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Quantitative T2* imaging of iron overload in a non-dedicated center – Normal variation, repeatability and reader variation

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ABSTRACT

Background: Patients with transfusion dependent anemia are at risk of complications from iron overload. Quantitative T2* magnetic resonance imaging (MRI) is the best non-invasive method to assess iron deposition in the liver and heart and to guide chelation therapy.
Purpose: To investigate the image quality and inter-observer variations in T2* measurements of the myocardium and the liver, and to obtain the lower limit of cardiac and hepatic quantitative T2* values in patients without suspicion of iron overload.
Material and methods: Thirty-eight patients referred for cardiac MRI were prospectively included in the study. Three patients were referred with, and 35 without suspicion of iron overload. Quantitative T2* parametric maps were obtained on a 1.5 T MRI system in the cardiac short axis and liver axial view. Two readers independently assessed the image quality and the representative and the lowest T2* value in the myocardium and the liver.
Results: The normal range of representative T2* values in the myocardium and liver was 24–45 ms and 14–37 ms, respectively. None of the 35 participants (0 %, 95 % confidence interval 0–11 %) in the normal reference group demonstrated representative T2* values below previously reported lower limits in the myocardium (20 ms) or the liver (8 ms). Focal myocardial areas with T2* values near the lower normal range, 19–20 ms, were seen in two patients. The readers generally reported good image quality.
Conclusion: T2* imaging for assessing iron overload can be performed in a non-dedicated center with sufficient image quality.

1. Introduction

In β-thalassemia, a major cause of mortality and morbidity is iron overload, due to transfusion dependence from early age [1]. Iron overload causes damage to different organ tissues as myocardium (cardiomyopatyhy), endocrine tissues (e.g. hypogonadism, diabetes mellitus) and liver (fibrosis and risk for cirrhosis and hepatocellular carcinoma) [2]. Control of iron overload, by monitoring and chelation therapy, is a cornerstone in the management of patients with transfusion dependent thalassemia [3,4].

Iron chelation therapy is usually initiated when the patient has received 10–20 packed red cell units or when serum ferritin levels exceed 1000 μg/L. Chelation needs to be continued for life and regularly monitored to allow for dose adjustments or alternative chelator medication. Serum ferritin, a simple and widely available blood sample test, is commonly used for routine monitoring of iron chelation therapy and iron burden. However, the ferritin analyses do not always correlate well with body iron stores, since ferritin levels are increased by inflammation and are also influenced by other factors, apart from iron burden [3].

A direct measurement of liver iron concentration (LIC) obtained from a transcutaneous biopsy is considered the most reliable indicator of body iron load. However, the procedure is invasive with associated side-effects. During the recent decades, techniques for non-invasive estimation of iron overload in specific organs using magnetic resonance imaging (MRI) have been introduced, in particular the liver and the heart [5–10].

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The purely quantitative T2* MRI technique and its reciprocal R2* are used for monitoring the chelation therapy. The measurement of the T2* relaxation time in the myocardium or the liver using MRI directly reflects the degree of iron deposition in the tissue [5]. Furthermore, the T2* value is highly predictive for arrhythmia and cardiac failure in patients with thalassemia. In these patients, a myocardial T2* value above 20 ms is considered normal, with low risk for cardiac complications [11]. Compared to echocardiography that visualize advanced stage cardiomyopathy, the T2* technique is more sensitive to myocardial iron overload, making it possible to optimize iron chelation before heart failure has developed [12,13].

The T2* assessment needs to be repeatable, and the normal range of myocardial and liver T2*-values needs to be known in relation to the limits used in monitoring the chelation therapy. Especially, this knowledge is needed since non-specialized centers may perform only a few clinical iron overload MRI each year.

Therefore, the aims of the current study were to: 1. Obtain the lower limit of cardiac and hepatic quantitative T2* values in patients without suspicion of iron overload. 2. Evaluate the repeatability and reader variation in T2* measurements. 3. Evaluate the image quality of T2* parametric maps of the heart and liver.

2. Material and methods

The regional research ethics board approved the study protocol of this prospective study. Patients were included after signed informed consent.

