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DOI
10.1088/1361-6560/ab7ef1

Publication date
2020

Document Version
Final published version

Published in
Physics in Medicine and Biology

Citation (APA)
Hermann, I., Uhrig, T., Chacon-Caldera, J., Akcakaya, M., Schad, L. R., & Weingartner, S. (2020). Towards measuring the effect of flow in blood T-1 assessed in a flow phantom and in vivo. Physics in Medicine and Biology, 65(9), [095001]. https://doi.org/10.1088/1361-6560/ab7ef1

Important note
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To cite this article: Ingo Hermann et al 2020 Phys. Med. Biol. 65 095001

View the article online for updates and enhancements.
Towards measuring the effect of flow in blood $T_1$ assessed in a flow phantom and in vivo

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Keywords: cardiac $T_1$ mapping, flow velocity dependency, flow phantom, blood $T_1$

Abstract
Measurement of the blood $T_1$ time using conventional myocardial $T_1$ mapping methods has gained clinical significance in the context of extracellular volume (ECV) mapping and synthetic hematocrit (Hct). However, its accuracy is potentially compromised by in-flow of non-inverted/non-saturated spins and in-flow of spins which are not partially saturated from previous imaging pulses. Bloch simulations were used to analyze various flow effects separately. $T_1$ measurements of gadolinium doped water were performed using a flow phantom with adjustable flow velocities at 3 T. Additionally, in vivo blood $T_1$ measurements were performed in 6 healthy subjects (26 ± 5 years, 2 female). To study the $T_1$ time as a function of the instantaneous flow velocity, $T_1$ times were evaluated in an axial imaging slice of the descending aorta. Velocity encoded cine measurements were performed to quantify the flow velocity throughout the cardiac cycle.

Simulation results show more than 30% loss in accuracy for 10% non-prepared in-flowing spins. However, in- and out-flow to the imaging plane only demonstrated minor impact on the $T_1$ time. Phantom $T_1$ times were decreased by up to 200 ms in the flow phantom, due to in-flow of non-prepared spins. High flow velocities cause in-flow of spins that lack partial saturation from the imaging pulses but only lead to negligible $T_1$ time deviation (less than 30 ms). In vivo measurements confirm a substantial variation of the $T_1$ time depending on the flow velocity. The highest aortic $T_1$ times are observed at the time point of minimal flow with increased flow velocity leading to reduction of the measured $T_1$ time by up to 130 ± 49 ms at peak velocity.

In this work we attempt to dissect the effects of flow on $T_1$ times, by using simulations, well-controlled, simplified phantom setup and the linear flow pattern in the descending aorta in vivo.

1. Introduction
Quantitative myocardial tissue characterization has increasingly gained attention in cardiac magnetic resonance imaging (MRI) over the past several years for its ability to non-invasively study the myocardial tissue state (Ferreira et al 2014, Hamlin et al 2014, Moon et al 2013, Messroghli et al 2004). Myocardial $T_1$ mapping is sensitive to changes in the macro-molecular environment and has demonstrated clinical value in various ischemic and non-ischemic cardiomyopathies (Dall’Armellina et al 2012, Radenkovic et al 2017, Puntmann et al 2016). Additionally, extracellular volume (ECV) mapping is widely used as a marker for
fibrotic remodeling of the myocardium in various pathologies (Moon et al 2013, Kim et al 2017, Haaf et al 2016, Messroghli et al 2017, Ntusi et al 2014). ECV maps are calculated based on native and post-contrast $T_1$ times in the myocardium and the blood-pool, and are normalized with the hematocrit (Hct). When hematocrit was not measured, or to achieve a more stream-lined process that does not require blood sampling and testing, it has been proposed to calculate a Hct estimate using blood $T_1$ times in a technique called synthetic Hct (Treibel et al 2016). Therefore, ECV and synthetic Hct values are highly dependent on the quality of blood $T_1$ measurements.

