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How to cite

CARNET, Emmanuelle et al. Superparamagnetic iron oxide particles and positive enhancement for myocardial perfusion studies assessed by subsecond T_1-weighted MRI. In: Magnetic resonance imaging, 1993, vol. 11, n° 8, p. 1139–1145. doi: 10.1016/0730-725x(93)90241-5

This publication URL: https://archive-ouverte.unige.ch//unige:166155
Publication DOI: 10.1016/0730-725x(93)90241-5

Magnetic Resonance Imaging, Vol. 11, pp. 1139–1145, 1993
Printed in the USA.

0730-725X/93 $6.00 + .00

● *Original Contribution*

SUPERPARAMAGNETIC IRON OXIDE PARTICLES AND POSITIVE ENHANCEMENT FOR MYOCARDIAL PERFUSION STUDIES ASSESSED BY SUBSECOND T_1-WEIGHTED MRI

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Superparamagnetic iron oxide particles (SPIOs) are usually referred to as T_2 MR contrast agents, reducing signal intensity (SI) on T_2-weighted MR images (negative enhancement). This study reports the original use of SPIOs as T_1-enhancing contrast agents, primarily assessed in vitro, and then applied to an in vivo investigation of a myocardial perfusion defect. Using a strongly T_1-weighted subsecond MR sequence with SPIOs intravenous (IV) bolus injection, MR imaging of myocardial vascularization after reperfusion was performed, on a dog model of coronary occlusion followed by reperfusion. Immediately after the intravenous bolus injection of 20 μmol/kg of SPIOs, a positive signal intensity enhancement was observed respectively, in the right and left ventricular cavity and in the nonischemic left myocardium. Moreover, compared to normal myocardium, the remaining ischemic myocardial region (anterior wall of the left ventricle) appeared as a lower and delayed SI enhancing area (cold spot). Mean peak SIE in the nonischemic myocardium (posterior wall) was significantly higher than in the ischemic myocardium (anterior wall) (110 ± 23% vs. 74 ± 22%, Mann-Whitney test $\alpha < 1\%$, $n_1 = 6$, $n_2 - n_1 = 0$, $U > 2$). In conclusion, the T_1 effect of SPIOs at low dose, during their first intravascular distribution, suggests their potential use as positive markers to investigate the regional myocardial blood flow and some perfusion defects such as the "no-reflow phenomenon."

Keywords: **Contrast media; Magnetic resonance (MR), contrast enhancement; Iron oxide; Heart perfusion; Myocardial ischemia.**

INTRODUCTION

Superparamagnetic MR contrast agents are usually referred to as T_2 or T_2^* contrast agents[1] and opposed to T_1 agents such as paramagnetic-gadolinium chelates. Another originality of Superparamagnetic Iron Oxide particles (SPIOs) over extracellular paramagnetic agents is their specific distribution.[2] After intravenous administration, they are removed from the vascular space by the mononuclear phagocytic system, and especially by the Kupffer cells of the liver.[3,4]

However, the initial intravascular period of SPIOs has been sparsely used to investigate microcirculation and tissue perfusion defect.[5,6] Recently, subsecond MR sequences had made it possible to follow up the distribution of various kinds of MR contrast agents, immediately after their bolus administration, when they could be considered as blood pool markers.[7–10]

Using the signal loss induced by the susceptibility effect of SPIOs, previous investigators have shown the ability of high dose of SPIOs to detect a myocardium damage after reperfusion.[11–13] In the present study, the effect of SPIOs on the longitudinal relaxation rate of protons (positive enhancement) was evaluated in vitro and in vivo, as a function of SPIOs concentration and MR sequence. In vivo, the potential use of SPIOs as both T_1 contrast agents and blood pool markers was investigated to explore the remaining myocardial

RECEIVED 3/4/93; ACCEPTED 6/16/93.