2.1. Patient selection

Between April 2015 and December 2018, 38 patients scheduled for cardiac MRI were prospectively included in the study, 35 patients in the normal reference group and three patients in a suspected iron deposition group. The inclusion criterium for the reference group was: Patient referred for cardiac MRI with clinical question including cardiac amyloid deposition disease or Arrhytmogenic Right Ventricular Disease (ARVD). Exclusion criteria were: 1. Patient age <18 or ≥60 years. 2. Clinical question in referral including iron deposition disease or clinical question including post-ischemic abnormalities. 3. Already included in the study.

In the suspected iron deposition group, the inclusion criterium was: Patient referred for cardiac MRI with clinical question including iron deposition disease. Exclusion criteria were 1. Patient age <18 or ≥60 years. 2. Already included in the study.

The inclusion criteria were designed to include a cohort of patients with similar age as the typical patient referred for chelation therapy monitoring and with mostly normal cardiac MRI examinations. The patient characteristics are detailed in Table 1.

2.2. T2* parametric maps

For each subject, T2* parametric maps were obtained in the cardiac short axis (SA) view and in the liver axial view, see Fig. 1. The cardiac SA view images were located midventricularly, perpendicular to the cardiac long axis. The image plane of liver axial view was perpendicular to the MRI gantry and the slice was placed through a section of the upper part of the liver, where both liver lobes were visible.

Table 1
Patient characteristics.

	Normal reference group (n = 35)	Suspected iron overload group (n = 3)
Age (years)	40 ± 13 [18–64]	28 [23–35]
Sex (M/F)	18/17	2/1
Body weight (kg)	79 ± 22 [53–159]	61 [47–74]

Note: values are mean ± standard deviation for reference group. Range is given within [brackets].

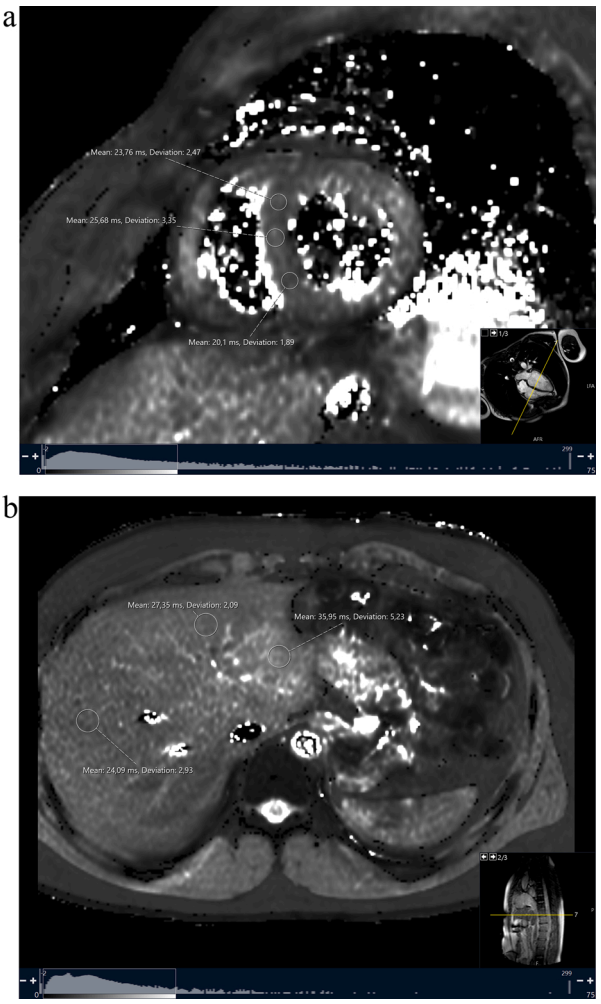

Fig. 1. (a) Myocardial T2* parametric map in the interventricular septum in one subject in the normal reference group. Example measurements of the representative (24 ms), lowest (20 ms) and highest (26 ms) measurements are shown. (b) Liver T2* parametric map in one subject in the normal reference group. Example measurements of the representative (27 ms), lowest (24 ms) and highest (36 ms) measurements are shown. (The demonstrated region of interests (ROI) are examples; the exact ROI locations for the readers in the study were not recorded. The parametric map intensity range between 0 ms and 75 ms is shown in the lowest part of the images.).

