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MRI-based blood oxygen saturation measurements in infants and children with congenital heart disease

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Abstract *Background*: Vessel oxygen saturation can be determined with MR oximetry using an in vivo measurement of signal decay (T2) and the calibration curve relating T2 to blood oxygen saturation ($\%HbO_2$), where: $1/T2 = 1/T2O + K(1–\%HbO_2/100)^2$ and K is a constant parameter which correlates with measured fibrinogen levels. The ability to noninvasively measure $\%HbO_2$ in cardiac chambers and vessels has enormous potential in children with congenital heart disease (CHD). *Objective*: The purpose of the study was to prospectively characterize the T2–$\%HbO_2$ relationship in infants where T2–$\%HbO_2$ is the realtionship between T2 and $\%HbO_2$ (blood oxygen saturation) expressed by the equation given above, and to determine whether adult values for K and T2O (where T2O is the T2 of fully oxygenated blood) can be extrapolated to pediatric patients with CHD. A second objective was to apply this method to calculate the $\%HbO_2$ in vivo using MR imaging in infants with CHD. *Materials and methods*: Fifteen patients with CHD undergoing cardiac catheterization (9 male; 6 female), median age 8 months, were recruited for the calibration study. T2O and K were measured directly from blood samples, compared with the values estimated from adult population statistics, and plotted against hematocrit and fibrinogen, respectively. In four studies of infants with CHD, T2 measurements were converted to $\%HbO_2$ using the calibration curve. *Results*: The T2–$\%HbO_2$ relationship in infants correlated with the adult calibration statistics (1/T2O vs. hematocrit, $r = 0.77$; K vs. fibrinogen, $r = 0.61$). Our initial in vivo studies demonstrated that the MR oximetry reflected the expected oxygen saturations. *Conclusion*: Adult values for T2–$\%HbO_2$ calibration can be used to measure blood oxygen saturation in vivo in children with CHD.

Keywords MR oximetry · Congenital heart disease · Blood oxygen saturation

Introduction

Blood vessel oxygen saturation, once measured only in the cardiac catheterization laboratory, can now be determined using the magnetic resonance (MR) oximetry technique [1, 2, 3]. Studies have shown that the T2 relaxation time of hydrogen in whole blood is directly related to the blood's oxygen saturation ($\%HbO_2$) [4, 5].

In normal healthy adults and those with congenital heart disease (CHD), the $\%HbO_2$ can be determined with MR oximetry using an in vivo blood T2 measurement

together with an empiric calibration curve, which depends on two parameters, K and T2O, where $1/T2 = 1/T2O + K(1–\%HbO_2/100)^2$ (Eq. 1). Typically, the parameters determining this relationship are measured directly from measured values of 1/T2 in samples of a subject's blood, which is oxygenated to various levels of $\%HbO_2$ in test tubes. A straight line is fit by plotting 1/T2 against $(1\text{-}HbO_2/100)^2$. This yields K as the slope and 1/T2O as the intercept.

The calibration technique is time consuming, prone to error, and requires a significant amount of blood (up to 15 cc), making it unsuitable for routine use in the pediatric age group.

Ideally, the relationship could instead be determined based on an understanding of the physics underlying the T2 dependence on oxygen saturation. This dependence can be explained as follows: 1/T2 describes the rate of signal decay. As the $\%HbO_2$ decreases, paramagnetic deoxyhemoglobin increases, perturbing the local magnetic field around red blood cells. Greater field perturbation leads to faster signal dephasing and hence, signal decay. The parameter K describes the strength of this effect. This parameter is typically determined by field strength and the intrinsic nature of the hemoglobin molecule.

