Original Research

Accurate Assessment of the Arterial Input Function during High-Dose Myocardial Perfusion Cardiovascular Magnetic Resonance

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Purpose: To develop a method for accurate measurement of the arterial input function (AIF) during high-dose, single-injection, quantitative T1-weighted myocardial perfusion cardiovascular magnetic resonance (CMR).

Materials and Methods: Fast injection of high-dose gadolinium with highly T1 sensitive myocardial perfusion imaging is normally incompatible with quantitative perfusion modeling because of distortion of the peak of the AIF caused by full recovery of the blood magnetization. We describe a new method that for each cardiac cycle uses a low-resolution short-axis (SA) image with a short saturation-recovery time immediately after the R-wave in order to measure the left ventricular (LV) blood pool signal, which is followed by a single SA high-resolution image with a long saturation-recovery time in order to measure the myocardial signal with high sensitivity. Fifteen subjects were studied. Using the new method, we compared the myocardial perfusion reserve (MPR) with that obtained from the dual-bolus technique (a low-dose bolus to measure the blood pool signal and a high-dose bolus to measure the myocardial signal).

Results: A small significant difference was found between MPRs calculated using the new method and the MPRs calculated using the dual-bolus method.

Conclusion: This new method for measuring the AIF introduced no major error, while removing the practical difficulties of the dual-bolus approach. This suggests that quantification of the MPR can be achieved using the simple high-dose single-bolus technique, which could also image multiple myocardial slices.

Key Words: heart; magnetic resonance; myocardial perfusion; gadolinium; first-pass; arterial input function
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QUANTITATIVE MYOCARDIAL perfusion cardiovascular magnetic resonance (CMR) requires measurement of the arterial input function (AIF), which is the concentration of gadolinium in the left ventricular (LV) or aortic blood pool as a function of time during its first pass. T1-weighted contrast is typically achieved by applying an inversion or saturation pulse before each image, saturation being generally preferred because of its immunity to cardiac interval variability. A long recovery delay (time from saturation pulse to the beginning of the readout) and high gadolinium dose are required for high T1 sensitivity and good myocardial signal intensity. However, a high gadolinium concentration causes full magnetization recovery with a long saturation delay (Fig. 1a), which may cause clipping of the AIF, and further increases in gadolinium concentration may even reduce the signal by T2* effects (1). The clipping of the AIF results in an underestimation of the AIF. Therefore, for accurate measurement of the myocardial perfusion reserve (MPR), it is preferable to use a low dose (Fig. 1b). This tension between the need for high-dose gadolinium for good myocardial response and low-dose gadolinium for accurate measurement of the AIF has not been adequately resolved to date. Previous proposed solutions include the T1-FARM (fast acquisition relaxation mapping) method (2), which computes a T1 map from two full-resolution images with response covering both the AIF and the myocardial tissue enhancement, and the dual-bolus technique (3), with a low dose for the AIF, followed by a large dose for the myocardium (i.e., the blood curve from Fig. 1b and the myocardial curve from Fig. 1a). However, both techniques have problems: the T1-FARM method has a low signal-to-noise ratio (SNR) and long imaging time, and the dual-bolus method is complicated to perform and care has to be taken to ensure the boluses are reproducible. In a third approach, using dual-inversion-time imaging for work on water exchange across the capillary wall, a 20-msec inversion recovery time gave the undistorted AIF, while both 20 and 600 msec were obtained in the myocardium (4), an approach similar to the method described in this article, except that the resolution was the same in both images. In a fourth method, multiple inversion times have been used for accurate multislice

