Published in final edited form as:

Magn Reson Med. 2019 July ; 82(1): 367–376. doi:10.1002/mrm.27721.

Mapping and Correcting Hyperpolarized Magnetization Decay with Radial Keyhole Imaging

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Abstract

Purpose—Hyperpolarized (HP) media enable biomedical imaging applications that cannot be achieved with conventional MRI contrast agents. Unfortunately, quantifying HP images is challenging, because relaxation and radio-frequency pulsing generate spatially varying signal decay during acquisition. We demonstrate that, by combining center-out k-space sampling with post-acquisition keyhole reconstruction, voxel-by-voxel maps of regional HP magnetization decay can be generated with no additional data collection.

Methods—Digital phantom, HP ¹²⁹Xe phantom, and *in vivo* ¹²⁹Xe human ($N = 4$ healthy; $N = 2$ with cystic fibrosis) imaging was performed using radial sampling. Datasets were reconstructed using a post-acquisition keyhole approach in which two temporally resolved images were created and used to generate maps of regional magnetization decay following a simple analytical model.

Results—Mean, keyhole-derived decay terms showed excellent agreement with the decay used in simulations ($R^2 = 0.996$) and with global attenuation terms in HP ¹²⁹Xe phantom imaging ($R^2 > 0.97$). Mean regional decay from *in vivo* imaging agreed well with global decay values and displayed spatial heterogeneity that matched expected variations in flip angle and oxygen partial pressure. Moreover, these maps could be used to correct variable signal decay across the image volume.

Conclusions—We have demonstrated that center-out trajectories combined with keyhole reconstruction can be used to map regional HP signal decay and to quantitatively correct images.

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This approach may be used to improve the accuracy of quantitative measures obtained from hyperpolarized media. Though validated with gaseous HP ^{129}Xe in this work, this technique can be generalized to any hyperpolarized agent.

1. Introduction

Advances in producing and detecting hyperpolarization (HP) media have enabled a wide range of basic and translational research applications that would otherwise be impossible (1–8). However, the wider utility of hyperpolarized agents—particularly for quantitative applications—is limited by the transient, non-recoverable nature of the hyperpolarized state (9–12). The *in vivo*, T_1 of HP nuclei is typically tens of seconds (13–18) and varies regionally, depending on factors including chemical environment, tissue composition, and O_2 partial pressure (pO_2) (13,17,19). Additionally, each RF excitation used to generate MR signal further depletes the available HP magnetization in a spatially varying manner.

This spatially-varying HP magnetization destruction can manifest as pronounced artifacts in reconstructed images and produce regional differences in image signal intensity independent of the concentration of the HP nuclei or contrast mechanism of interest (e.g., diffusion, chemical exchange, etc.) (17). Thus, to perform quantitative analysis on HP media images, spatially resolved knowledge of the signal decay is required, for which additional scans must be acquired to map B_1 field (i.e., flip angle) and T_1 (20). Alternatively, global signal can be held constant using variable flip angle techniques (21). However, many experiments make global assumptions about—or simply neglect—the effects of spatially varying T_1 and RF-induced magnetization depletion (22). In principal, both T_1 decay and RF depletion are encoded simultaneously with imaging data, suggesting that magnetization decay can be extracted directly from raw k-space data with an appropriate combination of imaging sequences and reconstruction algorithms.

A particularly promising class of imaging techniques for extracting HP magnetization decay are collectively termed ultra-short echo time (UTE) sequences (23–27). These sequences utilize imaging gradients applied immediately after the RF pulse and concurrent with data acquisition (26), thereby sampling from the center to the edge of k-space. As a result, center-out k-space trajectories sample the hyperpolarized signal intensity generated by each RF excitation, allowing global signal decay to be tracked trivially by examining the intensity at the k_0 point on each radial view (28–30).

Herein, we propose a technique by which signal decay may be mapped, voxel-by-voxel, from a single set of k-space data acquired using center-out, radial trajectories. Our method builds on the works of Miller *et al.* (31) and Marshall *et al.* (28) and uses a 3D radial sequence to encode k_0 decay alongside image data. Using a combination of pre- and post-processing and a simple theoretic model, imaging data are used to generate an HP ^{129}Xe ventilation image and to map and subsequently correct regional signal decay. This technique was validated using simulations, HP gas phantoms, and *in vivo* imaging. Importantly, while this work focused on HP ^{129}Xe ventilation imaging, the general approach can be extended to MR imaging of virtually any system with high nuclear polarization.

