Mapping Myocardial Microvascular Volume and Blood Oxygenation Using Iron Oxide Nanoparticles and Adenosine

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INTRODUCTION

The measurement of microvascular blood volume in the myocardium has great potential for evaluating disorders in myocardial microvascular physiology. With mild coronary artery stenosis, microvascular vasodilation occurs, in order to maintain a constant flow and perfusion.[1] Thus, myocardial microvascular volume changes occur before disturbances in flow and perfusion occur. In addition, newly proposed methods to measure myocardial oxygen extraction ratios using magnetic resonance imaging techniques depend on microvascular blood volume.[2,3] We propose a method of quantitatively determining blood volume, drug-induced microvascular volume changes, as well as drug-induced changes in blood oxygenation, in which the signal changes produced by an exogenous agent are used to calibrate those produced by physiological and pharmacological effects.

THEORY

We postulate that at high fields there is a contribution to transverse relaxation rates that reflects the presence of microvessels and depends on the oxygenation state of the blood. We therefore model the measured relaxation rate R_2^* as $R_2^* = R_2 + kV(X_b - X_t)$, where R_2 is the relaxation rate when the blood susceptibility matches that of tissue, and $kV(X_b - X_t)$ is the contribution from blood in the microcirculation (k is a proportionality constant that depends on field strength, V is the blood volume, and X_b and X_t are the susceptibilities of blood and tissue). X_b depends on the blood oxygenation state. In the presence of an intravascular contrast agent such as iron oxide, the rate becomes $R^*_{2a} = R_2 + kV(X_b + X_a - X_t)$, where X_a is the susceptibility of the agent. By measuring the R_2^* before and after administering the agent, and knowing the susceptibility of the agent, we can calculate kV. We thus obtain a map of relative blood volume in the tissue.

Administration of adenosine or dobutamine causes potential changes in both the blood volume and oxygenation. As R_2^* is dependent on the amount of deoxygenated hemoglobin in the blood, as well as the microvascular blood volume, the relaxation rate may then be modeled as $R^*_{2aden} = R_2 + k(V+\Delta V)(X_{aden} - X_t)$, , where X_{aden} is the blood susceptibility during the adenosine episode and is again a direct measure of the blood and tissue oxygenation change. For the same dose of adenosine in the presence of the intravascular MION contrast agent, $R^*_{2(aden+a)} = R_2 + k(V + \Delta V)(X_a + X_{aden} - X_t)$, from which we can compute the relative volume change, $(\Delta V/ V)$. We thus obtain a map of the fractional change in blood volume due to the effect of adenosine or dobutamine, using the value of kV obtained above. In addition, $R^*_{2aden} - R_2 = kV(1 + \Delta V/V)(X_{aden} - X_t)$ whereas, $R_2^* - R_2 = kV(X_b - X_t)$.

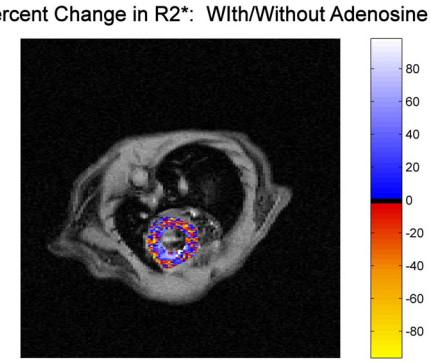
Thus, enough information is available to obtain maps of $(X_b - X_t)$ as well as of $(X_{aden} - X_b)$. The former should correlate directly with the baseline heterogeneous distribution of tissue and blood oxygenation, while the latter should correlate with the change in tissue and blood oxygenation from the effects of dobutamine. Whereas $(\Delta V/V)$ represents a measure of vascular reserve and reactivity within the tissue, $(X_{aden} - X_b)$ represents the corresponding change in oxygen. This simple model requires 4 measurements of R_2^*; baseline, with adenosine, back at baseline with iron oxide present, and then again with adenosine in the presence of iron oxide.

METHODS

Mice were imaged using a 4.7T Varian imaging system. Scout images were obtained to find the optimal short axis view for imaging. Maps of R2* were obtained using a multi-echo, gradient-echo sequence with the following parameters: TR/TE= 300/(3.7*n, n=1-12), FOV=35mmX35mm, RO/PE=256/128. The images were acquired using cardiac and respiratory gating, and the total imaging time for one $R2^*$ map was approximately six minutes. $R2^*$ maps were acquired with and without infusion of adenosine at a rate of 0.375 mg/kg·min.

RESULTS AND DISCUSSION

Myocardial maps of percent change in $R2^*$ due to adenosine were calculated. The maps reflect a proof of concept of the above theory. Many technical issues were encountered during the development of this protocol. The $T2^*$ of myocardium and blood are very short at high fields. Therefore, pulse sequences must be optimized to obtain images at very low echo times. The myocardial motion results in several sources of potential error. With reflex tachycardia, induced by adenosine, myocardial contractility increases, causing difficulty with the registration of myocardial tissue with and without adenosine. As can be seen, there exist some potential edge effects at the myocardial borders. Finally, the small total blood volume of the mouse severely limits the amount of adenosine and contrast agent that can be given. However, it is possible to make these measurements in a reasonable time and compute the quantities of theoretical interest with reasonable accuracy. In summary, we have developed a protocol based on gradient-echo relaxation theory that shows great potential for measuring microvascular blood volume changes, as well as blood and tissue oxygenation changes.



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