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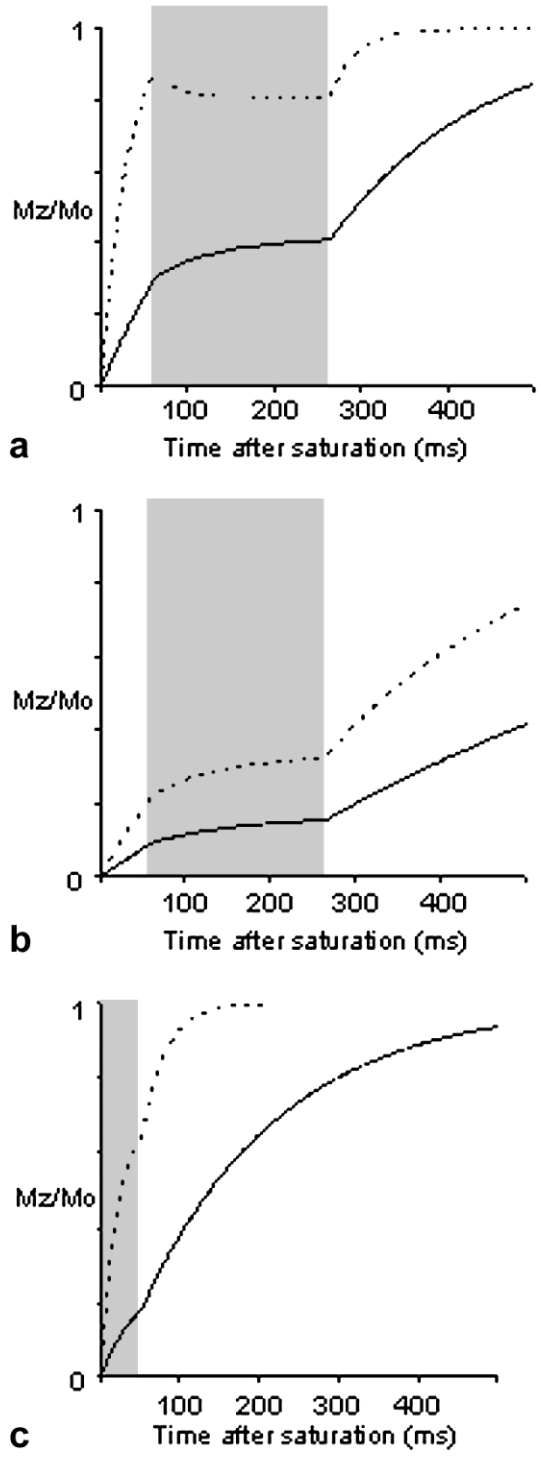
myocardial T1 measurements, but have so far been acquired too slowly to follow first-pass perfusion (5).

Longitudinal magnetization recovery is partially suppressed by fast-low-angle shot (FLASH) imaging (7) (Fig. 1) with the consequence, for longer T1 values, that most of the longitudinal magnetization recovery occurs between saturation and the start of FLASH imaging, with small further recovery in the remaining time before central k-space acquisition. For this reason, the saturation-recovery delay in the Materials and Methods section is defined as the recovery time before imaging starts. The remaining delay before central raw data acquisition is available from the sequence parameters. A simple exponential recovery model based on a single recovery time should be modified according to Larsson et al (7).

This work describes a new approach to the problem of accurate blood and myocardial measurements in high-dose fast-injection perfusion CMR. It compares MPR measurements by the new approach with those made using the dual-bolus technique (3).



MATERIALS AND METHODS

A 1.5-T scanner (Siemens Sonata) with four-channel body array coil and gradient performance up to 40 mT/m and 200 T/m/second was used, with a FLASH prototype sequence (Siemens IDEA pulse sequence programming software) modified to acquire two different resolution images of the same slice within each cardiac cycle. A single-shot image was obtained immediately after the R-wave, which was designed for measurement of LV blood pool signal with only low resolution. Single-shot FLASH was used to acquire 48 × 64 k-cells at field of view (FOV) = 30 × 40 cm, short saturation-recovery time = 3.4 msec (time from the 1-msec nonselective saturation pulse to the first FLASH excitation pulse), short TE = 0.5 msec, TR = 1 msec, linear ky order, no ky offset, and 3900 Hz/pixel, overall aiming for a response covering the peak blood gadolinium concentration. Figure 1c demonstrates how this low-resolution sequence acquires an accurate AIF with high-dose (0.1 mmol/kg) injection of gadolinium. The same 0.16-msec 10° flip angle slice-selective radio frequency (RF) pulse was used for this sequence and for the high-resolution FLASH sequence described below. Neither sequence used a partial echo. The increased possibility of signal dephasing by T2* within the large voxels of this image was partly offset by the very short TE. The effect of T2* was evaluated in vivo by comparing the peak signal with the unsaturated signal level prior to contrast agent injection.

Figure 1. Longitudinal magnetization (Mz) after saturation during gadolinium first pass. The broken line is the recovery curve for blood and the solid line is the recovery curve for myocardium. The magnetization was simulated using sequence parameters and the doses given in the Materials and Methods section, using the following estimated peak contrast agent concentrations: 7 mM high-dose blood, 1 mM myocardium, 0.7 mM low-dose blood, and 0.1 mM myocardium. The gray block shows the time of the FLASH sequence. **a:** Long saturation-recovery-delay high-dose FLASH perfusion; the blood pool (T1 ≈ 30 msec) has fully recovered by the time of image acquisition, meaning that the AIF is clipped. Myocardial SNR is high (T1 ≈ 175 msec). **b:** Long saturation-recovery-delay low-dose FLASH perfusion; the blood pool has not fully recovered (T1 ≈ 250 msec) and the AIF is not clipped. Myocardial SNR is low (T1 ≈ 640 msec) **c:** Short saturation-recovery low-resolution high-dose FLASH perfusion; the blood pool (T1 ≈ 30 msec) has not fully recovered and the AIF is not clipped.

