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Right/Left Ventricular Blood Pool T2 Ratio as an Innovative Cardiac MRI Screening Tool for the Identification of Left-to-Right Shunts in Patients With Right Ventricular Disease

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Background: Left-to-right (L-R) shunts are characterized by a pathological connection between high- and low-pressure systems, leading to a mixing of oxygen-rich blood with low oxygenated blood. They are typically diagnosed by phase-contrast cardiac magnetic resonance imaging (MRI) which requires extensive planning. T2 is sensitive to blood oxygenation and may be able to detect oxygenation differences between the left (LV) and right ventricles (RV) caused by L-R shunts.
Purpose: To test the feasibility of routine T2 mapping to detect L-R shunts.
Study Type: Retrospective.
Population: Patients with known L-R shunts ($N = 27$), patients with RV disease without L-R shunts ($N = 21$), and healthy volunteers (HV; $N = 52$).
Field Strength/Sequence: 1.5 and 3 T/balanced steady-state free-precession (bSSFP) sequence (cine imaging), T2-prepared bSSFP sequence (T2 mapping), and velocity sensitized gradient echo sequence (phase-contrast MRI).
Assessment: Aortic (Qs) and pulmonary (Qp) flow was measured by phase-contrast imaging, and the Qp/Qs ratio was calculated as a measure of shunt severity. T2 maps were used to measure T2 in the RV and LV and the RV/LV T2 ratio was calculated. Cine imaging was used to calculate RV end-diastolic volume index (RV-EDVi).
Statistical Tests: Wilcoxon test, paired *t*-tests, Spearmen correlation coefficient, receiver operating curve (ROC) analysis. Significance level $P < 0.05$.
Results: The Qp/Qs and T2 ratios in L-R shunt patients (1.84 ± 0.84 and 0.89 ± 0.07) were significantly higher compared to those in patients with RV disease (1.01 ± 0.03 and 0.72 ± 0.10) and in HV (1.04 ± 0.04 and 0.71 ± 0.09). A T2 ratio of >0.78 showed a sensitivity, specificity, and negative predictive value of 100%, 73.9%, and 100%, respectively, for the detection of L-R shunts. The T2 ratio was strongly correlated with the severity of the shunt ($r = 0.83$).
Data Conclusion: RV/LV T2 ratio is an imaging biomarker that may be able to detect or rule-out L-R shunts. Such a diagnostic tool may prevent unnecessary phase-contrast acquisitions in cases with RV dilatation of unknown etiology.
Level of Evidence: 3
Technical Efficacy: Stage 2

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Congenital heart diseases (CHD) affect 6 to 8 per 1000 neonates worldwide.[1] Advances in diagnostic and therapeutic strategies result in higher survival rates, increasing the prevalence of adult CHD in the general population.[2] Some CHD are not diagnosed in early childhood, but at a later age when symptoms develop.[3] In this diverse cohort of CHD, left-to-right (L-R) shunts, including intra-cardiac (such as atrial and ventricular septal defects) and extra-cardiac defects (such as abnormal return of pulmonary veins), are the most prevalent.[4] L-R shunts are characterized by a pathological connection between high- and low-pressure systems, leading to a mixing of oxygen-rich blood from the left heart with low oxygenated blood from the right heart. Both intra- and extra-cardiac shunts lead to volume overload and consequent right and left heart dilatation and failure, pulmonary hypertension, and ultimately adverse cardiac events.[5] Therefore, the timely and accurate diagnosis of L-R shunts is of interest.

Echocardiography, the first-line imaging modality in suspected CHD, is user-dependent, and its utility can be limited by, eg, acoustic windows that hinder the identification of certain defects as well as lower reproducibility and beam direction dependence of quantitative parameters.[6,7] Therefore, cardiac magnetic resonance imaging (MRI) has become the modality of choice in CHD, as it provides comprehensive evaluation of (potentially complex) cardiac anatomy and physiology in CHD and is regarded as the reference standard for quantification of biventricular volumes and shunts.[8] In addition, MRI is considered useful in adults with nonspecific findings such as murmurs and RV dilatation, potentially caused by shunts, that are otherwise difficult to diagnose by echocardiography.[9] Several other diseases such as advanced left heart failure, pulmonary and tricuspid valve regurgitation, and arrhythmogenic right ventricular cardiomyopathy (ARVC) may lead to right heart dilatation in the absence of L-R shunts.[10,11] Patients with suspected L-R shunts typically undergo phase-contrast MRI to compare the flow between the pulmonary and systemic circulation (Qp and Qs respectively).[9] Phase-contrast acquisitions require extensive planning leading to prolonged examination times, reduced patient comfort, and limited scanner efficiency.