In a recent survey of factors affecting K from measurements on the blood of 135 adults, fibrinogen concentration in blood (Fb) was found to correlate strongly with K although the physical source of this relationship is not understood. The parameter 1/T2O was also found to vary in a linear fashion with hematocrit (HCT), and describes the rate of signal decay without the effects of deoxyhemoglobin. The rate of signal decay is dominated by the concentration of macromolecules in the solution. This explains the effect of HCT: increasing the HCT increases the relative concentration of large proteins in blood. Thus, in adults, the T2–$\%HbO_2$ relationship for a 1.5-T GE Signa MR system can be determined from simple measurements of Fb and HCT from a blood laboratory [6]. The effects of HCT and Fb on 1/T2O and K have not yet been validated in the pediatric age group.

The primary objective of the study was to determine whether adult values for K and T2O could be extrapolated to pediatric patients with CHD, and whether K and T2O in children have the same linear relationship with Fb and HCT. We assumed that the majority of fetal hemoglobin has disappeared in infants by the age of 3–6 months, and therefore the previously validated values for K and T2O would be applicable in the infant population [7]. The secondary objective of the study was to prospectively measure the $\%HbO_2$ in vivo in infants with complex CHD in various vessels and chambers of the heart, and to compare the findings with both cardiac catheterization and pulse oximetry data.

Methods

Part 1: in vitro calibration

A total of 15 patients between 4 months and 3 years of age who were undergoing a diagnostic or interventional cardiac catheterization study at the Hospital for Sick Children were included in the study. All patients had a diagnosis of CHD or had undergone cardiac transplantation. All patients were under general anesthesia. Patients were excluded from the study if they weighed less than 5 kg, or if their parents had not given informed consent. The study was approved by the Hospital for Sick Children Research Ethics Board.

Data including patient age, sex, height, weight, underlying cardiac diagnosis, and previous surgical procedures, as well as baseline serum hemoglobin and HCT were recorded. Each patient had a sample of blood taken from the in situ venous catheter at the time of the catheterization study. A total of 8 cc of blood was drawn in patients who weighed between 5 and 7 kg; 10 cc of blood was drawn in patients who weighed more than 7 kg. The blood sample was packed on ice in a heparinized syringe.

The blood samples were divided into five test tubes and oxygenated to various levels (40–90%), immersed in a water bath at body temperature (36.7°C), and placed in a 1.5-T GE Signa MR scanner (GE Medical Systems, Milwaukee, Wis., USA). T2 for each sample was then measured using the same sequence used for in vivo T2 measurements [8]. Specifically, the sequence developed T2 weighting in a magnetization preparation interval with a nonselective 90° excitation, a train of refocusing 180° pulses separated by a refocusing interval of 24 ms, and a –90° pulse returning magnetization of the longitudinal axis. This T2-weighted magnetization is then excited with a slice-selective pulse followed by signal acquisition with position encoding via spiral gradient trajectories. The typical resolution is 1.5 mm in plane and 7 mm through plane over a 20-cm field of view. With repositioning of the magnetization preparation approximately every 1.5 s (cardiac-gated in vivo with respiratory motion compensation), a typical acquisition required about 4 min [9]. T2 decay constants were measured using images with four different T2 weightings corresponding to 12, 58, 105, and 198 ms of decay.

Hemoglobin (g/l), HCT (l/l), and Fb (g/l) levels were determined by standard hospital blood laboratory tests. The T2O and K values were determined for each sample from a least squares fit of Eq. 1. An estimated value for T2O (1/s) and K (1/s) was then computed for each patient based on the adult calibration curve data, adjusted for hemoglobin and HCT.

Statistical analysis

All values for estimated and measured T2O, K, as well as hemoglobin, HCT, and Fb were expressed as a mean ± SD. The quality of data fits to estimate blood T2 values and to estimate K and T2O were evaluated with chi-square analysis.

The relationship between T2O and HCT, and K and Fb, was determined and compared with previously published adult data from the same institution using an analysis of variance on regression parameters. Similarly, the correlation between measured K and T2O and estimates from adult data was established. A difference between the estimated T2O or K and the measured T2O or K of 10% or less was considered acceptable, as determined by the effect on $\%HbO_2$ accuracy.