Several cardiac $T_1$ mapping sequences have been proposed and can be clinically used for native $T_1$ and ECV mapping (Messroghli et al 2004, Chow et al 2014, Weingärtner et al 2014, Piechnik et al 2010, Weingärtner et al 2015). Modified Look-Locker inversion recovery (MOLLI) (Messroghli et al 2004) is the most widely used method for myocardial $T_1$ mapping and yields precise $T_1$ maps but lacks accuracy compared to other $T_1$ mapping methods (Roujol et al 2014). In MOLLI multiple images with different $T_1$-weightings are acquired following a non-selective inversion pulse. This repeated image acquisition perturbs the magnetization which is corrected for in the reconstruction (Deichmann correction) (Look et al 1970, Deichmann et al 1992). Saturation recovery single-shot acquisition (SASHA) (Chow et al 2014) was proposed as an alternative for $T_1$ mapping with increased accuracy. In SASHA images are acquired every heartbeat following a non-selective saturation pulse with varying saturation time. Due to a reduced dynamic range and suboptimal sampling of the recovery curve for long $T_1$ times, SASHA $T_1$ maps suffer from reduced precision compared with MOLLI (Weingärtner et al 2016).

Accuracy and precision of myocardial $T_1$ mapping are integral to its clinical value and have been thoroughly investigated in several recent studies (Kim et al 2017, Haaf et al 2016, Roujol et al 2014, Weingärtner et al 2016, Kellman and Hansen 2014, Cameron et al 2018). It was shown that the dominant variability in blood $T_1$ comes from the biological constituents such as hematocrit, iron, and HDL cholesterol (Rosmini et al 2019). However, blood $T_1$ times often fall out of the range for which myocardial $T_1$ mapping techniques are validated and multiple confounding mechanisms have been proposed (Choi et al 2013, Shang et al 2018). In particular it has been suggested that various flow effects compromise $T_1$ measurement of the blood-pool (Kellman and Hansen 2014). Given the implicit clinical use of blood $T_1$ times, thorough investigation of the effect of flow is warranted. However, complex flow patterns in the ventricle as well as a multitude of parameters determining the relevant flow hamper the holistic evaluation of this confounder in vivo.

In this study, we aim to analyze the impact of certain aspects of flow on $T_1$ measurements with two commonly used myocardial $T_1$ mapping techniques in well controlled experimental settings in order to further our understanding of flow as a confounding factor. Bloch simulations are performed to shed light on the relative contribution of different flow effects. These effects are then validated in a controlled flow phantom comprising a peristaltic pump with linear flow. Finally, the combined flow dependency of $T_1$ measurements is studied in vivo by imaging the descending aorta as a proxy, where flow patterns are largely linear and consistently varying across the cardiac cycle.

2. Methods

2.1. Flow effects on blood $T_1$ measurements

Blood $T_1$ measurements can be subject to three main flow effects (Kellman and Hansen 2014, Chow et al 2014, Cameron et al 2018) depending on the myocardial $T_1$ mapping technique (figure 1).

1. **Non-prepared spins:** In $T_1$ mapping multiple images are acquired with variable delay following a preparation pulse. During this delay spins that were not subject to the preparation (e.g. far outside the isocenter) can flow into the heart. This increases the signal intensity and therefore decreases the measured $T_1$ relaxation time.

2. **Beat-to-beat exchange:** For sequences such as MOLLI the same magnetization preparation is read out over multiple heartbeats. Spins flowing into the imaging plane from beat-to-beat are not subject to partial saturation by repeated imaging readouts, but are influenced by one slice selective readout only.

3. **In- and out-flowing spins:** Fast flowing spins that flow into the imaging plane during the readout lead to faster signal regrowth due to partial saturation by one train of imaging pulses.

