pH-Responsive MRI Contrast Enhancement of Isolated Perfused Rat Hearts with GdDOTA-4AmP

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Introduction

It is known that cardiac ischemia produces acidic regions in the ventricular musculature. The goal of this study was to evaluate the use of GdDOTA-4AmP as a pH-responsive contrast agent (pHCA) for highlighting those low pH regions by MRI. GdDOTA4AmP has been used successfully to map extracellular pH of kidneys in vivo by MRI (1). The pH-dependent T_1 relaxivity of this compound arises from the phosphonate-catalyzed exchange of protons from a single inner-sphere water molecule with bulk water (2). Prior data suggest that low concentrations of GdDOTA4AmP might be used to measure acidification levels of isolated perfused rat hearts upon ischemia by MRI.

Methods

We employed the standard SEMS and GEMS sequences to image both KCl-relaxed and cardiac-gated beating rat hearts isolated from 320-380 g Sprague-Dawley rats. Isolated hearts were subjected to retrograde perfusion with Krebs-Henseleit bicarbonate buffer containing 10 mM glucose in a 4.7T Varian Unity Inova vertical bore imaging system. Spin-echo T_1 and T_2 maps as well as gradient-echo T_2* images of the left ventricular main axis were obtained before, during and after perfusion with GdDOTA-4AmP, GdDOTP, or GdDTPA (~ 0.10 to 0.70 mM). Some experiments involved switching from GdDOTP or GdDTPA to GdDOTA-4AmP to see the difference in contrast enhancement (CE). Global ischemia was also induced in some hearts by stopping perfusion flow for 20 minutes and observing the CE during ischemia, and then, 20 minutes after reperfusion with contrast agent.

Results

Similar CE levels were observed with GdDOTP, GdDTPA, and GdDOTA-4AmP in perfused KCl-relaxed hearts prior to ischemia at low concentrations (~0.10 mM). The apparent T_1 contrast profile across the left ventricle prior to ischemia was small. No significant change was observed over most of the left ventricle before and after 20 minutes into perfusion with 0.10 mM GdDOTA-4AmP (Figure 1, A-B). The T1-weighted contrast prior to the GdDOTA-4AmP perfusion increased significantly upon 20 minutes into stop-flow ischemia with the pH-sensitive agent on board (Figure 1, B-C). The difference between the pre- and post-ischemia GdDOTA-4AmP perfusion was indicative of the response of the agent (Figure 1, B vs. D). Results suggest that the apparent biodistribution of GdDOTP within the left ventricular muscle was the same or similar to that of GdDOTA-4AmP at the low concentrations used for the pH mapping. Although GdDOTP and GdDTPA affected T_1 contrast upon ischemia (basis for concentration estimates), the effects of GdDOTA-4AmP were more pronounced (e.g.,with T_1 changes > 0.2 $mM^{-1}s^{-1}$ in some areas). These data indicate pH-response effects (Figure 2).

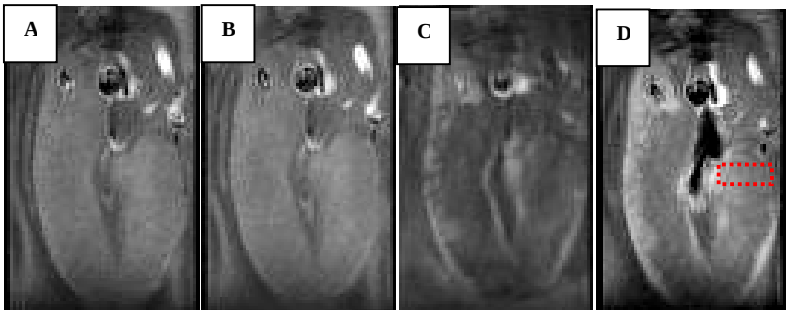

Figure 1. Spin-echo MR images of a KCl-relaxed rat heart (left ventricular main axis slice) before (A), and 20 minutes during perfusion with 0.10 mM GdDOTA-4AmP (B). Enhancement of the left ventricular musculature was more apparent upon *stop-flow* ischemia (C) but significant contrast enhancement was retained even 20 minutes after reperfusion with the same agent (D). Conditions: TR/TE = 600/8.2 ms.

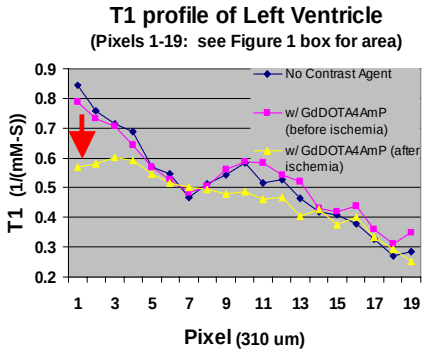

Figure 2. The T_1 profiles of the mid-section (~ 6 mm long) of the left ventricular wall (see Figure 1D box). T_1 hardly changed upon GdDOTA-4AmP perfusion due to the relatively low concentration (0.1 mM). The *inner* musculature showed significant effective T_1 enhancement after ischemia (red arrow).

Conclusion

T_1,T_2 and T_2* contrast enhancements were observed with GdDOTA-4AmP perfusion into KCl-arrested as well as beating rat hearts. Although the non-pH-responsive agents GdDTPA and GdDOTP showed significant contrast enhancement upon ischemia possibly due to distribution effects, the higher contrast enhancement observed with GdDOTA4AmP was attributed to pH gradients. This was consistent with the expected acidification profile that develops in the ventricles upon ischemia, i.e., some portions of the left ventricular musculature tend to acidify faster than others.

References (1) Raghunand et al., *MRM* 49:249-257 (2003). (2) Zhang et al., *Angew. Chem. Int.Ed.*. 38:21 (1999).