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MRI with gadofosveset: A potential marker for permeability in myocardial infarction

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ABSTRACT

Background and aims: Acute ischemia is associated with myocardial endothelial damage and microvessel formation, resulting in leakage of plasma albumin into the myocardial extravascular space. In this study, we tested whether an albumin-binding intravascular contrast agent (gadofosveset) allows for improved quantification of myocardial permeability compared to the conventional extracellular contrast agent Gd-DTPA using late gadolinium enhancement (LGE) and T1 mapping *in vivo*.

Methods: MI was induced in C57BL/6 mice (n = 6) and cardiac magnetic resonance imaging (CMR) was performed at 3, 10 and 21 days post-MI using Gd-DTPA and 24 h later using gadofosveset. Functional, LGE and T1 mapping protocols were performed 45 min post-injection of the contrast agent.

Results: LGE images showed that both contrast agents provided similar measurements of infarct area at all time points following MI. Importantly, the myocardial R_1 measurements after administration of gadofosveset were higher in the acute phase-day 3 (R1 [s^{-1}] = 6.29 ± 0.29) compared to the maturation phase-days 10 and 21 (R1 [s^{-1}] = 4.76 ± 0.30 and 4.48 ± 0.14), suggesting that the uptake of this agent could be used to stage myocardial remodeling. No differences in myocardial R1 were observed after administration of Gd-DTPA at different time points post-MI (R1 [s^{-1}] = 3d: 3.77 ± 0.37; 10d: 2.74 ± 0.06; 21d: 3.35 ± 0.26). The MRI results were validated by *ex vivo* histology that showed albumin leakage in the myocardium in the acute phase and microvessel formation at later stages.

Conclusions: We demonstrate the merits of an albumin-binding contrast agent for monitoring changes in myocardial permeability between acute ischemia and chronic post-MI myocardial remodeling.

1. Introduction

Myocardial infarction (MI) remains the leading cause of heart failure, morbidity and mortality in the Western societies [1]. Post-MI remodeling is generally thought to be subdivided in two successive and overlapping phases: an acute inflammatory stage and a chronic maturation stage [2]. The first is characterized by the influx of leukocytes (neutrophils and inflammatory monocytes) to release inflammatory mediators and remove cellular debris [3] while the second is initiated by the influx of reparative monocytes that orchestrate the healing response which includes the deposition of collagen and elastin and the formation of microvessels to restore blood supply [4]. These processes are regulated by a complex signaling cascade leading to transcriptional, structural, electrophysiological, and functional events occurring within the cardiomyocytes [5]. Remodeling is therefore a dynamic and time-dependent process, with changes occurring in both the necrotic region and the adjacent non-infarcted remote myocardium [6,7].

The extent of myocardial damage and its location within the left ventricle (LV) directly affects the magnitude of LV remodeling [8]. The underlying mechanisms of LV remodeling are closely related to the infarction itself, including cell death and loss of contractile activity within the affected zone and secondary ventricular dilation and remodeling in the LV regions remote to the infarct as a result of

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increased hemodynamic burden [9]. It is well established that the endothelium is significantly damaged during the acute stage of MI [10,11] and associated with an increase in the intercellular junction width [12,13]. Normal junctions allow the transport of small water-soluble molecules up to a diameter of 2 nm [14] whereas breaks in the tight junctions allows for the transport of molecules up to 20 nm diameter and more [15,16] facilitating the influx of serum albumin (diameter of ≈6 nm). At the late stage of MI, gap junction width seems to reverse to normal size based on electron microscopy studies [17], thereby decreasing leakage of large molecules into the diseased tissue [13].

Animal models of MI are important in research to understand the complex pathophysiology of ischemic heart disease [18] and are essential for testing therapeutic approaches for the treatment of MI. There are currently two widely used murine models of left anterior descending (LAD) ligation to induce myocardial infarction: a permanent ligation of the LAD, as used in this study, and an ischemia reperfusion injury model. Similar to human MI, interruption of blood flow to the myocardial territory supplied by the LAD produces profound ischemia in the anterolateral territory of the heart which then manifests as an acute MI. Both models have been extensively used for the better understanding of the underlying mechanisms of post-MI remodeling at the cellular and molecular levels [19–22]. Briefly, permanent ligation of the LAD is associated with ischemic necrosis and increased inflammation, whereas the ischemia-reperfusion injury model is associated to cell death via apoptosis and limited ischemic necrosis [23]. Additionally, these models have been used to assess the changes in cardiac function at different time points following injury using different imaging modalities. Both models lead to cardiac dysfunction including systolic and diastolic dysfunction associated with adverse myocardial remodeling that could lead to the development of heart failure [24–26]. Albumin is the most abundant protein in human plasma, accounting for half of all serum proteins [27]. Approximately 33% of albumin can be found in the intravascular compartment, while the remaining 67% is in the extravascular exchangeable and remote compartments [28]. In diseases such as atherosclerosis [29] and myocardial infarction [30], an increase in albumin leakage is expected due to acute endothelial damage and later microvessel formation [31].

