

Appendix S1

Intra- and Inter Reader Comparison for Healthy Volunteer

Intra class correlation coefficient (ICC) for T2 between the same reader was 0.97 (95% CI: 0.96–0.98) and ICC between two different readers was 0.95 (0.92–0.97). Bland Altman Analysis revealed no relevant bias between two reads by the same person and between two different persons (bias: 0.13 msec and 0.02 ms, respectively). See Figure S1 and Figure S2.

Phantom Data Intraobserver Comparison

The T2-bssfp 3RR phantom measurements were evaluated twice by the same reader. The ICC for T2 values was 1 (0.999–1). See Figure S3.

Extended Discussion

Suggestions for Mitigating Heart Rate Dependency and New T2 Mapping Sequence Developments

We advocate to use the same acquisition scheme in all patients as new site-specific reference ranges must be generated when acquisition parameters are changed (1). To allow sufficient magnetization recovery over a broad range of heart rates, a fixed recovery period (ie, 3 seconds) may be used, which has the advantage of providing the same predictable breath-hold time for all patients. Alternatively, a recovery period of 6 RR intervals, which would allow a recovery interval of 3 seconds even at a heart rate of 120 bpm could be used. The disadvantage of this is a relatively longer breath-hold duration at lower heart rates (eg, 18 seconds at 60 bpm). Accordingly, in a recent review, a resting period of three seconds was recommended (18). However, this variant was not available to us, and we were therefore unable to assess its heart rate dependency.

Recent sequence developments aimed to mitigate heart rate dependency in T₂ mapping approaches. T₂ sequences which used a nonselective 90° saturation prepulses prior to the acquisition module to reset the magnetization and avoid heart rate dependency have been described (26,27). Magnetic resonance fingerprinting (MRF) is a recently introduced approach (28), which offers simultaneous assessment of T₁ and T₂ relaxation times in a single breath-hold. In a MRF phantom study consistent T₁ and T₂ measurements over a range of heart rates between 40 and 120 could be shown (29). However, these sequences are not widely available, their accuracy and precision may vary, and clinical validation is required before entering routine employment.

Additional Factors Influencing Reproducibility of T2 Mapping Results

To ensure the reproducibility of T2 mapping results, factors such as scanner field strength, intravendor diversity, sequence parameters, scan parameters, and postprocessing approaches should be considered and kept as constant as possible (18). When controlled for these factors, T2 mapping results can be standardized across different sites (30). Nonetheless, in addition to these

major confounders and physiologic factors, as demonstrated in this study for heart rate, internal scanner settings, intrinsic physiologic properties of tissues and artifacts must be further considered.

Discrepancy between Reference and T2-bSSFP Derived T2 Values

The reference T2 values obtained via the spin echo (SE) sequence and the T2 prep-bSSFP mapping derived T2 values differed in our Bloch simulations and phantom study. This discrepancy can be attributed to the known differences between SE and bSSFP sequences, as well as the two-parameter fit model used, which does not account for changes in the T1/T2 contrast due to imaging pulses until the acquisition of the center of k-space or other imperfections in T2-prep RF pulses (31,32).

References

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Table S1

Phantom Measurements per Tube and Heart Rate (in bpm) for T2-balanced Steady-state Free Precession (bSSFP) 3-RR, Shown T2 Times (ms) are the Mean Value between the First and Second Measurement, CoV = Coefficient of Variation

| Heart Rate | Tube G | Tube D | Tube A | Tube B | Tube E | Tube H | Tube I | Tube F | Tube C |
|---------------|------------------|------------------|-------------------|--------------------|------------------|------------------|------------------|------------------|-------------------|
| 60 | 64.82 | 50.33 | 207.23 | 195.01 | 43.80 | 51.31 | 56.10 | 47.39 | 199.32 |
| 70 | 64.41 | 50.13 | 206.79 | 185.79 | 43.02 | 50.72 | 55.38 | 46.67 | 199.35 |
| 80 | 64.19 | 49.86 | 210.16 | 179.71 | 42.02 | 50.83 | 56.04 | 46.15 | 196.92 |
| 90 | 64.74 | 48.93 | 209.99 | 171.92 | 41.33 | 50.86 | 55.63 | 44.72 | 196.90 |
| 100 | 64.96 | 48.14 | 208.12 | 163.96 | 40.81 | 50.45 | 55.25 | 44.04 | 194.74 |
| 110 | 64.91 | 47.92 | 213.25 | 157.32 | 39.56 | 50.44 | 55.15 | 43.64 | 194.79 |
| 120 | 64.58 | 46.92 | 210.50 | 154.23 | 38.85 | 49.86 | 55.88 | 42.59 | 194.98 |
| 130 | 64.44 | 46.05 | 209.47 | 148.83 | 38.46 | 50.14 | 55.26 | 42.38 | 194.06 |
| Mean \pm SD | 64.62 \pm 0.46 | 48.53 \pm 1.47 | 209.43 \pm 2.71 | 169.59 \pm 15.36 | 40.98 \pm 1.83 | 50.57 \pm 0.53 | 55.58 \pm 0.41 | 44.69 \pm 1.77 | 196.38 \pm 2.43 |
| CoV (%) | 0.71 | 3.02 | 1.29 | 9.05 | 4.48 | 1.06 | 0.75 | 3.97 | 1.24 |

