Impact of the Choice of Native $T_1$ in Pixelwise Myocardial Blood Flow Quantification

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Background: Quantification of myocardial blood flow (MBF) from dynamic contrast-enhanced (DCE) MRI can be performed using a signal intensity model that incorporates $T_1$ values of blood and myocardium.

Purpose: To assess the impact of $T_1$ values on pixelwise MBF quantification, specifically to evaluate the influence of 1) study population-averaged vs. subject-specific, 2) diastolic vs. systolic, and 3) regional vs. global myocardial $T_1$ values.

Study Type: Prospective.

Subjects: Fifteen patients with chronic coronary heart disease.

Field Strength/Sequence: 3T; modified Look-Locker inversion recovery for $T_1$ mapping and saturation recovery gradient echo for DCE imaging, both acquired in a mid-ventricular short-axis slice in systole and diastole.

Assessment: MBF was estimated using Fermi modeling and signal intensity nonlinearity correction with different $T_1$ values: study population-averaged blood and myocardial, subject-specific systolic and diastolic, and segmental $T_1$ values. Myocardial segments with perfusion deficits were identified visually from DCE series.

Statistical Tests: The relationships between MBF parameters derived by different methods were analyzed by Bland–Altman analysis; corresponding mean values were compared by $t$-test.

Results:
- Using subject-specific diastolic $T_1$ values, global diastolic MBF was $0.61 \pm 0.13$ mL/(min·g). It did not differ from global MBF derived from the study population-averaged $T_1$ ($P = 0.88$), but the standard deviation of differences was large (0.07 mL/(min·g), 11% of mean MBF). Global diastolic and systolic MBF did not differ ($P = 0.12$), whereas global diastolic MBF using systolic ($0.62 \pm 0.13$ mL/(min·g)) and diastolic $T_1$ values differed ($P < 0.05$). If regional instead of global $T_1$ values were used, segmental MBF was lower in segments with perfusion deficits (bias = $-0.03$ mL/(min·g), $-7\%$ of mean MBF, $P < 0.05$) but higher in segments without perfusion deficits (bias = 0.01 mL/(min·g), 1% of mean MBF, $P < 0.05$).

Data Conclusion: Whereas cardiac phase-specific $T_1$ values have a minor impact on MBF estimates, subject-specific and myocardial segment-specific $T_1$ values substantially affect MBF quantification.

Level of Evidence: 3

Technical Efficacy Stage: 3

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Dynamic contrast-enhanced (DCE) cardiac magnetic resonance imaging (MRI) represents a recognized technique for the assessment of myocardial perfusion and ischemia.1,2 Whereas a series of longitudinal relaxation time ($T_1$)-weighted images acquired during the first passage of a bolus of contrast agent (CA) are typically inspected visually for regional myocardial perfusion deficits, corresponding temporal signal intensity changes provide quantitative information on myocardial blood flow (MBF). The accuracy of this technique depends on the reliability of the $T_1$-weighting, which is inherent to short-echo-time $T_1$-weighted sequences commonly used for DCE imaging. The value of $T_1$ is influenced by the solubility of the contrast agent and the local blood flow. The aim of this study was to evaluate the impact of different $T_1$ values on MBF quantification in patients with chronic coronary heart disease.
MBF relates temporal CA concentration changes in the left ventricular (LV) blood pool, represented by the arterial input function (AIF), with temporal CA concentration changes in myocardial tissue. Consequently, MBF estimation requires the conversion of measured SI in blood and myocardial tissue into corresponding CA concentrations, which is complicated by their typically nonlinear relationships. Various conversion methods have been introduced, including minimization of deviation from linearity directly during image acquisition, as performed by low-dosage, dual-bolus, and dual-sequence approaches, the use of retrospectively empirical calibration curves, or the application of SI models in combination with additional calibration images.

The usage of an SI model that incorporates native T₁ values of blood and myocardium for SI-to-CA-concentration conversion is tempting because of its universality and the integration of T₁ mapping into clinical cardiovascular MRI. While MBF estimation has been extensively studied employing native T₁ normal values, the first attempts were made to render the method more subject-specific by using native blood and myocardial T₁ values measured from native T₁ maps. The feasibility of pixelwise MBF quantification employing an SI model incorporating native T₁ values of blood and myocardium remains, however, to be examined. Studies show that native myocardial T₁ values differ between systole and diastole as well as between myocardial segments, the latter especially if infarcted regions are present. We therefore hypothesize that not only global, but also regional native myocardial T₁ values, as well as the cardiac phase of native T₁ maps, affect SI model-based MBF estimates.

