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VIABILITY

Influence of Contrast Agent Dose and Image Acquisition Timing on the Quantitative Determination of Nonviable Myocardial Tissue Using Delayed Contrast-Enhanced Magnetic Resonance Imaging

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ABSTRACT

Background: Delayed contrast-enhanced magnetic resonance imaging (ceMRI) has been shown to identify areas of irreversible myocardial injury due to infarction (MI) with high spatial resolution, allowing precise quantification of nonviable (hyperenhanced) myocardium. The aim of our study was to investigate the size of nonviable myocardium quantitatively as a function of time post-contrast when inversion time is held constant in patients post-myocardial infarction using two contrast agent (CA) doses. *Methods:* Nine patients with chronic MI underwent two MR scans on a 1.5 Tesla system. Contrast-enhanced MRI data in two short-axis (SA) slices were continuously acquired until 40 minutes after CA injection [gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA), 0.1 mmol/kg body weight = single dose] interrupted only for a complete stack of SA slices encompassing the entire left ventricle (LV) between minutes 20 and 28. Left ventricular mass showing hyperenhancement was determined. The measurement was repeated on the subsequent day with double dose CA (0.2 mmol/kg body weight). Differences of signal intensities for hyperenhanced, nonhyperenhanced myocardium, and LV cavity were calculated. *Results:* Total mass of hyperenhancement from a complete SA stack acquired between minutes 20 and 28 was lower for single dose CA [9.0% vs. 14.2% for single and

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double dose, respectively (p=0.03)]. Ten to 18 minutes after CA injection, there was no significant difference between the two doses and to an internal reference for both single and double dose. For single dose the image contrast between hyperenhancement and LV cavity was superior (minutes 10 to 16, $p<0.05$) but inferior between hyperenhanced and nonhyperenhanced myocardium (minutes 6 to 16, $p<0.05$). *Conclusion:* Myocardial infarct size measurements are a function of time postcontrast when inversion time is held constant regardless of the contrast agent dose. These data underscore the fact that a standardized imaging protocol that defines how the appropriate inversion time should be selected is needed for comparison of results obtained at various cMR sites.

Key Words: Contrast media; Magnetic resonance imaging; Myocardial infarction; Viability; Delayed enhancement.

INTRODUCTION

Delayed contrast-enhanced magnetic resonance imaging (ceMRI) has been shown to identify areas of irreversible myocardial injury due to infarction (MI) in the acute (Dendale et al., 1998; de Roos et al., 1989; Eichstaedt et al., 1989; Fieno et al., 2000; Judd et al., 1995; Kim et al., 1996, 1999; Kramer et al., 2000; Lima et al., 1995; Oshinski et al., 2001; Saeed et al., 2001; Van Rossum et al., 1990; Wu et al., 1998; Yokota et al., 1995), subacute (Choi et al., 2001; Fieno et al., 2000; Kim et al., 1999; Petersen et al., 2003; Rogers et al., 1999), and chronic phase (Choi et al., 2001; Fedele et al., 1994; Fieno et al., 2000; Kim et al., 1999, 2000; Lauerma et al., 2000; Petersen et al., 2003; Ramani et al., 1998; Rogers et al., 1999; Sandstede et al., 2000a) of MI. The high spatial resolution of the technique allows precise quantification of nonviable myocardium. Two developments have been seminal for this approach: First, in an animal model, Judd et al. (1995) described a close agreement between histological MI size and the MI size determined with ceMRI. Second, Simonetti et al. (2001) showed substantially enhanced image contrast between viable and nonviable myocardium with an inversion-recovery Turbo-FLASH (fast low-angle shot) sequence. The delayed enhancement technique has recently been widely used in animal models (Judd et al., 1995; Kim et al., 1996, 1999; Oshinski et al., 2001; Pereira et al., 1996, 2000a,b; Rehwald et al., 2002) and patients (Choi et al., 2001; Kim et al., 2000; Klein et al., 2002; Sandstede et al., 2000a,b; Wu et al., 1999) to identify irreversibly injured nonviable myocardium and is now considered the reference by many investigators. However, with the widespread use of this MR technique, different imaging protocols have evolved that vary with regard to contrast dose and timing of image acquisition after contrast injection and inversion time settings. Underlying mechanisms and factors influencing ceMRI image contrast remain to be fully defined. Thus, there is a need to optimize and standardize protocols for ceMRI, so that data obtained from different cMR sites are directly comparable.

