Supplementary Material
Supplementary Methods
Image Analysis

Endocardial and epicardial borders were manually defined on all conventional short-axis images for volumetric and wall motion measurements, and were then applied to all corresponding LGE, T2 and T1 map sequences for analysis with minimal manual adjustments. Regions of interest (ROIs) were determined using the standard 16-segment cardiac model with global myocardial values derived from an average of all 16 segments. After contouring, an additional epicardial and endocardial offset of 20% was applied automatically to minimise tissue interface for all T1 map analyses and artefact was excluded manually in a minority of cases only. In patients, additional ROIs were drawn according to regional pathology, corresponding to myocardial infarction as defined by LGE, or in areas of pathological myocardium defined by LGE, T1 and T2 mapping. For serial T1 imaging post-MnDPDP, manually drawn ROIs from the pre-contrast image were transferred to all subsequent post-contrast images to ensure consistency. Haematocrit from the day of scanning was used to calculate extracellular volume from pre- and post-gadolinium T1 maps.

Quantification of myocardial infarction with LGE

Infarct was assessed by LGE from 7 min after contrast injection. All images were analysed independently in a single batch by one expert operator (NS). To reduce variability, automated reference ROIs were generated in infarct and remote myocardium. Myocardial infarction size was quantified using the full-width-at-half-maximum technique expressed as percentages of the left ventricle as a whole, as well as the core infarct short-axis slice.

Quantification of area-at-risk (AAR) and peri-infarct regions

Area-at-risk (AAR) and functional impairment were assessed on T2 and native T1 maps. Endocardial and epicardial borders were derived from short-axis stack images with minimal
manual correction where necessary. A reference ROI was automatically generated in the remote myocardium as above, with minimal manual adjustment based on the opposing wall from the LGE-defined infarct and wall motion by cine sequences where necessary. Given the lack of established consensus on quantification, a threshold of 2 x SD above remote myocardium was used for both T2 and T1 AAR. Peri-infarct tissue was defined as LGE negative but with elevated T2 AAR (>2 x SD) in the infarct related artery territory.

Manganese-enhanced Magnetic Resonance Imaging

T1 mapping was performed pre-contrast with full short-axis ShMOLLI stack as above. A core infarct short-axis slice was identified by the supervising cardiologist according to the region of maximal wall motion abnormality. T1 mapping was then performed at this slice location every 2.5 min after starting contrast infusion for 40 min, at which point a full short-axis ShMOLLI stack was repeated post-contrast (Figure S1). This slice was matched visually by the same supervising cardiologist for repeat MEMRI scanning. For healthy volunteers, a mid-ventricular slice was chosen for serial T1 mapping post-MnDPDP. Heart rate and blood pressure were measured for the duration of the scan following MnDPDP administration. All participants were followed up by telephone 7 days following MEMRI to capture adverse events.

Quantification of functional impairment with MEMRI T1 mapping

Functional impairment by reduced calcium-channel activity was assessed on MEMRI T1 maps. In the absence of any existing data on quantification of injury or functional impairment with MEMRI T1 mapping, and as MEMRI shortens T1 in normal myocardium, an identical methodology to those employed for native T1 and T2 mapping was employed; with a threshold of 2 x SD above a remote reference myocardial ROI, expressed as a percentage of...
the core infarct short-axis slice. To quantify change in T1 over time, ROIs were drawn in infarct (LGE positive), remote (opposing wall to infarct) and peri-infarct regions, copied automatically to all slices from 0 to 40 min.

**Kinetic Modelling**

In brief, the model consists of (i) a reversible compartment \(v_e\), comparable to intravascular and interstitial space, and (ii) an irreversible compartment \(v_i\) where irreversible accumulation of the contrast agent is anticipated, comparable to the intracellular space. The arterial concentration (derived from blood pool T1) represents contrast agent delivery into myocardial tissue and constitutes the arterial input function (Supplementary Figure 2).

Skjöld and colleagues have previously derived a Patlak model adaptation for cardiac MEMRI,\(^3,4\) demonstrating an apparent unidirectional influx constant \(K_i\) for the transfer of manganese from plasma to irreversible compartments \(v_i\) can be measured using equation (1).\(^3\)

\[
\frac{C_t(t)}{C_a(t)} = K_i \int_0^t \frac{C_a(t')}{C_a(t)} \, dt' + v_e
\]

where \(C_t\) and \(C_a\) are the manganese concentration in myocardial tissue and blood pool (arterial input function) respectively. This expression is equivalent to the Patlak formulation and describes that if a contrast medium is irreversibly trapped in the tissue within the imaging time frame, the instantaneous tissue concentration divided by the instantaneous arterial concentration plotted against the integrated arterial concentration divided by the instantaneous arterial concentration, will result in linearisation of the data. The gradient of this line represents the apparent unidirectional influx constant \(K_i\), which in turn equals:
\[ K_i = \frac{k1 \cdot k3}{k2 + k3} \]  \hspace{1cm} (2)

where \( k1, k2 \) and \( k3 \) are the individual rate constants of the two-compartment model presented (Supplementary Figure 2). To derive the manganese concentrations \( C_t \) and \( C_a \) as a function of time to be used in equation (1), the following equation was used:

\[ R_1(t) = R_1(0) + r_1 C(t) \]  \hspace{1cm} (3)

where \( R_1 = 1/T_1 \), \( R_1(0) \) is the native longitudinal relaxation rate and \( R_1(t) \) is the longitudinal relaxation rate at time \( t \) of manganese contrast enhancement, \( r_1 \) is the relaxivity and \( C(t) \) is the concentration of the contrast agent at time \( t \). Using equation (3), \( C_t \) and \( C_a \) were calculated for each successive \( T_1 \) map derived in the tissue and blood pool before, during and after contrast infusion for the 40 min period of the MEMRI imaging protocol (Supplementary Figure 1).

The Patlak model employed here has previously been shown as an effective method of estimating intracellular influx of manganese in the context of imaging with MnDPDP in the same dose and formulation used in the present study.\(^3\)

**References:**

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Supplementary Figure 1. MEMRI imaging protocol.

MEMRI, Manganese-enhanced MRI; MnDPDP, manganese dipyridoxyl diphosphate
Supplementary Figure 2. Compartmental model

Two-compartment model used for Patlak formulation with reversible and irreversible uptake between combined intravascular/interstitial and intracellular compartments respectively.

Supplementary Figure 3. ECG parameters pre- and post-MEMRI

ECG parameters before (blue) and after (red) administration of MnDPDP (manganese dipyridoxyl diphosphate) in healthy volunteers (HV) and patients with ischaemic cardiomyopathy (ICM, both n=20).
Supplementary Figure 4. Haemodynamic during with Manganese-enhanced MRI

Blood pressure and heart rate after administration of MnDPDP (manganese dipyridoxyl diphosphate) in healthy volunteers (A) and patients with ischaemic cardiomyopathy (B, both n=20).
Supplementary Figure 5. Wall motion, LGE and MEMRI T1

Wall motion, LGE and MEMRI T1 mapping colour maps at the core infarct slice in remaining 15 patients, represented as 100-chord plots (anterior RV insertion as reference point). Values demonstrate stronger correlation between MEMRI T1 than LGE with reduced wall motion in every patient.

LGE, late gadolinium enhancement magnetic resonance imaging; MEMRI, manganese-enhanced magnetic resonance imaging; RV, right ventricle.