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perfusion defect after reperfusion (no reflow phenomenon), on a canine model of coronary artery occlusion followed by reperfusion.[14]

MATERIAL AND METHODS

Contrast Media

Superparamagnetic iron oxide particles were used in the form of a stable aqueous suspension of iron oxide-dextran, formulated at 200 μmol/l Fe (11.2 mg Fe/ml) (AMI-25, manufactured by Advanced Magnetics Inc., Cambridge, MA, and supplied by Guerbet, France, ENDOREM®). The reported relaxivity of this preparation is $3 \times 10^4\ s^{-1}\ M^{-1}$ for $1/T_1$ and $1 \times 10^5\ s^{-1}\ M^{-1}$ for $1/T_2$ in water (20 MHz, 37°C).[2] The iron core mean diameter is 4–6 nm, whereas the median diameter of the dextran-stabilized particles is distributed between 80–150 nm. After intravenous administration, SPIOs are rapidly removed from the vascular space by mononuclear phagocytic system cells and concentrated in liver, spleen and bone marrow. Consequently, their first application has been the investigation of liver and spleen pathologies. However, they were also employed to study myocardial ischemia and infarction in animal models of coronary artery occlusion, with or without reperfusion.[11–13,15] Concerning the tolerance of SPIOs, they have been shown to cause no tissue toxicity in rats and have been used in human trial studies as a MR contrast agent for the liver in the dose range of 10–50 μmol/kg.[2]

In Vitro Experiments

Correspondence between MR signal intensity and concentration of AMI-25 was established in vitro over a broad range of concentrations (0, 20, 40, 60, 120, 200, 400, and 800 μmol Fe/l, SPIOs diluted in water). MR images of the 20 mm diameter tubes filled with the different solutions, were performed in the head coil of a 1.5 T whole body MR System (Magnetom 63 SP, Siemens, Germany). Three different MR sequences were acquired: both a standard and a strongly T_1-weighted spin-echo (i.e., respectively, TR/TE = 500/22 ms and TR/TE = 200/22 ms) and a T_1-weighted Turbo-FLASH sequence with the same parameters as those selected for myocardial perfusion studies (i.e., TR/TE = 6.5 ms/3 ms, TI = 300 ms, flip angle = 11°, FOV = 250 mm, matrix size = 128 × 128).

Animal Model

All animal experiments were performed within the guidelines established in "Position of the American Heart Association on Research Animal Use" and following the recommendations of INSERM (France) for Animal Care. This dog model of myocardial ischemia followed by reperfusion has already been described by our group for ex-vivo imaging of another class of MR contrast media.[16]

Six beagle dogs (12–16 kg) were anesthetized by intravenous thiopental (Nesdonal®, 30 mg/kg) and ventilated with a Harvard respirator. After left thoracotomy, the occlusion of the left descending coronary artery (LAD) was performed and maintained for 2 hr, followed by 5 hr of reperfusion. MR imaging was realized after 5 hr of reperfusion and the animals were sacrificed by an overdose of thiopental at 6 hr of reperfusion. Infarct sizing (IS) was then performed by ex vivo blue Evans dye and TTC staining to allow the planimetry of the area of necrosis (infarct size = IS) and of the ischemic area (area at risk = AAR), compared to the total left ventricular area (LV).[16] All data are expressed as mean ± standard error of the mean.

In Vivo MR Imaging

The subsecond T_1-weighted Turbo-FLASH with a 180° preparation pulse (TR = 6.5 ms, TE = 3 ms, α = 11°, FOV = 300 mm, slice thickness = 15 mm, matrix size = 128 × 128, corresponding to a pixel area of 2.34 mm^2) was acquired on a 1.5 T Magnetom 63 SP (Siemens, Germany), in a double helmoltz surface coil. Slices were obtained in a true short axis orientation. An anatomic ECG-gated T_1-weighted spin-echo (TR = 250 ms, TE = 15 ms) was performed prior to contrast media administration, to select the proper level for the Turbo-FLASH acquisition (slice positioned at the middle part of the left ventricular cavity). The T_1 contrast of the Turbo-FLASH images was achieved by prefacing the data acquisition interval with a nonselective 180° inversion at the time of the QRS complex. The delay before the initiation of the data acquisition was selected to null the signal in the LV cavity and to minimize the signal of the myocardium (inversion time, TI = 300 ms). This enables the central encoding line of the sequence (corresponding to the major part of the image information) to be acquired 800 ms after QRS. A total of 17 measures were realized, 10 without any delay and the last 7 with an additional 3-s interscan delay.

