of P760 and 16% of P717. It can be assumed for P717 that due to the polydispersity of the dextran derivative ($I = 1.66$), a portion of small molecules may extravasate, which could explain why the compound is not fully intravascular at this time (5). P760 is not truly an intravascular agent because even at early times after injection, a small portion of the compound has already left the blood compartment. Due to its higher molecular volume, P760 presents a lower rate of interstitial diffusion than nonspecific agents (4).

The increase in the arterial blood concentration with blood pool agents in the postbolus phase leads to an increase in the temporal imaging window. This is of particular interest for territories like the coronary arteries, where a longer time interval is required (9,10). These data corroborate imaging results obtained with P717 and P760, where a significant enhancement was observed at later times after the contrast agent injection (11–13).

This model was developed to mimic an MRA protocol in the rabbit to analyze the influence of different parameters on blood gadolinium concentrations, which will determine signal efficacy. Two phases are identified: the bolus phase and the postbolus phase.

The injection parameters (injection rate, total duration of injection, volume, concentration of the solution, dose) strongly influence the pattern of the bolus phase. The postbolus phase is sensitive only to the injected dose.

In this model, blood pool agents present a similar bolus profile to Gd-DOTA, whereas in the postbolus phase, the intravascular restriction of these blood pool agents leads to higher blood concentrations than Gd-DOTA.

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Visualization Techniques for Blood Pool Contrast-enhanced Magnetic Resonance Angiography

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The conventional technique for processing time-of-flight and dynamic arterial phase contrast material–enhanced magnetic resonance (MR) angiographic images has been the maximum intensity pixel (MIP) projection algorithm. This is a powerful technique for creating projectional images from source data that are not very anatomically complex. However, in the case of images obtained using MR imaging blood pool contrast agents, the MIP technique does not provide images that are appropriate for most diagnostic purposes. This is due to the complex overlap of arterial and venous structures in the projectional images, which makes it nearly impossible to disentangle the vessels when they lie in close proximity. Therefore, alternative visualization techniques will be required to derive the full diagnostic benefit of these contrast agents.

The simplest technique to use includes viewing of source and multiplanar reformatted (MPR) images. Modern workstations permit rapid viewing of these large multislice data sets in a convenient and rapid fashion. MPR in planes orthogonal to the vessel axis can be especially useful in assessing cross-sectional vessel measurements, such as area stenosis, and in clearly separating adjacent arteries and veins. Currently available software packages permit the rapid placement of points along the course of a vascular bundle in two planes with rapid generation of a set of vessel-orthogonal MPR slices. Despite the power of these MPR techniques, they are still rather user-intensive in that the viewer must physically look at a large number of individual slices, either individually or in a cine format. It would be much more convenient for users to have access to panoramic viewing of these image sets so the viewer can come to a rapid diagnosis as to the general state of the vasculature, with dedicated viewing of source and MPR images reserved for selected areas where higher precision is needed.

The two basic approaches to this problem are (a) tagging of each image voxel on the basis of some physiologic feature during the acquisition of the image, and (b) pure postprocessing of high-resolution image data, relying on spatial relationships of vessels to separate arteries and veins.

In acquisition tagging, a physiologic feature measurable by MR imaging is associated with each voxel. This feature is then used to identify anatomic structures, such as arteries and veins, which can be differentiated by this feature. Images can be displayed by colonization with the magnitude of the feature displayed as color hue and the sign (if applicable) associated with different colors (eg, red or blue). Features that can be used for this purpose include the time of appearance of contrast, oxygenation, and flow direction.

With current MR sequences, full three-dimensional (3D) volumes can be acquired with temporal resolution of several (<10) seconds. This permits clear distinction of arterial and venous voxels. In one implementation, initial estimates of the arterial and venous volumes are made using a two-dimensional (2D) correlation plot. Initially, the sum of squared deviations between a voxel’s time values and those of the reference artery and vein curves are plotted on a 2D plot. Initial estimates of pure arterial and venous voxels are made from the peaks in the 2D plot. Temporally ambiguous voxels are assigned based on spatial connectivity. However, most of the segmentation is provided by the 2D correlation (1). In the case where higher resolution steady-state images are acquired with lower resolution dynamic images for temporal data, inter-
polation must be used to map the temporal data onto the steady-state image.