Table S2

Phantom Measurements per Tube and Heart Rate (in bpm) for T2-balanced Steady-state Free Precession (bSSFP) 6-RR, Shown T2 Times (ms) are the Mean Value between the First and Second Measurement, CoV = Coefficient of Variation

| Heart Rate | Tube G | Tube D | Tube A | Tube B | Tube E | Tube H | Tube I | Tube F | Tube C |
|---------------|------------------|------------------|-------------------|-------------------|------------------|-------------------|------------------|------------------|-------------------|
| 60 | 64.70 | 53.53 | 211.01 | 226.00 | 46.65 | 53.11 | 57.43 | 51.18 | 197.33 |
| 70 | 65.66 | 53.78 | 215.67 | 219.59 | 46.74 | 52.60 | 56.79 | 50.86 | 195.96 |
| 80 | 65.15 | 53.81 | 211.09 | 214.85 | 46.14 | 53.04 | 57.07 | 50.57 | 195.29 |
| 90 | 65.07 | 53.48 | 214.43 | 210.86 | 45.93 | 52.81 | 56.87 | 50.06 | 196.93 |
| 100 | 65.51 | 53.19 | 213.36 | 207.40 | 45.32 | 53.21 | 56.61 | 50.14 | 196.67 |
| 110 | 64.72 | 52.80 | 213.32 | 201.89 | 45.02 | 52.91 | 57.00 | 49.47 | 195.16 |
| 120 | 65.12 | 52.92 | 214.89 | 196.35 | 44.96 | 52.98 | 57.03 | 49.35 | 196.58 |
| 130 | 64.62 | 52.34 | 211.24 | 194.08 | 44.45 | 52.75 | 57.09 | 48.72 | 196.86 |
| Mean \pm SD | 65.07 \pm 0.36 | 53.23 \pm 0.48 | 213.13 \pm 1.72 | 52.92 \pm 10.46 | 45.65 \pm 0.78 | 208.88 \pm 0.19 | 56.98 \pm 0.23 | 50.04 \pm 0.78 | 196.34 \pm 0.74 |
| CoV (%) | 0.55 | 0.91 | 0.80 | 5.01 | 1.72 | 0.36 | 0.40 | 1.55 | 0.38 |

Table S3

Phantom Measurements per Tube and Heart Rate (in bpm) for T2-balanced Steady-state Free Precession (bSSFP) 9-RR, Shown T2 Times (ms) are the Mean Value between the First and Second Measurement, CoV = Coefficient of Variation

| Heart Rate | Tube G | Tube D | Tube A | Tube B | Tube E | Tube H | Tube I | Tube F | Tube C |
|---------------|------------------|------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|-------------------|
| 60 | 65.41 | 54.15 | 211.68 | 229.97 | 47.64 | 53.62 | 57.24 | 50.73 | 195.98 |
| 70 | 64.93 | 54.05 | 209.88 | 223.26 | 47.07 | 52.98 | 57.53 | 50.84 | 196.82 |
| 80 | 65.07 | 54.18 | 210.39 | 225.49 | 47.21 | 52.62 | 57.09 | 50.82 | 195.93 |
| 90 | 64.71 | 54.12 | 210.92 | 224.19 | 47.19 | 53.00 | 57.12 | 50.57 | 194.37 |
| 100 | 65.49 | 54.35 | 213.15 | 221.67 | 47.05 | 53.38 | 56.78 | 50.67 | 193.48 |
| 110 | 65.17 | 53.87 | 213.07 | 217.29 | 46.63 | 52.71 | 57.05 | 50.47 | 196.90 |
| 120 | 65.29 | 54.01 | 211.72 | 216.44 | 46.60 | 52.96 | 57.00 | 50.36 | 194.61 |
| 130 | 65.76 | 54.09 | 210.82 | 215.09 | 46.58 | 53.22 | 56.78 | 49.78 | 195.54 |
| Mean \pm SD | 65.23 \pm 0.31 | 54.10 \pm 0.13 | 211.45 \pm 1.11 | 221.67 \pm 4.77 | 46.99 \pm 0.35 | 53.06 \pm 0.31 | 57.07 \pm 0.23 | 50.53 \pm 0.32 | 195.45 \pm 1.13 |
| CoV (%) | 0.48 | 0.24 | 0.53 | 2.15 | 0.74 | 0.59 | 0.40 | 0.64 | 0.58 |