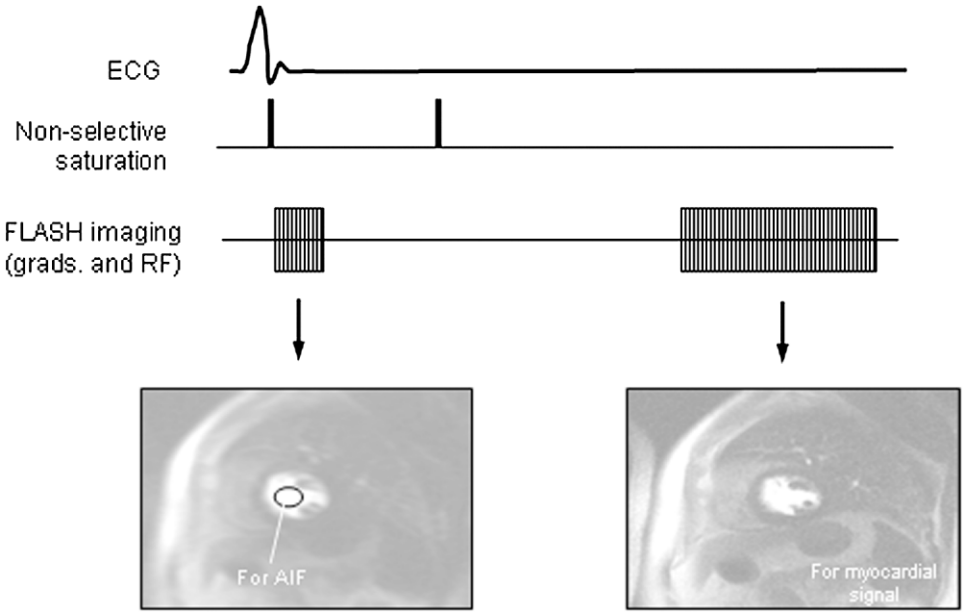


Figure 2. The dual-resolution perfusion sequence method. Immediately following each R-wave the fast low-resolution FLASH sequence is run, to provide the AIF, which is then followed by the high-resolution FLASH sequence to measure the myocardial signal.

The 48-msec blood pool image was followed later in the same cardiac cycle by a FLASH image for myocardial signal measurement. The myocardial imaging sequence was saturation-recovery high-resolution single-shot FLASH acquiring 108 × 256 k-cells in the same plane and FOV as the low-resolution image, with imaging time = 201 msec, long saturation-recovery time = 63.4 msec from the 1-msec nonselective saturation pulse to the first FLASH excitation pulse, TE = 1.2 msec, flip angle = 10°, TR = 1.86 msec, linear ky order, no ky offset, and 1500 Hz/pixel. Due to its long imaging time, the high-resolution FLASH was run in late diastole for minimal cardiac motion (Fig. 2). The long FLASH image was required by an ongoing research protocol to which this work was attached, but a single AIF image per cycle by the new method could apply to multislice myocardial imaging by any sequence. Images were obtained by magnitude reconstruction; both raw data arrays were zero-filled to 128 × 256 before fast Fourier transform. In the low-resolution blood pool images, Gibbs truncation artifacts were seen, but this did not interfere with blood pool analysis. The T1 sensitivities of the low-resolution and high-resolution FLASH sequences were compared using diluted contrast agent in saline in 60-mm-diameter bottles.

Subjects and Protocol

The new method was evaluated in 15 subjects. All patients gave informed consent and the project was approved by the local ethics committee. Volunteers were requested to abstain from caffeine consumption or other adenosine antagonists on the day of scanning. A mid-ventricular short-axis (SA) plane was selected and images were acquired for 50 cardiac cycles, during peripheral injection of the contrast agent through an 18-G cannula at 7 mL/second by power injection (Medrad) into the antecubital fossa. For the dual-bolus approach, the gadolinium contrast agent (Omniscan, Nycomed) was diluted to 0.05 M in saline, resulting in identical fluid volumes of injection for the low-dose (0.01 mmol/kg) and high-dose (0.1 mmol/kg) perfusion runs. After each injection, the lines were flushed with normal saline. The contrast agent was selected for its low viscosity before dilution, so that the two injections should be as similar and rapid as possible. The low dose was injected approximately 2 minutes before the high-dose injection. The power injector had two syringes (designed for contrast agent and saline), which were used for 0.05 and 0.5 M contrast agent in this work. Because no saline flush could be delivered, a fixed 5-mL line volume was preloaded with saline, and an additional 5-mL injection volume to that required for the dose was programmed to ensure complete dose delivery. The subjects were requested to hold their breath from the start of the perfusion sequence for as long as possible. After the rest study, adenosine was infused at 140 μg/minute/kg for four minutes and the full dual-bolus technique was repeated. The time between the rest and stress studies was 20–25 minutes. Each subject received a total of 0.22 mmol/kg of gadolinium contrast agent for this comparison protocol.

