

Noninvasive liver iron quantification by MRI using refocused gradient-echo (bSSFP): preliminary results

Nichtinvasive Quantifizierung des Lebereisengehalts mittels MRT unter Verwendung einer refokussierten Gradienten-Echo-Sequenz (bSSFP): erste Ergebnisse

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Key words

MR-imaging, iron, abdomen, hematologic

received 06.02.2023

accepted 29.03.2023

published online 03.05.2023

Bibliography

Fortschr Röntgenstr 2023; 195: 804–808

DOI 10.1055/a-2072-7148

ISSN 1438-9029

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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ABSTRACT

Purpose To evaluate the feasibility of using a balanced steady-state free precession sequence (bSSFP) to determine liver iron content (LIC).

Method Thirty-five consecutive patients with liver iron overload were examined with bSSFP. Signal intensity ratios of liver parenchyma to paraspinal muscles were retrospectively correlated with LIC values obtained by FerriScan, which was used as the reference method. Combinations of bSSFP protocols were also evaluated. The best combination was utilized to calculate LIC from bSSFP data. The sensitivity and specificity

for the therapeutically relevant LIC threshold of 80 $\mu\text{mol/g}$ (4.5 mg/g) were determined.

Results LIC values ranged from 24 to 756 $\mu\text{mol/g}$. The best SIR-to-LIC correlation of a single protocol was obtained with a 3.5-ms repetition time (TR) and 17° excitation flip angle (FA). A combination of protocols with TRs of 3.5, 5, and 6.5 ms, each at 17° FA, yielded a superior correlation. LIC values calculated using this combination resulted in a sensitivity/specificity of 0.91/0.85.

Conclusion bSSFP is basically suitable to determine LIC. Its advantages are high SNR efficiency and the ability to acquire the entire liver in a breath hold without acceleration techniques.

Key Points:

- The bSSFP sequence is suited to quantify liver iron overload.
- bSSFP has a high scanning efficiency and potential for LIC screening.
- Despite susceptibility artifacts, the LIC determined from bSSFP data showed high accuracy.

Citation Format

- Wunderlich AP, Cario H, Götz M et al. Noninvasive liver iron quantification by MRI using refocused gradient-echo (bSSFP): preliminary results. Fortschr Röntgenstr 2023; 195: 804–808

ZUSAMMENFASSUNG

Ziel Es wurde geprüft, ob die balancierte Steady-State-Free Precession-Sequenz (bSSFP) zur Bestimmung des Lebereisengehalts (LIC) geeignet ist.

Methode 35 konsekutive Patienten mit Eisenüberladung der Leber wurden mit bSSFP untersucht. Das Verhältnis der Signalintensität des Leberparenchyms zu den paraspinalen Muskeln wurde retrospektiv mit LIC-Werten korreliert, die mit FerriScan als Referenzmethode ermittelt wurden. Es wurden auch Kombinationen von bSSFP-Protokollen analysiert. Die beste Kombination wurde zur Berechnung des LIC aus den bSSFP-Daten verwendet. Sensitivität und Spezifität für den therapeutisch relevanten LIC-Schwellenwert von 80 $\mu\text{mol/g}$ (4,5 mg/g) wurden bestimmt.

Ergebnisse Die Spanne der LIC-Werte betrug 24 bis 756 $\mu\text{mol/g}$. Die beste Korrelation der SIR-Werte zum Referenz-

enz-LIC wurde bei einem einzelnen Protokoll mit einer Wiederholungszeit (TR) von 3,5 ms und einem Anregungs-Flip-Winkel (FA) von 17° ermittelt. Eine kombinierte multiple lineare Regression von Protokollen mit TRs von 3,5, 5 und 6,5 ms, jeweils bei 17° FA, führte zu einer verbesserten Korrelation. Die mit dieser Kombination berechneten LIC-Werte zeigten eine Sensitivität/Spezifität von 0,91/0,85.

Schlussfolgerung Die bSSFP-Sequenz ist grundsätzlich geeignet, um LIC-Werte zu bestimmen. Vorteile sind die hohe Effizienz, also ein gutes Signal-zu-Rausch-Verhältnis bei kurzer Scanzeit, sowie die Möglichkeit, die gesamte Leber in

einem Atemstillstand ohne Beschleunigungstechniken wie parallele Bildgebung zu erfassen.

Kernaussagen:

- Die bSSFP-Sequenz ist für die Quantifizierung der Eisenüberladung der Leber geeignet.
- Die bSSFP-Sequenz hat eine hohe Scaneffizienz und Potenzial für LIC-Screening.
- Trotz Suszeptibilitätsartefakten zeigte die aus bSSFP-Daten bestimmten LIC-Werte eine hohe Genauigkeit.