2. Theory

In MRI, fine image detail is encoded in the high-frequency periphery of k-space, while signal intensity is dominated by the center of k-space, k_0 (32–34). In some applications (e.g., contrast-enhanced angiography), variations in high frequency data are negligible compared to temporal variations in k_0 intensity. Thus, temporally-resolved subsets of low frequency data (keys) can be combined with a complete, temporally invariant high-frequency dataset (i.e., keyhole) to generate pseudo-dynamic images. Further, when these systems are imaged using radial sequences (34–36), which intrinsically oversample k_0 , it becomes possible to generate multiple, fully sampled images that depict regional dynamics with a single image acquisition (36).

For HP nuclei, low frequency data vary almost exclusively due to the decay of longitudinal HP magnetization, M_Z . In the absence of complexities such as changing pO_2 or chemical reactions, hyperpolarized magnetization decays monotonically to thermal equilibrium due to T_1 relaxation and RF depletion (9–12). If decay processes are assumed to be constant during data acquisition, the keyhole approach can be combined with an analytical expression for magnetization dynamics, allowing M_Z to be monitored spatially and temporally (Figure 1). Specifically, if the repetition time, TR , is much less than T_1 , M_Z decays from its initial value, $M_Z(0)$, as a function of view number, n , according to

$$M_z(n) = M_z(0) \left[\cos(\alpha) \exp\left(-\frac{TR}{T_1}\right) \right]^{n-1} = M_z(0) C_1^{n-1}, \quad (1)$$

where $C_1 \equiv \cos(\alpha) \exp(-TR/T_1)$ describes HP magnetization decay (37). Thus, the signal intensity originating from the n th RF pulse, s_n , is given by

$$s_n = M_z(0) \sin(\alpha) C_1^{n-1}. \quad (2)$$

Because k_0 is sampled with each excitation, the total signal intensity, S , of a radial image is the average of all S_n values and is given by

$$S = M_z(0) \sin(\alpha) \frac{1}{N} \sum_{n=1}^N C_1^{n-1} = M_z(0) \sin(\alpha) \frac{1}{N} \frac{1 - C_1^N}{1 - C_1}, \quad (3)$$

where N is the total number of radial views. The signal lost over the course of a radial acquisition can then be described by the fractional signal attenuation A ,

$$A = \frac{S(0) - S}{S(0)} = 1 - \frac{1}{N} \left(\frac{1 - C_1^N}{1 - C_1} \right), \quad (4)$$

where, $S(0) = M_Z(0) \sin(\alpha)$ is the image signal intensity in the absence of any magnetization decay (i.e., signal intensity of the first radial view).

When a radial acquisition is divided into K temporally resolved keys, Eq. 3 must be modified to account for previous signal decay, and the expression for the signal of a given key, s_{κ} , becomes

$$S_{\kappa} = M_z(0) \sin(\alpha) \frac{C_1^{(\kappa-1)N/K} (1 - C_1^{N/K})}{N/K}, \quad (5)$$

where κ denotes the key number.

To illustrate the utility of radial keyhole in HP imaging, we have chosen the simplest temporal subdivision ($K = 2$) Using Eq. 5 on two temporally adjacent keyhole images, the decay term C_1 can be extracted:

$$C_1 = \sqrt[N/2]{\frac{S_2}{S_1}}. \quad (6)$$

Therefore, the fractional signal attenuation can be calculated from the intensity of two key images by rewriting Eq. 4 as

$$A = 1 - \frac{1}{N} \left[\frac{1 - (S_2/S_1)^2}{1 - (S_2/S_1)^{2/N}} \right]. \quad (7)$$

Moreover, together Eqs. 4 and 6 allow the unattenuated image to be recovered from the original image and key images according to

$$S(0) = \frac{S}{1 - A} = S \cdot \frac{N(1 - C_1)}{1 - C_1^N} = S \cdot N \left[\frac{1 - (S_2/S_1)^{2/N}}{1 - (S_2/S_1)^2} \right]. \quad (8)$$

3. Methods

3.1 Simulations

Simulations were performed in MATLAB 20106a (Mathworks, Natick, MA) using a digital two dimensional Shepp-Logan phantom (matrix: 256×256, TR: 4 ms, radial views: 804). Simulated, radially-sampled k-space data was generated by modeling hyperpolarized magnetization behavior according to Eq. 2, using regionally varying flip angles and T_1 values. Flip angle was varied between 1° and 3° and T_1 between 10 and 30s and kept

constant throughout sampling. K-space was sampled with a 2D golden-angle radial pattern (38) and images were reconstructed and analyzed as described in sections 3.4 and 3.5.