During each injection of low-dose (LD) and high-dose (HD) gadolinium, two series of perfusion images were obtained: low resolution with low T1 sensitivity (LT) and high resolution with high T1 sensitivity (HT). Four series of perfusion images were therefore obtained at rest and repeated under stress. The four series (Fig. 3) are identified as follows: low-dose LT (LDLT) and low-dose HT (LDHT); high-dose LT (HDLT) and high-dose HT (HDHT). The LDLT images were not used since virtually no contrast enhancement was present. The first image of each series was acquired without saturation pulses to act as a reference for the full recovery level.

Analysis

For the AIF measurements, a 20-mm-diameter region of interest (ROI) was selected in the LV blood pool during the LDHT, HDLT, and HDHT series. For a total of 30

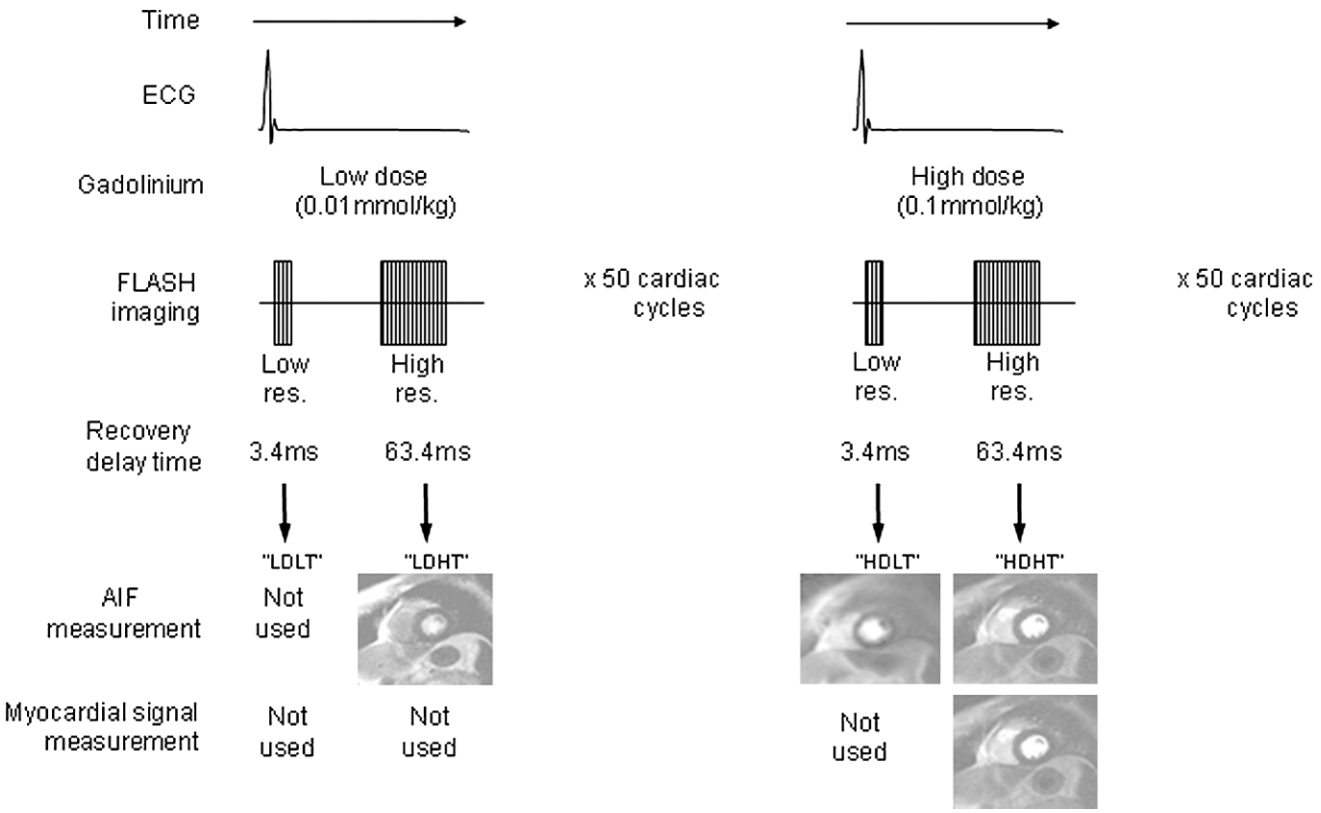


Figure 3. Diagram illustrating the sequences and images acquired. In each subject low-resolution and high-resolution images were acquired with low and high doses of gadolinium at rest and stress. This allowed three measurements of the AIF, only two of which were used in MPR calculations: low-dose low T1 sensitivity (LDLT) (unused), low-dose high T1 sensitivity (LDHT), high-dose low T1 sensitivity (HDLT), and high-dose high T1 sensitivity (HDHT). The HDHT AIF was used only to illustrate the clipping problem.