Introduction

Noninvasive quantification of liver iron content (LIC) is essential for patients with iron overload due to increased iron resorption or patients suffering, e. g., from anemia receiving blood transfusions. MRI methods are widely used for noninvasive LIC quantification. Overviews are given, e. g., by Sarigianni and Henninger [1, 2]. The majority of them use gradient-echo sequences, while a method employing spin-echo has been FDA-certified [3].

As far as we figured out, the refocused gradient echo sequence, also called balanced steady-state free precession (bSSFP) sequence, has not yet been investigated for its potential to quantify iron. This sequence is characterized by a high SNR efficiency, i. e., a high ratio of signal-to-image noise per scan time [4]. For this reason, the suitability of the bSSFP sequence for LIC quantification was investigated in this study.

Methods

According to the latest version of the Declaration of Helsinki (revision dated 2013, Fortaleza, Brazil) and after approval of our local ethics committee, patients referred to our institution for noninvasive LIC quantification between June 2014 and February 2015 were studied at 1.5 T (Magnetom Avanto, Siemens Healthcare GmbH, Erlangen, Germany). All patients, or, for minors, their parents, gave written informed consent. LIC was determined using the FerriScan procedure [3]. Images were acquired with the ap-

propriate protocols and transferred for centralized evaluation. These LIC values served as a reference. Additionally, eleven protocols with different contrasts were acquired in all patients with a bSSFP sequence in 3D mode with FoV of 315*420 mm, matrix size 192 x 112 x 26 and resolution 2.2 x 2.2 x 5 mm. Acquisition was performed in shallow breathing with long-term averaging of 3 acquisitions to avoid pulsation and breathing artifacts, resulting in a total acquisition time of seven minutes for all protocols together. Parameters deviating between the different bSSFP protocols are listed in ► **Table 1**. For signal homogeneity in the imaging plane, the body resonator was used as a receive coil.

The bSSFP data were retrospectively analyzed by manually positioning three circular regions of interest (ROIs) of predefined size (1.75 cm²) in the vessel-free liver parenchyma, preferably the right liver lobe, and two bilaterally in the paraspinal musculature (0.75 cm²), as shown in ► **Fig. 1**. ROI placement was performed in two different axial slices in each patient. Subsequently, the liver signal was divided by that of the muscle to obtain signal intensity ratio (SIR) values.

Statistical analysis was performed in SPSS (v. 27, 2020, IBM, Armonk, USA). Logarithms of SIR values of the different protocols were linearly correlated with the liver iron reference value. The coefficient of determination R² was used to determine the quality of correlations. Protocols showing the best correlation at this step were then used to test multiple linear correlations of SIR logarithms to LIC reference. Correlation parameters of this multiple linear correlation were used to derive a relationship to determine

► **Table 1** List of bSSFP protocols used.

Protocol no.	Echo time TE [ms]	Repetition time TR [ms]	Bandwidth [Hz/pixel]	Acquisition time [s]	Excitation flip angles FA [°]
1–3	1.75	3.5	668	29	7, 10, 17
4, 5	1.75	3.5	1184	29	30, 50
6–8	2.5	5	395	41	7, 17, 60
9–11	3.25	6.5	243	53	7, 17, 50

Overview of the bSSFP protocols used in this study.
Überblick über die bSSFP-Protokolle, die in dieser Studie verwendet wurden.



► **Fig. 1** Example of a bSSFP image at a TR of 3.5 ms and 17° FA with three liver ROIs and two in the paraspinal muscles.

► **Abb. 1** Beispiel eines bSSFP-Bildes mit einer Repetitionszeit TR von 3,5 ms und einem Anregungswinkel von 17° mit 3 ROIs in der Leber und 2 in der paraspinalen Muskulatur.