Contrast Media Administration

The SPIO particles were employed at the low dose of 20 μmol Fe/kg bw, which is the recommended dose for clinical trial, and injected via a femoral vein catheter. The bolus administration of SPIOs was performed in the magnet, 2 s after the onset of the Turbo-FLASH sequence, allowing the acquisition of at least two precontrast images.

Image Analysis

In vitro signal intensities (SI) of various SPIOs concentrations and in vivo SI evolution were determined

with automatic computer-assisted measurements of the mean in regions of interest (ROIs) of 32 pixels each. Signal intensity in Turbo-FLASH was found important enough with regard to noise (with a maximum SI of 550 compared with a mean of 3 for background noise), with little variations of background noise and signal to noise ratio from experiment to experiment. Consequently, absolute signal intensity was preferred to normalized SI for time-intensity curves in Turbo-FLASH, unlike SE sequences, where a signal intensity normalization with a reference phantom was necessarily required.

For myocardial perfusion studies, ROIs were positioned on 3 areas: left ventricular cavity (LV), postero-inferior wall (nonischemic myocardium = NI) and anteroseptal wall of the left ventricle (ischemic myocardium = I, corresponding to the LAD distribution). Time-intensity curves were obtained by recording variations of absolute SI within each ROI over the complete Turbo-FLASH acquisition (40 s).

Statistical Analysis

Mean SI with standard error of the mean (±SEM) from the left ventricular cavity and the two myocardial ROIs were plotted on time-density curves. Multiple factor repeated measure analysis of variance (ANOVA) was used to estimate differences in curve upslope (with a statistical significance defined as $p < .03$). SI at peak between the two myocardial areas was estimated with the nonparametric Mann-Whitney test with a statistical significance chosen for $\alpha < 1$.

RESULTS

In Vitro Experiments

In vitro experiments were performed to establish the relationship between signal intensity values on T_1-weighted Turbo-FLASH and SPIO concentration. As a result, curves of SI over SPIO concentration (SPIOs diluted in water) were realized with the three different T_1-weighted sequences (Fig. 1).

The objectives of this present in vitro study were to express the differences between SI with T_1 Turbo-FLASH and SI with different spin-echo sequences at low concentrations of SPIOs. Whereas, with spin-echo, SI response to SPIO concentration is known to be multiphasic (at least biphasic, as described recently by Chambon and co-workers,[15] with dilution of SPIOs in various media and T_1-weighted SE sequences), SI with T_1-weighted Turbo-FLASH appeared to increase monoexponentially with SPIO concentration up to 400 μmol Fe/l. Moreover, SI was found to be linearly proportional to SPIO concentration for the lowest concentrations (≤200 μmol Fe/kg), making it possible to establish an in vivo relationship between the SI enhancement during the dynamic MR acquisition and the SPIO wash-in after the bolus injection.