T2 mapping is a parametric technique that allows the estimation of voxel-wise T2 relaxation times.[12] While T2 mapping is mainly used to evaluate myocardial water content, it is also sensitive to the level of blood oxygenation.[13,14] We hypothesized that T2 mapping can detect blood oxygenation differences between the left (LV) and right ventricles (RV) caused by L-R shunts. Therefore, the aim of this study was to test the feasibility of using routine T2 mapping for L-R shunt detection in patients with RV disease compared to healthy volunteers (HVs).

Materials and Methods

Patient Population

The local institutional review boards of the two participating institutions (*blinded* and *blinded*) approved the protocol of this retrospective study with a waiver for written informed consent. Patients were enrolled based on the following inclusion criteria: 1) presence of any of the following: (a) L-R shunt; or (b) RV disease without L-R shunt defined by RV end-diastolic volume index (EDVi) >100 mL/m^2 or reduced RV ejection fraction (EF) <40%.[15] Unavailability of adequate MR data for dedicated flow measurements of pulmonary and systemic flow and T2 mapping in three short-axis orientations was regarded as exclusion criteria.

Healthy Volunteer Population

Subjects from our institution's HV cohort that we prospectively collected under a prior research initiative to establish institutional normal values at the *blinded* were retrospectively included. HVs provided written informed consent at the time of their MRI. Subjects were enrolled based on the following inclusion criteria: 1) >18 years of age; 2) no history of any cardiovascular disease; and 3) available MR data for dedicated flow measurement of pulmonary and systemic flow and T2 mapping in three short-axis orientations.

MR Acquisition

Subjects underwent MRI on 1.5 and 3 T systems (Magnetom Avanto and Prisma, Siemens Healthineers, Erlangen, Germany). Cine acquisitions, T2 mapping, and phase-contrast imaging were performed as a part of a comprehensive MRI protocol as part of our institutional standards which proposes a comprehensive assessment including parametric mapping, even if current guidelines do not recommend the specific use of this technique for certain indications. Therefore, every patient in our institutions will receive T2 mapping as part of their clinical routine. All subjects were scanned in a head-first supine position using 32-element spine and 18-element surface phased-array coils. All acquisitions were electrocardiographically triggered and performed during expiratory breath-hold. Based on initial scout images, 2D balanced steady-state free precession (bSSFP) cine images were acquired in long- and short-axis planes to completely cover the left and right heart. In addition, cine images were acquired to plan aortic and pulmonary flow measurements. T2 mapping was performed in three short-axis slices (basal, midventricular, and apical), using a commercially available T2 prepared bSSFP sequence with three preparation pulses of 0.0 msec, 30.0 msec, and 55.0 msec and a recovery period of three heartbeats to obtain T2 maps in diastolic phase. Through-plane phase-contrast images were acquired perpendicular to the bloodstream in the proximal aorta and the main pulmonary artery using a velocity sensitized gradient-echo sequence.[8,16] Typical pulse sequence parameters are summarized in Table 1.

Image Analysis

Image analysis was performed locally at the respective institutions. Two readers (TS and VB with 2 and 3 years of experience in cardiovascular imaging, respectively) performed the measurements under the supervision of two expert readers (TE and AS with 10 and

