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Research Article

Blood Oxygenation Can be Detected Using a T2 Preparation Pulse

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Abstract

Aim: So far, invasive procedures, such as heart catheterization, are state of the art to investigate blood oxygenation levels in humans. For patients who suffer of chronical heart disease and renal failure BOLD (blood oxygenation level dependent) is an effective, but still frail imaging method. This study aimed to validate the use of Magnetic Resonance Imaging (MRI) with a dynamic T2 preparation pulse and a weighted subtraction afterwards as a competitive imaging method to assess blood oxygenation in a phantom and healthy volunteers.

Methods: MRI was performed with a dynamic T2 preparation pulse followed by a weighted subtraction of the dynamic T2 sequences to investigate different blood oxygenation levels in an Extracorporeal Membrane Oxygenation (ECMO) pump (phantom). Afterwards, healthy volunteers (age 30 to 45 years without chronic disease) were enrolled and imaged with identical cardiac MRI protocols. Finally, we compared the oxygenation levels obtained with Blood Oxygenation Level-Dependent (BOLD) imaging and bedside gas analysis with those obtained with the dynamic T2 preparation pulse.

Results: The Signal-to-Noise Ratios (SNRs) of the subtracted images acquired with the T2 preparation pulse sequence for both the phantom and 19 healthy volunteers (mean age 25 ± 10 years) were significantly negatively correlated with the oxygenation level assessed by BOLD imaging (r = -0.6479, p = 0.0227 and r = -0.7754, p < 0.003, respectively). The phantom's Contrast-to-Noise Ratio (CNR) and the healthy volunteers' CNRs and SNRs in the ascending aorta and pulmonary artery measured on the T2 images were significantly correlated with the oxygenation level measured by blood gas analysis (p < 0.05). The BOLD imaging and blood gas analysis measurements of the oxygenation level were significantly negatively correlated (r = -0.965, p < 0.008), and the oxygenation levels in the pulmonary artery measured with BOLD imaging demonstrated a positive association with that as assessed by blood gas analysis (p < 0.05).

Conclusion: Non-invasive measurement of blood oxygenation using a dynamic T2 preparation pulse is feasible in healthy patients. Unlike existing state-of-the-art methods involving invasive measurements, this method does not require the use of radiation or contrast agents, thus critical patients with renal failure, could be investigated by cardiac MRI in a competitive method to BOLD. Further work is necessary to validate this technique in a clinical setting.

Translational Perspective: The dynamic T2 preparation pulse MRI sequence is able to distinguish between oxygenated and deoxygenated blood with little effort without the need for radiation or contrast agents and can therefore be implemented in clinical settings.

Abbreviations

ECMO: Extracorporeal Membrane Oxygenation; SNR: Signal-to-Noise Ratio; CNR: Contrast-to-Noise Ratio; BOLD: Blood Oxygenation Level-Dependent

Introduction

Patients with acute heart failure often suffer from peripheral hypoperfusion, which can lead to organ injury and final to renal impairment [1]. To assess the heart and the great vessels for oxygen saturation, combined left and heart coronary angiography is often performed, and blood gas analysis is needed to assess blood oxygen saturation in the great vessels. However, these methods put the patient at increased risk for radiation exposure and bleeding [2]. Non-invasive alternatives without the use of contrast agents would be especially useful for patients with renal failure [3]. In principle, Cardiac Magnetic Resonance Imaging (MRI) may be a good option for such patients and has some desirable advantages; there is no risk of radiation or bleeding, and therefore the scan is not harmful. Blood Oxygenation Level-Dependent (BOLD) imaging is one example of cardiac MRI that leverages the different magnetic susceptibilities of oxygenated and deoxygenated blood. However, this method is still criticized because of its low signal-to-noise and contrast-to-noise ratios [4], which are frequently used parameters for signal evaluation on MRI. Nonetheless, BOLD was used for the detection of viable myocardium with impaired left ventricular contraction [5] and BOLD has been used to assess myocardial oxygenation in severe aortic stenosis [6]. A short while ago, Wen et al have used

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QSM (quantitative susceptibility mapping) successfully for the detection of mixed venous saturation in heart chambers [7]. This technique was developed for quantifying the spatial resolution of magnetic susceptibility within biological tissue. QSM has its limits at background field removal [8].