Thus, the aims of this study were to assess the impact of native T₁ values on pixelwise MBF quantification by evaluating 1) the necessity for using subject-specific native T₁ values, 2) the influence of the cardiac phase, and 3) the need for using regional instead of global native myocardial T₁ values.

Materials and Methods

Study Population

This prospective study (ClinicalTrials.gov identifier, NCT0253835) was approved by the local Ethical Review Board, and all subjects gave written informed consent. Between February 2016 and April 2017, 20 adult patients with known chronic coronary heart disease (CHD) and without contraindications to contrast-enhanced MR underwent comprehensive cardiac MRI including myocardial DCE imaging and native and postcontrast T1 mapping. The feasibility of pixelwise MBF quantification employing an SI model incorporating native T₁ values of blood and myocardium remains, however, to be examined. Studies show that native myocardial T₁ values differ between systole and diastole as well as between myocardial segments, the latter especially if infarcted regions are present. We therefore hypothesize that not only global, but also regional native myocardial T₁ values, as well as the cardiac phase of native T₁ maps, affect SI model-based MBF estimates.

MR Image Acquisition

ECG-gated cardiac MR was performed with a 3T clinical MR scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) using an 18-channel body coil and 12 elements of a 32-channel spine coil with the patient in the supine position. T₁ maps and DCE series were acquired under a resting condition and inspiratory breath-holding in the same mid-ventricular short-axis slice.

An ECG-gated modified Look-Locker inversion recovery (MOLLI) sequence with single-shot balanced steady-state free precession (bSSFP) readout, motion correction, and automatic T₁ map generation was used to derive native T₁ maps at end-systole and diastasis. The MOLLI scheme was 5(5)3, meaning the acquisition of five images after the first inversion pulse and after a waiting period of five heartbeats the acquisition of three further images after a second inversion pulse. Protocol parameters of the bSSFP readout were repetition time (TR) = 2.7 msec; echo time (TE) = 1.1 msec; flip angle = 35°; bandwidth = 1085 Hz/pixel; generalized autocalibrating partially parallel acquisition (GRAPPA) factor = 2; partial Fourier reconstruction = 7/8; field of view (FOV) = 307 × 360 mm²; and voxel size = 2.1 × 1.4 × 8.0 mm³.

DCE imaging was performed with the CA gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) at a dose of 0.05 mmol/kg body weight. The CA was administered into the right antecubital vein by means of a power injector (Medrad, Volkach, Germany) at a rate of 4 mL/s, followed by a saline flush of 30 mL at the same rate. Starting with CA administration, its passage was imaged for 70 heartbeats employing an ECG-gated single-shot saturation recovery fast low-angle shot (SR FLASH) sequence; the breath-hold command given during acquisition targeted a breath-hold period from the arrival of the bolus in the LV until its second pass. The imaging time per frame of the SR FLASH sequence was 158.8 msec, which allowed imaging of the same mid-ventricular short-axis slice four to six times within each cardiac interval. Further protocol parameters were TR = 2.2 msec; TE = 1.1 msec; time between composite saturation pulse and central k-space line of image readout (TI) = 90 msec; flip angle = 12°; bandwidth = 930 Hz/Pixel; GRAPPA factor = 2; FOV = 330 × 360 mm²; voxel size = 2.7 × 1.9 × 0.0 mm³; and matrix = 124 × 192. Images of the DCE scan within the first two heartbeats were acquired without applying magnetization preparation at a low flip angle of 5°. The resulting (precontrast) proton density-weighted images were used to estimate the coil sensitivity of the receiver coils. This estimation, together with a surface coil correction as well as a nonrigid motion correction of every frame, was performed automatically during image reconstruction by the scanner software.

Immediately after the DCE scan, a second bolus of CA was administered at a dose of 0.10 mmol/kg body weight. Approximately 15 minutes after CA administration, myocardial late gadolinium enhancement (LGE) was imaged by T₁ mapping at diastasis employing the MOLLI sequence described above but with MOLLI scheme 4(1)3(1)2 (acquisition of 4, 3, and 2 images after the first, second, and third inversion pulse, respectively, with waiting periods of one heartbeat in between).
For detailed patient characterization, cardiac MR also included LV function and LGE imaging in inspiratory breath-holding. For details, see the Supporting Information.

