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Title: *Determination of Oxygen r1 at 3 Tesla using samples with a concentration range of dissolved oxygen*

Authors:

Svein Are Sirirud Vatnehol, MSc ^{a, b, c},

Per Kristian Hol, MD, PhD ^{a, b}

Atle Bjørnerud PhD ^{d, e}

Mahmood Amiry-Moghaddam MD, PhD ^{a, c}

Camilla Haglerød, PhD ^c

Tryggve Holck Storås, PhD ^f

Affiliations:

a: University of Oslo, Faculty of Medicine

b: Oslo University Hospital, The Intervention Centre

c: Oxy Solutions AS

d. University of Oslo, Department of physics

e: Oslo University Hospital, Division of Radiology and Nuclear Medicine, Computational Radiology and Artificial Intelligence

f: Oslo University Hospital, Department of Diagnostic Physics

Corresponding author

Svein Are Sirirud Vatnehol, sav@oxysolutions.com

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Running title

Determination of oxygen r1

Abstract

Objective: To investigate the sensitivity of Modified Look Locker Inversion Recovery (MOLLI) to measure changes in dissolved oxygen (DO) concentrations in water samples and to calculate sequence specific relaxivity (r_{1m}) and Limit of Detection (LOD).

Materials and methods

Ten water samples with a range of DO concentrations were scanned at 3T using two variations of MOLLI schemes. Using linear regression the r_1 of DO was estimated from the measured DO concentrations and T_1 relaxation rates (R_1). The results were combined with previously reported values on *in vivo* stability measures of the MOLLI sequences and used to estimate a limit of detection (LOD).

Results

DO concentrations ranged from 0.5 to 21.6 mg/L. A linear correlation between DO and R_1 was obtained with both MOLLI sequences, with an average correlation coefficient (R^2) 0.9 and an average estimated r_1 ($\widehat{r_1}$) of $4.45 \cdot 10^{-3} \text{ s}^{-1} \cdot \text{mg}^{-1} \cdot \text{L}$. Estimated LOD was $\approx 10 \text{ mg/L}$.

Conclusion

MOLLI T_1 -mapping sequences may be used for detecting dissolved oxygen *in vivo* at 3 T with an $\widehat{r_1}$ in the range $4.18 - 4.8 \cdot 10^{-3} \text{ s}^{-1} \cdot \text{mg}^{-1} \cdot \text{L}$ and a corresponding LOD for dissolved oxygen of approximately 10 mg/L. MOLLI based T_1 mapping may be a useful non-invasive tool for quantification of *in vivo* changes of DO concentration during oxygen challenges.

Introduction

Quantification of changes in T_1 relaxation rates (R_1) may be used to evaluate changes in tissue oxygenation. Previously several organs have been evaluated in such a fashion, including vitreous [1], CSF [2] kidneys [3,4] and tumours [5]. In oxygen challenge studies, the effect of breathing 100 % oxygen versus ambient air on T_1 has been shown to be dependent on target organ, field strength, and in some cases, also dietary status. In a study by O'Connor in 2007 [4] significant changes from baseline R_1 was found in spleen, liver, paraspinal muscle, renal cortex, and subcutaneous fat with ΔR_1 values ranging from 0.052 to 0.188 s^{-1} . Similar effects were observed by Jones et al in 2002 [3].

The R_1 is linearly dependent on dissolved oxygen (DO) concentration [6-8] described by

$$R_1 = R_{1b} + r_1[DO] \quad \text{Eq. 1}$$

where R_1 is the measured longitudinal relaxation rate (s^{-1}), R_{1b} is the relaxation rate without the presence of DO, r_1 is the relaxivity of oxygen in units of $s^{-1}[\text{concentration (in mg/L)}]^{-1}$ and DO concentration is in the unit of mg/L. Estimation of oxygen concentration can therefore be obtained if r_1 , R_1 and R_{1b} can be accurately measured. Knowledge of the concentration response of DO (quantified in terms of r_1) and limit of detection (LOD) for a given MRI based measurements technique may facilitate quantification of oxygen changes *in vivo*. Comparing the differences in r_1 and LOD between different MR sequences would also help selecting an optimal sequence when conducting oxygen challenge studies.