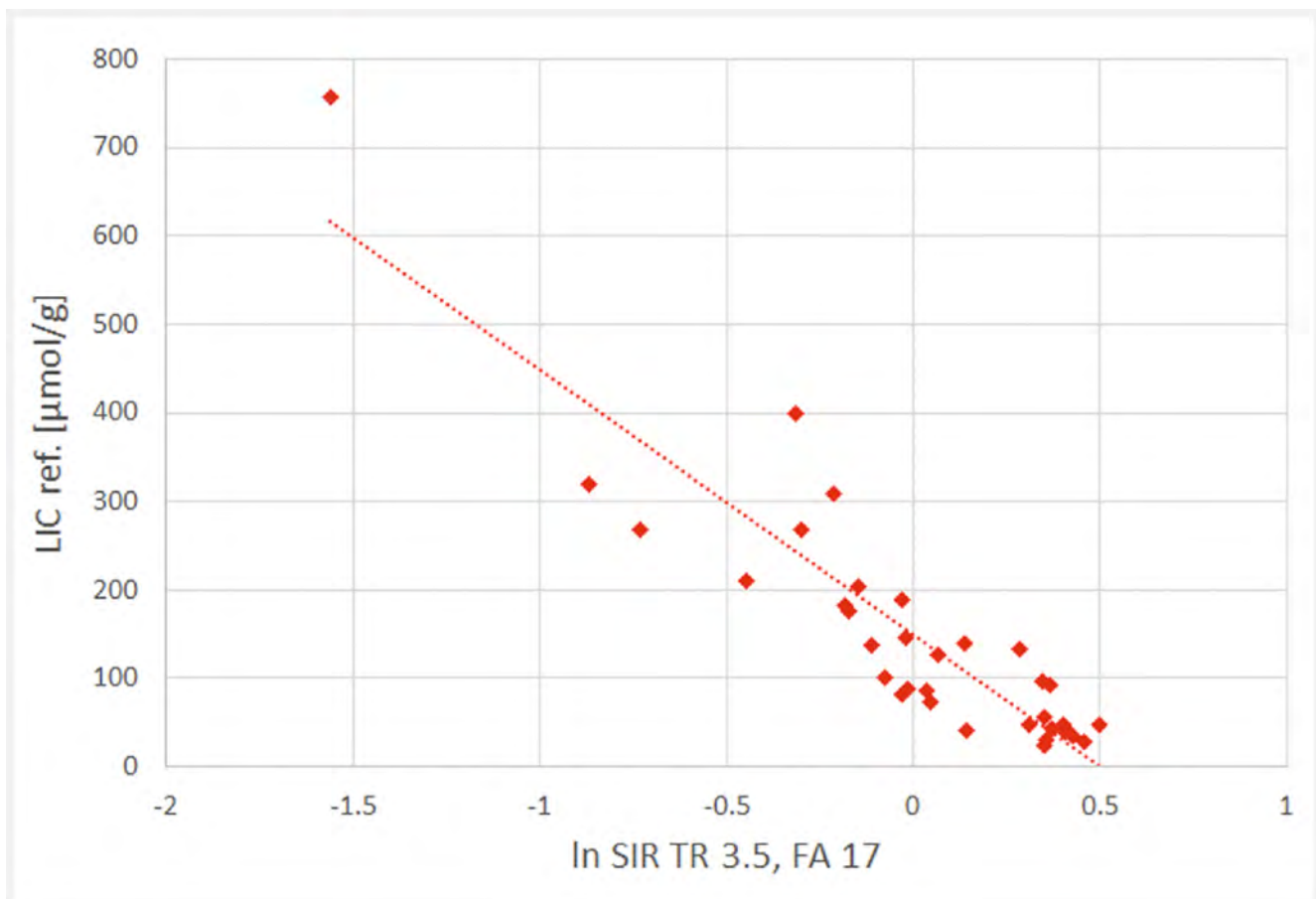
the LIC from bSSFP data. The sensitivity and specificity of these bSSFP-LIC values with respect to the reference method were studied for an LIC threshold of 80 $\mu\text{mol/g}$ (4.5 mg/g) relevant for iron chelation therapy [5].

Results

In the studied time interval, data of 35 patients (24 male, age range: 6.9 to 73 years, mean \pm standard deviation 24.2 \pm 14.4 years) were suitable for analysis and were evaluated.

