Measuring Blood Oxygenation using Variable Echo Spacing CPMG: Use of the Luz-Meiboom Equation

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Introduction

The accurate quantification of blood oxygenation is of critical importance in studying both pathological conditions, such as tumour angiogenesis, and normal physiology, such as the degree of neuronal activation via the BOLD effect of fMRI. However, non-invasive techniques to accomplish quantitative blood oximetry without invoking simplified tissue models are lacking. *In vivo* blood T_2 is typically much longer than other tissue types. We have used this characteristic of blood T_2 to achieve blood signal isolation through multi-exponential fitting, and have then exploited this isolation to accomplish quantitative blood oxygenation measurement using the well-described dependence of blood T_2 on oxygenation, validated in numerous *ex vivo* blood sample studies[1,2,3]. This new method is technically challenging, given the small systemic blood volume (approximately 3%) which causes blood T_2 isolation to be quite unstable. We describe here a multiple echo spacing, multiple echo, CPMG technique which exploits the known echo spacing dependence of blood T_2 to enhance the stability of blood signal isolation. This dependence relies on blood water fast exchange according to the Luz-Meiboom [4] equation. While the reliability of the Luz-Meiboom equation is well established in *ex vivo* blood samples [2,3], its validity *in vivo* is demonstrated by us for the first time here, as is the subsequent extraction of quantitative blood oxygenation in skeletal muscle by this approach.

Theory

The BOLD effect induces red blood cell intra and extra cellular field gradients as well as a resonance shift between compartments[5]. Water diffusion/exchange through this distribution of fields is fast enough to establish the fast exchange condition. For such a system, the CPMG echo spacing dependence of the observed blood relaxivity, R_{2bl}, is given by the Luz-Meiboom equation [4]. For the *in vivo* situation, we model the vasculature as a combined arterial and venous pool where the total blood pool signal fraction, f_{bl}, is the sum of the arterial, f_a, and venous, f_v, fractional signals. This permits our implementation of an *in vivo* Luz-Meiboom equation:

$$R_{2bl} = R_{2o} + \frac{1-fpe}{2\tau_{cpmg}} + R_{2dv}\left\{1-\frac{\tau}{\tau_{cpmg}}\tanh\left(\frac{\tau_{cpmg}}{\tau}\right)\right\}\left(1-\frac{f_a}{f_{bl}}\right) \qquad (1)$$

where τ_{cpmg} is the 90-180 echo spacing in a CPMG acquisition and τ is the exchange time. R_{2dv} is the diffusion induced relaxivity for the venous pool and R_{2o} is the relaxivity contributed from all other mechanisms. Diffusion induced relaxivity is assumed to be negligible for the arterial pool. The second term of eqn 1 is necessary in practice to account for imperfect refocus pulse efficiency characterized by the fraction, fpe. Equation 1 employs a *weighted R_2 assumption* where $R_{2bl} = (f_aR_{2a} + f_vR_{2v})/f_{bl}$ with R_{2a} and R_{2v} being the arterial and venous blood relaxivities. Equation 1 is a 5 parameter equation (R_{2o}, fpe, R_{2dv}, τ, f_a), with f_{bl} and R_{2bl} measured for every τ_{cpmg} (see methods).

From BOLD theory and the derivation of the Luz-Meiboom equation, we have R_{2dv} proportional to $B_o^2(1-Y)^2$ where B_o is field strength and Y is fractional venous blood oxygenation. Many others have validated the Luz-Meiboom relationship by varying both B_o [2] and Y [5] for *ex vivo* blood samples. By fitting the data of Gomori [2], we estimate a proportionality coefficient between R_{2dv} and $B_o^2(1-Y)^2$ of 6.35 $s^{-1}T^{-2}$. This relation is used to estimate Y.

Methods

All measurements were performed at 4T on a Varian/Siemens whole body imager. Three normal human volunteers placed their lower leg within a 17cm ID quadrature birdcage coil. A pulse sequence having a non-selective CPMG train of rectangular hard pulses followed by a 512ms FID acquisition with 2 kHz spectral bandwidth, was developed. The pulse widths of the 90° and 180° pulses were 300µs and 600µs respectively with τ_{cpmg} ranging from 1.5ms to 7ms by 0.5ms increments. Appropriate numbers of refocusing pulses were employed to produce 10 readout echo times exponentially spaced between 6ms and 600ms. Two signal averages and a 900ms post acquisition delay were employed to collect a complete data set for every τ_{cpmg} each 30sec. 10 identical acquisitions were collected for statistics.

