Manganese-hydroxypropyl-tetraacetic-acid as an MR contrast agent for detecting differences in myocardial blood flow

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INTRODUCTION

Investigation of myocardial perfusion with MR-imaging is today limited to first-pass imaging using gadolinium-based contrast agents and pharmacologic stress. Manganese ions (Mn^{2+}) have been shown to yield a persistent longitudinal relaxation rate (R_1) increase that could be used to increase the time available for imaging and enable the use of physiologic stress for this application. The persistent R1-increase can be explained by intracellular uptake and retention of the Mn^{2+} ions. Injections of free Mn^{2+} ions may affect the heart adversely since they interfere with the excitation-contraction coupling in the cardiomyocytes. This effect can be diminished by chelating the Mn^2 ions. The purpose of this study was to examine if the manganese chelate MnHPTA could be used to detect differences in myocardial blood flow by measuring relaxation rates in pig myocardium after injections at rest and during dobutamine-induced stress. An additional purpose of the study was to investigate the effect of two consecutive MnHPTA injections on R1.

METHOD

MnHPTA was administered to six pigs as two consecutive injections, one at rest and one during dobutamine-induced stress, with one hour of imaging time in between. 25µmol MnHPTA/kg bodyweight was administered intravenously. Three pigs received a first injection at rest followed by a second injection during dobutamine-induced stress. The other three pigs received the injections in reversed order. Imaging was performed using a Philips Gyroscan Intera 1,5T scanner, using a single-slice Look-Locker sequence to quantify relaxation rate in a short-axis view of the myocardium and in the left ventricular blood pool. Comparisons were made between the first injections, i.e., between the three pigs that received the first MnHPTA injection at rest and the other three that received the first injection during dobutamine stress (Fig. 1) Comparisons were also made between to consecutive injection in the same pig, either at rest first and stress last (Fig. 2) or vice versa (Fig. 3),

RESULTS

Myocardial R1 increased after MnHPTA administration, R1 peaked early and decreased to a plateau-level over the first 30 minutes post injection (Fig 1). In the left ventricular blood pool, R1 peaked early and decreased down to zero over the first 30 minutes (not shown). The myocardial R1-increase was higher in the presence of dobutamine stress (Fig. 1). However, the difference between two consecutive injections of MnHPTA in the same pig was only evident when the first injection was performed during dobutamine stress (Figs 2 and 3).

Fig 1

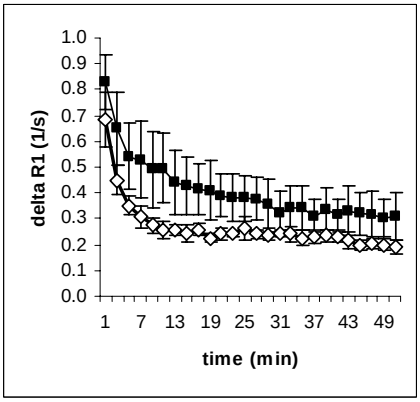

Fig 2

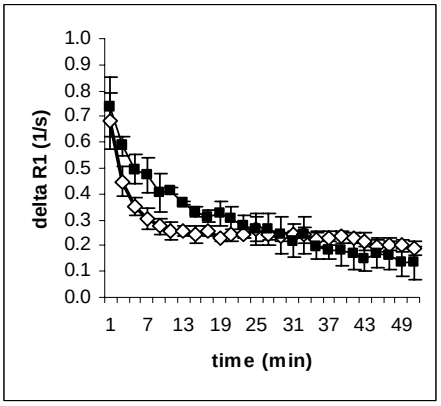

Fig 3

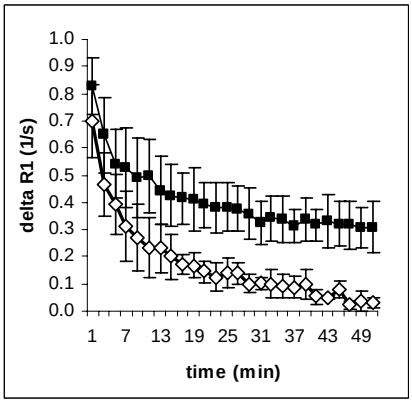

Fig. 1 shows the increase in R1 between administration at rest (open squares) and during dobutamine stress (filled squares) for a single first MnHPTA injection, i.e., injection of MnHPTA at either rest (n=3) or during dobutamine stress (n=3).

Fig. 2 shows the increase in R1 for each group after the MnHPTA administration at rest (open squares) as the first injection (n=3) and during stress (filled squares) as the last injection (n=3).

Fig. 3 shows the increase in R1 for each group after the MnHPTA administration during dobutamine-induced stress (filled squares) as the first injection (n=3) and at rest (open squares) as the last injection (n=3).

Error bars in all figures represent standard deviation.

DISCUSSION

The present study showed that MnHPTA increases R1 in the porcine myocardium significantly. The increase was lower than that previously shown for $MnCl_2$, but higher than that of MnDPDP[1]. For a single MnHPTA injection, dobutamine-induced stress increased myocardial R1, as previously shown for $MnCl_2$ in mice[2]. However, the difference between two consecutive injections of MnHPTA (the first at rest and the second during stress or vice versa) was only evident when the first injection was performed during stress. This may suggest that the MnHPTA dose is high enough to saturate uptake in the Mn^{2+}-retaining compartment (maybe the mitochondrial compartment). The shown effect may be used to increase the time available for imaging, which in turn may enable injection of contrast agent in the presence and absence of physiological stress outside the MR scanner. The possibility of saturated Mn^{2+} uptake as suggested from the present results may limit the usefulness of this technique in a conventional rest-stress test situation.

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2. Hu TC, Pautler RG, MacGowan GA, Koretsky AP. Manganese-enhanced MRI of mouse heart during changes in inotropy. Magn Reson Med 2001;46:884-890.