first-pass perfusion studies, the three versions of the AIF were assessed by plotting their baseline and peak values compared to the reference full recovery level. Only the AIFs from the LDHT and HDLT series were used for MPR analysis by deconvolution. The HDHT AIF was available gratis during the myocardium imaging and was used only to illustrate the clipping problem. For the myocardial signal response, the ROI included the entire myocardium in the HDHT images. The ROIs were moved manually to follow any in-plane respiratory motion.

All of the measurements were performed at rest and stress on each subject. Receiver gain and image reconstruction settings did not change. For each of the two blood input measurement methods with each myocardial region, MPR was calculated using constrained deconvolution with a Fermi function model (6) using in-house designed software (CMRtools, Imperial College, London, UK). A linear dependence of ROI magnitude on contrast agent concentration was assumed, and the baseline ROI value before bolus arrival was subtracted from the input function. The MPR values obtained using the different input functions were compared using the Wilcoxon matched-pairs test.

RESULTS

The Gd phantom results (Fig. 4) showed 90% of full recovery for the low- and high-resolution sequences at 14 and 4 mM concentrations of contrast agent, respectively.

Figure 5 shows one subject's resting examples of the AIFs measured from the HDHT, LDHT, and HDLT images. Peak clipping distorted the HDHT AIF (clipping, arrowed). Normal T1 recovery of blood during the 63.4-msec saturation-recovery time of the LDHT images explained their higher baseline mean ROI before bolus arrival, compared to the 3.4-msec saturation-recovery low-T1-sensitivity HDLT images. For the stress perfusion measurement (Fig. 6), the remaining contrast agent from the rest measurement typically increased

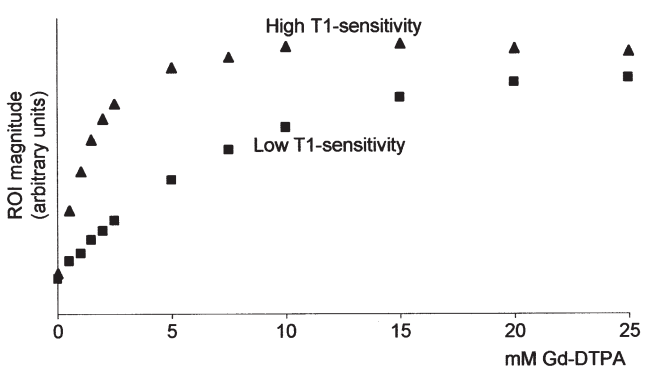


Figure 4. The T1 sensitivity of the two FLASH sequences for contrast agent diluted in saline.

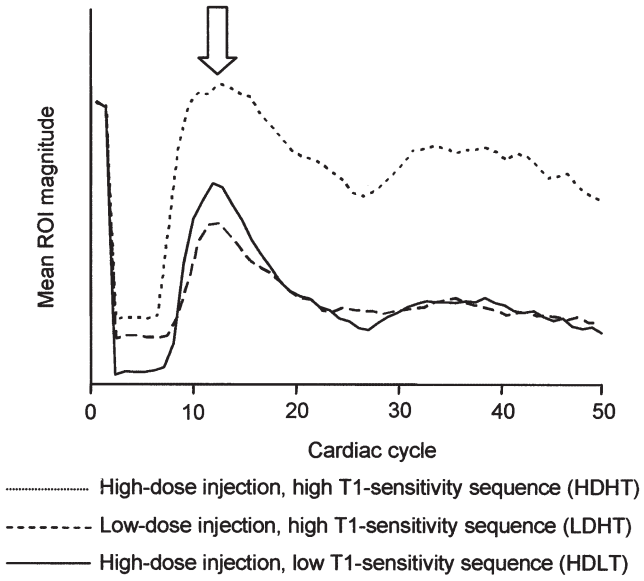


Figure 5. Rest Gd bolus measurements: the saturation pulse was turned off for the first images (see Materials and Methods), giving a full recovery value in the absence of Gd. Each method was scaled by its full recovery value to the same starting value. Full recovery caused clipping of the HDHT response (arrow) at a value higher than the initial value because of the small inherent T1 sensitivity of the FLASH image without a saturation pulse. The LDHT and HDLT responses are not clipped, but they differ in shape because they were obtained during two separate injections at low and high doses, and they differ in amplitude because of their different doses and T1 sensitivities. Except for the higher baseline of the high-T1-sensitivity response caused by the normal blood T1, and its peak clipping, the two AIFs obtained during the high-dose injection are similar on a beat-to-beat time-scale.