**Visual Analysis of Regional Myocardial Perfusion Deficits**

The mid-ventricular DCE series acquired in diastole were analyzed visually for regional myocardial perfusion deficits, which were interpreted according to the American Heart Association (AHA) model by three readers (C.R., V.N., and U.R. with 4, 5, and 20 years of experience, respectively). The discrimination between perfusion deficits and possible dark rim artifacts was based on localization and duration of reduced SI increase during the first passage of CA as well as the presence of LGE visualized in postcontrast T1 maps (Fig. 1). In particular, an AHA segment was counted as a perfusion deficit segment if the majority of readers identified reduced SI increase in at least 50% along the subendocardial border of the segment.

**Determination of Regional Native T1 Values**

Systolic and diastolic global native myocardial and blood T1 values were determined by manual segmentation of the endocardial and epicardial borders, as well as a region of interest (ROI) placed in the LV blood pool in the corresponding native T1 maps by a reader with 4 years of experience (C.K.) using dedicated cardiac image analysis software (cvi42, Circle Cardiovascular Imaging, Calgary, Canada). An offset of 25% from the drawn endo- and epicardial contours was chosen to ensure robust T1 mean value estimates. Moreover, diastolic T1 maps were evaluated according to the six AHA segments of the measured mid-ventricular slice, halves of these AHA segments, thirds of these AHA segments, and quarters of these AHA segments to derive the corresponding 12-, 18-, and 24-sectional mean native T1 values.

**Pixelwise and Regional MBF Determination**

DCE series in end-systole (systolic DCE series) and diastasis (diastolic DCE series) together with an estimate of native myocardial and blood T1 values were converted to pixelwise MBF maps and regional MBF estimates using in-house software implemented in MATLAB (MathWorks, Natick, MA). Figure 2 shows an overview of the image processing steps.

In a first step, the AIF was obtained from the DCE series as the mean signal from a central ROI in the LV blood pool, which was manually drawn onto one image of the perfusion series with suitable contrast between LV blood pool and myocardium, excluding papillary muscles. Then temporal SI changes of the AIF and every single pixel of the DCE series were converted to CA concentration changes using an SI model for the employed SR FLASH sequence:

$$SI = e \cdot \left( 1 - e^{-TD/T1} \right) \cdot a^{n-1} + \left( 1 - e^{-TR/T1} \right) \cdot \frac{1 - a^{n-1}}{1 - a}$$

with $a = \cos(\alpha) \cdot e^{-TR/T1}$

where $\alpha$ denotes the flip angle, $TR$ the repetition time per phase encoding, $n$ the number of phase encoding steps between acquisition.

**FIGURE 1:** Example of a perfusion deficit (a) and a dark rim artifact (b). In both cases, the DCE image during maximum SI in the LV (left panel) shows reduced SI increase in the myocardium (arrow). During maximum SI in the myocardium or equivalently some seconds later (center panel), only the perfusion deficit persists. Only the perfusion deficit demonstrates regional consistent late gadolinium enhancement in the postcontrast T1 map (right panel). DCE = dynamic contrast-enhanced; SI = signal intensity; LV = left ventricle.
start and k-space center (set to 31), and TD the time delay between the composite saturation pulse and the start of FLASH readout (set to 21.2 msec). $c$ is a scaling factor proportional to the equilibrium magnetization and is assumed to be constant throughout the DCE series.\(^{11}\) For every pixel, $c$ was estimated employing the native T1 value of blood or myocardium (for choices of native T1 values, see next section) as well as the baseline signal determined as the temporal median of the signal from start to CA arrival in the LV blood pool. Equation 1 was then used to determine the T1 values for each timepoint of the AIF and each pixel of the DCE series. CA concentrations corresponding to the calculated T1 values were determined using the relationship:

$$\frac{1}{T_1} = \frac{1}{T_{1,0}} + r_1 \cdot [\text{CA}] \quad (2)$$

where $T_{1,0}$ denotes the native T1 estimate, $r_1$ the T1 relaxivity constant of the contrast agent, and [CA] the contrast agent concentration. $r_1$ was set at 5.0 L-mmol\(^{-1}\)-s\(^{-1}\) and assumed to remain unchanged when the CA passed from blood into tissue.\(^{5,30}\)

Pixelwise MBF was quantified using Fermi function model constrained deconvolution, employing the AIF of the respective cardiac phase (eg, for DCE series in systole, the systolic AIF, which was converted to CA concentration with the systolic native T1 value).\(^{6}\) In doing so, the DCE series was restricted to the first passage of CA, with the end of the first passage identified as the valley point after the maximum of the AIF. The time shift between AIF and myocardial signal was identified as the one yielding the minimal fitting error between the deconvolution-determined and measured myocardial signal.\(^{31}\) Global and segmental MBF values were calculated as the mean MBF of all pixels of the corresponding myocardial region; without further specification, MBF refers to global MBF.