The main limitation of temporal labeling is that only a single field of view can be imaged throughout the dynamic and steady-state phases required. It would be helpful to have techniques that are applicable to the steady-state alone so multiple vascular regions could be imaged, taking full advantage of the longer temporal duration of the steady-state phase of contrast agent distribution. Phase-contrast agent imaging is one approach that meets this requirement. The physiologic feature that is most readily encodable using phase data is blood velocity, although differences in blood oxygenation may also be exploited to provide phase-contrast images (2). Phase-contrast imaging can be used to differentiate arteries and veins based on flow velocity (3) or flow direction (4). The use of flow direction is appealing, especially in regions where arteries and veins are closely entwined in vascular bundles, such as the lower extremity circulation. In such vascular territories, arterial and venous flows are strictly distinguishable based on flow direction relative to the axial plane. The upper extremity and carotid circulations are examples of other vascular territories that exhibit this feature. The fact that arterial and venous flows are in opposite directions also has the advantage that phase encoding only needs to be in a single direction, parallel to the vascular bundle.

Alternatively, pure postprocessing strategies may be applied to a high-resolution image. Volume rendering is a technique that incorporates data from all pixels in an image to provide a 3D representation. By incorporating cut planes to eliminate unwanted structures and by varying the degree of opacity of structures, image viewing may be optimized. This technique can be effective at depicting arteries and veins even when these structures are adjacent. By providing depth cues and with the ability to rotate the vessels in three dimensions, even complex anatomy of, for example, the carotid bifurcation can be analyzed quickly and accurately. This technique is most effective when used on vessels that, although adjacent, are not completely intertwined, such as the carotid artery and jugular vein. Another feature of the carotid artery that makes the volume-rendering approach especially effective is the fact that a focal area of the carotid artery, the carotid bifurcation, is of greatest interest, so the volume can be rotated with the aim of visualizing this specific region. In the peripheral circulation, this approach is less successful because the complex intertwining of artery and vein makes separating the vessels along their entire course a very tedious process, and it is necessary to fully visualize the entire length of the artery because disease can occur at any location along it.

In the periphery, another goal of postprocessing is to completely segment the arterial from the venous circulations. The simplest method of doing this is a connectivity approach, whereby a seed is placed within an arterial or venous voxel, and the program is asked to generate a structure based on pixels above a certain threshold that are connected to the seed point. Although attractive in principle, this simple approach has several limitations based on focal zones of diminished signal due to artifact as well as bridging between structures, which can occur with loss of just a single pixel separating them.

More advanced techniques for artery-vein segmentation are under investigation. Two recently described approaches are forward-looking graph search (5) and “fuzzy” connectedness (6). As an example, in the former technique, a graph search is performed on the 3D image data starting at a set of user-defined points. Node costs are determined by gray level, 3D edge strength, and a model of preferred branch direction. The graph search program then identifies the lowest-cost path through the 3D volume. Fuzzy connectedness aims to overcome the limitations of pure intensity thresholding by establishing affinity relationships between regions. These affinities can be composed of a variety of characteristics but, in practice, usually consist primarily of a signal homogeneity-based component and an object feature-based component. The strength of these postprocessing techniques is that they do not rely on special acquisitions but can be performed post hoc on any high-resolution data set. However, it will need to be seen how robust these techniques are in a range of pathologic conditions, including long occlusions.

In conclusion, intravascular contrast agents provide a unique opportunity for high-resolution MR imaging of vascular structures. However, to maximize the utility of these agents, it will be essential to have techniques to separate overlapping arteries and veins. Both acquisition-based and pure postprocessing approaches have shown promise; further work will be required to demonstrate which approaches will prove most robust in clinical use.