While there are accurate *in vitro* techniques available for measuring R_1 , *in vivo* measurements are more challenging, especially in the abdominal and thoracic regions due to respiratory and cardiac motion [9]. In addition, limitations on breath hold duration demands some concessions on image quality and sampling duration of the sequences.

The MODified Look-Locker Inversion Recovery (MOLLI) sequence is a robust and increasingly popular T_1 mapping technique based on adiabatic inversion pulses, followed by a sequence of single shot balanced steady state free precession (b-SSFP) images, sampling the recovery curve [10].

While MOLLI does allow for breath hold imaging of moving tissue, the measured T_1 is known to be biased and sensitive to several effects, among these T_2 relaxation and resonance offset which may both be modified by DO concentration [11,12]. For this reason, it is not evident that R_1 obtained by MOLLI is a good estimator of DO concentrations. As a pragmatic solution, we propose the use of a sequence specific r_1 (r_{1m}) to adjust for the bias in R_1 .

In preparation for future studies with oxygen challenges, the purpose of the current study was therefore to obtain sequence specific estimates of r_1 ($\widehat{r_{1m}}$) values for two schemes of MOLLI currently available for in vivo use and to estimate the limits of detection (LOD) for MOLLI based oxygen measurements.

Methods

Preparation of the water solutions with different DO concentrations

Ten samples were prepared by diluting water with DO concentration > 60 mg/L with anoxic water (DO concentration ≈ 0 mg/L). A patented process (WO 2016/071691 Oxy Solutions, Oslo, Norway) where oxygen and water are mixed in a chamber and passed through a piping system equipped with a venturi produced water with high DO concentrations. An anoxic chamber (Modified AW200SG Anaerobic Workstation, Electrotek, West Yorkshire, UK) supplied with gas consisting of 5% H_2 5% CO_2 , and 95% N_2 (Praxair, Guildford, UK) produced the anoxic water, and after 72 hours anoxic levels were confirmed using a Orion Star oxygen probe (Thermo Fisher, Waltham, Massachusetts, USA).

High DO- and anoxic- water samples were mixed to a total volume of 250 mL before being divided into; 100 mL for Winkler titration and 150 mL for MRI scanning. Winkler titration and MRI scanning were performed immediately after preparation of the water samples.

The experiment was repeated four times with pure water. To mimic *in vivo* R_1 the same experiment was performed four times with water where gadoterate meglumine (DotaremTM Guerbet, Roissy, France) was added to give a T_1 close to that of venous blood, which previously has been reported to be 1759 ms [9]. The amount of gadolinium needed was determined by titration, and a volume of 350 μ L DotaremTM diluted to 10% was used to achieve a final concentration of 0.116 mmol/L of gadolinium.

Measurements of DO levels using Winkler titration

All reagents used for DO concentration determination with Winkler titration were supplied by Sigma-Aldrich (St. Louis, MO, USA). Determination of DO concentrations was performed as described by Moen et al. [13]. Adding one mL of manganese sulphate (2.2M) and alkaline iodide solution (12M NaOH and 0.86M KI) to 100 mL of the water solutions resulted in sedimentation of $MnO(OH)_2$. Sediments were allowed to settle halfway twice before 3 mL of 95 - 98% sulfuric acid (H_2SO_4) was added to dissolve the sediment. Sodium thiosulfate (0.0375M) was titrated to the sample until the solution reached a pale yellow colour, and subsequently 2 mL of starch indicator was added to give the sample solution a deep blue colour. The solution was further titrated with sodium thiosulfate

until the solution was transparent. Estimates of DO concentrations in mg/L was subsequently calculated from the total volume of sodium thiosulfate used.