3.2 Phantom Imaging

Natural abundance or isotopically enriched (83% ^{129}Xe) xenon (Linde Specialty Gases) was polarized to >20% using a Polarean 9810 ^{129}Xe Hyperpolarizer (Polarean Imaging Ltd., Durham, NC). Imaging was performed using a 7T BioSpec (Bruker, Billerica, MA) preclinical scanner and a 3T Achieva (Philips Healthcare, Best, Netherlands) human scanner. On the preclinical system (26 scans), ~15 mL of HP ^{129}Xe was dispensed into a 26-mm inner-diameter, 60-mL syringe (Cole Parmer) placed in a 50-mm, quadrature ^{129}Xe birdcage coil. Imaging was performed using a 3D radial sequence with golden-means trajectories (39) (matrix: $40 \times 40 \times 40$, FOV: $40 \times 40 \times 40 \text{ mm}^3$, TR/TE: 6/0.7 ms, bandwidth: 50,000 Hz, radial views: 2514, and α : 1 to 3.5°). Prior to imaging, frequency and flip angle were calibrated using a thermally polarized phantom pressurized with 2.5 atm. xenon and 2 atm. O_2 .

Scanning on a human system used a 3D radial kooshball imaging sequence with 10 linear-projection-order interleaves and three coil/phantom combinations to assess the impact of coil size and homogeneity. For bag phantoms, natural abundance xenon was dispensed into 500 ml Tedlar bags (Jensen Inert Products, Coral Springs, FL). Imaging was performed with a $36 \times 40 \text{ cm}$ dual-loop chest coil intended for use on adults (11 scans) or a $32 \times 36 \text{ cm}$, dual-loop chest coil intended for pediatric use (7 scans) (40). In both cases, the loops were separated by 13 cm (average for use on human subjects). Scan parameters included matrix: $44 \times 44 \times 44$, FOV: $250 \times 250 \times 250 \text{ mm}^3$, TR/TE: 4/0.14 ms, bandwidth: 314 Hz/voxel, radial views: 1940; α : 0.5 to 3° . Additionally, imaging was performed using the $36 \times 40 \text{ cm}$ coil and a structured phantom (Dia. $13 \times$ Len. 19 cm) containing ~1L of isotopically-enriched xenon to examine the impact of image edges on the decay extraction method (Supporting Information, Figure S1). Acquisition parameters were: matrix: $60 \times 60 \times 60$, FOV: $300 \times 300 \times 300 \text{ mm}^3$, TR/TE: 4.5/0.15 ms, bandwidth: 265.0 Hz/voxel, radial views: 3600, and α : 1.8° . Prior to imaging, a series of 64, non-selective pulses ($\alpha \sim 11^\circ$) were applied to a bag of HP ^{129}Xe to calibrate frequency and flip angle. Flip angle values were chosen with lower bound dictated by system limits and upper bound by the maximum flip angle that could be used with 5% signal remaining after the scan.

3.3 In Vivo Imaging

Human studies were performed following Cincinnati Children's Hospital Medical Center, Institutional Review Board and FDA investigational new drug (IND 123,577) protocols. Written informed consent was obtained from all subjects prior to studies, and written assent was also obtained from pediatric subjects. Radial HP ^{129}Xe images were measured in four healthy (average age 15.5 ± 10.1 yrs) and two Cystic Fibrosis (CF) patients (ages 15, 18yrs) using a Philips 3T Achieva MRI scanner. Subjects were imaged in the supine position during a breath-hold (duration <16s). The $32 \times 36 \text{ cm}$ dual-loop coil described above was used with four subjects (Healthy-3, CF-1), while the $36 \times 40 \text{ cm}$ dual-loop coil was used with two subjects (Healthy-1, CF-1) (40). An initial dose containing 10% HP ^{129}Xe and 90% N_2 was used to calibrate the RF flip angle using a series of 64 non-selective pulses ($\alpha \sim 11^\circ$). Further doses used for imaging of subjects 18 yrs and younger contained a volume of HP ^{129}Xe