Table S4

Phantom Study; Confidence Intervals of Spearman's rho for the Correlation between Heart Rate (HR) and T2 (ms), Measured by bSSFP with 3-RR, 6-RR and 9-RR Resting Periods

| Confidence Intervals of Spearman's rho | | | | | |
|--|--------------------|---------------------|-------------------------|---|--------|
| Tube | Included Variables | Spearman's rho | Significance (2-tailed) | 95% Confidence Intervals (2-tailed) ^{b, c} | |
| | | | | Lower | Upper |
| D (1041/44 ms) | HR-T2 3-RR | -1.000 ^a | <0.001 | . | . |
| | HR-T2 6-RR | -0.881 | 0.004 | -0.979 | -0.444 |
| | HR-T2 9-RR | -0.405 | 0.320 | -0.870 | 0.441 |
| E (1534/40 ms) | HR-T2 3-RR | -1.000 ^a | <0.001 | . | . |
| | HR-T2 6-RR | -0.976 | <0.001 | -0.996 | -0.864 |
| | HR-T2 9-RR | -0.929 | <0.001 | -0.988 | -0.632 |
| F (1293/43 ms) | HR-T2 3-RR | -1.000 ^a | <0.001 | . | . |
| | HR-T2 6-RR | -0.976 | <0.001 | -0.996 | -0.864 |
| | HR-T2 9-RR | -0.905 | 0.002 | -0.984 | -0.534 |

^a Confidence Interval cannot be computed for this variable pair because the correlation is -1.

^b Estimation is based on Fisher's r-to-z transformation.

^c Estimation of standard error is based on the formula proposed by Fieller, Hartley, and Pearson.

Table S5

Intra-reader Comparison for Healthy Volunteer Data, Values are given as Mean \pm SD

| | Read 1 | Read 2 |
|--------|----------------|----------------|
| T2, ms | 51.1 \pm 2.3 | 51.3 \pm 2.4 |

Table S6**Association between Individual Factors and T2 Values in Healthy Volunteers**

| Factor | Regression Coefficient, Beta | 95% Confidence Interval | P | R ² |
|------------|------------------------------|-------------------------|-------|----------------|
| Heart rate | -0.075 | -0.128--0.021 | 0.007 | 0.114 |
| Age | 0.018 | -0.027--0.063 | 0.417 | 0.011 |
| Sex | -0.028 | -1.262--1.206 | 0.964 | 0.000 |

Note.—Linear regression analysis, association between heart rate (in bpm), age (years), sex (dichotom: male, female) and T2 (ms) as the dependent variable.

Table S7**Association between Heart Rate, Age, Sex and T2 in Healthy Volunteers, Multiple Linear Regression with Backward Selection and T2 (ms) as Dependent Variable**

| Coefficients ^a | | | | | | | | |
|---------------------------|------------|-----------------------------|------------|---------------------------|--------|--------|---------------------------------|-------------|
| Model | | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95,0% Confidence Interval for B | |
| | | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| 1 | (Constant) | 55.269 | 2.181 | | 25.340 | <0.001 | 50.902 | 59.637 |
| | HR | -0.069 | 0.028 | -0.314 | -2.492 | 0.016 | -0.125 | -0.014 |
| | Sex | -0.050 | 0.621 | -0.011 | -0.081 | 0.936 | -1.294 | 1.194 |
| | Age | 0.020 | 0.023 | 0.114 | 0.873 | 0.386 | -0.025 | 0.065 |
| 2 | (Constant) | 55.215 | 2.058 | | 26.832 | <0.001 | 51.096 | 59.335 |
| | HR | -0.069 | 0.027 | -0.313 | -2.521 | 0.014 | -0.124 | -0.014 |
| | Age | 0.020 | 0.021 | 0.117 | 0.941 | 0.350 | -0.023 | 0.063 |
| 3 | (Constant) | 55.888 | 1.928 | | 28.991 | <0.001 | 52.031 | 59.746 |
| | HR | -0.068 | 0.027 | -0.309 | -2.492 | 0.016 | -0.123 | -0.013 |

^a Dependent Variable: T2

Table S8**Adjusted Coefficient of Determination for Different Models to Predict T2 Values**

| Model | Adjusted R ² |
|----------------------|-------------------------|
| Heart rate, age, sex | 0.040 |
| Heart rate, age | 0.049 |
| Heart rate | 0.060 |

Note.—The adjusted R² demonstrates that the addition of age or sex does not genuinely improve the model.