# Effect of Nitric Oxide Inhibitor on Intra-Renal $R_2$* Measurements in Humans

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## INTRODUCTION

Nitric oxide (NO) is continuously synthesized by the endothelium and has a wide range of biological properties including relaxation of vascular tone [*Nature*. 1988;333:664-666]. In healthy subjects, administration of inhibitor of endothelial NO synthase blocks the synthesis of nitric oxide, and results in a constriction of the vessels, and an increase in blood pressure [*Am J Physiol*. 1993;264:F79-F87; *Am J Physiol*. 1995;268:R317-R323]. We had previously demonstrated that NO inhibitors reduced renal medullary $R_2$* in normotensive rats but not in hypertensive ones as evaluated by BOLD MRI technique [*JMRI* 2003;17: 671]. This preliminary study is a direct extension of these observations to the humans, where we have evaluated for the first time the renal medullary $R_2$* response to the administration of NO inhibitor $N^G$-monomethyl-L-arginine (L-NMMA) in healthy human volunteers.

## METHODS

To-date, three healthy young male volunteers (34.3±1.5 years old) have participated in this study. Each volunteer gave informed consent to a protocol approved by our Institutional Review Board. The subjects came to the study after abstaining from food and water for about 12 hours. The arterial blood pressure was monitored every 3 minutes using MRI compatible patient monitoring system (Magnitude, Invivo, USA). After obtaining baseline BOLD MRI data, L-NMMA (Clinalfa, Bad Soden, Germany) was infused intravenously using an infusion pump (Medfusion 2010 syringe pump, GA, USA). The dosing protocol consisted of a rapid infusion of 3mg/Kg over 6 min followed by a maintenance dose at a rate of 3 mg/kg/h infused over 24 min, resulting in a total dose of 4.25 mg/kg. Post-L-NMMA images were continually acquired from 5 axial slices located in the middle of the kidney throughout the infusion period at 3 minutes interval. The experiments were conducted on a GE Signa Vh*i* 3.0T whole body scanner (GE Medical Systems, Milwaukee, WI) using a multiple gradient echo (mGRE) sequence (TR/TE/Flip angle/BW=60/6.4-40.8ms/30/62.5 kHz) with selective water excitation pulse to acquire 16 $T_2$* weighted images within a single breath-hold of about 12 s. A FOV 36x27 cm with 256 by 256 matrix size applied. A standard four-coil torso array was used for signal reception. $R_2$* maps were constructed using FUNCTOOL by fitting a single exponential function to the signal intensity *vs.* echo time data on a pixel by pixel basis. Regions of interest (ROI) covering at least 10 pixels were drawn on the anatomic template from each of the 5 slices acquired and on both kidneys. The data were combined to obtain a single representative mean value of $R_2$* per subject per time point. The average of all points acquired after 30 minutes of L-NMMA administration was used as post-L-NMMA $R_2$*. The statistical significance was assessed using the two-tailed paired Student's t-test.

## RESULTS

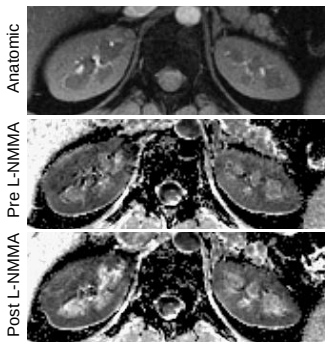


**Figure 1**

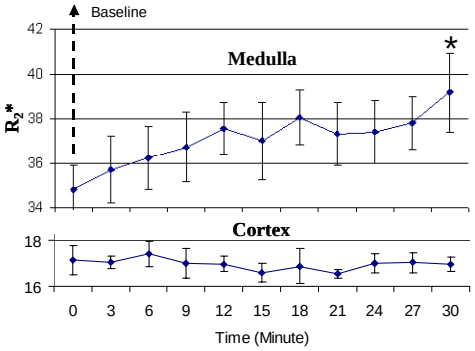


**Figure 2**

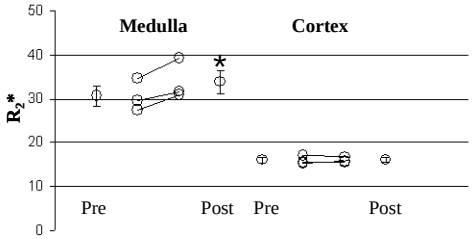


**Figure 3**

**Figure 1** shows representative pre- and post-L-NMMA $R_2$* maps from one volunteer. Note the relatively brighter medulla in the post-L-NMMA map as compared to pre-L-NMMA map, probably signifying a reduction in medullary oxygenation. The window and level settings for both the maps are exactly the same. The trend of increased $R_2$* values in the medulla post-L-NMMA is consistent with our previous published data in animal model [*JMRI* 2003;17: 671].

**Figure 2** shows representative $R_2$* *vs.* time during the *i.v.* administration of L-NMMA. Note the small but significant change in the medullary $R_2$* values over the measurement period, while the cortex shows no appreciable change.

**Figure 3** summarizes the individual changes post-L-NMMA in the three subjects. $R_2$* obtained at the 30 minute time point after start of L-NMMA administration was used as post-L-NMMA measurement. Mean $R_2$* values pre- and post-L-NAME in the renal medulla and cortex averaged over all subjects.

## DISCUSSION AND CONCLUSION

The preliminary data presented here are consistent with our previous data in rat kidneys [*JMRI* 2003;17: 671]. The major difference is the magnitude of change in $R_2$*. However, it should also be noted that the nitric oxide inhibitor used in rat studies was L-NAME ($N^G$-nitro-L-arginine methyl ester) and at a dose of 10 mg/kg. The reason for the use of L-NMMA was due to a relatively large number of published reports on its use in humans. Use of L-NAME in humans has been reported and has been shown that the blood pressure raising effect is much more potent compared to L-NMMA [*Hypertension* 1999; 33:937]. However, in the same study it was also found that L-NAME had greater potential for side effects compared with L-NMMA. For this preliminary study, we preferred to try the relatively safer drug. Given this background on efficacy of L-NMMA, and the fact that we were able to observe measurable changes in $R_2$* during L-NMMA administration indicates the sensitivity of BOLD MRI technique. Further studies in larger number of subjects is warranted.

These data do lend support to the feasibility of studying microvascular reactivity in the kidneys using BOLD MRI technique, similar brachial artery ultrasound studies to evaluate peripheral vascular reactivity [*Hypertension*. 2001; 38:1349].

## ACKNOWLEDGEMENTS

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