equal to 1/6 total lung capacity estimated by the subject's height according to American Thoracic Society standards (41). The dose size used for subjects older than 18 was 1L. Imaging was performed using a radial kooshball sequence (matrix: 60×60×60, FOV: 300×300×300 mm³, TR/TE: 4.5/0.15 ms, bandwidth: 265.0 Hz/voxel, radial views: 3600, α : 1.5°). For one volunteer (age 30 yrs), a second dose of HP ¹²⁹Xe was administered to measure an additional radial image with $\alpha = 1^\circ$. Flip angles were chosen to maximize the total signal intensity (1.5°) or to minimize the signal difference (k_0 intensity) between first and last radial acquisitions (1.0°).

3.4 Image Reconstruction

Low frequency k-space data was separated into two temporally separate datasets and combined with all high frequency data. To ensure that the low-frequency region within the key is fully sampled, the cutoff between high- and low-frequency data was set to the Nyquist radius. For a given number of radial views, N , and number of keys, K , this “keyhole radius” r_{key} , is given by (34)

$$r_{key} = \frac{N}{2\pi K} \quad (2D)$$

$$r_{key} = \sqrt{\frac{N}{4\pi K}} \quad (3D)$$

Because sharp changes in k-space signal intensity can lead to reconstruction artifacts (35), the high frequency data was scaled view-by-view by the average of the k_0 points in each key (Supporting Information, Figure S1). Key images were then reconstructed using iterative density compensation (42) and either in-house reconstruction software based on the groups of Pipe (43) and Fessler (44) or reconstruction routines in the graphical programming interface (GPI) (45).

3.5 Data Analysis

Extracted decay and attenuation maps were calculated from equations 6 and 7 using routines written in MATLAB. To confine analysis to the lung volume and airways, a binary mask was created using thresholding at the Rose criterion (SNR > 5) of each key image followed by an erosion and dilation (kernel radius = 2). Manual intervention was used where necessary to improve segmentation and include ventilation defects excluded by the SNR threshold. All other data analysis (e.g. regional keyhole decay extraction, global k_0 decay fitting, calculation of means and standard deviations, and Bland-Altman analysis) were performed in MATLAB.

4. Results

4.1 Simulations

The digital phantom (Fig. 2a) was decayed and sampled as outlined in Fig. 1, following Eq. 2 and the pattern shown in Fig. 2f. The intensity of the resulting k_0 values from each radial view decayed monotonically with a global C_1 value of 0.9988, in excellent agreement with the pixel-by-pixel average C_1 of 0.9990 ± 0.0004 extracted from the simulation within the phantom area. Moreover, the signal intensity of the reconstructed image Key 1, and Key 2 (2b, 2c, 2d) displayed a grid pattern identical to the one shown in 2f. C_1 (2g) and attenuation maps (2h) were constructed following Eq. 6 and 7. In addition to the patterns seen in 2f and 2g agreeing visually, the C_1 values from the extracted map correlate exceptionally well (Fig. 2j, $R^2 = 0.996$), with only minor discrepancies due to reconstruction imperfections. When corrected for magnetization depletion (2i), some residual signal intensity variation remained in the image due to the $\sin(\alpha)$ dependence in Eq. 3 (Fig. 2k).

4.2 Phantom Imaging

In phantoms, T_1 is long with respect to the imaging time (~2hrs vs 15s), so signal depletion is dominated by RF-induced depolarization, and $C_1 \cong \cos(\alpha)$ (46). Therefore, flip angle maps can be extracted from key images using Eq. 6 (Fig. 3). The spatial average of these flip angle maps correlated well with the global overall value obtained from fitting k_0 decay ($R^2 > 0.98$) (3e). While the birdcage coil used at 7T has greater homogeneity than the human-sized dual-loop used at 3T, the HP ^{129}Xe -containing phantom occupied ~40% of the coil volume at 7T compared to <5% of the coil volumes at 3T, leading to greater deviation of extracted flip angle at 7T. Also of note, small deviations from linearity are visible at the lowest flip angles ($\alpha = 1^\circ$), likely due to lower SNR and amplifier nonlinearities at low RF power. Bland-Altman analysis (Fig. 3f) showed no systematic difference between global and mean flip angle values. Similarly, our keyhole method of generating flip angle maps also agreed well ($R^2 = 0.98$) with the FLASH-based method of flip angle measurement proposed by Miller et al. (31) (data not shown).