Also, T2 mapping was used to visualize different blood oxygenation levels via cardiac MRI in patients with cardiovascular diseases whilst utilizing multiple T2 measurements with different inter-echo pulse spacings [9]. However, whether this method is flow-independent and thus delivering constant measurements in all cardiac structures still needs to be discussed in detail. Thus, T2 preparation MRI, a flow-independent method with sufficient signal and adequate signal-to-noise and contrast-to-noise differences, was introduced for the non-invasive assessment of oxygenation [10]. In this method, a weighted subtraction of an image acquired with a dynamic T2 preparation pulse from an image acquired without T2 preparation is performed [11]. A dynamic T2 preparation pulse is easy to use during daily clinical routine and is therefore a competitive imaging method for detection of oxygen saturation. Rodriguez-Soto et al used balanced Steady-State Free Precession (bSSFP) with a T2 preparation pulse to quantify whole-blood oxygenation at a field strength of 1.5 T in healthy volunteers compared to blood gas analysis [12]. Still, a dynamic T2 preparation pulse with dynamic implementation was not yet used for the analysis the blood oxygenation levels of the great vessels. Here, we aimed to investigate the ability of a dynamic T2 preparation pulse to measure blood oxygenation in the cardiac vessels of a proxy system, an Extracorporeal Membrane Oxygenation (ECMO) device as a phantom, and healthy volunteers, employing BOLD MRI and a bedside blood gas analyser as standards for comparison.

Results

Phantom Study

The scanned tubes of the extracorporeal membrane oxygenation were compared to blood gas analysis. They showed good correlation compared to blood gas analysis after weighted subtraction (B-1,8A) (Figure 1). Also, the correlation between the Signal-to-Noise Ratio (SNR) obtained with the T2 preparation pulse and oxygen saturation (SaO2) in ECMO. A) SNR *vs.* SaO2 with the dynamic T2 preparation pulse (r = -0.6479). B) SNR *vs.* SaO2 without the dynamic T2 preparation pulse (r = -0.7754, p < 0.003) (Figure 2).

Study Population

We recruited 19 healthy volunteers (age 30 to 45 years without chronic disease). They were scanned with a dynamic T2 preparation pulse with weighted subtraction. Afterwards, SNR and CNR analyses of the images were compared with oxygen saturation.

SNR and CNR Analyses

The SNR in the phantom's and volunteers' subtracted images for the T2 preparation pulse were significantly negatively correlated with the level of oxygenation assessed by blood gas analysis (r = -0.6479, p < 0.0227, respectively; (Figure 2A). r = -0.7754, p < 0.003 (Figure 2B). The CNR and SNR in the ascending aorta and pulmonary vessels of the healthy volunteers were correlated with oxygen saturation (p < 0.05; (Figure 3)) [13]. Furthermore, the BOLD imaging and blood gas analysis measurements of oxygenation level were significantly correlated (r = -0.965, p < 0.008), and BOLD imaging in the pulmonary artery was correlated with the oxygenation level as assessed by blood gas analysis (p < 0.05). Additionally, the SNR in the ECMO images tended to correspond to the level of oxygenation, but not to a statistically significant degree (p < 0.097). The ECMO and healthy volunteer CNRs and SNRs were significantly correlated with the level of oxygenation as measured by blood gas analysis (p < 0.05).

However, the BOLD-based oxygenation level was significantly correlated with SNR in the ascending aorta (p < 0.008) and in the pulmonary artery (p < 0.05) (Figure 3). While using the dynamic T2 preparation pulse technique in healthy volunteers, we obtained different findings between images acquired in systole or in diastole (Figure 4A,B). For images acquired in diastole, the descending aorta remained dark, indicating that there was no

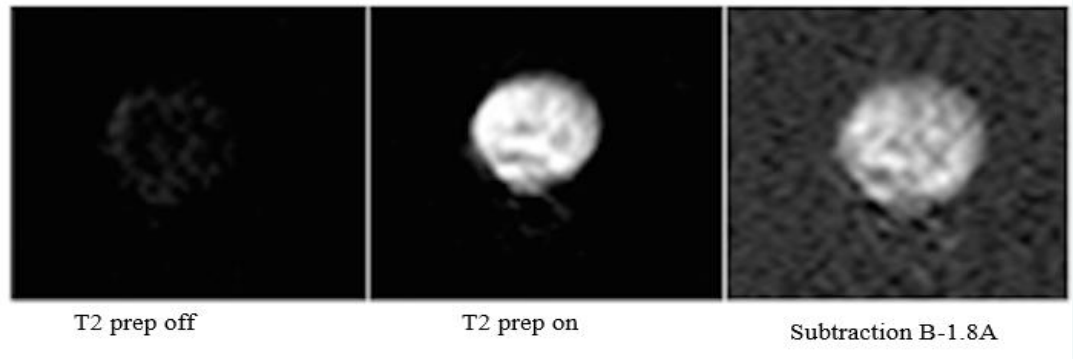

Figure 1 Cross-section images of an ECMO tube obtained
A. without the T2 preparation pulse and
B. with the T2 preparation pulse, as well as
C. the subtraction image (B-1.8A).