Part 2: in vivo demonstration

In the second part of the study, four patients, median age 5.2 months (range 3.2–7.6 months), with complex CHD were recruited as part of an ongoing prospective cardiac MR study at the same institution between January 2000 and April 2000. The cardiac diagnoses included tricuspid atresia s/p right Blalock-Taussig

($n=1$), unrepaired tricuspid atresia with pulmonary stenosis ($n=1$), double outlet right ventricle s/p Norwood I ($n=1$), and hypoplastic left heart syndrome s/p bidirectional Glenn ($n=1$).

All patients had undergone a cardiac catheterization study under general anesthesia in room air within 2 weeks of the MR study. During the catheterization study, oxygen saturations in the vessels of interest were obtained directly from a blood sample via a venous catheter, including the superior vena cava, ascending aorta, and main pulmonary artery and left atrium when possible.

For the MR study, patients were sedated with either oral chloral hydrate (dose of 80 mg/kg) if less than 6 months of age, or sedated with intravenous Nembutal (dose of 5 mg/kg) if over 6 months of age, and were placed in a 1.5-T GE Signa MR scanner (GE Medical Systems, Milwaukee, Wis., USA). Pulse oximetry oxygen saturations were monitored in room air for the duration of the study. A series of T2-weighted images with different echo times were obtained from two axial imaging planes; one showing the cross sections of the ascending aorta, main pulmonary artery, and superior vena cava, and the other traversing the middle of the left atrium. The MR sequences used for the second part of the study were identical to those used for the in vitro calibration part of the study. All images were acquired with cardiac gating and respiratory compensation to minimize motion artifact. A slice thickness of 4 mm was used. T2 was measured for each of the four regions of interest using a weighted least squares fit to the T2-weighted signals. The oxygen saturation for each vessel was then determined by choosing the region of interest and fitting the acquired intensity data to an exponential decay, yielding an estimate of the time constant, T2. Using the adult in vitro calibration data adjusted for measured HCT, the $\%HbO_2$ was determined [8]. Oxygen saturation measurements were taken in the superior vena cava, main pulmonary artery, ascending aorta, and left atrium.

Statistical analysis

The T2 blood oxygen saturation was then compared with the oxygen saturation obtained during the patient's cardiac catheterization study using the paired t test and regression analysis.

Results

Part 1

A total of 15 patients (9 male; 6 female), median age 8 months (range 4–60 months), were enrolled in the study between August 1999 and December 2000. The underlying cardiac diagnoses included: atrial septal defect ($n=2$); complex single ventricle s/p bidirectional cavo-pulmonary anastomosis ($n=4$) and s/p right Blalock-Taussig shunt ($n=3$); transposition of the great arteries s/p repair ($n=1$); truncus arteriosus s/p repair ($n=1$); Tetralogy of Fallot s/p repair ($n=1$); s/p patent ductus arteriosus coil occlusion ($n=1$); and there were two postcardiac transplantation patients.

The measured hemoglobin, HCT, Fb, K, T2O, as well as K and T2O estimated from adult relationships are shown in Table 1. There was a statistically significant relationship between T2O and HCT, as shown in Fig. 1a, that plots 1/T2O against HCT using the linear fit equation: $1/T2O = 1.17(\pm 0.043) + 5.87(\pm 1.24)$ HCT. We compared this to the adult linear fit equation for 1/T2O vs. HCT: $1/T2O = 1.2(\pm 0.316) + 6.5(\pm 0.75)$ HCT (Fig. 1b). The r value for the pediatric data set was 0.77, compared with an r value of 0.604 using the adult data [6].

The value for K was then plotted against Fb, again using a linear fit equation (Fig. 2a, b). The r value was less significant than the r value for T2O vs. HCT, but was nonetheless significant ($r=0.61$ vs. adult $r=0.623$). There was also a higher variability in the K–Fb fits in children, where $K = 74.98(\pm 11.34) – 16.61(\pm 6.04)$ Fb vs. adult $K = 66.29(\pm 3.28) – 10.59(\pm 1.38)$ Fb.