**Experiments on the Impact of Native T1 Values on MBF**

At the SI-to-CA-concentration conversion processing step, several experiments were performed to evaluate the influence of native T1 values on pixelwise MBF estimates. MBF maps were determined:

1. without nonlinearity correction (by only subtracting the baseline SI),
2. using ranges of native blood and myocardial T1 normal values at 3T as well as the study population-averaged native blood and global myocardial T1 values,\(^{32-36}\)
3. employing individual patients’ native blood and global myocardial T1 values,
4. for the perfusion series in the systolic and diastolic phase, one time using native T1 values of the respective cardiac phase and one time using the native T1 values of the other cardiac phase,
5. using successively smaller native myocardial T1 regions, ranging from six AHA segments of the mid-ventricular slice up to 24 sections.

Apart from the cardiac phase comparisons (experiment 4), all evaluations were performed employing diastolic DCE series. In experiments 3 and 5, diastolic native T1 values were used. Additionally, the impact of the cardiac phase in which the AIF was measured was investigated by applying the systolic AIF to diastolic DCE series in experiments 1–4.

**Statistical Analysis**

Statistical analysis was performed with MedCalc (MedCalc Software, Ostend, Belgium), considering $P < 0.05$ as significant. Mean values are specified together with standard deviations.

Equality of variances of distributions of perfusion and T1 parameters was tested by the variance ratio test, their normality by the Kolmogorov–Smirnov test. Study population mean values of
perfusion and T₁ parameters were compared by paired t-test or by Wilcoxon test, in case of nonnormality of the differences. Differences between perfusion and T₁ parameters in AHA segments with and without perfusion deficits were analyzed by means of unpaired t-test, Welch test, in case of unequal variances, or Mann–Whitney test, in case of nonnormality. Relationships between MBF and T₁ parameters were analyzed by the Pearson correlation coefficient (r) and its significance level. Relationships between global, segmental, and pixelwise MBF parameters derived by different methods were studied again by Pearson correlation analysis as well as linear regression and Bland–Altman analysis.

Results

Study Population

Demographic as well as LV function parameters of the study population are summarized in Supporting Information Table S1.

Whereas systolic and diastolic native blood T₁ values (1897 ± 138 msec vs. 1891 ± 136 msec) did not differ significantly (P = 0.07), systolic and diastolic global native myocardial T₁ values (1249 ± 65 msec vs. 1259 ± 80 msec) differed (P < 0.05). However, systolic and diastolic native T₁ values correlated strongly (r = 1.00 for blood and r = 0.99 for myocardium, P < 0.05 in both cases).

Myocardial perfusion deficits were identified in seven patients and 13 AHA segments; except for one AHA segment, this was agreed upon by all three observers. All perfusion deficits were surrounded by LGE (for further details, see Supporting Information). Mean diastolic native T₁ values in myocardial segments with perfusion deficits were significantly higher than in segments without perfusion deficits (1425 ± 170 msec vs. 1235 ± 66 msec, P < 0.05).

MBF Quantification Without Subject-Specific Native T₁ Values

MBF determined without nonlinearity correction was significantly higher than MBF determined using subject-specific global native T₁ values (MBF SI = 0.71 ± 0.11 mL/(min·g) vs. MBF subject-specific T₁ = 0.61 ± 0.13 mL/(min·g), P < 0.05) and they correlated strongly (r = 0.85, P < 0.05).