Post processing involved Fourier transforming each FID acquisition to the spectral domain and performing first order phase correction. A variance normalized NNLS transform for each spectral frequency bin was then performed[6]. Tissue and blood chemical shift spectra were constructed through summation within the T_2 ranges of 5ms-50ms and 50ms-500ms respectively for each spectral frequency bin. Summation of these spectra over the central 80hz (water peak) generated the estimate for blood relaxivity, R_{2bl}, and fractional blood signal, f_{bl}.

Results and Discussion

Figure 1 is a plot of the measured total blood pool relaxivity, R_{2bl}, and the extracted venous blood relaxivity, R_{2v}, versus τ_{cpmg} for subject #1. R_{2v} is derived from the weighted R_2 assumption equation and fitted parameters of equation 1 in the theory section. The result of this fit for R_{2v} is indicated by the solid curve of figure 1. Error bars represent the standard error of repeated measures. While the total blood pool relaxivity, R_{2bl}, is very unstable, R_{2v} is considerably more stable and is well represented by the *in vivo* Luz-Meiboom eqn fit. This is a result of the strong co-variation between R_{2bl} and f_{bl} (data not shown). Though these parameters are individually unstable, their collective influence in determining R_{2v} through fitting equation 1 is considerably more stable.

Table 1 contains the fitted parameters of eqn 1 for each of the 3 subjects along with the χ^2 for the fit. All fits were excellent with χ^2 well below unity. Table 1 also has venous blood oxygenation estimates based on R_{2dv}. The mean Y was 61.7% for all subjects. The mean τ was 0.89ms, in reasonable agreement with the *ex vivo* blood sample estimate of 0.6ms provided by Thulborn [1] and characteristic of diffusion through intracellular field gradients.

Conclusions

We have described, to our knowledge, the first *in vivo* demonstration of venous blood T_2 variation in accordance with Luz-Meiboom theory. The arrayed τ_{cpmg} experimental approach has been shown to greatly stabilize the separation of blood and tissue signal, permitting more reliable blood T_2 estimates. We have used parameters derived from the Luz-Meiboom equation fit, in conjunction with literature *ex vivo* blood sample results, to *directly* estimate baseline venous blood oxygenation of human skeletal muscle.

References

[1] Thulborn et al, Biochimica et Biophysica Acta **714**: 265-70 (1982)
[2] Gomori et al, JCAT **11**(4): 684-690 (1987)
[3] Bryant et al, MRM **13**: 133-144 (1990)
[4] Luz and Meiboom, J. Chem. Phys. **39**(2): 366-370 (1963)
[5] Ye and Allen, MRM **34**: 713-720 (1995)
[6] Bowen and Rutt, ISMRM 7th proc: 2160 (1999)

Figure 1: Luz-Meiboom equation fit to venous blood R_2 variation

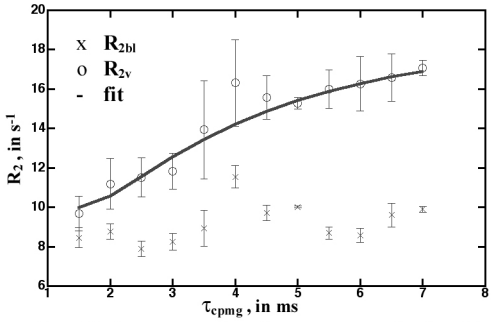

Table 1: Luz-Meiboom equation fit parameters for 3 subjects

	τ (ms)	R_{2dv} (s^{-1})	R_{2o} (s^{-1})	fpe	f_a	χ^2	Y (%)
Sub #1	1.76	19.8	0.9	0.984	3.5	0.5	55.8
Sub #2	0.33	14.3	0	1	1.5	0.3	62.5
Sub #3	0.59	11.2	4.1	1	3.8	0.2	66.8