Part 2

A total of seven oxygen saturation measurements from cardiac catheterization and T2 MR were available from four patients. The results of the T2 MR and cardiac catheterization are shown in Table 2. The T2 measurements of oxygen saturation strongly correlated with the cardiac catheterization measurements ($r=0.9$; $p=0.01$).

An example of a T2 data set in a child with CHD is shown in Fig. 3.

Table 1. Measured hemoglobin (*Hgb*), hematocrit (*HCT*), fibrinogen (*Fb*), K and T2O (*M* male, *F* female)

Patient number	Age (months)	Sex	Measured K (1/s)	Measured T2O (1/s)	Hgb (g/l)	HCT (l/l)	Fibrinogen (g/l)	Estimated K (1/s)	Estimated T2O (1/s)
1	60	F	46.937	287.4	119	0.348	1.7	48.279	287.272
2	72	M	43.317	299.5	114	0.334	1.9	46.160	293.392
3	48	F	38.943	263.9	119	0.348	1.7	48.279	287.272
5	8	M	52.767	256.2	163	0.48	1.8	47.219	229.572
7	6	F	59.395	325.5	131	0.382	1.3	52.517	272.410
8	6	M	21.883	372.2	75	0.243	2.2	42.981	333.170
9	6	M	48.292	339.9	114	0.333	2	45.100	293.829
10	12	M	39.33	273.3	130	0.377	2	45.100	274.596
11	6	M	52.526	277.6	146	0.419	1.3	52.517	256.237
12	4	F	48.447	323.4	131	0.401	2	45.1	264.105
13	7	M	39.69	353.7	92	0.265	2.1	44.041	323.553
14	10	F	44.88	325.2	109	0.323	1.9	46.160	298.200
15	10	F	37.32	336.8	98	0.278	1.8	47.219	317.871
Mean	19.62		44.133	310.354	118.4	0.347	1.823	46.975	287.739
SD	23.63		9.283	36.603	22.503	0.065	0.274	2.907	28.363

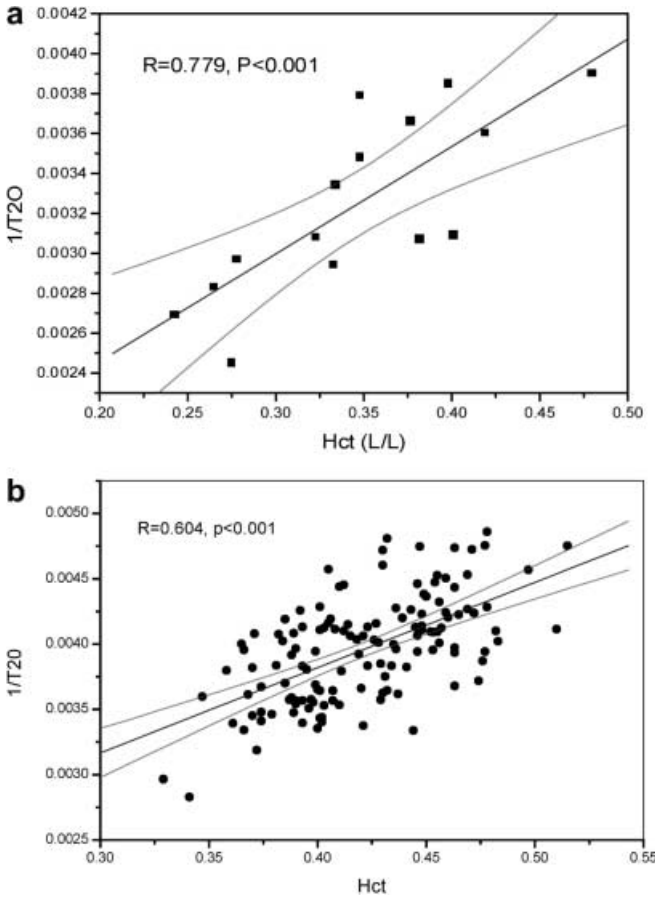

Fig. 1. **a** 1/T2O (*1/s*) vs. hematocrit (*Hct*, *l/l*) relationship in children. **b** 1/T2O (*1/s*) vs. hematocrit (*l/l*) relationship in adults [1]