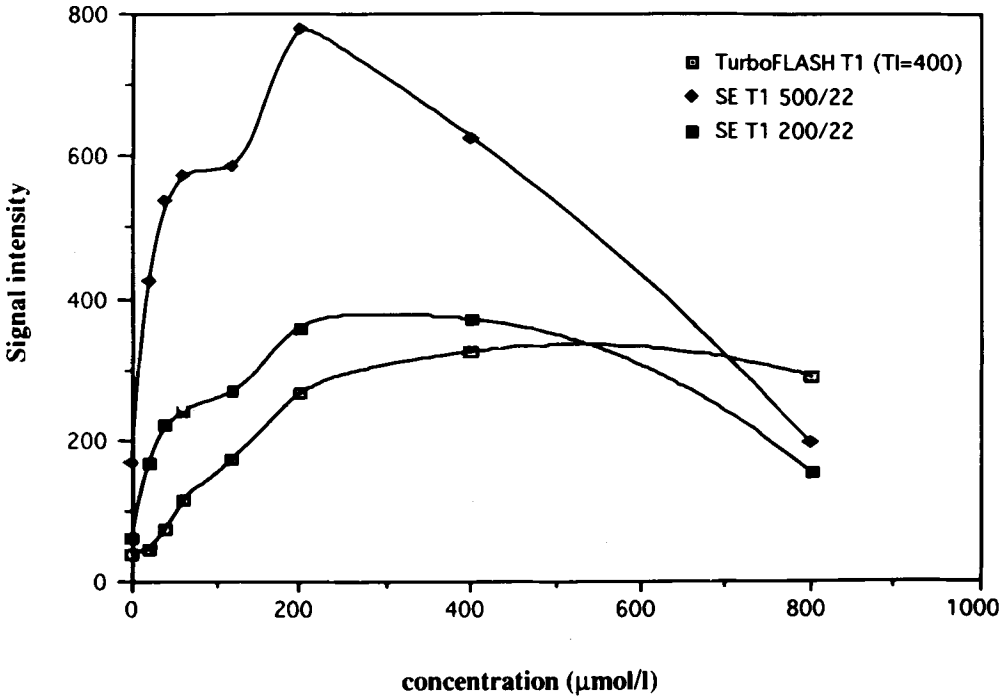


Fig. 1. Signal intensity vs. SPIOs concentration with three different T_1-weighted sequences (two T_1 spin-echo, with TR/TE = 500/22 ms and 200/22 ms, and the T_1-weighted Turbo-FLASH, with TR/TE = 6.5/3 ms and TI = 300 ms). Note the good linearity of increased SI using the T_1-weighted Turbo-FLASH with SPIO concentration up to 200 μmol Fe/kg.

Ex Vivo Infarct Sizing

All animals developed a myocardial infarction in the subendocardial area of the LAD related myocardial wall. Mean infarct size ($n = 6$) expressed as a percent of LV area was IS/LV = 14.3 ± 2.4%. The area at risk as a percent of LV area was AAR/LV = 25 ± 2.7%, and the infarct size related to the area at risk was IS/AAR = 54.8 ± 7.4%.

In Vivo MR Imaging

Before SPIOs, the LV cavity appeared as a dark area and there was no regional differences in myocardial SI (Fig. 2A). The arrival of SPIOs in the LV cavity induced a positive SI enhancement of the blood pool, as predicted by the in vitro SI response at a low concentration of SPIOs. Following this, the SPIOs wash-in occurred in the normally perfused myocardium (postero-inferior wall), whereas the hypoperfused myocardium (anterior wall) remained as a dark subendocardial zone (Fig. 2B).

Image Analysis

Time-intensity curves from the same subject were automatically reconstructed on the three ROIs previously defined (i.e., LV cavity, NI and I myocardium) (Fig. 2C). Before contrast media administration (Figs. 2A and 2C: first data points), the blood pool in the LV cavity appeared as a low SI and there was no significant difference in SI between normal and ischemic myocardium. After the SPIOs inflow, SI of the nonischemic myocardium enhanced more rapidly and reached a higher level than SI of the ischemic myocardium (Fig. 2C).

Averaged measurements for six dogs were plotted on Fig. 3. Maximum enhancement of the blood pool (LV cavity) occurred a few seconds after SPIOs bolus administration with a mean percentage enhancement > 500%. The peak SI enhancement (SIE) of the non ischemic myocardium was significantly greater (110 ± 23%) than the SIE of the ischemic myocardium (74 ± 22%) (Mann–Whitney test with $\alpha < 1\%$, $n_1 = 6$, $n_2 - n_1 = 0$, $U > 2$). Multiple factor repeated measure analysis of variance showed statistical differences between mean intensity of enhanced LV postero-inferior wall (NI) and LV anteroseptal wall (I) ($p < .03$), during SPIOs inflow (upslope, first five data points after bolus injection, considering the inherent interscan delay and the relatively low temporal resolution of this 128 × 128 matrix).