REFERENCES


Ultrasmall Superparamagnetic Iron Oxide–enhanced MR Imaging of Atherosclerotic Plaque in Hyperlipidemic Rabbits

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RATIONALE AND OBJECTIVES

Chronic inflammatory changes of the arterial wall are inherent in the genesis of atherosclerosis (1). Despite the inhomogeneous makeup of atherosclerotic plaque, it is assumed that atherosclerotic changes originate from fatty streaks that occur early in life and tend to progress to advanced lesions (2,3). Particular plaque configurations yield high risks for thrombosis independent of the degree of associated luminal narrowing (4). Whereas conventional angiographic techniques display luminal narrowing, the presented strategy aims at the detection of atherosclerosis-associated inflammatory changes in the vessel wall, based on the observation that ultrasmall superparamagnetic iron oxide (USPIO) particles undergo phagocytosis by cells of the mononuclear phagocytic system (5).

The purpose of this study was to evaluate the performance of USPIO (Sinerem; Laboratoire Guerbet, Aulnay Sous Bois, France) as a marker of macrophage activity in atherosclerotic plaque.

MATERIALS AND METHODS

Experiments were conducted on five heritable hyperlipidemic rabbits aged 6–10 months. Three white New Zealand rabbits served as a control group. The studies were performed in accordance with all regulations governing animal experiments.

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Magnetic resonance (MR) imaging was performed with the rabbits fully anesthetized. To maximize the signal-to-noise ratio, a quadrature transmit/receive head coil was used. The protocol was as follows:

1. All rabbits underwent three-dimensional (3D) contrast material–enhanced MR angiography of the thoracic aorta with 2 mL of gadoterate meglumine (Gd-DOTA) (Dotarem; Laboratoire Guerbet, Aulnay Sous Bois, France) diluted with 10 mL of saline. Contrast material injection was performed with an automated injector at a flow rate of 0.1 mL/sec.

2. At least 1 day (maximum, 10 days) after the 3D MR angiography, USPIO (Sinerem) was injected intravenously at a dose of 1 mmol Fe/kg. MR imaging with a 3D ejection fraction gradient-recalled echo (GRE) sequence (6.7/1.6 [repetition time msec/echo time msec], 30° flip angle, field of view of 28 × 19.6 cm, and two signals acquired) was performed daily up to 5 days after USPIO application. Maximum intensity projections of the 3D data sets were reconstructed. Subsequently, the rabbits were killed for ex vivo imaging of the aorta and histopathologic evaluation.

3. For ex vivo imaging, the aortic specimens were closed with surgical thread at both ends, filled with 1:50 diluted Gd-DOTA, and placed in a small plastic container filled with saline. 3D MR data sets were obtained with the parameters described previously.

4. Histopathologic evaluation of the aorta was performed, including histochemical staining (Prussian blue staining).

RESULTS

3D MR angiography with Gd-DOTA (Dotarem) revealed no abnormal findings in either the five hyperlipidemic or three control rabbits (Fig 1). After application of the USPIO (Sinerem), the signal intensity in the vessel lumen steadily increased over the 5-day imaging period, paralleling the de-
crease in T2*—effects due to the decreasing concentration of USPIO (Sinerem). Luminal signal intensity reached its maximum (best angiographic effect) after 4–5 days. On the 3D GRE images, the aorta of the hyperlipidemic rabbits showed marked susceptibility artifacts in the vessel wall in vivo (Fig 2), as well as ex vivo.

In the atherosclerotic rabbits, histopathologic examination proved marked uptake of Fe particles in macrophages embedded in atherosclerotic plaque found in the aortic wall. No such changes were seen in the control rabbits. Similarly, no such changes were seen in one hyperlipidemic rabbit killed before receiving the USPIO (Sinerem).

CONCLUSION

The results of the study indicate that USPIOs, which undergo phagocytosis by macrophages in atherosclerotic plaques of the aortic wall, lead to susceptibility artifacts that can be readily detected with 3D GRE sequences. USPIO uptake may thus serve as a marker of early atherosclerotic changes before luminal narrowing is present. The presented imaging protocol is suited to combine MR angiographic imaging with the detection of early atherosclerotic wall changes.