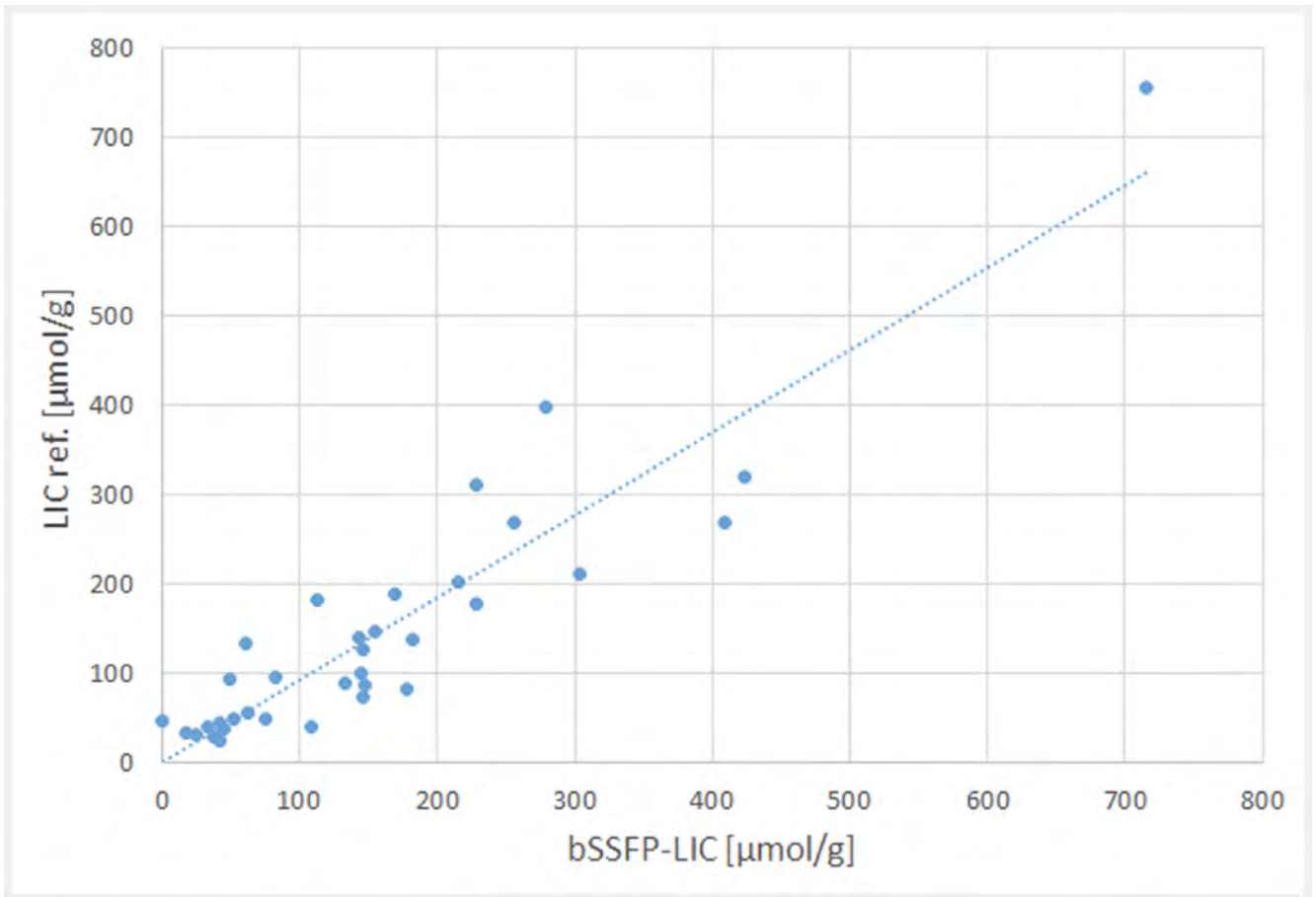
LIC reference values ranged from 24 to 756 $\mu\text{mol/g}$ (MW \pm stdDev 145 \pm 143 $\mu\text{mol/g}$) in our patient cohort. Yet, their distribution was not uniform: most LIC reference values were observed between 20 and 200 $\mu\text{mol/g}$, only a few were between 200 and 400 $\mu\text{mol/g}$, and there was only one rather high value of 756 $\mu\text{mol/g}$.

The best correlation of a single protocol was obtained with a repetition time TR of 3.5 ms at a flip angle (FA) of 17° with a coefficient of determination R^2 of 0.82. ► **Fig. 2** shows a scatterplot of these data. For the other TRs, FA of 17° also yielded the best results. A multiple linear correlation of the three protocols with TRs of 3.5, 5, and 6.5 ms, each at an FA of 17°, resulted in a coeffi-



► **Fig. 2** Scatterplot of LIC reference values vs. ln (SIR). The dotted line is the regression line.

► **Abb. 2** Punktegrafik der Referenzwerte der Lebereisenkonzentration als Funktion der Logarithmen der Signal-Intensitäts-Verhältnisse. Die gepunktete Linie ist die Regressionsgerade.



► **Fig. 3** Scatterplot of LIC reference values vs. bSSFP-LIC. The dotted line is the regression line.

► **Abb. 3** Punktgrafik der Referenzwerte der Leber-Eisen-Konzentration gegenüber den mit der bSSFP-Methode ermittelten Werten. Die gepunktete Linie ist die Regressionsgerade.

cient of determination of 0.85. ► **Fig. 3** shows a scatterplot of bSSFP-LIC values determined using the resulting relationship, and the corresponding 2-by-2 table for the LIC threshold of 80 µmol/g (4.5 mg/g) is given in ► **Table 2**. We found a sensitivity/specificity of 0.91/0.85.