Therefore, the aim of our study was to investigate the size of nonviable myocardium quantitatively as a function of time post-contrast when inversion time is held constant in patients post-myocardial infarction using two contrast agent (CA) doses.

METHODS

Patient Group

Patients with a history of chronic (older than 8 weeks) anterior myocardial infarction and typical electrocardiogram (ECG) changes were included [n=9, all male, age 54.3±9.8 (mean±SD)] in the study. None of the patients had a contraindication to MRI, and all gave written informed consent to the study protocol, which had been approved by the local ethics committee.

Study Protocol

Two MR scans (Fig. 1) were performed on consecutive days on a 1.5 Tesla MR system (Sonata Siemens Medical Solutions, Erlangen, Germany). On day 1, Cine TrueFISP sequences were performed to identify the area of myocardial infarction via altered regional wall motion [repetition time/echo time (TR/TE) 34.8/1.6 ms, field of view (FoV) 340×340 mm^2, matrix 183×256, slice thickness 7 mm, slice distance 10 mm, temporal resolution 35 ms]. Vertical (VLA) and horizontal (HLA) long-axis and short-axis (SA) cines encompassing the entire left ventricle were acquired. To follow image contrast changes over time, two SA slices with altered regional wall motion were chosen for ceMRI. These were then acquired in an

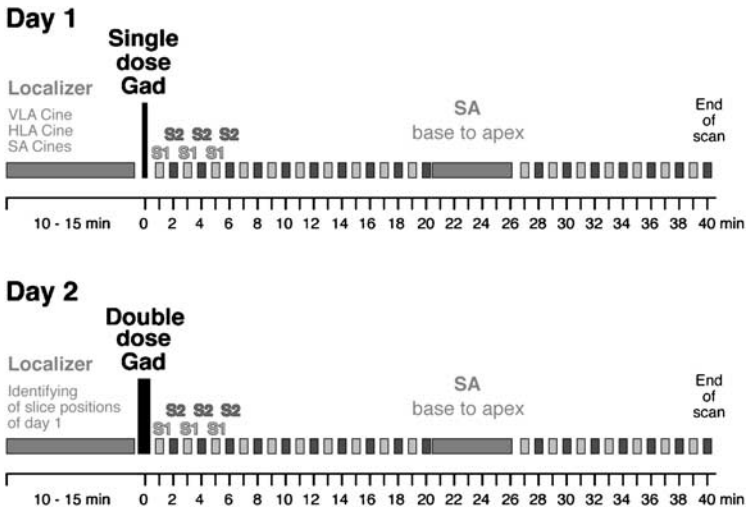

Figure 1. Study protocol (Gad=Gadolinium-DTPA, VLA=vertical long axis, HLA=horizontal long axis, SA=short axis, S1=slice 1, S2=slice 2).

alternating order every other minute (i.e., slice 1 at minute 1, 3, 5, etc. and slice 2 at minute 2, 4, 6, etc.) until 40 minutes after contrast agent injection [Gadolinium-DTPA (Gd-DTPA), 0.1 mmol/kg body weight= single dose, segmented inversion-recovery TurboFLASH, TR/TE 750/4.4 ms, constant TI of 260 ms, slice thickness 6 mm, slice distance 10 mm, FoV 276×340 mm^2, matrix 166×256]. To quantify the total mass of nonviable myocardium, between minutes 20 and 28, VLA, HLA, and SA ceMRI images encompassing the entire left ventricle were acquired.