Using the range of native myocardial and blood T₁ normal values for MBF estimation yielded lower mean MBF for higher native myocardial T₁ values and higher mean MBF for higher native blood T₁ values (Fig. 3a,b). Figure 3c,d

![FIGURE 3: MBF determined using normal ranges of native blood and myocardial T₁ values at 3T. The mean of MBF of all patients at varying myocardial T₁ values while keeping the blood T₁ value fixed (a) and at varying blood T₁ values while keeping the myocardial T₁ value fixed (b). The mean of MBF of all patients at varying differences between blood and myocardial T₁ values while keeping the blood T₁ value fixed (c) and while keeping the myocardial T₁ value fixed (d). MBF = myocardial blood flow.](image-url)
demonstrate that mean MBF becomes higher predominantly with the difference of native blood and myocardial T1 values, irrespective of absolute blood or myocardial T1 values. The mean MBF determined with the study population-averaged diastolic native T1 values resulted in 0.62 ± 0.15 mL/(min/g). Whereas this mean value did not differ from the mean MBF determined with subject-specific native T1 values (P = 0.88) and MBF estimates correlated strongly (r = 0.89, P < 0.05), MBF values of single patients deviated substantially from the mean difference (Fig. 4).

Of note, whereas mean MBF estimates were lower for higher native myocardial T1 normal values and lower native blood T1 normal values, the subject-specific MBF values did not correlate significantly either with the subject-specific native myocardial (r = 0.26, P = 0.35) or blood T1 values (r = 0.12, P = 0.64) or their difference (r = 0.04, P = 0.88).

**MBF Quantification With Systolic and Diastolic Native T1 Values**

Systolic MBF determined using systolic native myocardial and blood T1 values did not differ significantly from diastolic MBF determined with diastolic native myocardial and blood T1 values (systolic MBF with systolic T1 = 0.59 ± 0.14 mL/(min-g) vs. diastolic MBF with diastolic T1 = 0.61 ± 0.13 mL/(min-g), P = 0.12). Moreover, a strong correlation between systolic and diastolic MBF estimates was observed (Fig. 5). However, MBF estimates calculated from native T1 values at different cardiac phases differed significantly (systolic MBF with systolic T1 = 0.59 ± 0.14 mL/(min-g) vs. systolic MBF with diastolic T1 = 0.58 ± 0.14 mL/(min-g), P < 0.05; diastolic MBF with systolic T1 = 0.62 ± 0.13 mL/(min-g) vs. diastolic MBF with diastolic T1 = 0.61 ± 0.13 mL/(min-g), P < 0.05). Bland–Altman and regression plots of the comparisons are given in Fig. 6.

The maximum values of systolic and diastolic AIFs were not significantly different, either for SI curves (systolic AIFmax = 663 ± 194 vs. diastolic AIFmax = 657 ± 187, P = 0.53) or for CA concentration signals (systolic AIFmax = 3.72 ± 1.14 mmol/L vs. diastolic AIFmax = 3.67 ± 1.13 mmol/L, P = 0.64). Correspondingly, using the systolic AIF instead of the AIF of the respective cardiac phase did not change the results of the global MBF comparisons above (MBF SI vs. MBF subject-specific T1, MBF study population-averaged T1 vs. MBF subject-specific T1, systolic MBF vs. diastolic MBF, systolic MBF with systolic T1 vs. systolic MBF with diastolic T1, diastolic MBF with diastolic T1 vs. diastolic MBF with systolic T1).

**MBF Quantification Using Regional Native Myocardial T1 Values**

Global MBF estimates determined with global native myocardial T1 values did not differ significantly from global MBF estimates determined with AHA-segmental (6-segmental) native myocardial T1 values (MBF global T1 = 0.61 ± 0.13 mL/(min-g) vs. MBF 6-segmental T1 = 0.61 ± 0.13 mL/(min-g), P = 0.11). The comparison of all 6-segmental MBF values calculated with global and 6-segmental native myocardial T1 values also did not yield a significant difference (P = 0.44; Fig. 7a). However, if the segments without and with perfusion deficits were considered individually, a significant difference between 6-segmental MBF estimates determined with global and 6-segmental native myocardial T1 values was observed: Segments without perfusion deficits showed higher MBF when 6-segmental instead of global
**FIGURE 5:** Bland–Altman (a) and linear regression (b) plots for comparison of systolic and diastolic MBF estimates determined with systolic and diastolic native T1 values, respectively. The dark gray bar indicates the 95% confidence limits of the bias. MBF = myocardial blood flow; MBF_{sys} = systolic MBF with systolic native T1 values; MBF_{dia} = diastolic MBF with diastolic native T1 values; SD = standard deviation of differences; LoA = limits of agreement; $r$ = Pearson correlation coefficient.