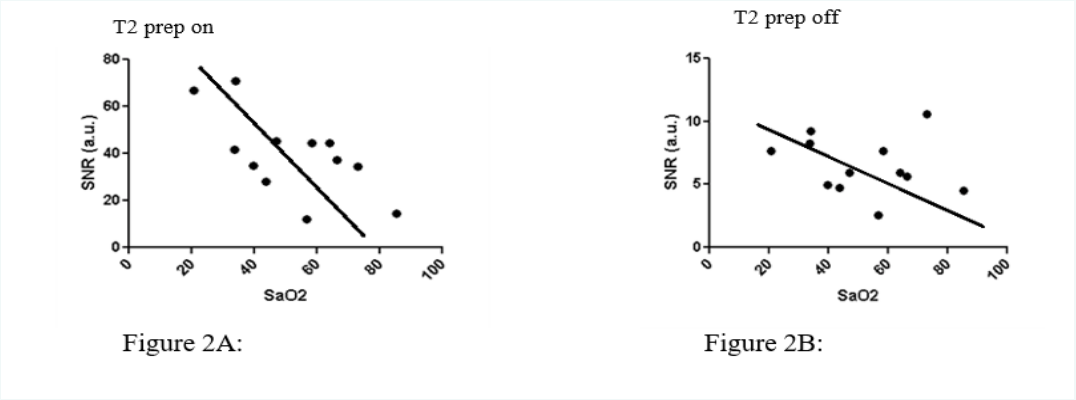

Figure 2 Correlation between the Signal-to-Noise Ratio (SNR) obtained with the T2 preparation pulse and oxygen saturation (SaO2) in the phantom.
A. SNR *vs.* SaO2 with the dynamic T2 preparation pulse (r = -0.6479).
B. SNR *vs.* SaO2 without the dynamic T2 preparation pulse (r = -0.7754, $p < 0.003$).