DISCUSSION

SPIOs are well known for their effect on transverse relaxation[1,2] and their susceptibility effect.[5,6] However, their action on the longitudinal relaxation rate of protons, despite its early demonstration,[17] had been sparsely explored.[18–20] Recently, new interest in theories of relaxation mechanisms has emerged, with SPIOs and USPIOs (a smaller particle size preparation, with prolonged intravascular retention), especially for their T_1 relaxivity and its expression on MR images.[15,20,21]

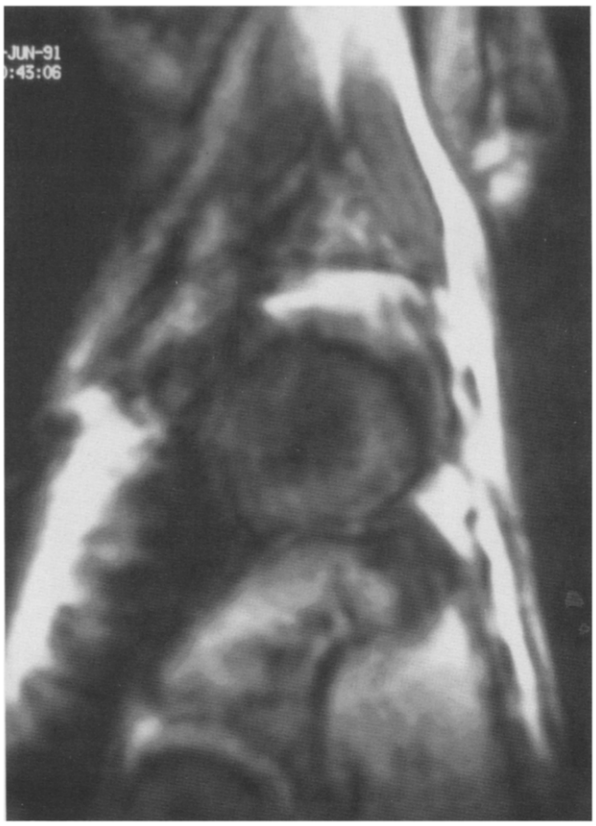
Moreover, AMI-25, a particulate contrast media from the SPIOs class, may be considered as an intravascular contrast agent and an indicator of tissue microcirculation during its initial time period after intravenous injection.[5,6,22] Using a strongly T_1-weighted sequence, we were able to demonstrate in vitro and in vivo the potentiality of AMI-25 to be used as a T_1 contrast agent (low dose of AMI-25, strongly T_1-weighted MR sequence). Furthermore, this property was originally applied to explore myocardial perfusion abnormalities in a model of reperfused myocardial infarction in dogs.

Previous investigators have already used ultrafast T_1 sequence combined with a Gadolinium chelate bolus injection to perform myocardial perfusion studies.[7–9,23]

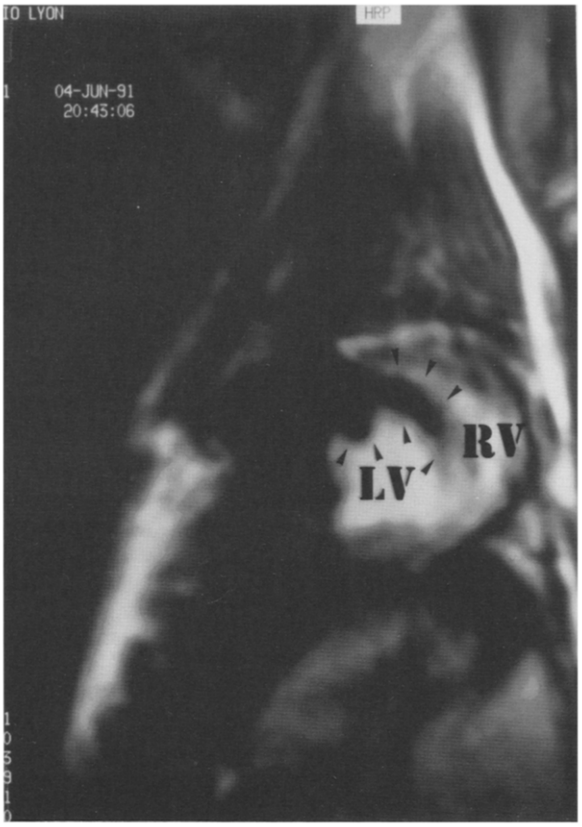
Thus, with this relative ultrafast T_1-weighted MR sequence, AMI-25 has been demonstrated as a potential positive blood pool contrast agent, and not only as a negative one,[22] during its initial intravascular distribution. Furthermore, this could be a new application of SPIOs (and USPIOs) in the field of regional blood flow measurements, more closer to the nuclear medicine concept of blood pool tracers (with the time-indicator dilution theory), as only a low dose (even lower than the one chosen here, unpublished data) is required for in vivo T_1 efficiency.

