

EFFECT OF NITRIC OXIDE ON T1-WEIGHTED SIGNAL INTENSITY

Nitric oxide increases the signal intensity of the T1-weighted magnetic resonance image of blood

RONALD W. DAY, M.D.,^{1,*} KEITH S. WHITE,² and GARY L. HEDLUND²

¹Department of Pediatrics, University of Utah, Salt Lake City, Utah, USA

²Department of Pediatric Radiology, Primary Children's Medical Center, Salt Lake City, Utah, USA

Human blood was infused through a gas permeable membrane to determine if treatment with nitric oxide affects the signal intensity of its T1-weighted magnetic resonance image. Equal volumes of blood with increasing concentrations of methemoglobin were placed in glass tubes. T1-weighted images of the samples were obtained with a 1.5T magnetic resonance scanner. There was a linear correlation between the signal intensity of the T1-weighted images and the amount of methemoglobin in each sample ($r^2 = 0.94$, $p = 0.0015$). Thus, blood that has been treated with nitric oxide can potentially be used as an autologous intravascular contrast agent for magnetic resonance imaging.

Key Words: Magnetic resonance imaging; Methemoglobin; Nitric oxide

1. Introduction

Magnetic resonance imaging is an important noninvasive method, which can accurately define the anatomy of pulmonary and systemic blood vessels. Contrast agents have been developed to enhance the signal intensity of blood. Gadolinium is currently the most frequently used contrast agent in clinical practice. It is relatively safe and effective (1). However, it is not an ideal agent if multiple sequences of a specific vascular region must be performed. Methemoglobin and nitrosylhemoglobin are paramagnetic compounds, which may change the relaxation of neighboring protons and influence the signal intensity of blood during T1-, T2-, and T2*-weighted magnetic resonance imaging (2–4). Sub-optimal imaging of the renal vasculature occurred when methemoglobin values were increased following an infusion of dimethylaminophenol in rabbits. However, a bolus of blood contrast containing methemoglobin may be necessary to effectively image a specific vascular region. Methemoglobin and nitrosylhemoglobin are produced when deoxyhemoglobin and oxyhemoglobin undergo oxidation by nitric oxide. This experiment was performed to determine whether the signal intensity of the T1-weighted image of blood is increased after treatment with nitric oxide through a gas permeable polymer membrane.

2. Methods

A sample of whole blood (120 mL) was drawn from the vein of a healthy volunteer and treated with heparin (600 units). Aliquots of this blood were placed into 6 glass tubes containing ethylene-diaminetetraacetic acid. The remaining blood was slowly infused through a silicon polymer membrane, which is clinically used for extracorporeal membrane oxygenation (Medtronic, Minneapolis, MN). The blood was treated by diffusion with a gas mixture of 800 parts per million nitric oxide and nitrogen (SensorMedics, Yorba Linda, CA) at a flow rate of 1.5 L/min. The system was flushed with normal saline until an adequate volume of blood was recovered to combine with the aliquots of untreated blood as listed in Table 1. A T1-weighted spin-echo sequence (TR 500 msec, TE 9 msec, 2 NEX, FOV 260 mm) was performed with a 1.5T magnetic resonance scanner (GE Medical Systems Horizon LX, Milwaukee, WI). The samples were placed together on a plastic rack and gently mixed prior to imaging. Ten cross-sectional slices of 4 mm in thickness with a spacing interval of 5 mm were evaluated for each tube. At each level, the mean intensity and standard deviation of the T1-weighted signal were measured by defining an equal region of interest for each sample (GE Advantage Workstation, Milwaukee, WI). At each level, the mean intensity and standard deviation of the surrounding background noise were also measured for each sample. The measurements from each level were combined to calculate the collective mean signal intensity for each sample and its surrounding background noise. Hemoglobin and methemoglobin measurements were performed by co-oximetry (Radiometer, Copenhagen, Denmark) approximately

Received 15 September 2004; accepted 14 April 2005.

