Quantification of L-type Calcium Channel Activity by Manganese-Enhanced MRI in Murine Hearts in Vivo

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Introduction

Calcium (Ca^{2+}) influx via the voltage-gated L-type Ca^{2+} channels is of key importance in cardiac Ca^{2+} cycling. However, limited imaging techniques exist for noninvasive measurement of Ca^{2+} channel activity. Manganese (Mn^{2+})-enhanced magnetic resonance imaging (MEMRI) provides the possibility for in vivo assessment of Ca^{2+} uptake. In the current study, a fast T_1 mapping method, saturation recovery Look-Locker (SRLL), was used to simultaneously quantify the dynamics of Mn^{2+}-induced T_1 changes in both blood and myocardium at a temporal resolution of ~3 min. A compartment model was developed for quantitative assessment of the L-type Ca^{2+} channel activity by least-square fitting of the model to experimental MEMRI data.

Materials and Methods

MRI Study The MRI study was performed on a horizontal 7T animal scanner (Bruker Biospin, Billerica, MA). An 18-cm long volume coil (Bruker, Billerica MA) and a 3-cm surface coil (Bruker, Billerica MA) were used as the transmitter and receiver, respectively. The SRLL pulse sequence consisted of a saturation module, applied at the beginning of each phase encoding step, followed by a series of ECG-triggered FLASH acquisitions during the magnetization recovery.

Four-month old C57BL/6J mice were used. $MnCl_2$ solution was infused via tail vein for 30 min at the rates of 7 (n = 6, referred to as the low dose group) and 14 (n = 8, referred to as the high dose group) nmol/min/g body weight (BW), followed by 30 min washout period. Continuous T_1 maps of the mid-ventricular slice at diastole were acquired using the following parameters: TE, 1.7 ms; nominal TR, 2.5 s; number of FLASH images, 9~12; flip angle, 10°; slice thickness, 1.5 mm; number of averages, 1; FOV, 3x3 cm^2; matrix size, 128x128/64 (baseline/post-contrast). The equilibrium magnetization was measured at baseline with a TR of 5 s and a matrix size of 128x128.

Compartment Model A compartment model was developed that included the plasma, extracellular, and intracellular spaces (Fig. 1). Changes in extracellular ($C_e(t)$) and intracellular ($C_i(t)$) Mn^{2+} concentration were described by the following kinetic equations:

$$\frac{dC_e(t)}{dt} = k_p\left[C_p(t) - C_e(t)\right] - k_{in}C_e(t) + k_{out}C_i(t)\frac{V_i}{V_e} \quad [1]$$

$$\frac{dC_i(t)}{dt} = k_{in}C_e(t)\frac{V_e}{V_i} - k_{out}C_i(t) \quad [2]$$

where $C_p(t)$ is the Mn^{2+} concentration in plasma, and V_p, V_e, and V_i are the corresponding volume fraction of the three spaces. The relaxation rate R_1 ($1/T_1$) in each imaging pixel is linearly related to the average Mn^{2+} concentration in that pixel, C_T, as $R_1(t)=R_0+r_1C_T(t)$, where C_T is the volume-weighted sum of Mn^{2+} concentration in each compartment, i.e., $C_T(t)=C_e(t)V_e+C_i(t)V_i+C_p(t)V_p$.

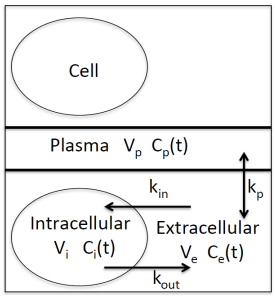

Figure 1. Compartment Model

For in vivo study, $C_p(t)$ is the arterial input function which is linearly proportional to the dynamic R_1 changes in blood. R_0 and r_1 in blood and myocardium were measured experimentally using MRI and flame atomic absorption spectrophotometry, respectively. The value of k_p was fixed to a large value (100 min^{-1}) with the underlying assumption that the exchange rate between plasma and extracellular spaces far exceeds the temporal resolution of data acquisition. The rate of Mn^{2+} uptake (k_{in}) and efflux (k_{out}) was determined by least-square fitting of the model to experimentally measured R_1 changes.

Results and Discussion

Simultaneous T_1 quantification in blood and myocardium at high temporal resolution was accomplished by the proposed method. Representative R_1 maps in blood and myocardium at baseline (Fig. 2a), the end of Mn^{2+} infusion (Fig. 2b) and washout (Fig. 2c) are shown. Dynamic R_1 changes in blood are shown in Fig. 2d. MRI-measured and model-fitted R_1 curves in myocardium are shown in Fig. 2e. Experimentally determined r_1 in blood and myocardium were 2.99 and 2.85 $mM^{-1}s^{-1}$, respectively.

As shown in Fig. 3, model-fitted k_{in} and k_{out} were 0.68±0.32 and 0.016±0.017 min^{-1} for the high dose group and 0.53±0.20 and 0.015±0.016 min^{-1} for the low dose group. Statistical analysis showed no difference in the fitted rate constants between the two groups.

Conclusion

In the current study, the SRLL method allowed quantification of both the arterial input function and the kinetics of Mn^{2+} uptake in mouse myocardium at high temporal resolution. A compartment model was developed for quantitative evaluation of Mn^{2+} uptake and efflux in vivo by fitting the model to the MEMRI data. Kinetic analysis yields similar rate constants for Mn^{2+} uptake and exclusion in the high and low dose groups.

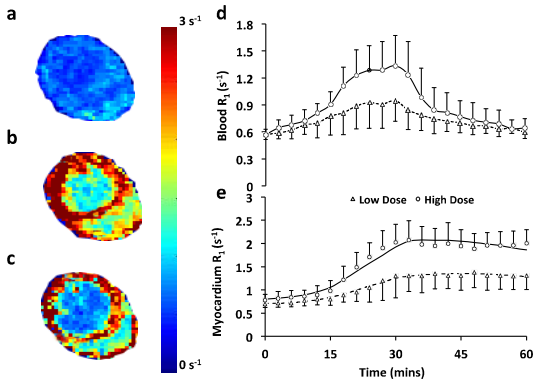

Figure 2. Quantification of the dynamic R_1 changes in blood and myocardium. (a-c) Representative R_1 maps at baseline, the end of Mn^{2+} infusion and washout. (d-e) Dynamic R_1 changes in blood and myocardium.

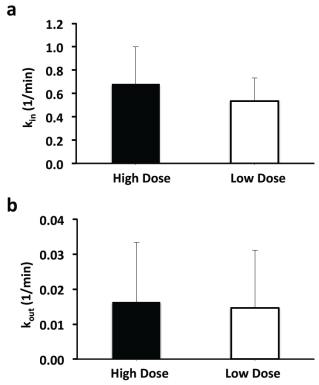

Figure 3. Estimated rate constants k_{in} (a) and k_{out} (b) at two Mn^{2+} dose.