MRI

MRI was performed using a 3T Philips Ingenia system (Philips Medical Systems, Best, The Netherlands) equipped with an embedded posterior and anterior coil. The bottles with the sample solutions were placed in a 10 L plastic container filled with sun seed oil to the level of the bottle caps. The container was placed in the MR scanner and the anterior coil was laid to rest on the top of the container.

Based on a previous study on *in vivo* stability [9] two MOLLI schemes of 10(5)5 and 5(3)3 were selected. Table 1 shows selected sequence parameters for both sequences. Parameters relevant for contrast were; flip angle 20, TR/TE shortest (2.4/1.07ms and 2.6/1.2ms) and minimum TI 178.3 and 196.1ms for the MOLLI 10(5)5 and 5(3)3 respectively. A simulated ECG signal was used for image triggering at a rate of 60 beats per minute.

Following localizer images, the sequences for quantitative estimation of T_1 were acquired six times for each sequence. Tests were performed at room temperature and the temperature was measured in the sun seed oil before and after scanning. Average temperature measured was 22.6 °C (range 21.5 - 24.0) in the non- gadolinium and 23.0 °C (range 22 - 24,5) in the gadolinium group respectively.

Image analysis

Parametric R_1 and corresponding goodness of fit maps showing sum of square residual (χ^2) maps were generated and analysed using nordicICE (NordicNeuroLab, Bergen, Norway) with Look Locker Correction enabled. Since χ^2 values are the square of differences between a measured point and the fitted curve, χ^2 maps, and values, allow for detection of areas with sub-par R_1 estimations. For this reason, ellipsoid ROIs were drawn on the χ^2 map in the centre of each bottle avoiding areas of visual artefacts (high χ^2 values) and the bottle walls. ROI positions and geometry were subsequently copied to parametric R_1 maps.

Statistical analysis

R_1 values were then correlated with DO concentrations using linear regression to give the calculated $\widehat{r_{1m}}$ and coefficient of correlation (R^2). (IBM SPSS Statistics for Windows, IBM Corp. Armonk, NY, USA) To check for bias between the measurements techniques Bland Altman analysis was performed to compare the R_1 between MOLLI 10(5)5 and MOLLI 5(3)3.

Estimation of in vivo Limits of Detection (LOD).

The limits of detection were estimated according to $LOD = \frac{F \cdot SD}{r_1}$ where F is a factor set to 3.3 and SD is the standard deviation of R_1 . [14] A factor of 3.3 results in a conservative LOD, the calculations were therefore also performed with F=2 to give a confidence interval of 95%. The SD values used were based on the results on the *in vivo* longitudinal stability of the applied sequences [9].

Results

Figure 1a-b shows representative R_1 maps from the MOLLI 5(3)3 and 10(5)5 with and without addition of gadolinium. The DO levels in each compartment are shown in the MOLLI 5(3)3 maps. A summary of the measured DO levels is presented in Figure 2a

The $\widehat{r_{1m}}$ values ranged between 4.18 and $4.8 \cdot 10^{-3} \text{ s}^{-1} \cdot \text{mg}^{-1} \cdot \text{L}$, while R^2 values ranged between 0.88 and 0.924. See Table 2 for details and Figures 2b-c for scatter plots. Comparing $\widehat{r_{1m}}$ gave no significant differences between the two MOLLI sequences, either with or without gadolinium (Table 2). Estimated LOD were 8.5 mg/L and 12.3 mg/L for the 10(5)5 and 5(3)3 schemes, respectively. Table 2 summarizes the measured r_1 and estimated LOD for both MOLLI schemes.

Average DO concentrations in the samples ranged from 0.5 – 21.6 mg/L, as measured by Winkler titration (Figure 2a). R_1 increased from 0.3 s^{-1} to 0.56 s^{-1} in the samples with lowest DO concentration.