*Address correspondence to Ronald W. Day, M.D., Division of Pediatric Cardiology, Primary Children's Medical Center, 100 North Medical Drive, Salt Lake City, UT 84113, USA; Fax: (801) 588-2612; E-mail: perday@ihc.com

Table 1. Measurements of blood samples

Sample	1	2	3	4	5	6
Proportion of blood volume treated with nitric oxide	0	0.2	0.4	0.6	0.8	1.0
Hemoglobin, g/dl	15.2	13.5	12.1	10.8	9.4	8.5
Methemoglobin, %	0.4	1.2	2.1	3.7	6.4	7.9
Methemoglobin, g/dl	0.061	0.162	0.254	0.400	0.602	0.672
Sample signal intensity, mean ^a	302 ± 10	352 ± 4	379 ± 4	402 ± 4	426 ± 4	452 ± 5
Sample signal intensity, SD ^b	17.5 ± 0.7	15.9 ± 0.5	14.6 ± 0.5	17.7 ± 0.7	19.1 ± 0.4	22.2 ± 1.6
Noise signal intensity, mean ^a	5.42 ± 0.06	5.89 ± 0.06	6.03 ± 0.04	6.08 ± 0.06	5.92 ± 0.08	5.55 ± 0.06
Noise signal intensity, SD ^b	3.81 ± 0.05	4.12 ± 0.05	4.31 ± 0.05	4.27 ± 0.05	4.20 ± 0.05	3.84 ± 0.05
Sample to noise ratio of mean signal intensity	55.7 ± 1.6	59.8 ± 1.1	62.9 ± 0.8	66.1 ± 0.6	72.1 ± 1.2	81.5 ± 1.3

^aMean of the magnetic resonance signal image intensity of T1-weighted images in arbitrary units, collective mean ± standard error of the mean.

^bStandard deviation (SD) of the magnetic resonance signal image intensity of T1-weighted images in arbitrary units, collective mean ± standard error of the mean.

30 minutes after the blood was treated with nitric oxide. The samples were scanned 90 to 120 minutes after the blood was treated with nitric oxide. The stability of the signal change was not evaluated over time.

3. Results

The total hemoglobin, percent methemoglobin, and total methemoglobin values are listed in Table 1 with the mean measurements (mean and standard deviation) of the signal intensity for the T1-weighted images of each sample and its surrounding background noise. Figure 1 shows cross-sectional images of the 6 samples with a corresponding increase in signal intensity as the amount of methemoglobin increases. There is a linear correlation between the mean signal intensities of the blood samples and 1) the values of percent methemoglobin ($r^2 = 0.89$, $P < 0.005$) and 2) the values of total methemoglobin ($r^2 = 0.94$, $P < 0.002$). There is also a linear correlation between the mean signal to noise ratios and 1) the values of percent methemoglobin ($r^2 = 0.97$, $P < 0.001$) and 2) the values of total methemoglobin ($r^2 = 0.94$, $P < 0.002$).

4. Discussion

This is the first report which describes how the magnetic resonance signal intensity of blood can be enhanced by simply using a gas permeable polymer as an interface for nitric oxide treatment. Modest changes in the amount of methemoglobin were associated with significant increases in the intensity of the T1-weighted image. Methemoglobin is a paramagnetic compound. However, other paramagnetic compounds, which were not measured, may have also contributed to the observed change in the image of blood. Additional studies are needed to determine whether the T1-weighted signal is primarily enhanced by methemoglobin or other factors. If enhancement results from an increase in methemoglobin or nitrosylhemoglobin, blood contrast may respect the blood-brain barrier and be appropriate for selected cases of cerebral vascular imaging.