REFERENCES

Noninvasive Assessment of Wound-healing Angiogenesis with Contrast-enhanced MRI

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RATIONALE AND OBJECTIVES

Angiogenesis is a process by which new vessels grow toward and into the tissue (1,2) and is a critical component of the wound-healing process. During this process, angiogenesis leads to increased endothelial permeability of the microvasculature, which is triggered by plasma proteins such as the vascular endothelial growth factor (1,2). Based on physiologic data, there are similarities between wounds and tumors (1). Previous studies demonstrated that macromolecular contrast material–enhanced magnetic resonance imaging (MRI) is able to quantify microvascular permeability and plasma volume, representatives of angiogenesis, in tumors (3,4).

The purpose of this study was twofold: (a) to quantitatively assess the time course of microvascular permeability and fractional plasma volume (fPV), representatives of angiogenesis, in an established wound-healing model induced in rodents; and (b) to correlate the MRI parameters with histologic and physiologic data of the wound-healing process.

MATERIALS AND METHODS

Twelve healthy young adult female Sprague-Dawley rats weighing 225–250 g were used for all wound model implantations. Polypropylene woven mesh cylinders were constructed from $27 \times 27$-mm square pieces of mesh with a mesh opening of 1,000 μm and a thickness of 1,020 μm (Spectrum, Houston, Tex), using a method of construction similar to stainless steel wire mesh Hunt-Schilling wound chambers (5). Final dimensions of the cylinder were an internal diameter of 8 mm and length of 28 mm. Rats were anesthetized with pentobarbital (35 mg/kg, intraperitoneal), buprenorphine hydrochloride (0.05 mg/kg, intraperitoneal), and atropine (0.8 mg/kg, intraperitoneal). Four cylinders were inserted through two 1-cm dorsal midline incisions and implanted into two pairs of bilateral subcutaneous pockets. Wound fluid was aspirated on days 1, 4, 9, and 22 after implantation using brief halothane anesthesia. For histologic purposes, three rats were killed on each of days 1, 4, 9, and 22. When aspirated, wound fluid was taken from a cylinder in which fluid had not been previously drawn. Vascular endothelial growth factor (VEGF) levels were assayed by commercial enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minn) from the wound fluid.

MRI was performed on an imaging system (Omega CSI-II System; Bruker Instruments, Fremont, Calif) operating at 2 T. This system is equipped with self-shielded gradient coils ($\pm 20$ G/cm, 15-cm inner diameter) (Acustar S-150; Bruker Instruments). Before MRI, pentobarbital (Abbott Laboratories, North Chicago, Ill) was injected intraperitoneally at a dosage of 50 mg/kg of body weight. For contrast medium injection during MRI, a 23-gauge butterfly cannula (Abbott Laboratories) was inserted into a tail vein of each animal. Animals were placed supine in a “birdcage” radio-frequency coil. A dilute gadopentetate–containing phantom was included in the field of view, close to each animal. Wound chambers were examined with a T1-weighted three-dimensional...
spoiled gradient-refocused (3D-SPGR) acquisition in a steady state. 3D-SPGR images were obtained with the following parameter settings: echo time (TE), 1.4 msec; repetition time (TR), 50 msec; one acquisition; flip angle, 90°; matrix, 128 × 128 × 16; section thickness, 3 mm; field of view, 50 × 50 × 48 mm; and acquisition time, 1 minute 42 seconds per volume of 16 sections. Precontrast longitudinal relaxation rates ($R_1$ = 1/T1) were calculated based on a set of seven similar SPGR sequences with varying TR values between 50 and 3,200 msec. To monitor albumin–(Gd-DTPA)$_{30}$ enhancement, three initial precontrast images and 30 dynamic postcontrast images (with fixed TR at 50 msec) were acquired over a 1-hour period. Albumin–(Gd-DTPA)$_{30}$, a prototype macromolecular contrast medium for MRI, was administered in a dose of 0.03 mmol of Gd per kilogram of body weight (6).

Animals were imaged on days 1, 4, 9, and 22 after wound chamber implantation. For histologic purposes, three rats were killed on each of days 1, 4, 9, and 22 immediately after MRI and wound fluid aspiration.

