Effect of Oxygen Free Radical Scavenger on Renal Medullary Oxygenation in Hypertensive Rats as Evaluated by BOLD MRI

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SYNOPSIS

We had previously shown that kidneys with hypertension have reduced response to nitric oxide synthase inhibition, as evaluated by BOLD MRI. This was consistent with the fact that hypertension involves increased oxygen free radical production, and hence reduced bioavailability of nitric oxide. In this study, we investigated the effect of administration of Tempol, an oxygen free radical scavenger on renal blood flow using BOLD MRI technique. Five spontaneously hypertensive rats (SHR) were used in this study. The R_2* in the renal medulla and cortex showed significant drop (40.6±9.8 to 31.7±10.7 and 31.8±4.4 to 25.9±5.3 s^{-1} respectively) after administration of Tempol.

INTRODUCTION

SHR is associated with reduced blood flow to the renal medulla due to reduced bioavailability of endothelium-dependent vasodilators like nitric oxide (NO) in the vessel wall by increase in production of free radicals such as superoxide[1]. Administration of Tempol-a membrane-permeable mimetic of superoxide dismutase - has been shown to reduce arterial pressure (by ~20mmHg) and increase medullary blood flow (by 35-50%) in SHR, as compared with untreated controls [2,3].
We have previously shown that BOLD MRI is useful in evaluating intra-renal oxygenation non-invasively[4,5] and more specifically showed that the measurements are sensitive to NO synthase (NOS) inhibition[6]. We further showed that kidneys in hypertensive rats lack a response to NOS inhibition[6], probably owing to the inherent reduction in the bioavailability of NO. In the present study, we extend those observations to see if administration of free radical scavenger could reverse the response in hypertensive rats.

METHODS

All our studies were performed on a 1.5 T Twin speed scanner equipped with Excite technology (General Electric Medical Systems, Milwaukee, WI) using a multiple gradient echo (mGRE) sequence (TR/TE/Flip angle = 75 m/8-50.4 ms/20°) to acquire 16 T_2* weighted images. Other relevant parameters include: FOV of 13 cm with a 256x256 matrix, slice thickness of 1.6mm, NEX = 12, BW = 42kHz**.** A standard quadrature extremity coil was used for signal reception. The signal intensity *vs.* time data was fit to a single exponential function to obtain R_2*, using the FUNCTOOL software available on the scanner platform. Studies were performed in anesthetized (Inactin 100 mgkg) SHR (n=5; wt: 344.6±14.6 gm) rats. The SHR were 19 weeks old, the age by which they are known to become hypertensive. After obtaining a set of baseline R_2* maps, the Tempol (Sigma-Aldrich, St. Louis, MO) solution (180µmol/kg) was administered *i.v* via jugular vein. R_2* maps were obtained every 3 mins for at least 30 mins. Regions of interest (ROIs) of at least 4 pixels were placed on renal medulla and cortex to obtain values for the mean and standard deviation of R_2*.

RESULTS

Figure 1 shows R_2* maps from one representative animal, pre and post administration of Tempol. The relatively darker medulla in the post-R_2* images of SHR indicate that the oxygenation improved due to increased blood flow. Figure 2 is the R_2* vs. time data from the same animal as in figure 1 (first 3 points were baseline). Figure 3 is the summary of R_2* from all 5 animals. Shown are baseline, 10 to 20 minutes and 30 minutes later after bolus injection of Tempol (180µmol/kg).

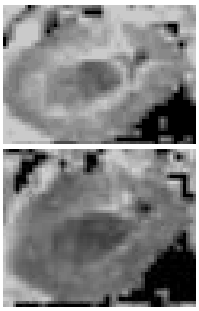

Fig. 1. Top: pre Tempol. Bottom: post Tempol.

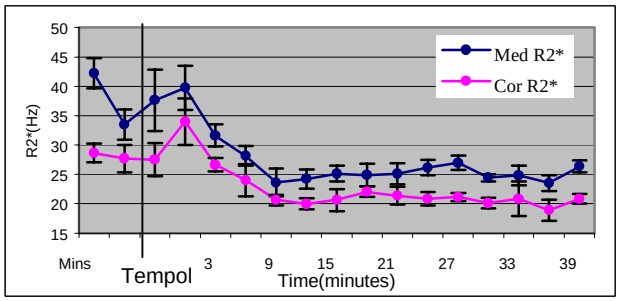

Figure 2. R2* vs time in tha same animal as in figure 1. Tempol injected at time 0.

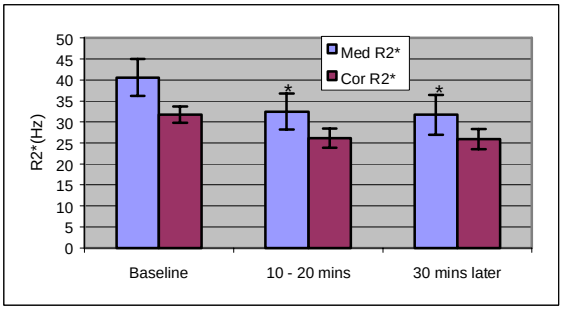

Figure 3. Summary of 5 SHR (Mean±St.Err). * implies $p < 0.01$ compared to baseline by paired two tail t-test

DISCUSSION

It is well accepted that renal NO system is impaired in SHR[7]. Administration of Tempol has been shown to reduce blood pressure and the effect is known to be a consequence of free radical scavenging, which improves endogenous NO bioavailability [2,3]. Our results shown here are consistent with this fact. R_2* decreased post Tempol administration suggesting improved oxygenation probably brought about by the improved blood flow. This result combined with our previous data[6] illustrating differences in response to NO inhibition in kidneys with hypertension support the feasibility of using BOLD MRI as a way of monitoring novel therapeutic maneuvers for hypertension. Further studies in humans are warranted to prove this feasibility. Further studies are also necessary to validate the BOLD MRI response against invasive "gold-standard" methods such as microelectrodes and laser Doppler probes.

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