TABLE 1. Pulse Sequence Parameters

	Cine		Phase-Contrast			T2 Mapping
	1.5 T	3 T	1.5 T	3 T	1.5 T	3 T
Repetition time (msec)	3.06	3.27	4.64	4.64	2.49	3.15
Temporal resolution (msec)	40.04	39.24	40.8	37.12	N/A	N/A
Reconstructed temporal resolution (msec)[a]	40.00	40.00	33.33	33.33	N/A	N/A
Phases/cardiac cycle	25	25	30	30	N/A	N/A
Acquisition window (msec)[a]	N/A	N/A	N/A	N/A	202	202
Echo time (msec)	1.28	1.39	2.47	2.47	1.06	1.32
Matrix	256 × 256	240 × 198	192 × 192	192 × 119	256 × 256	192 × 112
Field of view (mm^2)	350 × 300	360 × 297	340 × 214	346 × 214	360 × 210	360 × 210
Flip angle (°)	90	48	20	20	70	12
Voxel size (mm^3)	1.4 × 1.4 × 7	1.5 × 1.5 × 8	1.8 × 1.8 × 6	1.8 × 1.8 × 6	1.4 × 1.4 × 8	1.9 × 1.9 × 8
Band-width (Hz/pxl)	930	945	449	449	1149	1185

[a]For a heart rate of 60 bpm.

12 years of experience in cardiovascular imaging, respectively). Assessment of LV and RV volumes, RV mass, and aortic and pulmonary flow was performed using a commercial software solution (cvi42, Circle Cardiovascular Imaging, Calgary, Canada) according to current guidelines.[8] Qp/Qs was calculated as the ratio of pulmonary and aortic (systemic) flow. For the assessment of the RV/LV T2 ratio, regions of interest were drawn in the lumen of the RV and LV, with careful avoidance of papillary muscles and myocardium. Subsequently, the T2 ratio between the RV and LV blood pool was calculated for every slice and averaged to generate a global value.

A subset of 40 subjects was assessed by two readers (TS and VB) for inter-reader correlation. After a hiatus of at least 14 days to minimize recall bias, one of the readers (TS) re-evaluated 40 random cases for intra-reader correlation.

Statistical Analysis

Statistical analysis was performed using SPSS v27 (IBM Corporation, Armonk, NY, USA) and plots were created in MedCalc 19.4 (MedCalc, Ostend, Belgium). The Kolmogorov–Smirnov test was used to test continuous data for normality. Normally distributed continuous variables are reported as means ± SDs, while those with non-normal distribution are given as a median with an interquartile range. Categoric variables are reported as absolute frequencies and proportions. Differences between subject groups were compared using paired-samples *t*-tests or Wilcoxon rank-sum tests, depending on distribution. Single rater intraclass correlations (ICC) with two-way mixed effects and absolute agreement were used to assess inter-reader and intra-reader agreement and were interpreted as follows: 0.0–0.3, lack of agreement; 0.31–0.5, weak agreement; 0.51–0.7, moderate agreement; 0.71–0.9, strong agreement; and 0.91–1.00, very strong agreement. Receiver operating curve (ROC) analysis was performed to calculate sensitivity, specificity, and negative predictive value (NPV) for the detection of L-R shunts, and the area under the curve (AUC) was determined. Comparisons of AUCs were assessed using DeLong's method. Subgroup comparisons were performed to determine the effect of the magnetic field (1.5 vs. 3 T), to detect clinically relevant shunts defined as Qp/Qs > 1.5,[5] and to evaluate the effect of the extent of RV dilatation on the discriminatory power of the T2 ratio. An EDVi cut-off of 100 mL/m^2 was chosen to define RV dilatation, which represents the average upper limit for normal RV EDVi among genders and different age groups.[15] Correlation between Qp/Qs and RV/LV T2 ratio was assessed using Spearman's correlation coefficient (*r*). A *P*-value <0.05 was considered significant.

Results

The overall study population consisted of 100 subjects, including 52 HVs and 48 patients including 27 with L-R shunts and 21 with various RV diseases. The etiology of L-R shunts included atrial septal defect (ASD, $N = 15$, 55.6%), partial anomalous pulmonary venous return ($N = 8$, 29.6%), and ventricular septal defect ($N = 4$, 14.8%). The cohort of patients with RV disease without L-R shunt represented the following diseases: ARVC ($N = 10$, 47.6%), repaired tetralogy of Fallot ($N = 7$, 33.3%), pulmonary valve disease ($N = 3$, 14.4%), and tricuspid valve disease ($N = 1$, 4.7%). Baseline characteristics including volumetric MRI parameters are summarized in Table 2.