The purpose of this work was to demonstrate the potentiality of SPIOs as T_1 agents during their intravascular time. Consequently, as the initial postinjection distribution of SPIOs was the prime object of this study, examinations of later contrast agent distribution and infarct sizing with SPIOs were beyond the scope of this study and have been reported elsewhere.[24]

Although functional MR imaging of the heart is still at its very first stage, recent implementation of ultrafast MR sequences requiring only a fraction of a second (subsecond) coupled with bolus administration of a paramagnetic contrast agent provided the opportunity to approach tissue perfusion.[9,15,23] In addition, susceptibility effects induced by SPIO particle transit proved to be potentially suited for cerebral[22] and myocardial[11,13] perfusion studies. In this study, using the property of positive tissue enhancement during the SPIOs inflow, we were able to visually define a normally perfused and a hypoperfused myocardial zone by following the differences in SI enhancement of tissues.[25] This particular phenomenon of perfusion de-



(A)



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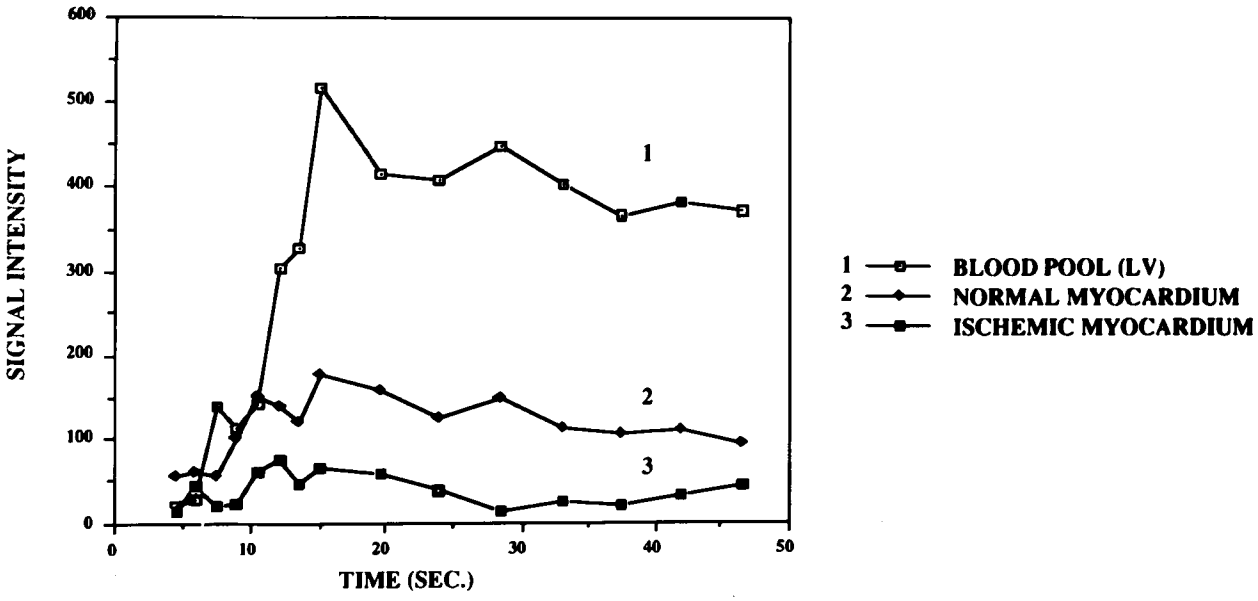

(C)

Fig. 2. Short axis view of the mid-left ventricular cavity before (A) and 10 seconds after (B) the IV bolus administration of SPIOs (20 μmol Fe/kg b.w.). Before injection (A), imaging parameters were chosen to lower the signal intensity from flowing blood and myocardial tissue. After injection (B), the blood pool in the right (RV) and left ventricular (LV) cavities presented a marked positive enhancement. The hypoperfused myocardium related to the LAD distribution (anterior LV wall) (arrowheads) demonstrated a lower enhancement (cold spot)[25] compared with the normally perfused myocardium (posterior-inferior wall). Individual time-intensity curves (C) of this dog were constructed by automatic ROIs computer-assisted measurements of the mean signal intensity.