this baseline and swamped the response to the low-dose injection, whereas the HDLT measurement was relatively unaffected by this problem. Figure 7 shows the AIFs at baseline and peak for the 15 subjects at rest

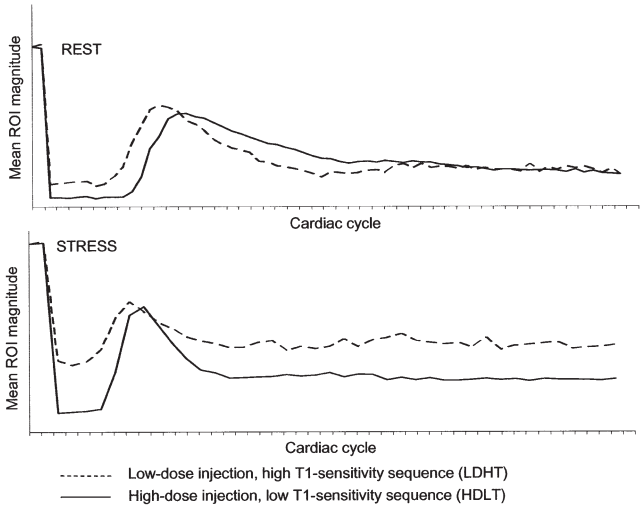


Figure 6. The effect of the remaining contrast agent on AIF measurements in the same subject. The second (stress) LDHT AIF is most affected by the remaining contrast agent from the first (rest) scan.

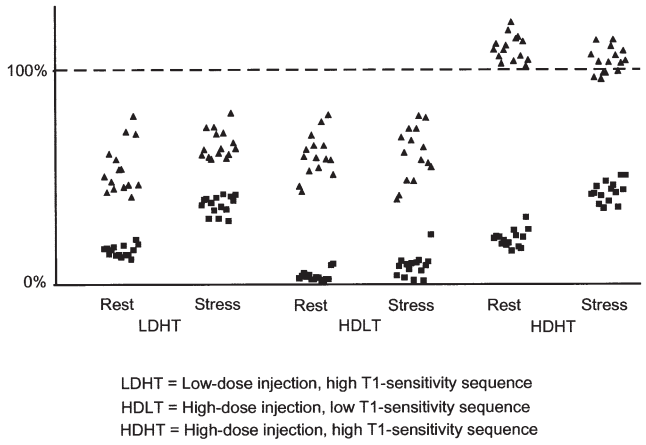


Figure 7. The AIF baseline (square) and peak (triangle) values of ROI mean magnitude, at rest and stress, for all 15 patients with all three methods. The 100% reference level was measured from the images acquired with no saturation pulse.

and stress. The 100% reference level was measured from the image acquired with no saturation pulse. In the HDHT image, designed to measure myocardial signal response, full recovery caused the blood signal to reach its maximum at contrast agent concentrations lower than the peak; this peak clipping effect is not to be confused with any maximum pixel value clipping by image reconstruction and display software. At high levels of Gd, this level exceeded the 100% reference due to the T1 sensitivity of the FLASH sequence itself. For the LDHT and HDLT methods, taking each AIF amplitude = peak – baseline, the AIF amplitudes were compared (Fig. 8), where linear regression analyses showed a

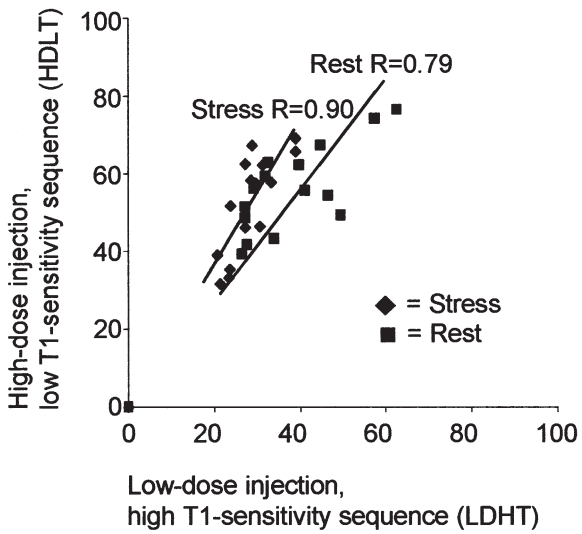


Figure 8. Comparison of the AIF amplitudes (= peak – baseline, from uncalibrated ROI mean magnitudes in the left ventricle) measured by the HDLT and LDHT methods. One hundred percent on the axes represents an amplitude equal to the reference level of Fig. 7. There is a reduction in the AIF amplitude measured by the LDHT method at stress compared to rest. Linear regression fits are shown separately for rest and stress.

