Imaging Cyclic Change of Myocardial Blood Volume During Cardiac Cycle Using Steady-state Susceptibility Effect of Superparamagnetic Nanoparticles

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INTRODUCTION Steady-state coronary vascular volume is known to vary with coronary perfusion pressure and cardiac contraction [1]. Cyclic change of regional myocardial blood volume (MBV) reflects the microvascular change during the cardiac cycle [2]. Knowledge of cyclic MBV change would enhance our understanding of the functional characteristics of intramyocardial capacitance and resistance vessels and possible transmural differences. Potentially it can serve as an index of microvascular potency. The magnitude of the cyclic MBV change may also serve as an index of the local intramyocardial compressive forces. However, such study has been hampered by lack of non-invasive techniques to map cyclic MBV changes in vivo with sufficient spatial and temporal resolution. In this study, the steady-state susceptibility effect of a superparamagnetic contrast agent was utilized to map the cyclic MBV changes during the cardiac cycle in normal murine myocardium.

METHODS Superparamagnetic contrast agent MION has a strong T1 and T2 shortening effect and a long half-life in blood. In myocardium, the T1 effect is complicated by water exchange [3]. However, at relatively high dosage, the MION effect is dominated by the T2 shortening. This is because, in tissue, the achievable T_1 shortening effect is limited and tends to saturate at high dosage since the dipolar relaxation only affects protons within very close proximity of the iron oxide nanoparticles. Although water exchange between the intra- and extravascular compartments helps to increase the T_1 relaxation, its effect is limited by the relatively slow exchange that is believed to occur at the rate of 0.5-2 s^{-1} in myocardium [4]. Wild-type mice (N=5, 25g, C57BL6/J) were studied on a Bruker 9.4T NMR microimaging system (400WB). Pre- and post-contrast short-axis images were acquired using an ECG gated flow-compensated 3D GE cine sequence with TR/TE = 24ms/1.3ms, 5 cardiac points, 15° flip angle, and 12 min scan time. The in-plane resolution and slice thickness were 200 μm and 500 μm, respectively. Mice were anesthetized with 1.5% isoflurane and he heart rate was maintained around 450 bpm during imaging. MION dosage of 10 mg Fe/kg was administered intravenously. Note that this relatively high dosage also minimized the interference from the cyclic myocardial oxygenation change [5]. With this dosage and voxel dimension, the long-range susceptibility effect of the high concentration MION in ventricles on the transmural signal variations was also estimated to be negligible. MBV maps at five cardiac points were computed pixel by pixel from the steady-state images as $MBV \propto ln(S_{pre}/S_{post})/TE$. Three consecutive central short-axis slices from each data set were selected to produce the MBV maps used for ROI analysis. To define ROIs, the left ventricular myocardium was divided into 8 evenly distributed polar angular segments and 3 transmural layers of equal thickness based on the pre-MION images at ED and ES.

RESULTS Consistent spatial and temporal MBV distributions in the left ventricular myocardium during the cardiac cycle were observed in the five normal mice studied. **Fig. 1** shows the pre- (**a**), post-MION images (**b**), and computed MBV maps (**c**) of a single short-axis slice at five evenly spaced cardiac points, with light blue color indicating high MBV values. High MBV was noted in these images in the areas near the left anterior descending artery (LAD) and posterior descending artery (PDA). **Fig. 2** shows the average MBV values in the lateral wall and septum in each single layer at ED (**a**) and ES (**b**), as well as in all three layers (**c**). These were relative values, expressed as the ΔR_2^* for 10 mg/kg MION dosage. **Fig. 2d** displays the average MBV values in each angular segment/layer in grayscale with the left and right hemispheres corresponding to lateral wall and septum, respectively. Note the general decrease of MBV at ES as well as the transmural heterogeneity of the MBV distribution. This was consistent with the well-known physiology that arterial inflow occurs at ED while venous outflow occurs at ES, and that overall vascular space decreases at ES [6]. From to ED to ES, the MBV percent decreases in the endocardial layer (layer 1), mid-myocardial layer (layer 2), and epicardial layer (layer 3) in lateral wall were 22.7±5.6% ($p<0.003$), 20.1±10.7% ($p<0.02$), and 17.2±10.0% ($p<0.006$), respectively. The trend was consistent with a recent in vitro study using μCT [2]. Those in the septum were 33.1±7.1% ($p<0.0009$), 25.8±7.8% ($p<0.004$), and 17.6±4.0% ($p<0.0003$). The average MBV in all three layers decreased at ES by 16.2±6.6% ($p<0.03$) and 24.7±3.1% ($p<0.0002$) in the lateral wall and septum, respectively. Note that the largest MBV decrease from ED to ES occurred in the left ventricular septal endocardial layer, namely 33.1%. Fig. 2 also reveals a difference between lateral wall and septum in transmural MBV distribution.