The Deichmann correction has been introduced to compensate for signal attenuation by continuous FLASH imaging pulses during inversion recovery of static tissue (Deichmann et al 1992) and is used in MOLLI to reduce the impact of the imaging readout on the $T_1$ time. However, in the presence of flow, the correction factor will also be subject to various flow-effects, including reduced effect of the repeated imaging readout and imperfect inversion due to in-flow of non-prepared spins.
Figure 1. Illustration of different flow effects on $T_1$. Illustration of the three different flow effects corrupting the measurement of blood $T_1$ times with myocardial $T_1$ mapping methods. The top panel (a) shows the effect of a $T_1$ recovery curve over multiple heartbeats, e.g. as seen in MOLLI. In the bottom panel (b) sample magnetization packages (arrows) are depicted during magnetization recovery in various flow scenarios. The signal intensity is encoded by the background shading. The first row shows the recovery in the absence of flow. Rows two to four illustrate the following three flow effects. In-flow of non-prepared spins: An increasing amount of non-prepared spins enter the imaging volume and contribute to faster signal recovery. Beat-to-Beat exchange: Flow between the imaging periods in successive heartbeats eliminates the signal attenuation that is seen with repeated imaging pulses in static tissue. Flow during the imaging readout: Spins that are not affected by previous imaging pulses flow into the imaging volume between two imaging pulses are played and thus mitigate the signal attenuation during an individual readout.

In this study, we try to disentangle the relative contributions of the in-flow of non-prepared spins, beat-to-beat exchange and the flow effect during the imaging readout. We study the effect on the $T_1$ time, as well as the uncorrected $T_1^*$ for MOLLI and $T_1$ times calculated with 2- (Kellman et al 2014b) and 3-parameter models in SASHA.

2.2. Sequence parameters

$T_1$ maps were generated using a 5(3 s)3 MOLLI (Kellman et al 2012) scheme with and without Deichmann correction (MOLLI $T_1$ /MOLLI $T_1^*$) for balanced steady-state free precession (bSSFP) readout and for gradient-echo (GRE) readout (MOLLIGRE $T_1$ /MOLLIGRE $T_1^*$). MOLLI maps are reconstructed by a 3-parameter fit with and without the Deichmann correction. SASHA is reconstructed with 3 and 2 parameter fits (SASHA/SASHA 2P) (Chow et al 2014, Kellman et al 2014b). Reference $T_1$ times in the phantom were measured with an inversion recovery (IR) in the absence of flow. $T_1$ maps were reconstructed with a voxel-wise Levenberg-Marquardt non-linear least-square curve fit implemented in-line on the scanner (Markwardt Craig 1980, Maier et al 2019, Lundervold et al 2019). All measurements were performed in a 3 T MRI scanner (Magnetom Skyra; Siemens Healthineers, Erlangen, Germany) with a 28-channel receiver coil array and shared the following common imaging parameters: FOV = 240 $\times$ 240 mm$^2$, matrix size (base resolution) = 192 $\times$ 192 (1.3 $\times$ 1.3 mm), slice thickness = 8 mm, bandwidth = 1085 Hz/px, GRAPPA-factor 2 and partial Fourier 6/8. SSFP imaging was performed with TR/TE = 3.6 ms/1.8 ms and high flip angle of
60°, as recommended in flow and SASHA (Kellman and Hansen 2014), and GRE imaging with TR/TE/\(\alpha\) = 2.9 ms/1.7 ms/8°.

Flow velocity measurements were performed with velocity-encoded retrogated cine using TR/TE/\(\alpha\) = 53.28 ms/4.37 ms/20°, FOV = 166 × 240 mm², matrix size = 166 × 240, slice thickness = 8 mm and interpolated phases = 30 and velocity encoding gradient strength \(V_{\text{max}} = 20\,\text{cm s}^{-1}\) in phantom and \(V_{\text{max}} = 500\,\text{cm s}^{-1}\) in vivo.