**FIGURE 6:** Bland–Altman and linear regression plots for comparison of systolic (a) and diastolic (b) MBF estimates determined with native T1 values of the respective cardiac phase and native T1 values of the other cardiac phase. The dark gray bar indicates the 95% confidence limits of the bias. MBF = myocardial blood flow; MBF_{sys, match} = systolic MBF with systolic native T1 values; MBF_{sys, mismatch} = systolic MBF with diastolic native T1 values; MBF_{dia, match} = diastolic MBF with diastolic native T1 values; MBF_{dia, mismatch} = diastolic MBF with systolic native T1 values; SD = standard deviation of differences; LoA = limits of agreement; $r$ = Pearson correlation coefficient.
native myocardial T1 values were used ($P < 0.05$; Fig. 7b), while segments with perfusion deficits exhibited lower MBF ($P < 0.05$; Fig. 7c).

Figure 8 demonstrates boxplots of MBF estimates in segments with and without perfusion deficits, calculated without nonlinearity correction (a), with global native T1 values (b), and with 6-segmental native T1 values (c). Mean MBF is indicated by $\times$ and stated with the standard deviation, $P$ refers to the comparison of the means. MBF = myocardial blood flow; MBF global T1 = MBF with global native T1 values; MBF 6-seg T1 = MBF with 6-segmental native T1 values.

FIGURE 7: Bland–Altman and linear regression plots comparing 6-segmental mean MBF values determined with global and 6-segmental native myocardial T1 values. MBF of all segments of all patients (a), all segments without perfusion deficits (b), and all segments exhibiting perfusion deficits (c). The dark gray bar indicates the 95% confidence limits of the bias. MBF = myocardial blood flow; MBF global = MBF with global native T1 values; MBF 6-seg = MBF with 6-segmental native T1 values; SD = standard deviation of differences; LoA = limits of agreement; $r$ = Pearson correlation coefficient.

FIGURE 8: Boxplots of MBF in segments with and without perfusion deficits, calculated without nonlinearity correction (a), with global native T1 values (b), and with 6-segmental native T1 values (c). Mean MBF is indicated by $\times$ and stated with the standard deviation, $P$ refers to the comparison of the means. MBF = myocardial blood flow; MBF global T1 = MBF with global native T1 values; MBF 6-seg T1 = MBF with 6-segmental native T1 values.
native T1 when comparing to MBF determined without non-linearity correction. Comparisons of pixelwise MBF values determined with a successively larger number of native myocardial T1 sections revealed that the largest impact of T1-sectioning occurs from global to 6-segmental, considering the pixelwise MBF correlations and standard deviations of pixelwise differences (Table 1).

**Discussion**

The main findings of this study are 1) pixelwise MBF quantification using native T1 mapping for SI model-based nonlinearity correction is feasible; 2) using native T1 normal values for blood and myocardium may lead to large variations in MBF estimates; 3) the cardiac phase in which native T1 values are acquired significantly affects MBF estimates, even though the resulting MBF bias is small; and 4) MBF should be determined using regional instead of global native T1 values.

**Pixelwise MBF Quantification**

While previous studies on pixelwise MBF estimation in humans either used SI nonlinearity correction at image acquisition or employed native T1 normal values for the SI model, the present study determined pixelwise MBF employing a clinical DCE protocol in combination with routinely acquired subject-specific native T1 maps for SI model-based nonlinearity correction. Both the average global MBF value of our study population and the mean MBF value in segments without perfusion deficits were within the range of published rest perfusion estimates (0.51 mL/(min-g) to 1.03 L/(min-g)), which shows that the employed SI nonlinearity correction method yields reasonable MBF estimates. The comparably low MBF values of the present study can be explained by chronic CHD patients being very likely to exhibit (globally) reduced myocardial perfusion even at rest.

**MBF Quantification Without Subject-Specific Native T1 Values**

As observed previously, MBF estimates determined without nonlinearity correction were significantly higher than those determined using SI model-based nonlinearity correction with subject-specific native T1 values. Interestingly, employing native T1 normal values in nonlinearity correction (experiment 2) might result in an even higher MBF bias.

Experiment 2 also showed that variations in native myocardial and blood T1 values have a similarly strong effect on MBF estimates. It is therefore necessary to measure both native myocardial and blood T1 values subject-wise instead of using fixed native T1 reference values. This is further supported by the large limits of agreement in the Bland–Altman plot comparing MBF estimates determined with the study population-averaged native T1 values and subject-specific native T1 values.

