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A New Collagen Iii-specific MRI Imaging Probe to Assess Cardiac Fibrosis

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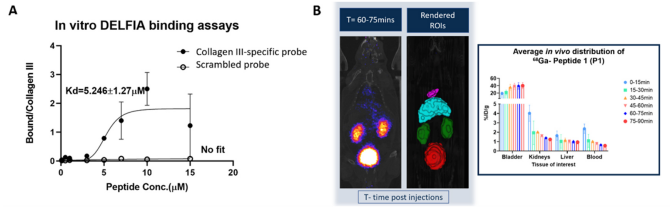
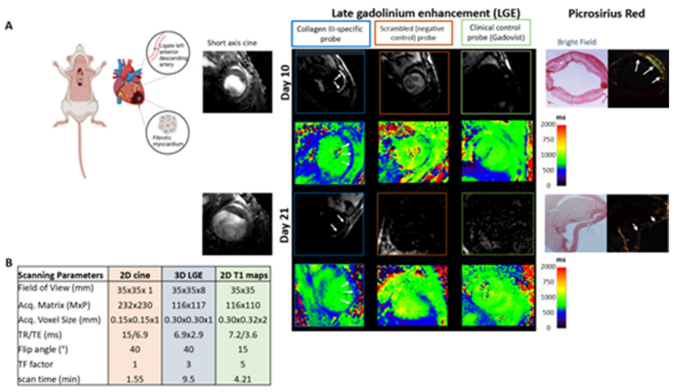
Background: Heart failure (HF) remains a major cause of morbidity and death affecting 64 million people globally[1]. Myocardial fibrosis, characterised by changes in type I (COL1) and III (COL3) collagen levels, may lead to HF[2,3]. Cardiac magnetic resonance (CMR) is a preferred method to detect fibrosis non-invasively, however it provides indirect measurements of fibrosis. Molecular imaging can directly visualise fibrosis, but current imaging probes target COL1. This study combines quantitative CMR and a novel COL3-binding probe for direct imaging of COL3, allowing quantification of previously undetectable COL3 and monitoring of treatment response.

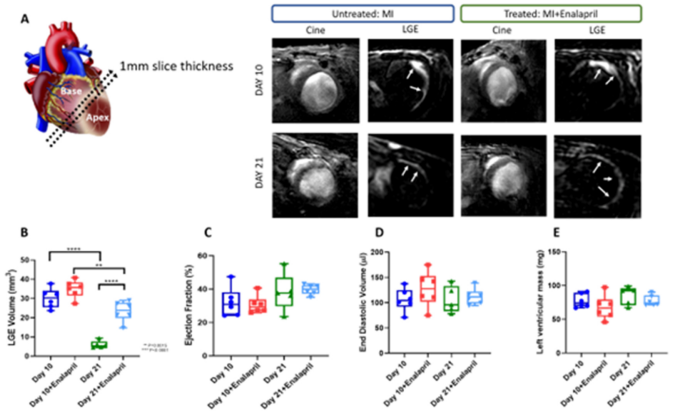
Methods: To develop a COL3-binding probe, a small peptide was conjugated to a DOTA-chelator and tagged with Europium [Eu(III)] for *in vitro* binding studies, gallium [^{68}Ga] for *in vivo* PET/CT distribution analysis, and gadolinium [Gd(III)] for *in vivo* CMR. For functional and molecular CMR, a 3T clinical MRI scanner was used on days 10 and 21 post-MI (n = 6/group). The same mice underwent imaging using a negative control probe and Gadovist (n = 3). The probe was used to monitor the effects of Enalapril on myocardial fibrosis post-MI. Mice received Enalapril (20mg/kg/day) immediately after MI and were imaged on days 10 and 21 (n = 6/group). Cardiac function was analysed through 2D short axis cine images of the LV. Furthermore, T_1-weighted 3D inversion recovery (IR) images were captured 60 minutes post-intravenous injection (0.2mmol/kg), enabling the acquisition of late gadolinium enhancement (LGE) images of the LV. T_1 mapping involved a 2D Look-Locker sequence with an inversion pulse, followed by capturing 30 IR images. For specifics of MRI acquisition parameters, refer to **Fig.2B**.

Results: We developed a high-affinity imaging probe that specifically binds to COL3 (Kd = 5.3μM) (**Fig. 1A**). The probe showed fast blood clearance and no unspecific binding (**Fig. 1B**). Molecular CMR, using the COL3-probe, showed high signal on day 10 which decreased on day 21 as COL3 was replaced by COL1 (**Fig. 2A**). Histology validated the imaging findings. Quantitative T_1 maps showed lower T_1 values in the infarct compared with the remote myocardium. Importantly, no enhancement was observed with the negative probe or clinical agent Gadovist. Enalapril-treated mice exhibited similar enhancement on day 10 compared to untreated mice (**Fig. 3A-B**). However, by day 21, enalapril-treated mice displayed greater LGE volume than untreated mice (**Fig. 3A-B**), suggesting that enalapril might extend the deposition of COL3, potentially delaying COL1 onset (**Fig. 3B**). Cardiac function was similar between the groups (**Fig. 3C-E**), indicating that molecular changes in COL3 may precede changes in cardiac function.

Conclusion: Quantitative molecular CMR imaging of COL3 enabled visualisation of changes in COL3 after MI and in response to treatment for the first time. This may bridge the knowledge gap enabling early fibrosis detection, disease staging, and a tool to monitor therapeutics.







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