To determine the influence of contrast agent dose, the protocol was repeated on day 2 with double dose contrast agent (0.2 mmol Gd-DTPA/kg body weight), using the identical imaging planes and acquisition protocol (Fig. 2).

MRI Data Analysis

Planimetric quantification of the areas of hyperenhancement was performed using Adobe® Photoshop 5.0; results were expressed as percentage of the

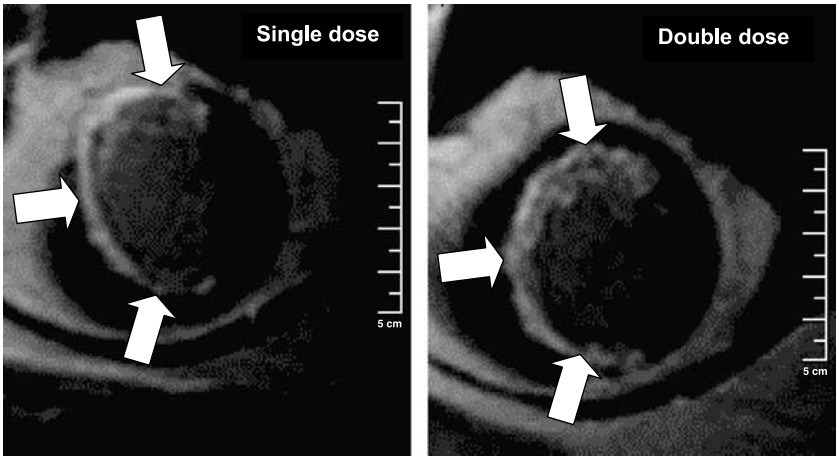

Figure 2. Agreement between areas of hyperenhancement in single dose (left panel) and double dose (right panel) short-axis slices in the same patient. White arrows pointing to hyperenhancement in the anterior, septal, and inferior myocardium. Left panel acquired with single dose (0.1 mmol/kg Gd-DTPA, 8 minutes after contrast agent administration), right panel with double dose contrast agent (0.2 mmol/kg Gd-DTPA, 24 minutes after contrast agent administration) using an ECG-triggered segmented inversion-recovery turboFLASH sequence in breath-holding with an inversion time held constant (TI 260 ms).

left ventricular mass in that slice. The mass of hyperenhancement in two short-axis slices was studied over time for both contrast agent doses, and the total mass of hyperenhancement (complete short axis stack) was calculated for both doses between minute 20 and 28.

The signal intensities in hyperenhanced and nonhyperenhanced myocardium as well as in the left ventricular cavity were measured over the time course with the Siemens software Mean Curve (part of the MR Syngo 2002B, Siemens Medical Solutions, Erlangen, Germany). Contrast of delayed enhancement images was evaluated by the difference of signal intensities between hyperenhanced myocardium and nonhyperenhanced myocardium and between hyperenhanced myocardium and left ventricular cavity. A higher absolute value is a marker for superior delineation regardless of positive or negative values.

Statistical Analysis

Total mass of hyperenhancement and image contrast parameters were tested for differences between single and double dose contrast agent using the Wilcoxon's signed rank test as this test does not rely on the assumption of a Gaussian distribution of the data (Kusuoka and Hoffman, 2002). The same test was applied for each acquisition time point in the time course study to analyze differences of mass of hyperenhancement to the internal reference double dose contrast agent at 20 minutes and between both contrast agent doses. The internal reference was defined in absence of a histological gold standard (e.g., triphenyltetrazolium chloride staining) and based on the protocols used by Kim et al. (2000), this being a standard that has been comprehensively validated. The level of significance was $p<0.05$. Values are given as mean±standard error of the estimate (SEE) unless stated otherwise.

RESULTS

Total Hyperenhanced Left Ventricular Mass

All nine patients showed an area of hyperenhancement in the anterior myocardium and an associated regional wall motion abnormality in this area.