**MBF Quantification With Systolic and Diastolic Native T1 Values**

Although the study population’s mean MBF was lower in systole, this difference did not reach statistical significance because of the comparably large standard deviation of differences. This lack of phasic variation of MBF is in accordance with previous rest perfusion experiments.

Experiment 4 implies that a bias is introduced if native T1 values are not measured in the same cardiac phase as the perfusion series, which seems to be a direct consequence of the slightly different but strongly correlating systolic and diastolic native T1 values. However, since the corresponding bias and standard deviation of differences were rather small compared to the systolic-to-diastolic MBF variation and even more to MBF differences between segments with and without perfusion deficits, it seems reasonable to measure native T1 values in only one cardiac phase. Moreover, extrapolating from the mid-ventricular short-axis slice to the whole LV, the order of acquisition of slices in a clinical perfusion study, typically acquiring slices in different cardiac phases, should not play an essential role for MBF quantification.

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**Table 1. Comparisons of Pixelwise MBF Values of All Patients Determined With a Successively Larger Number of Native Myocardial T1 Sections**

| Comparisons of pixelwise MBF | r   | Difference of MBF (mL/(min-g)) | P value |
|-------------------------------|-----|-------------------------------|---------|
| Global T1 vs. 6-segmental T1  | 0.99| 0.0015 ± 0.0306 (0.25 ± 5.05%)| <0.05   |
| 6-segmental T1 vs. 12-sectional T1 | 1.00| 0.0012 ± 0.0159 (0.19 ± 2.61%)| <0.05   |
| 12-sectional T1 vs. 18-sectional T1 | 1.00| 0.0004 ± 0.0141 (0.07 ± 2.32%)| 0.33    |
| 18-sectional T1 vs. 24-sectional T1 | 1.00| 0.0002 ± 0.0114 (0.04 ± 1.87%)| 0.10    |

r indicates the Pearson correlation coefficient; P value refers to Wilcoxon test.
Previous perfusion studies performing cardiac phase comparisons used the same systolic or diastolic AIF for MBF calculation to avoid potential AIF-dependent effects. The present study found no significant differences between MBF estimates determined using the same systolic AIF and MBF estimates determined using AIFs of the corresponding cardiac phases. Moreover, in contrast to MBF studies on healthy volunteers, the present study did not find that AIF_{max} was consistently lower in either systole or diastole.

**MBF Quantification Using Regional Native Myocardial T1 Values**

Whereas there was no significant intersubject correlation between native myocardial T1 and global MBF values, MBF estimates tend to be lower if the native myocardial T1 values used for MBF estimation are higher (experiment 2). Consequently, MBF values of segments with perfusion deficits are overestimated and MBF values of segments without perfusion deficits are underestimated when using global instead of 6-segmental native myocardial T1 values for nonlinearity correction. Moreover, while visually detected perfusion deficits demonstrated lower MBF values, irrespective of the employed native T1 values, the MBF difference between segments with and without perfusion deficits was largest in the case of MBF calculated with 6-segmental native T1 values. It is therefore appropriate to measure native myocardial T1 values regionally in at least six segments to analyze possible perfusion deficits. Experiment 5 demonstrates that further T1-sectioning of the myocardium leads to a reduced effect on pixelwise MBF estimates.

**Limitations**

First of all, the patient number of the study was small and no healthy controls were investigated. Perfusion imaging was performed at rest only. However, since more than a third of the patients exhibited a rest perfusion deficit, a proof of principle was feasible without stress perfusion data. Findings on the influence of native T1 values on MBF estimates can be expected to also hold for stress perfusion experiments. The use of positron emission tomography (PET) perfusion imaging as a gold standard comparison was not feasible. However, the global MBF estimates obtained were in accordance with the results of other MR rest perfusion studies.

Only images at the same mid-ventricular location were acquired, which was necessary for assessing the impact of systole and diastole on native T1 values and MBF estimates. However, it can be assumed that the main findings of the present study would apply to basal and apical short-axis slices as well.

The MOLLI sequence is known to underestimate the T1 value; nevertheless, it was chosen for native T1 mapping due to its robustness and high signal-to-noise ratio. Furthermore, the presence of a small native T1 bias in all patients would not change the main findings of this study.

**Conclusion**

Whereas cardiac phase-specific native T1 values have a minor impact on MBF estimates, subject-specific and myocardial segment-specific native T1 values substantially affect MBF quantification.

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