All MR examinations were performed on a clinical 1.5 T Philips Achieva system (Philips Healthcare, Best, the Netherlands) using the five channel SENSE cardiac coil for all measurements. The T2* relaxation time measurements were performed following the procedure described in earlier work [8,14]. The cardiac SA and axial liver images were acquired using a multiecho, gradient-echo pulse sequence. Typical imaging parameters were for axial liver/SA acquisitions, respectively: TR = 15.1/16 ms, TE = (2.4–13.7) / (2.7–14.4) ms (6 echoes separated by 2,3 ms), field-of-view (FOV) 320 mm, acquisition matrix 180 × 128, and then resampled to 256 × 256 image matrix with in-plane resolution of 1.25 × 1.25 mm^2, flip angle 30° and a slice thickness 10 mm. Each image was acquired during breath-hold. From the source T2* weighted images, the T2* parametric maps were automatically created by the scanner's software.

The cardiac and liver T2* maps were repeated for each subject for assessment of inter-scan repeatability. However, repeated cardiac T2* maps were unavailable in two patients, and repeated liver T2* maps

were unavailable in one patient.

2.3. Image evaluation

Two readers, radiologists with 7 and 0 years cardiac MRI experience, independently assessed the cardiac SA and liver axial T2* parametric maps. The readers were blinded for clinical information, including reason for referral. Only the source T2* weighted images and resulting T2* parametric maps were available for the readers in the study. The readers used the circular region of interest (ROI) tool in Sectra IDS7 radiological workstation to obtain a mean value of pixel intensities (scaled to correspond to milliseconds) within the ROI in the T2* parametric map.

Each reader performed the measurements in two sessions, separated with at least six months. In the first session, the first of the two acquired image sets for each patient was analyzed and in the second session, the second image set. In the first reading, cardiac SA and liver axial images were available in all 38 patients. In the second reading, cardiac images were available in 36 patients and liver images in 37 patients.

2.3.1. Cardiac T2*

The cardiac T2* value was evaluated within the interventricular septum in the single cardiac SA T2* parametric map, using a circular ROI as large as possible without including any part of the cardiac cavities. The main outcome that the readers were instructed to obtain was a T2* value representative for the myocardium, corresponding to what would have been reported in a clinical report. The readers were also instructed to obtain the lowest and the highest T2* value in a ROI in the septum, placed in area relatively free from artefacts, Fig. 1.

2.3.2. Liver T2*

The hepatic T2* value was evaluated in the axial liver parametric map. Similar to the cardiac T2* evaluation, the readers obtained a representative T2* value, and the lowest and highest T2* value measurable in areas relatively free from artefacts, avoiding large vessel and bile ducts. The readers were instructed to use a ROI of sufficient size, generally approximately 1 cm diameter.

2.3.3. Image quality

For each assessment, the readers provided an image quality score on the following scale:

1 Severe artifacts precluding confident assessment of T2*.
2 Substantial artifacts, assessment of T2* possible with low confidence.
3 Some artifacts, assessment of T2* possible with moderate confidence.
4 No or minimal artifacts, confident assessment of T2* possible.

When reported image quality score was 1 (severe artifacts), no measurements of T2* were reported.

2.4. Statistics

Standard descriptive statistics were used for T2* measurements. The distribution of T2* values in the normal reference group and the suspected iron deposition group were compared with Wilcoxon rank sum test. Matlab R2018b (The Mathworks Inc) was used for statistics.

3. Results

3.1. Myocardial T2*-measurements

The range of representative myocardial T2*-values in the normal reference group was 24−45 ms, see Fig. 2. None (0 %, 95 % C.I 0 %–10 %) of the 35 subjects had representative T2*-value below the commonly reported normal limit 20 ms. All three subjects in the suspected iron deposition group had normal myocardial T2*-values, consistent with no signs of myocardial iron deposition.