4.3 In Vivo Imaging

When imaging HP ^{129}Xe *in vivo*, relaxation is non-negligible, so C_1 depends on both RF and T_1 (Eq. 1). As seen in Table 1, the average C_1 decay rate from keyhole extraction matches well with the global value. However, examination of the individual decay maps reveals larger regional differences than were observed in the phantom imaging. These variations result from the RF heterogeneity of the dual-loop coils across the larger lung volume (~7% over centered 1L volume for large coil, ~22% for small coil) (39) and regional variations in T_1 (i.e., oxygen partial pressure) (18,47,48) (Supporting Information Figure S2).

In CF patients with ventilation defects, a wide range of C_1 values were extracted from regions of defect—approximately double the range of C_1 values extracted from well-ventilated regions of the lungs. This led to attenuation values in CF lungs ranging from 0 to 70% with the whole lung average being 32%. Correcting images for signal decay using Eq. 7 (Fig. 4c) leads to a marked visual change in subjects with defects. Defects with increased

decay (i.e. small C_1) become less pronounced (4c) with correction while defects with weak decay (i.e. large C_1), become more pronounced. In contrast, the images from healthy subjects remained visually unchanged following correction.

5. Discussion

Simulations were performed using conditions that mimicked the T_1 and RF effects expected when imaging hyperpolarized media *in vivo*. For all simulated data, radial imaging produces accurate reconstructed images of both keys and provided quantitative decay attenuation via keyhole that closely matched values used in the simulations.

At both 3T and 7T, imaging HP gas phantoms further validated the radial keyhole approach to extract regional HP magnetization decay. From each data set, flip angle maps were generated that correlated well with the global flip angle obtained from k_0 decay. Minor deviations from linearity at low flip angle ($\alpha < 1^\circ$) likely result from lower SNR and RF amplifier non-linearity. However, as the flip angle was increased to values comparable to those used in human imaging, the effectiveness and accuracy of keyhole decay extraction improved substantially.

Although flip angle could not be directly extracted *in vivo*, the voxel-by-voxel mean C_1 obtained from both healthy and CF subjects agreed well with the global decay term extracted from k_0 . Once regional decay was calculated, the resulting attenuation maps were used to correct images for decay. Despite residual signal inhomogeneity due to coil sensitivity, the corrected images provide a superior estimate of regional ^{129}Xe content. While the correction had minor visual effect on the relatively homogenous images obtained from healthy subjects, significant improvements were observed in the appearance of images from CF patients. More importantly, using bias field correction (49) alongside keyhole decay extraction could further improve the accuracy of quantitative measurements of regional ventilation.

6. Conclusions

We have demonstrated a method that combines 3D imaging using center-out trajectories with keyhole reconstruction to map hyperpolarized magnetization decay with no additional data collection. This technique was validated via simulation and phantom imaging alongside *in vivo* ventilation imaging using hyperpolarized ^{129}Xe . In each case, decay maps were produced that closely correlated with global HP signal depletion and expected regional variations in decay. Importantly, the principles behind our keyhole decay extraction method are not limited only to HP gas imaging, but can be generalized to any hyperpolarized agent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. Bastiaan Driehuys for lending us the structured, hyperpolarized gas phantom; Dr. Laura Walkup for assistance with the human HP ^{129}Xe experiments; Andrew Bryan for polarizing HP ^{129}Xe ; and Drs. Jean Tkach, Greg Lee, Hui Wang, and Jinbang Guo for helpful discussions. This work was supported by the NIH

(R00HL111217, R44HL123299, and T32HL007752), the Cystic Fibrosis Foundation (Clinical Research Award CLEVEL16A0), and the Cincinnati Children's Research Foundation.

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Figure 1.

Workflow schematic for hyperpolarized decay extraction with radial keyhole. *i.* The object is radially sampled to generate k-space data. *ii.* During acquisition, longitudinal magnetization decays (green arrow) from its initial value $M_z(0)$ due to RF depletion and T_1 relaxation. *iii.* Following acquisition, data are divided into high- and low-frequency components, and two temporally resolved data subsets are constructed from low frequency data. The low-frequency Nyquist radius for two keys is depicted by the yellow dots. *iv.* Low frequency keys are inserted into the high frequency keyhole to create two fully sampled datasets. *v.* High frequency keyhole data are scaled by the average value of k_0 to mitigate blurring artifacts. *vi.* Images are reconstructed from both keyhole data sets. *vii.* The ratio of key signal intensities are calculated from which C_I can be trivially calculated. *viii.* Attenuation maps are calculated using Eq. 7.