TABLE 2. Subject Characteristics; Cine Imaging-Based Cardiac Volumes and Function Displayed as Mean and SD or Median With [Interquartile Range] Depending on Data Distribution

	L-R Shunt	RV Dilatation	Healthy Volunteers
N (%)	27 (27)	21 (21)	52 (52)
Age (years)	17.0 (16.0/24.0)	27.0 (15.5/37.5)	23.0 (18.0/29.0)
Gender (male)	12 (44.4%)	14 (66.7%)	30 (57.7%)
BMI (kg/m^2)	22.6 ± 5.4	23.9 ± 4.9	22.3 ± 3.1
LV EF (%)	63.6 ± 7.9	59.2 ± 9.4	62.8 ± 5.6
LV EDVi (mL/m^2)	75.1 ± 15.2	87.3 ± 19.5	87.5 ± 10.1
LV mass (g/m^2)	68.9 ± 25.9	79.2 ± 36.2	92.7 ± 31.4
RV EF (%)	55.6 ± 9.5	50.0 (43.1/55.5)	53.4 ± 5.5
RV EDVi (mL/m^2)	123.4 ± 42.8	127.8 ± 34.6	95.3 ± 16.7
RV mass (g/m^2)	47.4 ± 13.7	46.3 (34.3/63.9)	39.3 ± 9.1

BMI = body mass index; LV = left ventricle; RV = right ventricle; EF = ejection fraction; EDVi = end-diastolic volume index; L-R = left-to-right.

RV-EDVi in L-R-shunt patients (123.4 ± 42.8 mL/m^2) was significantly higher compared to HV (95.3 ± 16.7 mL/m^2), but not in comparison to patients with RV disease (127.8 ± 34.6 mL/m^2; $P = 0.315$). The Qp/Qs and T2 ratios (see Table 3 and Fig. 1) in L-R shunt patients were significantly higher compared to those in RV disease and in HV. Representative cases comparing RV and LV T2 relaxation times in a HV, a patient with ASD, and a subject with ARVC are provided in Fig. 2.

An RV/LV T2 ratio cut-off of 0.78 demonstrated an overall excellent diagnostic performance for the detection of L-R shunts (sensitivity 100.0%, specificity 73.9%, and AUC 0.965), leading to a 100% NPV. RV/LV T2 ratio showed superior performance compared to RV-EDVi (AUC: 0.712) for the discrimination between L-R-shunt and HVs, against Qp/Qs as reference standard (Fig. 3). A subgroup analysis demonstrated comparable AUCs at 1.5 T ($N = 29$, including 18 L-R shunt patients; AUC 0.955) and 3 T ($N = 71$, including nine L-R shunt patients; AUC 0.961, $P = 0.888$). There was a strong positive correlation between shunt severity and the RV/LV T2 ratio in patients with L-R-shunt ($r = 0.83$), Fig. 4. The RV/LV T2 ratio showed a comparable diagnostic performance in detecting L-R shunts in shunt patients with ($N = 10$ with RV EDVi <100 mL/m^2; AUC 0.943) vs. without RV dilatation ($N = 17$ with RV EDVI >100 mL/m^2; AUC 0.955, $P = 0.784$). In addition, an RV/LV T2 ratio >0.83 was able to detect clinically relevant shunts (defined by Qp/Qs-ratio >1.5) with high confidence ($N = 13$ with Qp/Qs > 1.5: sensitivity 100.0%, specificity 95.4%, AUC 0.99), resulting in a positive predictive value of 81.3% and an NPV of 100%.

TABLE 3. Qp/Qs and RV/LV T2 Ratio Among the Study Groups

	L-R Shunt	RV Dilatation	HV
Qp/Qs	1.84 ± 0.84	1.01 ± 0.03	1.04 ± 0.04
RV/LV T2 ratio	0.89 ± 0.07	0.72 ± 0.10	0.71 ± 0.09

RV = right ventricle; LV = left ventricle; L-R = left-to-right; HV = healthy volunteer; Qp/Qs = pulmonary and aortic flow.