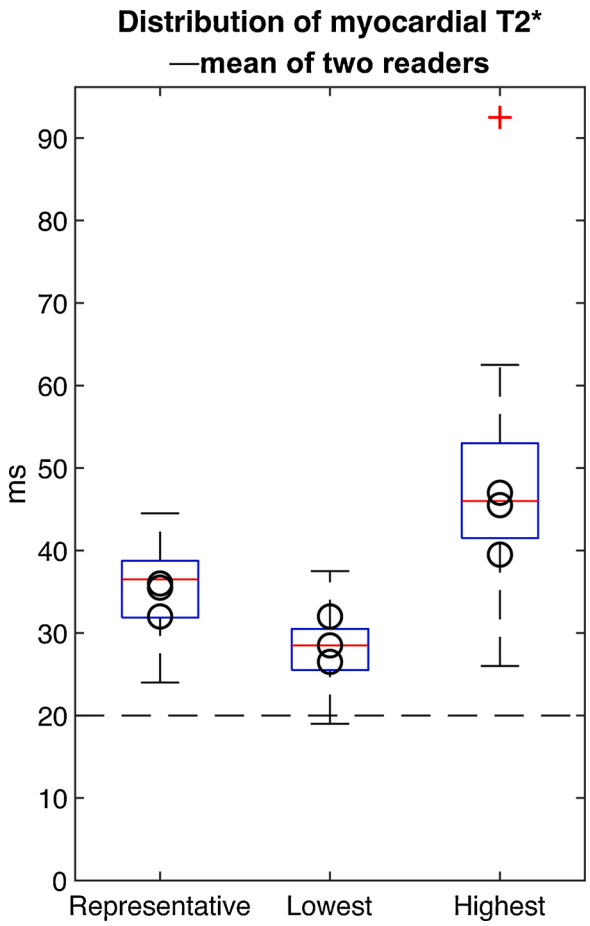

Fig. 2. Distribution of myocardial T2* measurements of the interventricular septum. The boxplots shows the representative, lowest and highest value of the normal reference group. The three subjects in the suspected iron deposition group are shown as black circles.

The variation of T2*-values within the myocardium was evaluated by placing a ROI in the area with the highest and lowest value in a location relatively free from artifacts in the interventricular septum. In two subjects in the normal reference group, the lowest measurements were 19 ms and 20 ms, respectively, see Figs. 1 and 2. This indicates that even in subjects without suspicion of iron overload, there are inhomogeneities in the myocardial T2* measurements, where occasionally an otherwise pathological value can be measured.

3.2. Liver T2*-measurements

The range of representative hepatic T2*-values in the normal reference group was 14−37 ms, see Fig. 3. None of the 33 subjects (0 %, 95 % C.I 0 %–11 %) in the normal reference group had representative liver T2*-value below 8 ms, while two out of three subjects in the suspected iron deposition group had clearly pathological T2*-values of <2 ms, indicating severe iron deposition in the liver [15], see Fig. 3. The T2* values were significantly lower ($p = 0.008$) in the suspected iron deposition group compared to the reference group.

Compared to the cardiac T2* values, the liver T2* showed less variation towards the lower normal limit in the normal reference group. The range of lowest T2* in the liver was 12−28 ms. In contrast to the myocardium, all reported lowest T2* values of the liver were above the commonly used lower normal level of 8 ms.

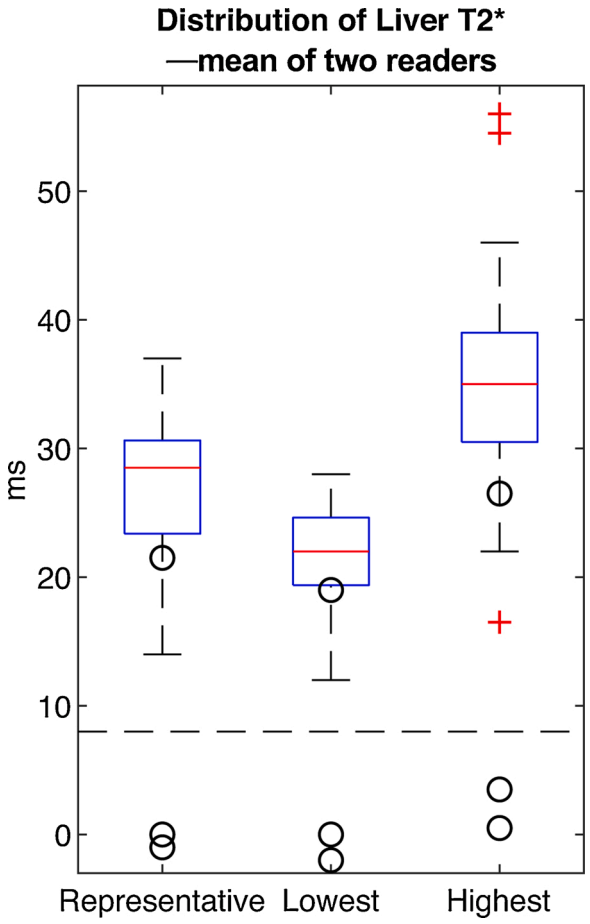

Fig. 3. Distribution of T2* measurements of the liver. The boxplots shows the representative, lowest and highest value of the normal reference group. The three subjects in the suspected iron deposition group are shown as black circles.