According to the Bland Altman plots (Figure 3) MOLLI 10(5)5 reported lower values than MOLLI 5(3)3 scheme (Bias -0.0066 $p < 0.001$ in the gadolinium group and -0.0081 $p < 0.001$ in the non gadolinium group). In the experiments with gadolinium added there was a positive correlation in the bias between MOLLI 10(5)5 and 5(3)3 as a function of R_1 (coefficient = 0.090, $R^2 = 0.550$ $p < 0.001$). In the experiments without gadolinium the correlation between MOLLI 10(5)5 and 5(3)3 was negative (coefficient = -0.058, $R^2 = 0.311$ $p < 0.001$).

Comparing the average Chi^2 values across all experiments and ROI's were 0.265 (SD 0.133) and 0.046 (SD 0.037) in the non-gadolinium group and 0.187 (SD 0.004) and 0.03 (SD 0.015) in gadolinium group for MOLLI 5(3)3 and 10(5)5 respectively.

A total of six samples were removed from the study due to errors in DO measurements from Winkler measurements ($n = 5$) and errors in adding gadolinium under preparation ($n = 1$).

Discussion

Our results confirm that the strong linear relationship between R_1 and DO concentration is also valid for MOLLI-based estimations of R_1 . The measured sequence specific $\widehat{r_{1m}}$ is in accordance with the value obtained with other MR based quantitative T1-mapping techniques such as Inversion Recovery and Look-Locker. [1,8] The addition of 0.116 mmol/L Gadolinium resulted in R_1 values similar to what has previously been measured in portal vein venous blood using these sequences (0.56 and 0.57 s⁻¹ for MOLLI 10(5)5 and 5(3)3 respectively) [9]. Which indicates that the titration resulted in a correct amount of gadolinium.

The linear correlation found between R_1 obtained with MOLLI and DO concentration facilitates the use of this robust breath hold sequence in oxygen challenge studies targeting organs or tumours in the abdomen or thoracic area. The ability for quantification of changes in R_1 might potentially yield additional information during oxygen challenges compared to that of a pure qualitative approach. The Bland-Altman plots revealed a slight bias in R_1 depending on the MOLLI scheme. While the MOLLI 10(5)5 consistently reported values lower than the MOLLI 5(3)3 we found a negative correlation between bias and R_1 in the experiments without gadolinium added, and a positive correlation in the experiments where 0.116mmol/L gadolinium was added. This might be an indication that the actual correlation is dependent on the range of R_1 measurements.

The estimated LOD indicates an *in vivo* detection threshold of approximately 10 mg/L oxygenation change; corresponding to a change in R_1 of $4.8 \cdot 10^{-2} \text{ s}^{-1}$. Although not directly comparable due to the difference in magnetic field strength, this indicates that the MOLLI 10(5)5 should be able to detect the changes reported in previous oxygen challenge studies [3,4]. O'Connor et al.[4] states that under normal conditions the dissolved oxygen content of systemic arterial and venous blood is 98 and 39 mmHg, which corresponds to 4.34 and 1.73 mg/L. During inspiration of 100% oxygen this increases to 600 and 48 mmHg which corresponds to 26.57 and 2.12 mg/L. Comparing this to our results, this would indicate that the MOLLI schemes in this study should be able to detect changes in the arterial blood but not venous blood.

Theoretically, the r_1 of DO at a given field strength and temperature should be a physical constant of oxygen and not dependent on choice of T₁-mapping sequence. In practice, however, the measured r_1 values depend on measurement method, as in our study is reflected in the slight difference in r_1 obtained with the two tested MOLLI schemes type and also baseline R_1 -values (with or without Gd-doped water). The slight, but significant ($p < 0.001$), difference between the r_1 estimated from the two MOLLI schemes in the gadolinium group is interesting as it also affects the limit of detection reported by these sequences and might indicate a difference in sensitivity. The lower Chi² values in the 10(5)5 variation is a further indication for higher sensitivity. These applied *in vivo* data, however

are based on young healthy volunteers. The longer required breath hold of MOLLI 10(5)5 might turn this around in another population.

Limitations

Estimation of DO r_1 requires accurate measurements of DO concentrations in the sample solutions, as well as stable and accurate measurements of R_1 . A limitations of this study is therefore linked to correct measurement of DO concentration and R_1 .