Blood that is treated with nitric oxide may be an appropriate alternative contrast agent for patients who have experienced an adverse reaction to gadolinium. It may also be an effective agent for real-time imaging or clinical settings where multiple injections of contrast are desired. Blood samples from the patient can easily be monitored to limit the

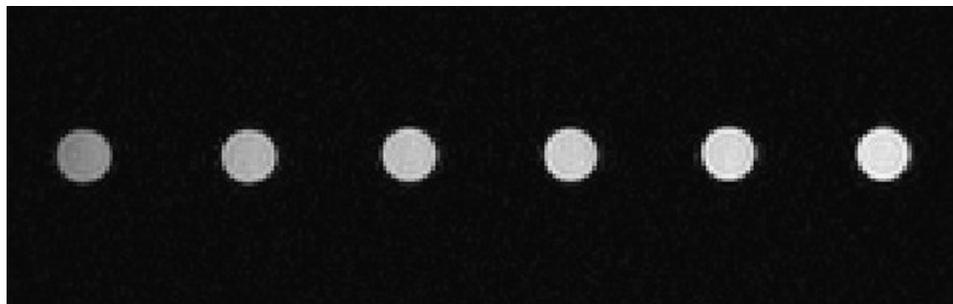


Figure 1. Cross-sectional images of blood samples. The T1-weighted signal intensity increases as the volume of blood treated with nitric oxide and the amount of methemoglobin increase from left to right.

number of serial injections of blood contrast and prevent an excessive accumulation of methemoglobin. Supplemental oxygen may be used to decrease a potential risk of impaired oxygen delivery if methemoglobinemia occurs. Patients may also be treated with ascorbic acid after blood has been drawn for treatment with nitric oxide to decrease the likelihood of developing a clinically significant degree of methemoglobinemia. Additional studies are needed to determine the amount of methemoglobin in a bolus of blood contrast and the amount of methemoglobinemia that are safe in a clinical setting.

It is possible that an injection of blood, treated with nitric oxide, will not adequately enhance the signal intensity of blood as it flows through vessels *in vivo*. Additional studies are needed to determine the volume of blood contrast, the concentration of methemoglobin and the optimal pulse sequence that are necessary to replicate the quality of vascular imaging that is currently achieved with gadolinium. Such studies may also determine whether differences in observer judgment of signal intensity are clinically important.

A change in the signal intensity of the T1-weighted images was identified at an interval of 90 to 120 minutes after blood was treated with nitric oxide. This interval would be adequate for this technology to be effective in a clinical setting. However, the stability of the signal change over time will need to be determined in additional studies.

A relatively large polymer membrane was used as an interface to prepare blood with nitric oxide in this experiment. Ideally, a more efficient gas permeable system must be developed to allow small volumes to be prepared without losing a substantial amount of blood during the process. A greater difference in the signal intensities in Fig. 1 may have

been achieved if the total hemoglobin values were comparable for each sample. A nitric oxide concentration of 800 parts per million was used in this experiment. It is possible that a higher concentration of nitric oxide may prepare the blood more efficiently. Various agents react with blood to form methemoglobin. The systemic use of these agents, and their potential adverse effects, can be avoided when nitric oxide alone is used to prepare a contrast agent from an autologous sample of blood.

5. Conclusion

In conclusion, this experiment demonstrates that whole blood can be treated with nitric oxide to form a contrast agent, which influences T1 relaxation and may potentially improve vascular imaging.

References

1. Lundby B, Gordon P, Hugo F. MRI in children given gadodiamide injection: safety and efficacy in CNS and body injections. *Eur J Radiol* 1996; 23:190–196.
2. DUEWELL SH, KASSERRA CE, JEZZARD P, BALABAN RS. Evaluation of methemoglobin as an autologous intravascular MRI contrast agent. *Magn Reson Med* 1996; 35:787–789.
3. Di Salle F, Barone P, Hacker H, Smaltino F, d'Ischia M. Nitric oxide-haemoglobin interaction: a new biochemical hypothesis for signal changes in fMRI. *NeuroReport* 1997; 8:461–464.
4. Nagano T, Yoshimura T. Bioimaging of nitric oxide. *Chem Rev* 2002; 102:1235–1269.