3.3. Repeatability of T2* measurements

The inter-reader repeatability was calculated from measurements by the two readers in the first reading. Liver axial images from two subjects were excluded because of insufficient image quality (image quality score 1 by at least one reader).

The inter-scan repeatability was calculated from subjects with available images from two acquisitions, and where both readers reported image quality of at least 2 in both readings. Measurements of myocardial T2* from all 36 subjects with available images were used. Measurements of liver T2* from 35 subjects were used. Repeated liver axial images were unavailable in one subject and images from two subjects were excluded because of insufficient image quality.

3.3.1. Cardiac T2* measurements

The Bland-Altman limits of agreement for inter-reader and between-scan repeatability of cardiac T2* measurements were -2 ± 9 ms and 0 ± 9 ms, respectively, see Fig. 4.

3.3.2. Liver T2* measurements

The Bland-Altman limits of agreement for inter-reader and between-scan repeatability of liver T2* measurements in the liver axial image were -2 ± 9 ms and 0 ± 8 ms, respectively, see Fig. 5. As demonstrated in the figure, there was low inter-reader and inter-scan variation for the two T2* values of <2 ms, corresponding to severe iron overload, whereas the variation was mainly seen in subjects with high liver T2* values within the normal range.

3.4. Image quality

The first reading with parametric maps from all 38 included subjects were used for the image quality analysis.

3.4.1. Cardiac T2* imaging

The median image quality score in the first reading was 4 (confident assessment of T2* possible) by reader 1, who had previous experience of T2* evaluation and 3 (assessment of T2* possible with moderate confidence) by reader 2, without previous experience. The distribution of image quality scores for the interventricular septum is shown in Fig. 6a.

3.4.2. Liver T2* imaging

The median image quality score in the liver axial view was 4 (confident assessment of T2* possible) by reader 1, and 3 (assessment of T2* possible with moderate confidence) by reader 2. In total, three images were scored 1 (severe artifacts) by at least one of the readers, see

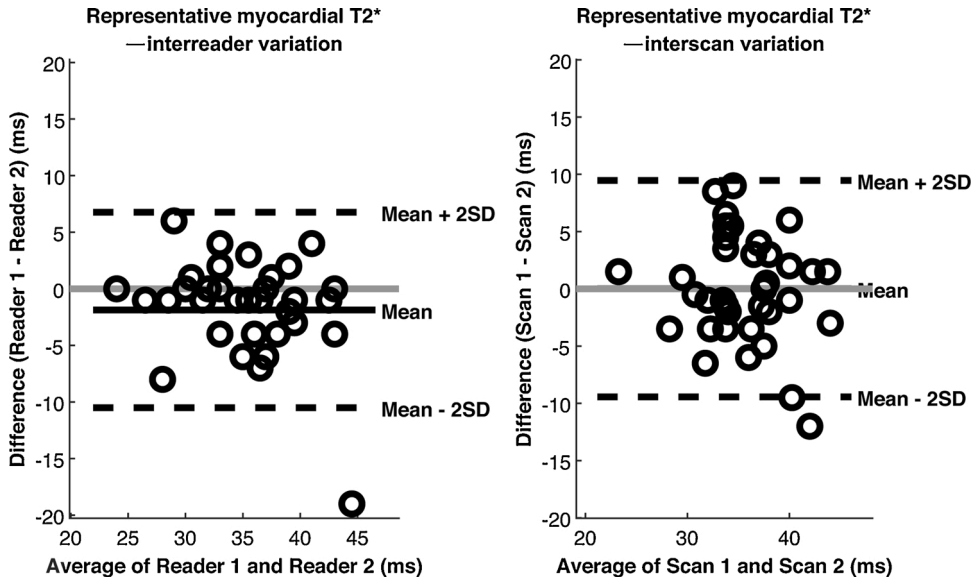

Fig. 4. Bland-Altman plots demonstrating the repeatability of myocardial T2* measurements in interventricular septum. a. Inter-reader variation. b. Inter-scan variation.