Total mass of hyperenhancement was significantly lower for the single dose group for the short-axis stack of images acquired between 20 and 28 minutes [Fig. 3; 9.0% vs. 14.2% for single and double dose, respectively ($p=0.03$)].

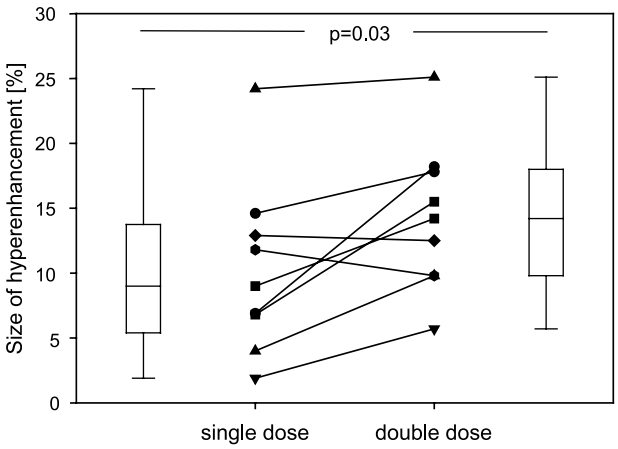

Figure 3. Size of hyperenhancement [%] between minutes 20 and 28.

Time Course of Delayed Enhancement

Extent of Delayed Enhancement

After the administration of contrast agent, over the first 10 minutes a sharp increase of the area of hyperenhancement was observed for both doses (Fig. 4). After this upslope, the curves reached a plateau phase. Thirty minutes post contrast agent administration the extent of hyperenhancement decreased rapidly for single dose, whereas for double dose it remained constantly elevated. Between 4 and 18 minutes post Gd-DTPA injection there was no significant difference between single and double dose ($p>0.05$). No significant difference between mass of hyperenhancement and the internal reference (mass of hyperenhancement at 20 minutes with double dose contrast agent) was seen between 6 and 20 minutes for single dose and between 10 and 40 minutes for double dose. Overall, between 10 and 18 minutes post Gd-DTPA administration there was no significant difference between the two dose groups nor did they differ significantly from the internal reference. The percentage difference between the extent of hyperenhancement to the internal reference [Change (%)=100*mass of hyperenhancement/internal reference] for single dose was highest for minute 2 (−74.9%) and lowest for minute 18 (1.3%). For double dose the maximal difference was −93.9% at minute 2 and 0% at minute 20 (internal reference). Mean differences for the period 10 to 18 minutes post

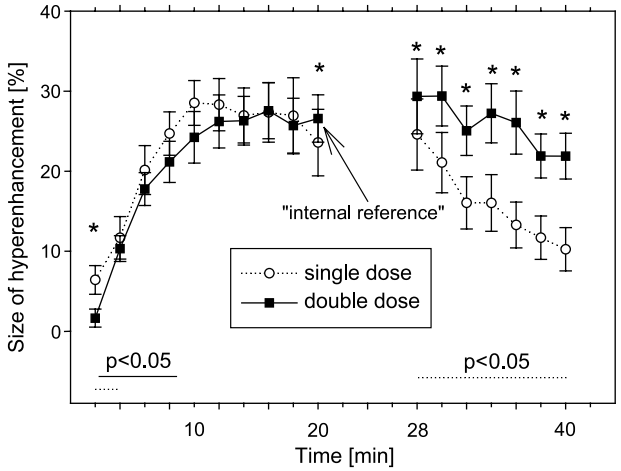

Figure 4. Time course of size of hyperenhancement (%) (slices 1 and 2) (* denotes statistical significance $p < 0.05$ between single and double dose contrast agent; significance between each dataset and the internal reference double dose at minute 20 is shown as a dotted line for single dose and as a solid line for double dose contrast agent).

Gd-DTPA injection were 3.9% and −2.2% for single and double dose, respectively.

Image Contrast

The delayed enhancement contrast between hyperenhanced, nonhyperenhanced myocardium, and the left ventricular cavity also changed over time (Figs. 5 and 6).