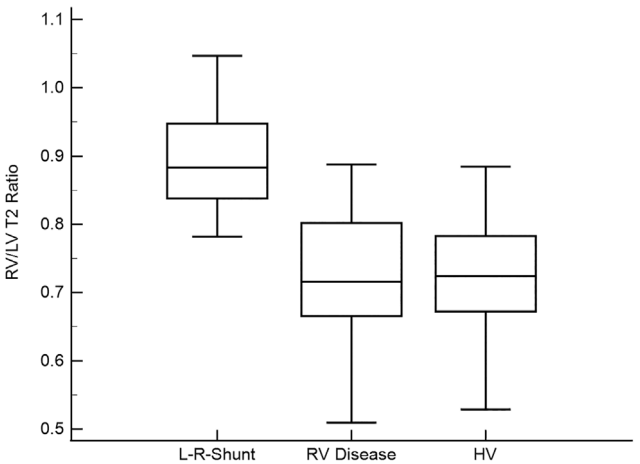

FIGURE 1: Boxplot visualization of RV/LV T2 ratio among L-R shunt and RV disease and HV. RV = right ventricle; LV = left ventricle; L-R = left-to-right.

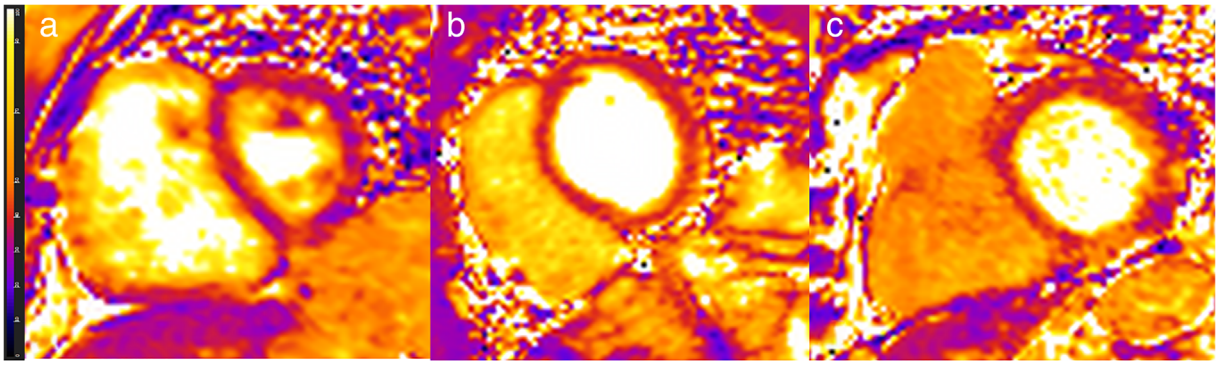

FIGURE 2: Representative image example demonstrating differences in blood T2 relaxation times between a patient with L-R shunt (a), a healthy volunteer (b), and a patient with RV disease without L-R shunt (c). L-R = left-to-right; RV = right ventricle.

Inter- and intra-reader assessment demonstrated excellent agreement between RV/LV T2 ratio measurements (inter-rater: ICC = 0.98, intra-rater: ICC = 0.99).

Discussion

In this study, we investigated the feasibility of routine T2 mapping to detect changes in RV blood oxygenation in order to identify patients with L-R shunts. We demonstrated a high diagnostic performance of RV/LV T2 ratio to rule-out L-R shunts among HVs and patients with non-shunt-related RV diseases. In addition, our results showed a strong correlation between RV/LV T2 ratio and shunt severity.

T2 mapping is often used to evaluate acuteness of disease, eg, it is recommended in acute myocarditis and is also useful for quantifying areas at risk in acute myocardial infarction.[17,18] Here, we presented another potential clinical application of T2 mapping that supports the evaluation of suspected L-R shunts and can be efficiently used as a screening tool to avoid time-consuming phase-contrast imaging and/or three-dimensional (3D) MR angiography acquisitions to rule-out an L-R shunt. For instance, measuring Qp/Qs typically needs eight breath-holds (three breath-holds for perpendicular cine acquisitions and one breath-hold for phase-contrast imaging per valve), while the here proposed RV/LV T2 ratio can be acquired in three breath-holds. In addition, RV/LV T2 ratio is calculated based on a rather simple and time-efficient post-processing approach using regions of interest in the blood-pool, compared to precise segmentations that are needed for accurate measurements of Qp/Qs. Various publications have explored the capability of MRI to assess blood oxygenation levels.[13,19–23] However, the methods used in these studies have limitations such as utilizing investigational T2 techniques, reliance on navigator-based acquisitions, and internal calibrations. For example, Wen et al proposed a 3D quantitative susceptibility mapping method,