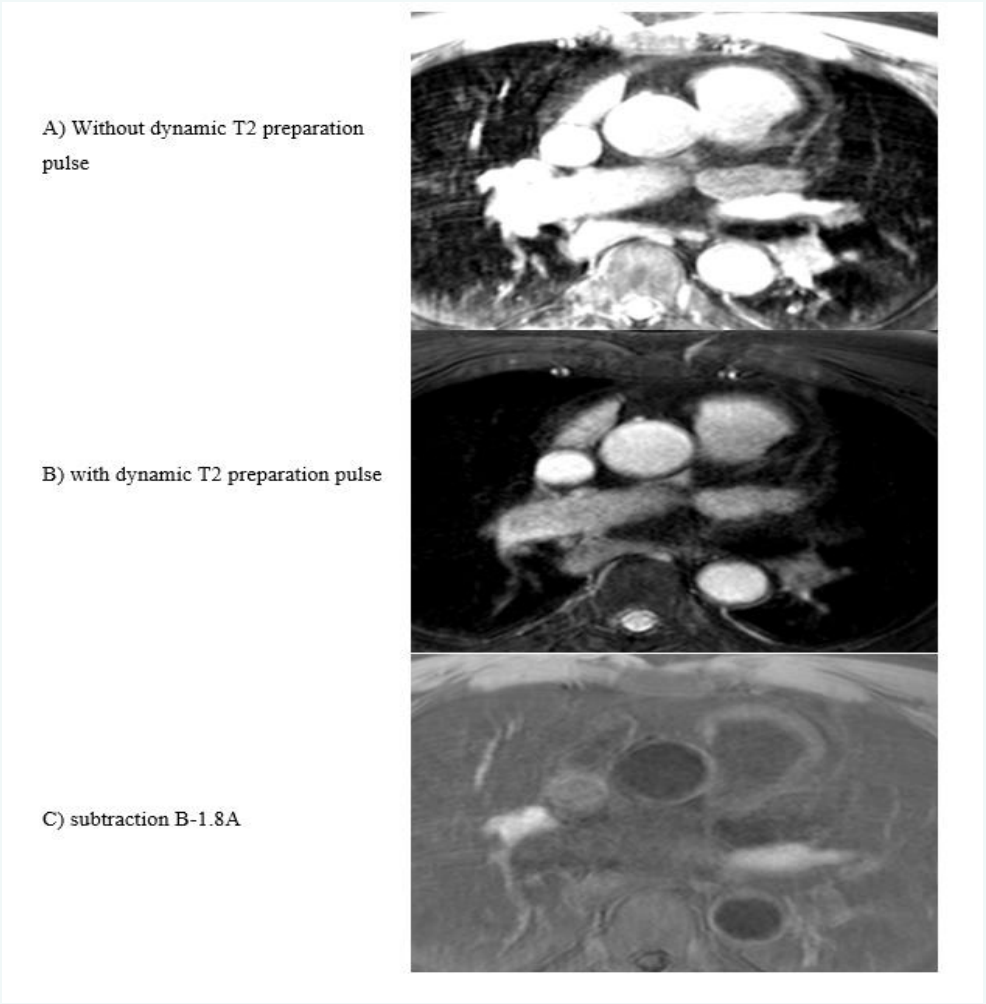

Figure 3 Images of the great arteries in healthy volunteers
A. without dynamic T2 preparation pulse,
B. with dynamic T preparation pulse and
C. with weighted subtraction (B-1.8A).

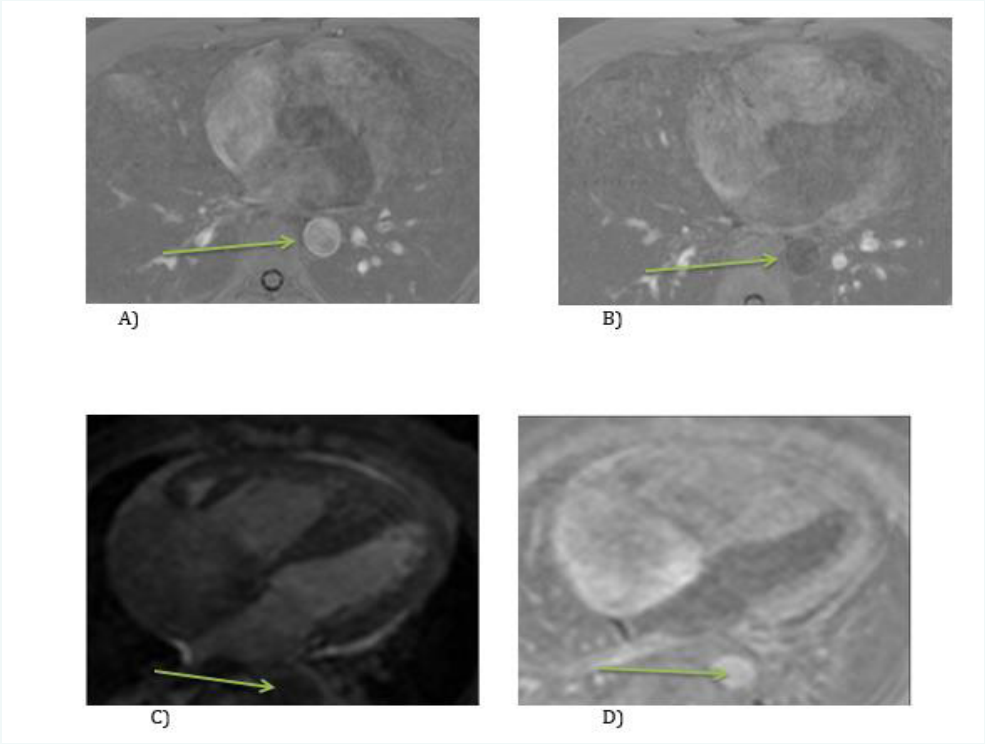

Figure 4 A. Subtracted image of a healthy volunteer acquired in systole (arrow, descending aorta) in SSFP.
B. Subtracted image of the same volunteer acquired in diastole (arrow, descending aorta) in SSFP.
C. Unsubtracted image in systole with T2 preparation pulse on in gradient echo (arrow, descending aorta).
D. Unsubtracted image in systole with T2 preparation pulse off in gradient echo (arrow, descending aorta).

flow dependency of the dynamic T2 preparation pulse (green arrow in (Figure 4)). For images are acquired in systole, there appeared to be a flow dependency of the operated dynamic T2 preparation pulse, as the descending aorta became bright. There were no statistically relevant differences whether the images were acquired with SSFP (Figure 4A,B) or with a gradient echo sequence (Figure 4C,D). Under conditions of constant flow, as in the ECMO tubes, the SNR remained relatively stable. Regarding the CNRs compared to blood oxygenation levels, there were no statistically relevant differences for either the phantom scan (ECMO) or the healthy volunteers.