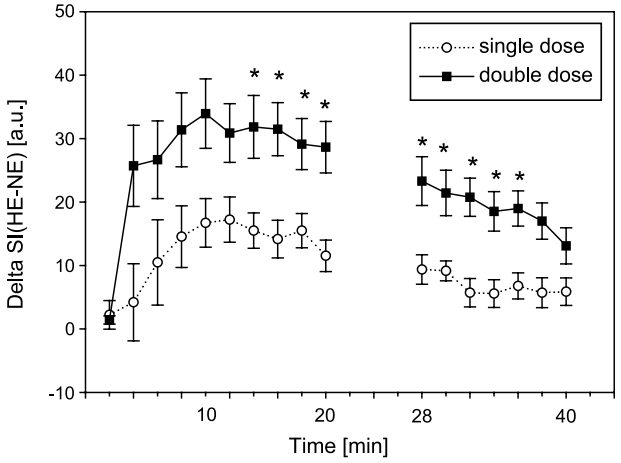

Figure 5. Time course of contrast between hyperenhanced and nonenhanced myocardium [* denotes statistical significance $p<0.05$ between single and double dose contrast agent; Delta SI(HE − NE) = difference of signal intensities between hyperenhanced and nonenhanced myocardium].

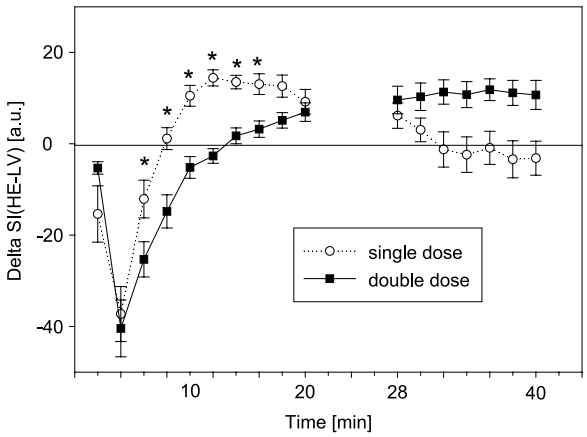

Figure 6. Time course of contrast between hyperenhanced myocardium and left ventricular cavity [* denotes statistical significance $p < 0.05$ between single and double dose contrast agent; Delta SI(HE − LV) = difference of signal intensities between hyperenhanced myocardium and left ventricular cavity].

The contrast between hyperenhanced and non-hyperenhanced myocardium (Fig. 5) was significantly higher for double dose for each time point between 14 and 36 minutes compared to single dose ($p<0.05$).

The time course of image contrast between hyperenhanced myocardium and the left ventricular cavity for the two contrast agent doses showed a significant difference for each time point between 6 and 16 minutes ($p<0.05$, Fig. 6). Negative values in the early phase of contrast agent distribution represented higher signal in the left ventricular cavity. Positive values at a late image acquisition time were due to the hyperenhanced regions showing higher signal intensity than the left ventricular cavity. Conversely, this contrast inversion was reached earlier for single dose (minute 8) compared to double dose contrast agent (minute 14 post administration of contrast agent). The absolute value of this image contrast parameter was higher for single dose between minutes 10 to 16 and higher for double dose between minutes 6 to 8.

DISCUSSION

Our study demonstrates, for the first time in humans, that quantification of infarct size by ceMRI is influenced by both contrast agent dose and timing of image acquisition when the TI is kept constant.

Between 10 and 18 minutes after contrast agent injection, there was no significant difference for infarct size between the two contrast agent doses and to the defined internal reference double dose at 20 minutes. The image contrast for single dose, however, was superior between hyperenhanced myocardium and the left ventricular cavity but inferior between hyperenhanced and nonhyperenhanced myocardium. Importantly, for both contrast agent doses, the contrast for distinction between hyperenhanced and nonhyperenhanced myocardium was sufficient for easy delineation.