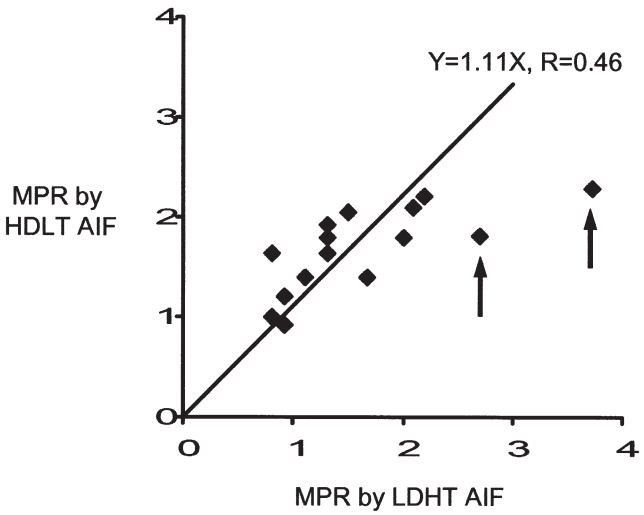


Figure 9. Comparison of MPR values calculated using AIFs measured from the new method HDLT images and the dual-bolus method LDHT images. In two cases (arrowed), the signal from the residual gadolinium from the first rest study was particularly high, and therefore the stress low-dose input was underestimated, resulting in a high LDHT MPR being calculated. Omitting these two points, the results showed an 11% overestimate of the MPR by the HDLT AIF, which has not been explained.

close agreement between the AIF amplitudes by the two methods. A change in the response of the LDHT method between rest and stress is apparent from Fig. 8 (see Discussion section).

For the 15 subjects, the MPR values (Fig. 9) using the LDHT and HDLT methods appear to demonstrate two effects. First, in some subjects the MPR calculated was markedly higher using the LDHT rather than the HDLT for the AIF (arrows). Second, eliminating the two most evident outliers, the MPR was higher using the HDLT AIF method (MPR by HDLT = 1.11 ($\pm$ 0.07) $\times$ MPR by LDHT).

In one extra subject, to examine possible T2* effects during the high-dose first pass, the mean ROI blood signal was measured (Fig. 10) in the ascending aorta using the HDLT sequence alone without saturation pulses. It showed no drop in the signal, unlike the neighboring caval vein. Furthermore, on the HDLT AIFs (Fig. 7) the consistent occurrence of peak bolus amplitudes approximately 50% to 60% of full recovery indicated that no severe T2* loss occurred. Finally, the phantom results (Fig. 4) were obtained from small bottles approximating diastolic LV blood cavity dimensions.

DISCUSSION

Accurate AIF measurement should avoid a concentration and T1 sensitivity arrangement that makes use of near full recovery, where the distorted response to [Gd] effectively clips the peak. The phantom experiments demonstrated how the dual-bolus and dual-T1-sensitivity methods avoid the problem: for an estimated peak concentration of 5 mM, the high-T1-sensitivity sequence exceeded 90% recovery, whereas the low-T1-sensitivity sequence was approximately 50% recovered. The dual-bolus method implemented here at 0.01 mmol/kg would result in an estimated 0.5 mM peak concentration, which drove the high-T1-sensitivity sequence to approximately 40% recovery. Although the HDLT and LDHT methods therefore had similar responses, no attempt was made to make them match precisely.

The reasonable in vivo agreement between the proposed new method and the dual-bolus method suggests that the new approach may be valuable because of the problems of using the dual-bolus approach. In spite of careful efforts to use the same injection volume and viscosity for both low and high doses, differences may still have occurred between the injections of the dual-bolus approach, such as cardiac timing and effects of breath holding on venous return. This concern remains even if the dual-bolus method is performed with more practical ease.