Discussion

The balanced gradient echo sequence (bSSFP) has a complex signal behavior. Due to the necessary balance of all gradients, it is favorable to choose the echo time TE as half the repetition time TR. In this case, the bSSFP signal does not depend on T_2^* , but on T_2 , like spin-echo. However, contrast is influenced also by longitudinal relaxation T_1 . In detail, contrast depends on the T_2 to T_1 ratio [6, 7]. Another parameter influencing contrast is the excitation angle, which is freely selectable within the maximum possible energy deposition. Short echo times are advantageous for this sequence, but require fast gradient switching and imply high energy exposure to the patients because of the fast repetition rate of excitation pulses. Hence, the maximal flip angle is limited.

► **Table 2** 2-by-2 table: bSSFP vs. reference method.

		LIC bSSFP		Sum
		Negative	Positive	
LIC reference	Neg	11	2	13
	Pos	2	20	22
Sum		13	22	35

2 × 2 table of LIC values calculated from bSSFP data vs. LIC reference values for the threshold of 80 µmol/g (4.5 mg/g), important for therapy management.

Vierfeldertafel der aus den bSSFP-Daten ermittelten Leber-Eisen-Konzentrationen gegenüber den Werten der Referenzmethode für die therapeutisch wichtige Schwelle von 80 µmol/g.

As the presented data show, bSSFP is in principle suitable to quantify liver iron content. Its advantages are high scanning efficiency, i. e., high signal-to-noise ratio achieved in short acquisition times. This allows imaging of the entire liver in a single breath-

hold without additional acceleration techniques such as parallel imaging, which require multiple receive coils and multiple receiver channels, but increase image noise. In our approach, breath hold could not be used in order to minimize pulsation artifacts. This was efficient for short TR protocols, but worse with increasing TR (data not shown).

The sequence used was a standard sequence that is generally available and easily applicable in the clinical routine.

In total, eleven protocols were studied since it was not clear which combination of acquisition parameters was best suited for LIC quantification. Originally, it was intended to determine the tissue parameters T1 and T2 with a nonlinear fitting process. To evaluate the feasibility of this, multiple parameter combinations seemed necessary and advantageous. Unfortunately, we were not successful (data not shown). Probably, this was caused by RF inhomogeneity, which was present in some patients at varying locations, and/or by banding artifacts. For SIR analysis, which also was planned from the beginning, it was unclear which parameters perform best and if, for the wide range of LIC values expected for our patients, a step-wise approach as proposed by Gandon would have been required [8].

The paraspinal muscle signal as internal reference was proposed by Alustiza and Gandon to quantify LIC with GRE [8, 9]. The motivation to investigate the correlation of the natural logarithm of SIR values rather than the SIR values themselves was previously published work on the SIR of gradient echo data [10].

The sensitivity and specificity previously reported for a sophisticated spoiled gradient echo (GRE) method requiring only a single breath hold were 0.98/0.67 for the 80 $\mu\text{mol/g}$ (4.5 mg/g) threshold [11]. In this preliminary study we found superior specificity for bSSFP, which, however, still needs to be verified in larger patient numbers. Sensitivity was higher for GRE. Probably, a combination of GRE and bSSFP would be advantageous for reliable patient management.

The major advantage of the method presented here is the simple mathematical approach avoiding an extensive fitting process. Compared to other SIR approaches at 1.5 T, bSSFP has the benefit of covering a large LIC range, avoiding the need for an additional protocol to address excessive iron overload [12]. With these benefits, bSSFP is probably suited for liver iron overload screening.

Limitations

The high sensitivity of the bSSFP sequence to magnetic field inhomogeneities is probably one reason for the scatter of the measured SIR values, since a standard bSSFP sequence was used. Maybe, results could be enhanced using proposed measures to reduce bSSFP signal reduction caused by susceptibility effects [13, 14].

The number of patients studied was small. Furthermore, LIC reference values were not normally distributed. In detail, a single value was nearly double the second largest. Therefore, the obtained calibration equation may be not very reliable. Further studies with larger patient numbers and a distribution of LIC reference

values closer to Gaussian distribution are needed to evaluate the suitability of the bSSFP sequence more thoroughly.

Despite these limitations, we were able to show that bSSFP, an efficient and fast sequence that is, however, sensitive to susceptibility effects, is suitable for the quantification of liver iron content. Sequence variants which are more robust against susceptibility artifacts should be studied for their potential to improve the method.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement

We acknowledge Karla Miller for her striking talk on bSSFP at the ISMRM 2022 meeting in London which encouraged us to re-evaluate our data.

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