Discussion

In this study, we demonstrated a correlation between both the SNR and CNR from images acquired with a T2 preparation pulse and the oxygenation levels analysed with blood gas analysis for bedside diagnosis in phantom MRI scans. These results demonstrate that blood oxygenation can be feasibly detected by using a dynamic T2 preparation in cardiac MRI without the need for more invasive measurements of blood oxygenation levels. Compared with BOLD-imaging, our T2 preparation technique demonstrated stable results. Recently, T2 mapping approaches for detection of blood oxygenation levels achieved impressive results [9]. Whether T2 mapping is a flow-independent method or robust for partial volume effects remain unclear. Additionally, diseases of the cardiac muscle might influence the incoming signal when using a T2 mapping method. Mapping tissue inhomogeneity was already described during acute myocarditis [14]. Although we have seen our limitations with images acquired in systole with a dynamic T2 preparation pulse due to flow dependency, we have created a competitive method, which is easy and fast to use during daily clinical routine in diastole for the heart as well as the great vessels.

As Rodriguez-Soto et al used balanced Steady-State Free Precession (bSSFP) with a T2 preparation pulse to quantify whole-blood oxygenation at a field strength of 1.5T in healthy volunteers compared to blood gas analysis, they have not investigated the blood oxygenation of the great vessels [11]. A dynamic T2 preparation pulse can provide accurate, non-invasive assessments of blood oxygenation levels in patients because the SNR in the images acquired is well correlated with blood oxygenation levels in constant flow conditions. We like to transport our findings into a clinical setting. However, here we want to compare our images with further invasive measurements. Our findings fit into the bigger picture of scanning options without the use of contrast agent for patients with CAD and renal failure.

Methods

Phantom

The inner tubes of an ECMO perfusion system were scanned. The ECMO perfusion system consisted of a centrifugal pump, a

pressure-controlled biocompatible heparin-coated silicone-membrane oxygenator, Medos 7000LT (MEDOS Medizintechnik AG, Stolberg, Germany= and a heat exchanger. As pump was used a Levitronix CentriMag (Levitronix GmbH, Zurich, Switzerland). The ECMO flow was initiated with human blood at 1.5-2.0L/min and manually adjusted. The inner tubes of the ECMO device were placed into the scanner and were imaged via a three-dimensional gradient echo with a dynamic (on/off) T2 preparation pulse (voxel size 0.45 × 0.45 × 30 mm, flip angle 30°, echo time (TE) 2.9 ms, repetition time (TR) 9.9 ms, slice thickness 30 mm) on a 1.5-T scanner (Achieva, Philips, Best, the Netherlands) with a 32-channel coil. Oxygenation levels were manually changed (100%, 90%, 80%, 70% and 60%) in the inner tubes of the ECMO device, analysed using a standard bedside blood gas analyser (ABL 90 Flex, Radiometer, Brønshøj, Denmark) and correlated with the signal-to-noise and contrast-to-noise measurements of the MRI images. Previously, images were obtained by subtracting the T2 prep "on" images from the "off" images and the weighted subtraction at the scanner. A subtraction factor of 1.8 was used for the "on" images to obtain consistent blood signal subtraction (indicated as B-1.8A). Osirix software (version 5.9, Geneva, Switzerland) was used to measure signal intensity using the formula ($mean_{blood\ of\ the\ inner\ tube}$ - $mean_{air}$)/air_{StDev}. All inner tubes of the ECMO were quantitatively analysed to obtain the CNR and SNR using Osirix software (version 3.7.1). Regions of Interest (ROIs) were defined to determine the signal (S) from blood (S_{Blood}).

Study Population

19 healthy volunteers were prospectively recruited between January and December 2014 at the University Hospital of Duesseldorf, Germany. The study was approved by the Institutional Review Board (IRB) of the University of Duesseldorf and was conducted according to the Declaration of Helsinki. Informed consent was obtained, and exclusion criteria (chronic heart and kidney disease) were applied.