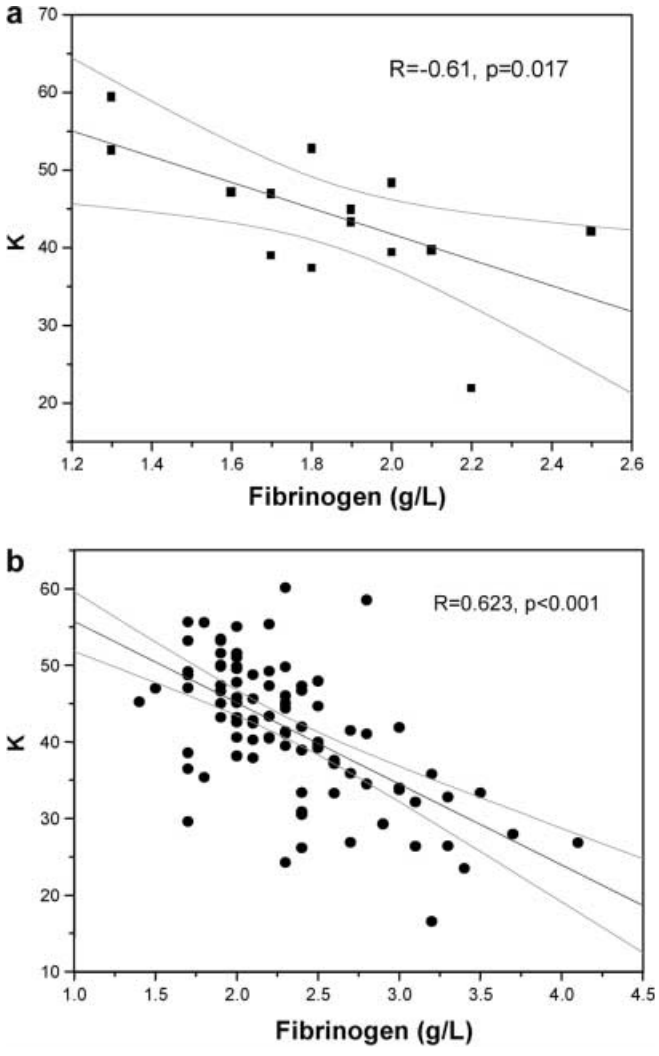

Fig. 2. **a** K (*1/s*) vs. fibrinogen (*g/l*) relationship in children. **b** K (*1/s*) vs. fibrinogen (*g/l*) relationship in adults [1]

Discussion

This study is the first to measure vessel oxygen saturation using T2 MR oximetry in children. It is also the first to establish normal values for K and T2O in children with CHD. We demonstrated that, as with adults, there is a strong correlation between 1/T2O and HCT. There was no statistically significant difference in the corresponding calibration parameters in infants and children with CHD compared to parametric values in adults. An estimated value for T2O can therefore be obtained if the HCT of the patient is known. We believe that the adult equation to estimate T2O can be used in infants older than 3 months and in children. However, the equation to estimate the value of T2O may not be applicable in newborns in whom blood characteristics are different from those of adults and older children, given the higher concentration of fetal hemoglobin. Further study is necessary to evaluate the effect of fetal hemoglobin on T2O in this population.