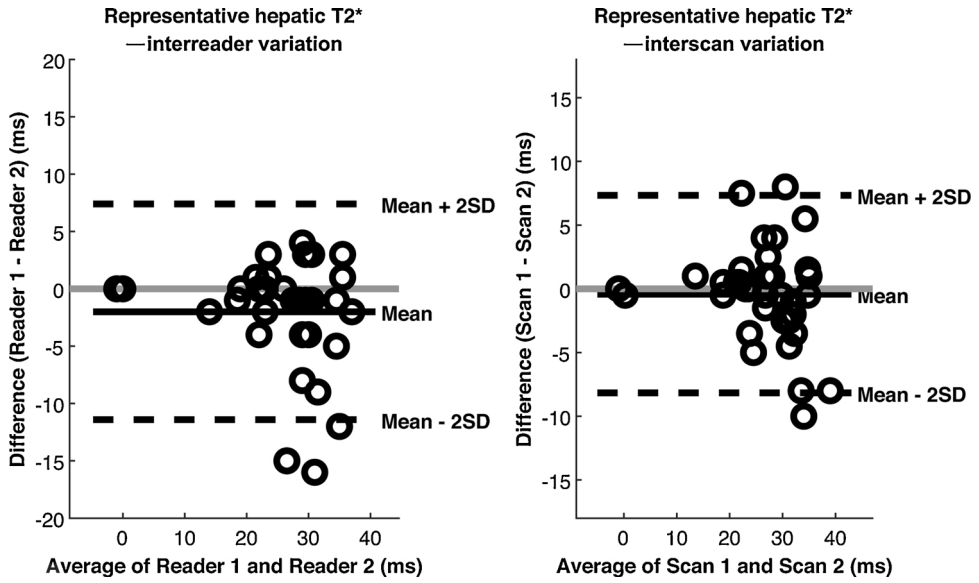

Fig. 5. Bland-Altman plots demonstrating the repeatability of hepatic T2* measurements in the liver axial image. a. Inter-reader variation. b. Inter-scan variation.