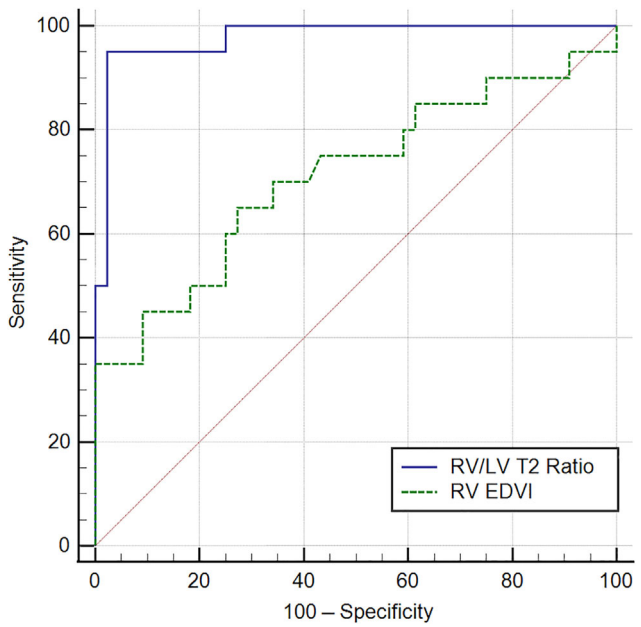

FIGURE 3: ROC analysis comparing the diagnostic performance of RV/LV T2 ratio and RV EDVi to differentiate between patients with L-R shunts and healthy volunteers using Qp/Qs as reference standard. ROC = receiver operating curve; RV = right ventricle; LV = left ventricle; EDVi = end-diastolic volume index; L-R = left-to-right; Qp/Qs = pulmonary and aortic flow.

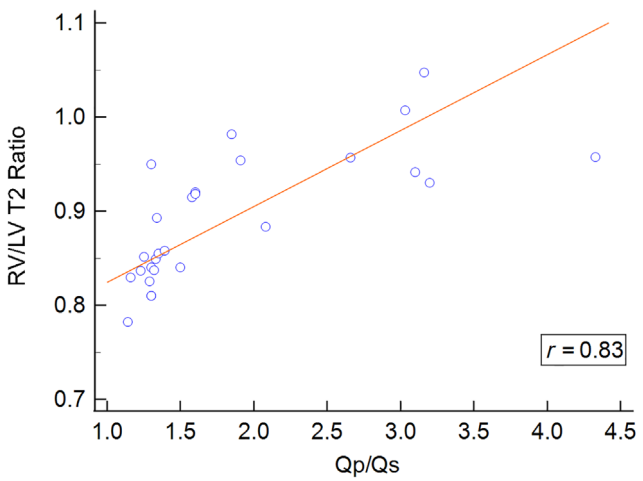

FIGURE 4: Scatter plot demonstrating significant correlation between RV/LV T2 ratio and Qp/Qs ratio. RV = right ventricle; LV = left ventricle; Qp/Qs = pulmonary and aortic flow.

which relied on the differentiation between the oxygenated diamagnetic and the deoxygenated paramagnetic states of iron in the hemoglobin molecule, with a high agreement to invasive measurements of oxygen saturation in the LV and RV.[23] The clinical application of these methods, however, is limited by the time-consuming nature of the acquisitions, which can reach up to 4–7 minutes. Another method proposed by Varghese et al used multiple T2 measurements with different inter-echo pulse spacings[22] processed in a Luz-Meiboom model to estimate oxygen saturation in both ventricles. Although this method provided an excellent agreement to invasive blood gas analysis, it has not been extended to clinical applications due to its investigational nature.