All MRI data were transferred to a workstation (Sun Sparc 10; Sun Microsystems, Mountain View, Calif). Signal intensity (SI) values for each time point were obtained from regions of interest (ROIs) defined in the most enhancing areas close to the wound chamber. Three to five ROIs over several different anatomic image sections were summed and evaluated using an image analysis program (MRVision, Menlo Park, Calif). In addition, signal in the inferior vena cava (IVC) and signal in a gadolinium phantom in the field of view were measured.

The mean SI values from the tumor and the IVC blood were corrected for spectrometer variation over time by dividing the SI at each time point by the SI of the phantom. Precontrast $R_1$ (1/T1) estimates for tumors were obtained by curve fittings based on seven unenhanced SPGR sets with TRs varying from 50 to 3,200 msec. The precontrast $R_1$ value for IVC blood was assumed to be 0.752 sec$^{-1}$ (1/1.33) (7). Postcontrast $R_1$ values can be calculated based on SI and knowledge of precontrast $R_1$ values (7,8). The difference between the postcontrast $R_1$ value at each time point and the precontrast $R_1$, $\Delta R_1(t)$, is taken to be directly proportional to the local gadolinium concentration in tissue at time $t$ (9). Our techniques for determining the fractional plasma volume of the tumor tissue (fPV, in mmol cc$^{-1}$ of tissue) and the permeability of the tumor tissue to a particular contrast agent, as estimated by the endothelial transfer coefficient (Kps, in mL min$^{-1}$ 100 cc$^{-1}$ of tissue), have been reported in detail elsewhere (10). Briefly, a two-compartment model including microvascular permeability was fitted to the $\Delta R_1(t)$ data from IVC and tumor after the former was corrected for hematocrit assuming a value of 0.42 (10). The $\Delta R_1(t)$ from the IVC, fitted by a monoexponential function for macromolecular contrast medium, served as forcing functions for the tumor tissue model, which had a two-compartment structure corresponding to plasma and interstitial water spaces. The model was fitted to the data using the SAAM II software (SAAM Institute, Seattle, Wash).

Immediately after MRI, animals were killed by an overdose of pentobarbital. Wound chambers were resected, fixed in methylmethacrylate (Technovit 9100; Heraeus Kulzer, Wehrheim, Germany), sectioned (100 μm) in the same plane as the MRI with a low-speed saw (Buehler, Lakebluff, Ill), and stained with epoxy tissue. For each specimen, 5–10 areas with the highest microvascular density (MVD) were chosen for vessel counting at low power (×40 and ×100).

RESULTS

The results of the permeability parameters (Kps, fPV), VEGF levels, and the MVD obtained from the wound models on days 1, 4, 9, and 22 in all 12 animals are summarized in the Table. Microvascular permeability of the wound, characterized by Kps, increased significantly from day 1 (Kps = 0 mL min$^{-1}$ 100 cc$^{-1}$ of tissue) to day 9 (Kps = 0.046 mL min$^{-1}$ 100 cc$^{-1}$ of tissue; $P < .01$) and remained constant through day 22 (Kps = 0.053 mL min$^{-1}$ 100 cc$^{-1}$ of tissue). The fPV increased progressively with time (day 1, fPV = 0.03 mL cc$^{-1}$ of tissue; day 22, fPV = 0.07 mL cc$^{-1}$ of tissue). The VEGF levels increased significantly from day 1 (489.5 pg/dL) to day 9 (1,215.9 pg/dL) and decreased on day 22 (849.6 pg/dL). The correlation between MRI data and VEGF levels was weak ($r = 0.3$; Spearman correlation). However, protease, which is known to interact with the VEGF, seems to be a reasonable explanation for these results. The MVD increased significantly with time (day 1 = 0; day 22 = 6.4). Both Kps and fPV correlated closely with vessel counts of the wounds.

CONCLUSION

Our results demonstrate that contrast-enhanced MRI is able to quantitatively assess the time-dependent changes of angiogenesis in the wound-healing process. Representatives of microvasculature, such as Kps, correspond with the histologic and physiologic parameters of the wound-
healing angiogenesis. Thus, MRI may offer a noninvasive quantitative assay for the wound-healing process and may be used to monitor treatment response.

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