Cardiac MRI Protocol

Volunteers were scanned in supine position with a protocol identical to that used to scan the ECMO phantom above using either a gradient echo or SSFP sequence, and identical parameters were used for the dynamic T2 preparation pulse and BOLD imaging. The volunteers were scanned on a 1.5-Tesla scanner (Achieva, Philips Healthcare, Best, the Netherlands) with a 32-channel, five-element sensitivity encoding (SENSE) cardiac receiver coil. Patients were scanned in supine position. An initial survey and reference scan were obtained adjacent to the position of the imaging area to yield coil sensitivity maps. The imaging area include the thorax with the heart and lung areas. After this survey, either the end-systolic or end-diastolic cardiac rest period was identified using a high temporal resolution, balanced-SSFP, two-dimensional cine MRI sequence in a four-chamber view orientation (repetition time = 4.7 ms, echo time = 2.3 ms, flip angle = 70°, slice thickness = 10 mm, Field of View [FOV] = 400 mm). Either the mid-systolic or the mid-diastolic rest period was detected from the cine images and used to define the trigger delay and acquisition window for the dynamic T2 images.

Next, an Electrocardiogram (ECG)-triggered and navigator-gated dynamic T2-prepared, three-dimensional SSFP gradient echo sequence was applied. Multislice, multiphase cine imaging was performed using a standard SSFP pulse sequence in the short axis (slice thickness, 8 mm; gap, 0 mm; 76 phases; FOV 350 × 370 × 96 mm) covering the entirety of the left and right ventricles. Three-dimensional gradient echo with a dynamic T2 preparation pulse was acquired (voxel size, 1.3 × 1.3 × 4 mm; flip angle, 30°; TE, 1.4 ms; TR, 4.5 ms; 40 slices).

Cardiac MRI Analysis

The cine images were analysed on a Philips workstation to assess left and right ventricular volumes and myocardial mass. Endocardial and epicardial borders were manually contoured at end-diastole and end-systole, and the following formula was applied: (epicardial volume-endocardial volume × myocardial density [1.05g/cm^3]); the values were indexed to body surface area. Images were obtained by subtracting the T2 prep "on" images from the "off" images and the weighted subtraction at the scanner. A subtraction factor of 1.8 was used for the "on" images to obtain consistent blood signal subtraction (indicated as B-1.8A). Osirix software (version 5.9, Geneva, Switzerland) was used to measure signal intensity using the formula ($mean_{myocardium}$ – $mean_{air}$)/air_{StDev}. All cardiac chambers and great vessels of the volunteers were quantitatively analysed to obtain the CNR and SNR using Osirix software (version 3.7.1). Regions of Interest (ROIs) were defined to determine the signal (S) from blood (S_{Blood}) in the Left Ventricle (LV), Right Ventricle (RV), Pulmonary Artery (PA), ascending and descending aorta (Ao), and Pulmonary Veins (PVs) relative to that of the reference tissue ($S_{Myocardium}$). The (N) level in these regions was estimated according to the standard deviation of the respective ROIs. The CNR was defined with the following equation: CNR = (S_{Blood} -$S_{Myocardium}$)/(0.5 × [N_{Blood}+$N_{Myocardium}$]), where all variables are the means. The SNR was defined with the equation SNR = (S_{Blood})/(N_{Blood}) [13]. Image processing and reformatting were performed with commercially available analysis software (View Forum; Philips Healthcare). The subtracted images were analysed by two experienced viewers with more than five years of experience.

Blood Gas Analysis

A standard bedside gas analyser was used to obtain the oxygen saturation of the inner ECMO-tubes. For this reason, 2 ml of blood after every ten minutes were sampled for each oxygenation status (100% of oxygen saturation, 80% of oxygen saturation, 70% of oxygen saturation and 60% of oxygen saturation) and compared with the imaging results.

Statistical Analysis

Prism (version 5.0, GraphPad, San Diego, USA) was used to analyse signal intensity data and compare blood oxygenation levels with correlation analyses. It was performed in SPSS (version 2017, IBM, Armonk, USA). Subsequently, we treated $P < 0.05$ as statistically significant when performing the t-test for describing the relation of SNR and CNR to BOLD.

Ethical statement

All human studies have been approved by the appropriate ethics committee and have therefor been performed in accordance with the ethical standards laid down in the 1963 Declaration of Helsinki and its later amendments.

Author Contributions Statement

Britta Elkenhans wrote the main manuscript and conducted the experiments. Tinush Rassaf, Tarique Hussain, Gerald Greil and Rene Botnar supervised the study Markus Henningsson programmed the sequence. Ingmar Vieregge edited the manuscript.

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