Figure 2.

Simulated radial keyhole imaging. (a) Digital Shepp-Logan Phantom. (b) Reconstructed image after radial k-space sampling. (c) Image reconstructed from Key 1. (d) Image from Key 2. (e) Applied decay pattern with signal attenuated view-to-view following Eq. 2. Flip angle increases from 1° to 3° (top to bottom), and T_1 increases from 10 s to 30 s (left to right). (f) Decay map with the same color scale as (e) extracted following Eq. 6. (g) Ratio of Key 2 to Key 1 signal intensity. (h) Map of fraction signal attenuation calculated using Eq. 7. (i) Image corrected for RF depletion and T_1 relaxation using Eq. 8. (j) Correlation of mean extracted C_1 from within each region of the grid in (b) vs. the regional C_1 value used in the simulation. Line is a linear, least-squares fit to the data, and vertical bars are standard deviations. (k) Flip angle obtained from the ratio of corrected image to original digital phantom plotted vs applied flip angle. Small circles are means of flip angle from each different decay region while large circles are means of lines of constant α . Line shows a linear, least-squares fit to the data. Vertical bars are standard deviations.

Figure 3.

Signal decay in HP ^{129}Xe phantoms. Note, $T_1 \sim 2$ hours, and can therefore be neglected during the 15 s image acquisition [i.e., $C_1 \approx \cos(\alpha)$]. Representative (a) Key 1 and (b) Key 2 images obtained at 3T and at 7T with SNR shown below images. (c) Ratios of Key images and (d) flip angle maps calculated using Eq. 6. Nominal global flip angles and the field strength are shown at the top of each column. (e) Correlations between mean extracted flip angle and global fitting to Eq. 2 are shown for 3T and 7T data. The dotted line shows the line $y = x$. Horizontal bars are fitting errors, and vertical bars are standard deviations. (f) Bland-Altman plot comparing global flip angle extracted from the decay of k_0 point on each FID and mean flip angle from the keyhole-derived maps for all phantom images measured. Green horizontal lines are 95% confidence intervals.

Figure 4.

Signal decay correction. **(a)** Representative axial slices from radial images measured with the small dual-loop coil and reconstructed from all of k-space are shown from a healthy subject and a CF patient. **(b)** Decay and **(c)** attenuation maps corresponding to (a) calculated from Eqs. 6 and 7. **(d)** Signal corrected images obtained by combining (a) and (c) according to Eq. 8.

Table 1.

Global and mean extracted values of key ratio, decay, and attenuation for each of the subjects studied via HP ^{129}Xe radial MRI.

Subject	Gas Volume Delivered	Applied RF Flip Angle	Key 1 : Key 2 SNR	Mean S_2/S_1 $\pm$ Std. Dev	Global C_1	Mean Extracted C_1 $\pm$ Std. Dev.	Mean Fractional Signal Attenuation $\pm$ Std. Dev.
30 y.o. H Female	1.00 L	1.0°	13.9:13.7	0.61 ± 0.10	0.99969	0.99972 ± 0.00008	(37 $\pm$ 14)%
30 y.o. H Female	1.00 L	1.5°	10.7:10.8	0.48 ± 0.09	0.99954	0.99959 ± 0.00008	(48 $\pm$ 12)%
11 y.o. H Male	0.77 L		12.7:16.3	0.52 ± 0.11	0.99938	0.99963 ± 0.00012	(44 $\pm$ 13)%
14 y.o. H Male	0.93 L		19.6:25.8	0.55 ± 0.11	0.99946	0.99965 ± 0.00012	(42 $\pm$ 15)%
7 y.o. H Female	0.40 L		21.9:25.3	0.53 ± 0.10	0.99943	0.99964 ± 0.00010	(44 $\pm$ 9)%
15 y.o. CF Female	0.75 L		14.6:17.8	0.56 ± 0.17	0.99949	0.99964 ± 0.00013	(42 $\pm$ 13)%
18 y.o. CF Male	0.82 L		4.5:5.0	0.45 ± 0.12	0.99928	0.99947 ± 0.00019	(53 $\pm$ 11)%