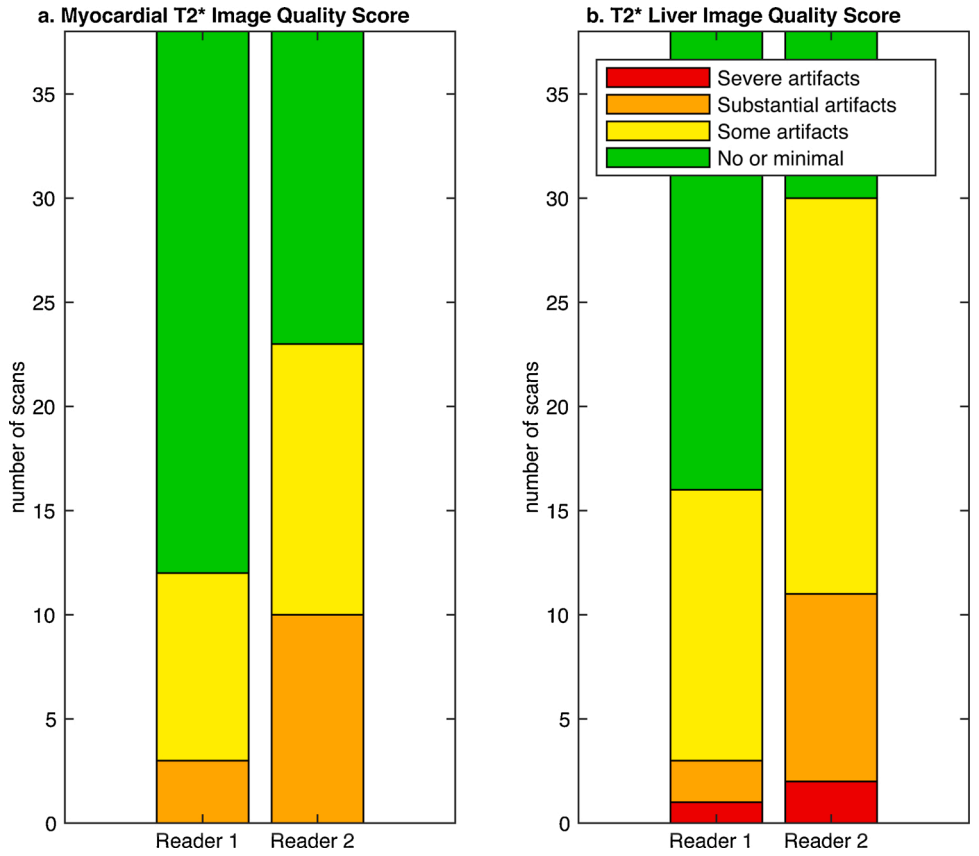

Fig. 6. (a) Myocardial image quality score. No images were score as demonstrating severe artifacts by any reader. (b) Liver T2* image quality score.

Fig. 6b.

4. Discussion

In the present study, quantitative MRI iron overload imaging using T2* parametric maps of the myocardium and liver was evaluated. There was one important result in the present study: Although the representative myocardial T2* value in the normal cohort was above the normal threshold of 20 ms in all subjects, there were inhomogenieties within the septum with areas demonstrating below 20 ms even in some individuals where no iron deposition was suspected.

Quantitative MRI measurements of T2*, the reciprocal R2* (defined as 1/T2*), and the related R2 has been shown to be closely related to invasively measured LIC. There are calibrations curves published based on a limited number of patients [6–8,10]. Although a consensus T2* to LIC conversion table has not been defined, the quantitative liver T2*

value is used in itself for therapy monitoring. A liver T2* between 4 and 8 ms indicates mild iron overload, T2* between 2 and 4 ms indicates moderate iron overload and T2* below 2 ms indicates severe iron overload [15].

Previous studies have shown good inter-scanner reproducibility and low inter-observer variations of cardiac and liver T2* and R2* in patients with suspected iron overload [10,16]. In the present study, a larger variation, between readers and between repeated scans, was seen in normal subjects with T2* values high above the normal threshold. Measurements in the two subjects with severe liver iron overload showed low inter-observer and inter-scan variations.

An important finding in the present study is the variations of obtained T2* measurements within the septum. Although the representative T2* value was above the threshold of 20 ms in all subjects in the normal reference cohort, the lowest measurements in areas relatively free from artifacts within the septum in two subjects were 19 ms and 20 ms. This is an important finding, that indicates that small foci with T2* around 20 ms not necessarily indicate iron deposition in patients with otherwise normal myocardial T2*.

The image quality for cardiac and liver T2* assessment was generally good, which supports that T2* iron overload imaging can be performed in non-dedicated centers.

There are several limitations in the study. A larger cohort would increase the precision of the normal interval. Only two subjects in the suspected iron overload cohort demonstrated signs of liver iron deposition and there were no findings of iron overload in the myocardium. Therefore, the repeatability of measurements in patients with different degrees of iron overload could not be assessed.

In conclusion, T2* imaging for assessing iron overload can be performed in a non-dedicated center with sufficient image quality. Patients without iron overload are not likely to demonstrate abnormal T2* values. However, occasional small foci with T2* close to or below the 20 ms normal limit in otherwise normal myocardium does not necessarily indicate iron deposition.

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Ethical statement

The regional research ethics board approved the study protocol, reference number Uppsala 2014/422. Participants were included after signed informed consent.