While the above methods may allow the direct quantification of blood oxygenation with or without the need to use scanner-specific calibrations, our proposed technique used a widely available, commercial T2 mapping sequence that required only a single breath-hold per slice Using the RV/LV T2 ratio established in our study, we demonstrated the feasibility of detection of differences in blood oxygenation levels regardless of the magnetic field strength, which is known to affect the magnitude of absolute blood T2 relaxation times.[24] While our method does not directly quantify blood oxygenation, the relative difference between T2 values of the LV and RV blood pools was able to detect abnormal blood oxygenation in the RV, which is a typical feature of L-R shunts. Vice versa, a normal RV/LV T2 ratio had a high NPV that excluded the presence of an L-R shunt. The method proposed in this study showed excellent inter- and intra-reader reproducibility and can be performed directly on the scanner without the need for additional software and/or post-processing tools. Although a comparable approach has been applied in fetal imaging using T1 and T2 mapping to estimate fetal oxygenation and hematocrit,[25,26] such a method has not been evaluated in children and adults with CHD and shunts.

We used the average of the RV/LV T2 ratio in the three short-axis oriented slices. Using T2 maps to estimate blood relaxation times can be challenging and influenced by a variety of factors, such as flow turbulence, B1 magnetic field inhomogeneity, and partial volume effects.[26] This is especially true for pulse sequences using a T2 preparation pulse and a single-shot bSSFP readout which may be sensitive to flow, resulting in potential signal loss and underestimation of T2.[27] Hence, we averaged the T2 ratios derived from the three T2 maps to reduce the impact of localized artifacts. However, some false positive RV/LV T2 ratios may still occur due to the influence of artifacts that affect blood relaxation times. The overall diagnostic performance of RV/LV T2 ratio for the detection of L-R shunts was sufficient and is especially promising as a screening tool due to its excellent NPV. From a practical standpoint, the clinical potential of using the RV/LV T2 ratio is 3-fold: first, T2 ratio may be used to detect L-R shunts in patients with normal-appearing RVs, but with clinical suspicion for an L-R shunt. Second, it may be used to rule-in/rule-out L-R shunts in patients with dilated RV and hence, to guide the necessity of flow measurements. Third, an RV/LV T2 ratio over 0.83 may be used to detect clinically relevant shunts (Qp/Qs > 1.5) that likely need surgical correction with high confidence. While we investigated this method only for detection of L-R shunts, it has further potential for additional applications, such as assessing the difference in blood oxygenation between the ventricles as a parameter of cardiac performance, eg, in exercise MRI or in patients with heart failure with and without preserved EF. LV dysfunction on exercise leads to an increased oxygen consumption that increases the delivery of deoxygenated blood to the right heart. Therefore, an abnormal RV/LV T2 ratio can indicate cardiac failure, and may be used to guide patient management comparable to invasive methods.[28,29]

Limitations

Our results are based on a single vendor study and require further evaluation on other scanner models and with different T2 mapping sequences. Due to the retrospective study design, validation of the MR measurements by invasively acquired blood oxygenation levels was not available and potentially requires further exploration. Notably, the here proposed method would not be able to diagnose shunts on an arterial level (persistent ductus arteriosus), which do not alter the oxygenation of the RV blood. Shunt patients mainly consisted of patients with shunts on atrial level and only four patients presented with a VSD. Therefore, we were not able to compare the diagnostic performance of the T2 ratio between different shunt levels, which may result in differences in RV blood oxygenation. The T2 mapping sequence used in our protocol was developed for the assessment of the myocardium and was not optimized for the measurement of blood T2 relaxation that can be affected by various parameters such as turbulent blood flow. This may have potentially lead to false-positive results in cases without L-R shunts or false-negative results in patients with L-R shunts and an optimized MR protocol may be required in the future. The overall sample size in this study was relatively small; however, post hoc analysis demonstrated sufficient power to detect significant differences with a power level of 0.8.

Conclusion

In conclusion, the RV/LV T2 ratio is an imaging biomarker that may detect L-R shunts with a high correlation to shunt severity. A T2 ratio <0.78 can accurately rule-out L-R shunts, independent of RV-EDVi and magnetic field strength. This diagnostic tool may prevent unnecessary phase-contrast acquisitions in cases with RV dilatation of unknown etiology.

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