In order to investigate focal changes in myocardial permeability, which may provide a non-invasive tool for the assessment of ischemic endothelial damage in infarcted myocardium [32] and microvessel formation, we used cardiac magnetic resonance imaging (CMR). Late gadolinium enhancement (LGE) MRI is the gold-standard technique to estimate infarct area after injection of Gd-DTPA (gadolinium diethylene triamine pentaacetic acid) [33–35]. We hypothesize that injection of the intravascular albumin-binding contrast agent gadofosveset may provide a measure of infarct area using LGE (similar to conventional Gd-DTPA) but also unveils temporal changes in myocardial permeability in acute ischemia using T1 mapping. To quantify gadofosveset uptake as a non-invasive surrogate measure of permeability we performed T1 mapping of the myocardium in addition to high resolution LGE imaging for direct infarct visualization. Gadofosveset, commercially known as Ablavar®, is a clinically approved gadolinium-based blood pool contrast agent that reversibly binds to serum albumin, resulting in a prolonged vascular presence and a 5–10-fold increase in relaxivity (r1) [36–38]. Gadofosveset may enter the interstitium through leaky microvessels [39] and mechanically damaged endothelium as we previously demonstrated in a mouse model of atherosclerosis [39–43]. We sought to investigate whether contrast-enhanced MRI using gadofosveset could provide information on changes in myocardial permeability to differentiate between acute ischemia and chronic post-MI remodeling using LGE and T1 mapping *in vivo* at high field.

2. Materials and methods

2.1. Animal model

In this longitudinal study, 6 female wild-type C57BL/6 mice weighing 18–24 g were purchased from Harlan Laboratories (Blackthorn, United Kingdom). Left coronary artery permanent ligation was used to induce myocardial infarction (MI). The protocol design is detailed in Fig. 1. Surgery was performed with 1.5%

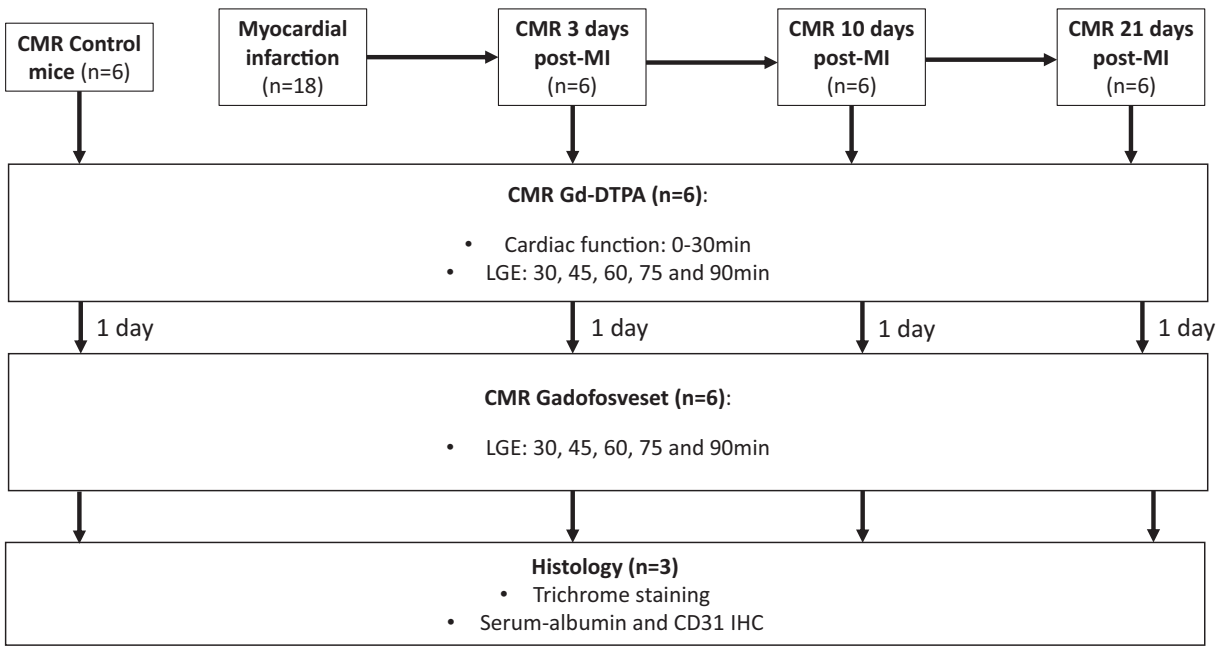

Fig. 1. Experimental protocol, contrast agents used, timing of MRI scans and histological protocols performed.

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