An additional problem with the dual-bolus technique is that the second low-dose bolus, given during adenosine infusion, is prone to being swamped by the residual gadolinium from the rest perfusion study. This effect may explain the two points arrowed on Fig. 9: in these two cases, the level of residual gadolinium from the first rest study remained high at the time of commencing the stress study. The residual Gd had a greater effect on the high-T1-sensitivity image (LDHT image) used for the dual-bolus technique for stress than it had upon the low-T1-sensitivity image (HDLT image). In Fig. 6, the residual Gd elevated the initial LDHT baseline before the arrival of the new Gd bolus injection and shifted the response to the Gd bolus further up the recovery curve than during the rest study. (The simple linear conversion of pixel magnitude to contrast agent concentration after baseline subtraction underestimated the AIF when the pixel magnitudes were higher up the curve toward full recovery.) It appears likely that the stress AIF was therefore sometimes underestimated by the LDHT images, as indicated by Fig. 8. Consequently, the MPR could be overestimated using this AIF, compared to using the AIF from HDLT images. Finally, omitting the points most obviously overestimated by the MPR calculated using the LDHT AIF, the

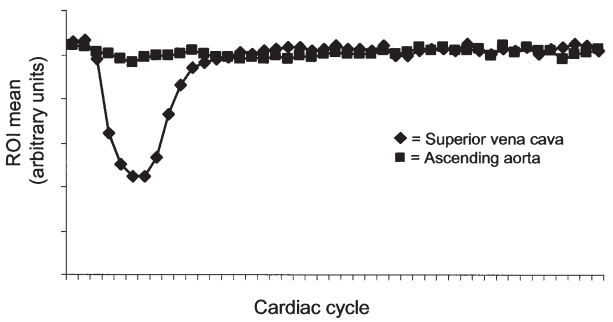


Figure 10. High-dose contrast agent first pass imaged by the low-resolution low-T1-sensitivity sequence (HDLT images). The T2* effect of the peak concentration reduced the signal in the superior vena cava, while no effect was seen in the neighboring ascending aorta.

results showed an 11% overestimate of the MPR by the HDLT AIF. The discrepancy in these results has not been explained. For each purpose (blood and myocardium T1 assessment), there is a limited range of saturation-recovery times that avoid peak AIF clipping while maximizing the sensitivity, and the calibration images obtained without saturation pulses at the start assisted in evaluating this range. We found empirically that 3.4-msec saturation-recovery delay worked well for LV blood pool with the injection parameters used. For the myocardium, a long saturation-recovery delay such as 63.4 msec might allow complete recovery of the vascular volume; however, the vascular volume is a small fraction (13 mL/100 g) of the myocardium, of which mainly the arterial (15%) and capillary (5%) components may contribute to a small multicompartment error in the myocardial mean ROI signal as a function of extracellular contrast agent concentration (7). Further concerns exist about the potential breakdown of the fast-exchange assumption at high concentrations of gadolinium; at the highest gadolinium concentrations in the extravascular extracellular volume (the interstitial fluid), the rate at which water protons are exchanged between extracellular and intracellular volumes may be slow compared to the relaxation time in the interstitial fluid, so that the tissue magnetization now has two separate extravascular components, and its longitudinal magnetization recovery cannot be modeled as a single exponential term (4,8). If this complex issue, where work is still in progress, is assumed to have a negligible impact, a final possible source of distortion must be considered for high-dose high-T1-sensitivity myocardial imaging. If the contrast agent in the interstitial fluid reached such a high concentration that its magnetization recovered fully in 63.4 msec after saturation, this method would have introduced myocardial response clipping; however, the initial calibration images with the saturation switched off proved that this limit was not reached even at the peak stress perfusion.

At 3.4-msec saturation-recovery delay, longitudinal magnetization in some regions of the HDLT images was partially saturated, and in other regions it had been driven negative and not yet recovered through zero. This effect was observed prior to the contrast agent injection, and the described regions could be shifted by changing the transmitter calibration—it was thought due to B_1 nonuniformity and inherent sensitivity of saturation to B_1 calibration (9). The nonuniform saturation was more apparent using the short saturation-recovery delay of 3.4 msec than the long recovery delay, when all relevant regions of the FOV had recovered through zero. The spatial effectiveness of the saturation varied between subjects, varying with tissue absorption and B1 calibration. In extreme cases the relationship between ROI magnitude and contrast agent concentration in the high-dose low-T1-sensitivity image was distorted (by a zero-crossing having lost the sign of the magnitude).

In conclusion, although the use of short saturation-recovery delay to reduce peak distortion of the AIF is well known, and the overestimation compared to the dual-bolus method in this work could not be explained, the proposed new method provided this data during the same first-pass of gadolinium as a highly sensitive high-resolution myocardial measurement. The new method may also apply to normalized upslope analysis. For multislice imaging, one AIF image by the new method may replace AIFs from the myocardial slices, where peak clipping may still occur at lower T1 sensitivity than in this work. The separate blood imaging sequence also provides new flexibility, e.g., the position of the separate blood measurement (10) or no longer needing a bright blood signal in the myocardial image.

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