There was only a weak correlation between K and Fb when we compared the pediatric with the adult data. However, the range of Fb values in the pediatric population (1.3–2.5 g/l) was substantially smaller than in the adults (1.3–4.1 g/l). The wider range of Fb levels in

Table 2. Comparison between T2 MR blood oxygen and cardiac catheterization blood oxygen measurements (*SVC* superior vena cava, *LA* left atrium, O_2 oxygen)

Location	MR O_2 saturation (%)	Catheterization O_2 saturation (%)
SVC	50	55
	63	51
Aorta	75	81
	88	94
	69	74
	68	
LA	70	73
r value		0.909
p value		0.012

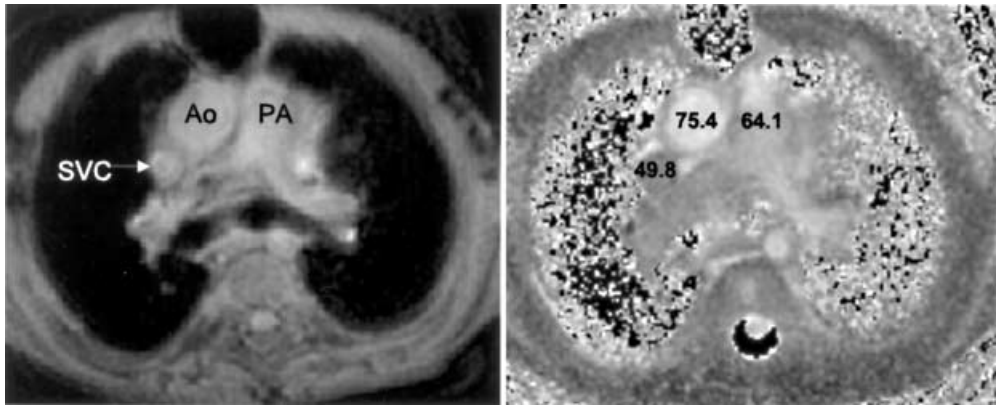

Fig. 3. T2 map for three major vessels from a child with tricuspid atresia and pulmonary stenosis. The ascending aorta (*Ao*) has the brightest signal intensity indicating the highest oxygen saturation. The superior vena cava (*SVC*), on the contrary, has the lowest signal intensity because of its low oxygen saturation level. *PA* main pulmonary artery

adults is influenced primarily by the women in the cohort. We hypothesize that the higher Fb levels found in women are due to hormonal effects. In our prepubertal series of patients, these hormonal effects do not occur. Based on the narrower range of Fb levels found in children, we therefore suggest that a constant value for K (43.73 1/s), for a refocusing interval of 24 ms, can be used in children younger than 12 years. For children older than 12 years, we suggest that the K value should be adjusted for Fb levels, as in adults [6].

The measurement of blood oxygen saturation is frequently used to determine the cardiac output and the degree of vascular shunting across the pulmonary bed and chambers of the heart. The potential for a noninvasive measurement of oxygen saturation in the blood vessels and chambers of the heart has tremendous implications for infants and children with various forms of CHD, especially children with more complex CHD, such as those with single ventricle physiology. At present, children with complex CHD requiring palliative surgery need multiple cardiac catheterizations in the first few years of life to delineate anatomy, measure pressures and resistance, and measure vessel oxygen saturation. The measurement of oxygen saturation in the various chambers and vessels of the heart serves to quantify the degree of intracardiac shunting, to diagnose important systemic venous or arterial collateral vessels, and to determine the cardiac output and pulmonary blood flow. With standard values for T2O and K, we can proceed to in vivo estimates of vessel oxygen saturation in children. Validating this noninvasive technique will potentially preclude the need for cardiac catheterization in certain situations, and will thus avoid the risks associated with cardiac catheterization, including stroke, hemorrhage, and thrombosis [10].

A larger, prospective study is currently underway at our institution to determine the accuracy of vessel oxygen measurement by T2 MR compared with cardiac catheterization and pulse oximetry in children with complex CHD.

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