The underlying mechanisms of delayed enhancement in areas of irreversibly nonviable myocardial tissue remain to be fully understood. This phenomenon is believed to be due to a change of distribution volumes in favor of extracellular space in acute, subacute, and chronic infarction (Mahrholdt et al., 2002). In the acute and subacute phase this may be due to ruptured cell membranes and edema. Scar tissue, in contrast, is characterized by an increased extracellular space with an excess of collagen matrix.

Gd-DTPA is not a necrosis-specific contrast agent such as porphyrin-based contrast media (Saeed et al., 1999), and it is important to define the factors that influence the quantification of nonviable myocardial tissue by the Gd-DTPA late enhancement technique. Currently, little information is available with regard to this, mainly from animal studies. For example, Oshinski et al. (2001) have demonstrated the critical role of image acquisition timing after Gd-DTPA injection in a rat model of acute MI with variable durations of ischemia and reperfusion. To define the influence of contrast agent dose and image acquisition timing we investigated a study population with chronic myocardial infarction after scar tissue formation in order to avoid underlying changes in delayed enhancement that may occur over time in the acute and subacute phases following myocardial infarction.

The shape of the time curves for mass of hyperenhancement for both contrast agent doses reported here differs from the results of Oshinski et al. (2001): They demonstrated a steady decrease of ceMRI mass of hyperenhancement over time, which lead to overestimation of true infarct size in measurements made too early and an underestimation in very late image acquisition. In contrast, our results, obtained in humans, suggest an underestimation of infarct size in images either acquired too early or too late when inversion time is held constant.

Limitations of the Study

The study was designed to analyze the dependent variable mass of hyperenhancement and image contrast over a time period of 40 minutes with the independent variable contrast agent dose. To avoid confounding of the dependent variables by changing TI values, we used a constant TI of 260 ms for all patients and both contrast agent doses, despite the drawback that the signal intensity of viable myocardium was not perfectly nulled in some instances. This study design, therefore, cannot answer the effects of changing TI values on the dependent variables mass of hyperenhancement and image contrast. Lower contrast agent concentration (i.e., single dose and later image acquisition) and consequently higher T1 values necessitate a longer TI for optimal image contrast (Mahrholdt et al., 2002; Simonetti et al., 2001). Future studies should aim to investigate the influence of variable TI and acquisition timing on quantitative MI size determination using delayed enhancement. A study design could now be performed with the recent advent of breath-hold sequences that use varying TI values to identify the optimal TI. The data presented in this manuscript should be interpreted bearing in mind that individually optimizing the TI improves image contrast and could minimize differences of mass of hyperenhancement. Using a nonoptimal TI could lead to an underestimation of infarction due to two reasons: firstly, mistakenly nulling edges of the myocardial infarctions that may have differing T1 values than the core of the infarction and secondly, poor image contrast that does not allow the clear demarcation of areas with high signal intensities. From a practical point of view, optimizing the TI manually needs time (and was thus not feasible in our study design) and experience, because contrast dose, timing of acquisition, trigger pulse settings, and heart rate [i.e., time for the signal to recover after the inversion pulse according to the Bloch equation $S=S0*(1-2e^{-t/T1})$] need to be taken into account. This tedious adjustment may become dispensable with recently described phase-sensitive reconstruction methods (Kellman et al., 2002).

Unlike in animal experiments, the areas of hyperenhancement in our study of patients with chronic MI could not be compared to a histological ''gold standard'' of myocardial nonviable tissue (e.g., triphenyltetrazolium chloride staining). Instead, delayed enhancement image acquisition at 20 minutes after contrast agent administration was used as an internal reference in our study based on the original method described by Kim et al. (2000).

CONCLUSION

Myocardial infarct size measurements are a function of time post contrast when inversion time is

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held constant regardless of contrast agent dose. These data underscore the fact that a standardized imaging protocol that defines how the appropriate inversion time should be selected is needed for comparison of results obtained at various cMR sites.

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