CRediT authorship contribution statement

Mats Lidén: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Supervision, Project administration. **David Adrian:** Investigation. **Jonas Widell:** Investigation. **Bertil Uggla:** Writing - review & editing. **Per Thunberg:** Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] B. Modell, M. Khan, M. Darlison, Survival in β-thalassaemia major in the UK: data from the UK thalassaemia register, Lancet 355 (2000) 2051–2052, https://doi.org/10.1016/S0140-6736(00)02357-6.
[2] N.F. Olivieri, G.M. Brittenham, Iron-chelating therapy and the treatment of thalassemia, Blood 89 (1997) 739–761. http://www.ncbi.nlm.nih.gov/pubmed/9028304.
[3] A.V. Hoffbrand, A. Taher, M.D. Cappellini, How I treat transfusional iron overload, Blood 120 (2012) 3657–3669, https://doi.org/10.1182/blood-2012-05-370098.
[4] B. Modell, M. Khan, M. Darlison, M.A. Westwood, D. Ingram, D.J. Pennell, Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance, J. Cardiovasc. Magn. Reson. 10 (2008) 1–8, https://doi.org/10.1186/1532-429X-10-42.
[5] J.C. Wood, Guidelines for quantifying iron overload, Hematol. Am. Soc. Hematol. Educ. Progr. 2014 (2014) 210–215, https://doi.org/10.1182/asheducation-2014.1.210.
[6] J.C. Wood, C. Enriquez, N. Ghugre, J.M. Tyzka, S. Carson, M.D. Nelson, T. D. Coates, MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients, Blood 106 (2005) 1460–1465, https://doi.org/10.1182/blood-2004-10-3982.
[7] T.G. St Pierre, P.R. Clark, W. Chua-anusorn, A.J. Fleming, G.P. Jeffrey, J.K. Olynyk, P. Pootrakul, E. Robins, R. Lindeman, Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance, Blood 105 (2005) 855–861, https://doi.org/10.1182/blood-2004-01-0177.
[8] L.J. Anderson, S. Holden, B. Davis, E. Prescott, C.C. Charrier, N.H. Bunce, D. N. Firmin, B. Wonke, J. Porter, J.M. Walker, D.J. Pennell, Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload, Eur. Heart J. 22 (2001) 2171–2179, https://doi.org/10.1053/euhj.2001.2822.
[9] J.C. Wood, J.M. Tyszka, S. Carson, M.D. Nelson, T.D. Coates, Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease, Blood 103 (2004) 1934–1936, https://doi.org/10.1182/blood-2003-06-1919.
[10] J.S. Hankins, M.B. McCarville, R.B. Loeffler, M.P. Smeltzer, M. Onciu, F.A. Hoffer, C.-S. Li, W.C. Wang, R.E. Ware, C.M. Hillenbrand, R2* magnetic resonance imaging of the liver in patients with iron overload, Blood 113 (2009) 4853–4855, https://doi.org/10.1182/blood-2008-12-191643.
[11] P. Kirk, M. Roughton, J.B. Porter, J.M. Walker, M.A. Tanner, J. Patel, D. Wu, J. Taylor, M.A. Westwood, L.J. Anderson, D.J. Pennell, Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major, Circulation 120 (2009) 1961–1968, https://doi.org/10.1161/CIRCULATIONAHA.109.874487.
[12] M.D. Cappellini, A. Cohen, J. Porter, A. Taher, V. Viprakasit, Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), 3rd ed., Thalass. Int. Fed., 2014. https://www.ncbi.nlm.nih.gov/books/NBK269371/?report=reader.
[13] M.A. Westwood, B. Wonke, A.M. Maceira, E. Prescott, J.M. Walker, J.B. Porter, D. J. Pennell, Left ventricular diastolic function compared with T2* cardiovascular magnetic resonance for early detection of myocardial iron overload in thalassemia major, J. Magn. Reson. Imaging 22 (2005) 229–233, https://doi.org/10.1002/jmri.20379.
[14] M. Westwood, L.J. Anderson, D.N. Firmin, P.D. Gatehouse, C.C. Charrier, B. Wonke, D.J. Pennell, A single breath-hold multiecho T2* cardiovascular magnetic resonance technique for diagnosis of myocardial iron overload, J. Magn. Reson. Imaging 18 (2003) 33–39, https://doi.org/10.1002/jmri.10332.
[15] R. Labranche, G. Gilbert, M. Cerny, K.-N. Vu, D. Soulières, D. Olivié, J.-S. Billiard, T. Yokoo, A. Tang, Liver Iron quantification with MR imaging: a primer for radiologists, Radiographics 38 (2018) 392–412, https://doi.org/10.1148/rg.2018170079.
[16] P. Kirk, T. He, L.J. Anderson, M. Roughton, M.A. Tanner, W.W.M. Lam, W.Y. Au, W.C.W. Chu, G. Chan, R. Galanello, G. Matta, M. Fogel, A.R. Cohen, R.S. Tan, K. Chen, I. Ng, A. Lai, S. Fucharoen, J. Laothamata, S. Chuncharunee, S. Jongjirasiri, D.N. Firmin, G.C. Smith, D.J. Pennell, International reproducibility of single breathhold T2* MR for cardiac and liver iron assessment among five thalassemia centers, J. Magn. Reson. Imaging 32 (2010) 315–319, https://doi.org/10.1002/jmri.22245.