Winkler titration is considered an accurate and reliable technique, which is often used as a gold standard for DO measurements. [15] The main confounding factor for Winkler titration in this study is that the procedure is performed manually, which may give higher variations than with an automatic approach. Also, since the Winkler titrations were not performed in a vacuum, the ambient oxygen levels could potentially affect the measurements. To minimize these errors several steps were taken. Firstly, the reagents used were added immediately after preparation, which minimize the potential for contamination of the specimens from atmospheric O_2 levels. Future studies may benefit from further optimization of the Winkler titration technique, potentially by using specialized equipment or chemicals that would further minimize the potential of atmospheric oxygen contamination.[15]

R_1 may be affected by the potential presence of other paramagnetic substances, as well as sample temperature. By using the same water for all sample solutions, it is unlikely that there is a significant difference in the concentration of other solvents beyond the controlled difference in DO concentrations. The addition of gadolinium was performed per bottle using a micropipette and small concentration differences were unavoidable both between bottles in the same experiment, and across different experiments. To minimise the potential variation gadolinium was diluted to 10% and the same diluted solution was used for all gadolinium experiments.

In the current setup, we were unable to control the temperature during scanning, thus temperature control is a limitation. To achieve a stable temperature as possible the sun seed oil used for the experiments were stored in the scanner room which is a combined scanner and operation theatre with strict temperature regulation. The temperature was also measured before and after scanning in all but one of the examinations. The interested reader are referred to the online supplements Figure 1 and Table 1 where scatterplots and regression analysis are presented in temperature groups. To

1 increase the reliability in future studies a stricter temperature control and measurements should be
2 performed during the experiments, preferably by a constant logging of temperature during scanning.
3

4 In conclusion, MOLLI based T_1 -mapping sequences may be used for detecting dissolved oxygen at 3
5 T, and the r_1 of DO *in vitro* was estimated to be in the range $4.18 - 4.8 \cdot 10^{-3} \text{ s}^{-1} \cdot \text{mg}^{-1} \cdot \text{L}^{-1}$. The
6 corresponding LOD for dissolved oxygen was approximately 10 mg/L. The obtained $\widehat{r_{1m}}$ is in good
7 agreement with r_1 values reported in literature. Our results support the feasibility of using the MOLLI
8 sequence for detection and quantification of DO concentrations *in vivo*.
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13

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15 Compliance with ethical standards.

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21

22 Conflict of interest:

23
24 Vatnehol is an employee of Oxy Solutions A/S a biotech company working with oxygenation of
25 liquids.
26

27
28 Haglerød is an employee of Oxy Solutions A/S a biotech company working with oxygenation of
29 liquids.
30
31

32
33 Amiry-Moghaddam is an employee of Oxy Solutions A/S a biotech company working with
34 oxygenation of liquids.
35
36

37 Hol declares that he has no conflict of interest.
38

39
40 Storås declares that he has no conflict of interest.
41

42 Bjørnerud declares that he has no conflict of interest.
43
44

45 Ethical approval: This article does not contain any studies with human participants or animals
46 performed by any of the authors
47
48

49 Authors Contribution:

50
51 Vatnehol; Study conception and design, Acquisition of data, Analysis and interpretation of data,
52 drafting of manuscript, Critical revision.
53
54

55 Hol: Study conception and design, Drafting of manuscript, Critical revision.
56
57

58 Bjørnerud: Study conception and design, Drafting of manuscript, Critical revision.
59
60

61 Haglerød: Study conception and design, Drafting of manuscript, Critical revision.
62
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1 Storås; Study conception and design, Drafting of manuscript, Critical revision.
2
3

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Figure Legend.