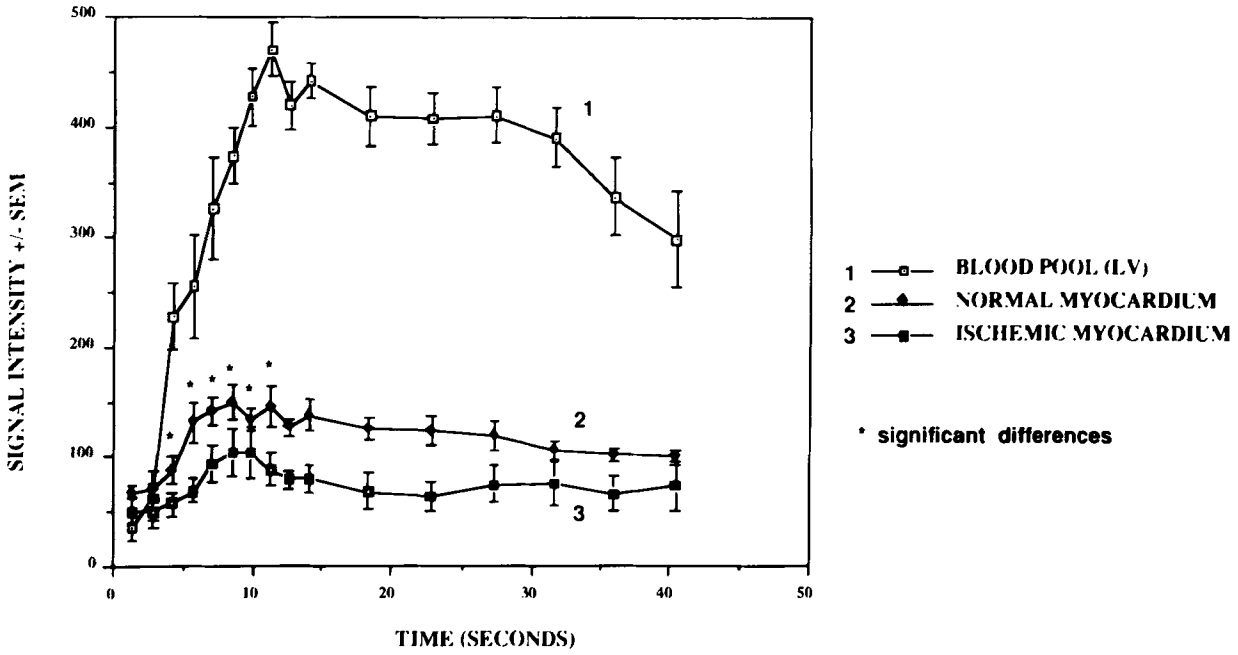

Fig. 3. Averaged time-intensity curves (n = 6) demonstrated a significant differential enhancement between normal (non-ischemic = NI) myocardium and ischemic (I) myocardium (Mann-Whitney test = $p < .03$).

fect occurring after an episode of ischemia followed by reperfusion is known as the no-reflow phenomenon and has been reported to be well-established at 5 hr of reperfusion with this dog model.[14]

In conclusion, a low dose of SPIOs in conjunction with ultrafast T_1 MR imaging may be well suited to assess noninvasively a myocardial perfusion defect. Therefore, to apply this potential new application of SPIOs to regional myocardial blood flow evaluation, a preliminary correlation with invasive gold standard techniques such as radioactive microspheres should be done, in an attempt to quantify absolute perfusion.

Despite these limitations concerning absolute perfusion quantification, using this property of positive tissue enhancement after SPIO inflow, relative MR perfusion studies would be possible,[25-27] provided that a higher temporal resolution and a more precise relationship between SI with SPIOs and flow phenomenon could be achieved.

Acknowledgments—This work was supported by a grant from Laboratoire Guerbet (Aulnay-sous-bois, France). We thank Dr. C. Chambon for valuable discussions.

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