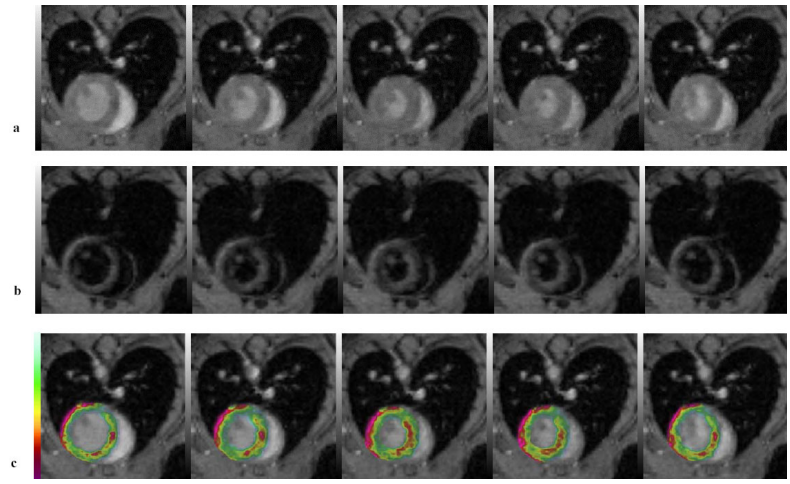

Fig. 1

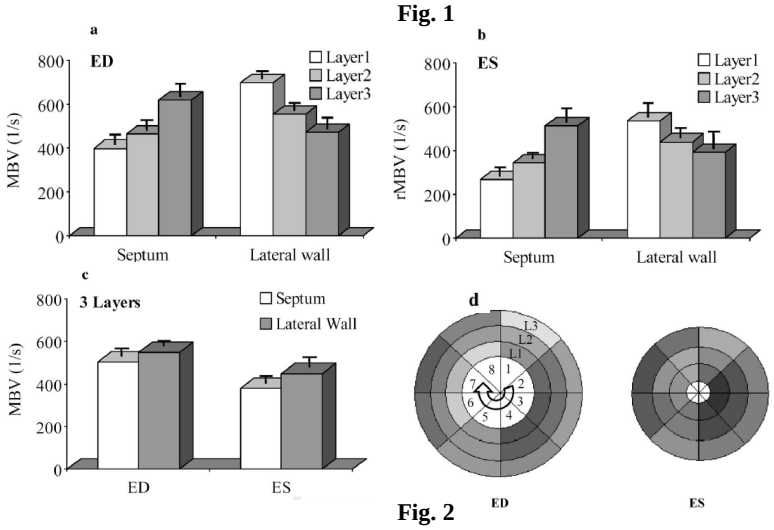

Fig. 2

DISCUSSION AND CONCLUSION Several factors that may influence the accuracy of this measurement remain to be explored. The first is the possible cyclic change of morphologic characteristics of the vasculature that might lead to an apparent cyclic ΔR_2^* change and interfere with the measurement of cyclic MBV changes. The second factor is the directional characteristics of microvasculature in myocardium. Capillaries, the dominating vasculature, are mostly aligned in parallel with the myofibers and their orientations are known to vary transmurally [7]. In summary, this preliminary study demonstrated the feasibility of mapping cyclic MBV change using the steady-state MION susceptibility effect in normal mouse hearts. Given the nature of coronary hemodynamics, cyclic MBV changes may reveal new physiologic information because they are a function of coronary perfusion pressure and myocardial contraction. The technique is potentially applicable to the study of normal human heart physiology. It may also be useful to the study of certain pathologic conditions (e.g., cardiomyopathy where myocardial vasculature is not leaky and MION can remain in the intravascular space) and pharmacological interventions.

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