Fig 1

Representative R_1 maps from the MOLLI 5(3)3 and 10(5)5 sequences without gadolinium (A) and with gadolinium (B). The upper left and lower right compartments in B are produced without gadolinium to serve as controls. DO of each compartment are shown in the MOLLI 5(3)3 maps. Average Chi^2 values were 0.265 (SD 0.133) and 0.046 (SD 0.037) in A and 0.187 (SD 0.004) and 0.03 (SD 0.015) in B for MOLLI 5(3)3 and 10(5)5 respectively. The colour scale is set from 0.29 to 0.43 s^{-1} in A and 0.29 to 0.65 s^{-1} in B. DO levels (in reading order starting top left) were: 0.3, 0.9, 1.2, 1.8, 2.1, 3.0, 9.0, 10.8, 14.1 and 23.7 mg/L in A and: 0.45, 0.45, 1.2, 1.8, 2.4, 3.45, 3.9, 9.3, 10.8, 12.9, 20.3 and 21.3 mg/L in B

Fig 2

(A) shows the average DO concentration as measured by Winkler Titration of the samples in the 10 compartments (black dots) and the mean DO concentration of each compartment (gray line). (B-C) The $\widehat{R}_1$ in each compartment plotted against the DO concentration of the two sequences, without gadolinium in B and with in C. The fitted regression lines are shown in gray solid lines (MOLLI 10(5)5) and dotted black lines (MOLLI 5(3)3).

Fig 3

Bland Altman plots comparing MOLLI 5(3)3 and MOLLI 10(5)5 in the non gadolinium group (A) gadolinium group (B) The plots show that the MOLLI 10(5)5 has a negative bias that is most profound in the lower DO levels. Red lines are mean bias, and blue lines are standard deviations * 1.96

Table 1

Selected sequence parameters for the MOLLI sequences

Table 2

The $\widehat{r}_1$, R^2 and LOD of the two MOLLI sequences with the p-values of differences in the regression analysis. LOD was only included for the sequences with gadolinium.

Supplemental Figure 1.

Scatter plots showing the measured R_1 vs DO in the two MOLLI sequences with regression lines broken down into different temperature groups. The graphs show that the R_1 increases with decreasing temperature.

Supplemental Table 1.

Regression analysis of R_1 against DO for both MOLLI sequences and gadolinium groups broken down into temperature showing the r_1 from each experiment and the average r_1 .

Table 1

Parameter	MOLLI 10(5)5	MOLLI 5(3)3
Field Of View (FOV)	360 x 360	360 x 360
Matrix	240 x 240	240 x 240
Resolution	1.5 x 1.5	1.5 x 1.5
Repetiton Time (TR)	Shortest (2.4 ms)	Shortest (2.6 ms)
Echo Time (TE)	Shortest (1.07 ms)	Shortest (1.2 ms)
Flip Angle	20°	20°
SENSE	2	2
Minimum Inversion time	178.3 ms	196.1 ms
Scan time	20 seconds	11 seconds

Table 2

Sequence	Without Gadolinium		With Gadolinium		
	r_1 ($s^{-1} \cdot mg^{-1} \cdot L$) (95% confidence interval) (standard deviation)	R^2	r_1 ($s^{-1} \cdot mg^{-1} \cdot L$) (95% confidence interval) (standard deviation)	R^2	LOD (mg/L)
MOLLI 10(5)5	$4,18 \cdot 10^{-3}$ ($3,7 - 4,6 \cdot 10^{-3}$) ($0,23 \cdot 10^{-3}$)	0,883	$4,8 \cdot 10^{-3}$ ($4,3 - 5,3 \cdot 10^{-3}$) ($0,25 \cdot 10^{-3}$)	0,911	8.5
MOLLI 5(3)3	$4,39 \cdot 10^{-3}$ ($3,9 - 4,9 \cdot 10^{-3}$) ($0,23 \cdot 10^{-3}$)	0,89	$4,41 \cdot 10^{-3}$ ($4 - 4,8 \cdot 10^{-3}$) ($0,2 \cdot 10^{-3}$)	0,924	12.3
p-value of r_1 between the MOLLI sequences	0.53		<0.001		
					p-value of r_1 with and without GD
					0,083
					.946

Figure 2

Figure 1B