2.3. Simulations
We used flow-sensitive Bloch-simulations to determine the relative contribution of the various flow effects for MOLLI and SASHA imaging sequences with bSSFP and GRE readout. All pulse sequences were simulated with the above listed sequence parameters.

For the no flow case, time periods of free relaxation/precession were simulated as

\[
\begin{pmatrix}
M_x(t+1) \\
M_y(t+1) \\
M_z(t+1)
\end{pmatrix} =
\begin{pmatrix}
E_2 & 0 & 0 \\
0 & E_2 & 0 \\
0 & 0 & E_1
\end{pmatrix}
\cdot
\begin{pmatrix}
M_x(t) \\
M_y(t) \\
M_z(t)
\end{pmatrix} +
\begin{pmatrix}
0 \\
0 \\
1 - E_1
\end{pmatrix},
\]

with \(E_1 = \exp(t/T_1)\), \(E_2 = \exp(t/T_2)\) and the time step \(t\). Center of k-space was chosen to calculate the magnitude with \(\sqrt{M_x^2 + M_y^2}\). Imaging and preparation pulses were simulated with corresponding rotation matrices. This magnitude is used for fitting MOLLI and SASHA relaxation curves. Along with the undisturbed relaxation curve without saturation by the readout pulses (no excitation pulses simulated), used as a reference relaxation curve, three different scenarios were simulated: 1) Stationary spins which are repeatedly saturated by the imaging pulses at every heartbeat. 2) Non-prepared spins flowing from the scan periphery into the imaging plane. 3) In-flow of unsaturated spins into the imaging plane during the readout at different flow velocities. For flow simulations, the magnetization vector was split in 1000 magnetization packages with fully relaxed magnetization vectors (1, 0, 0)\(^T\). All simulated spins are influenced by only one slice selective imaging readout, as fresh spins are flowing into the imaging plane from beat to beat. Therefore, between heartbeats the magnetization vectors are set to the magnetization of the undisturbed spins. The cardiac cycle was simulated with R-R intervals = 1000 ms and blood relaxation times were simulated as \(T_1 = 2000\,\text{ms}\) (Qin et al 2010, Varela et al 2011, Li et al 2017, Liu et al 2016) and \(T_2 = 200\,\text{ms}\) (Liu et al 2016, Chen et al 2009). For a given velocity the proportion of unsaturated spins flowing into the imaging plane per time step was calculated as follows:

\[
\text{percentage of in-flowing spins per time step} = \frac{\text{flow velocity} \cdot \text{time step}}{\text{slice thickness} \cdot \text{readout duration}}.
\]

This percentage is used to calculate the amount of magnetization vectors per time step, which are exchanged by the corresponding magnetization vector (all vectors in the magnetization package are the same) from the reference relaxation curve at that time step.

2.4. Phantom experiments
A 30 cm long peristaltic pump (Watson-Marlow-Bredel, 300 Series Laboratory Tube Pumps) was used to circulate gadolinium-doped water from a reservoir outside the scanner bore through a pipe into a dialysis filter (filter with increased diameter, consisting of small fibers). From there the water circulated back outside the bore to the reservoir (figure 2). A dialysis filter with a diameter of 6 cm was used. The dialysis filter and a reference probe (3 cm in diameter) with non-flowing solution were placed in a posterior imaging slice (figure 2). Additionally, imaging was performed in an anterior slice comprising only the dialysis filter. Imaging was performed at five different flow velocities in both flow directions. \(T_1\) measurements were performed using IR, MOLLI \(T_1/T_1^*\), MOLLIGRE \(T_1/T_1^*\), SASHA and SASHA 2P. Additionally, MOLLI and SASHA were performed with a reduced slice thickness of 4 mm to evaluate the flow effect of in-plane saturation. Reference flow velocities were determined by velocity encoded (VENC) cine measurements in the dialysis filter.

2.5. In vivo experiments
\textit{In vivo} measurements were performed in six healthy subjects (26 ± 5 years, 2 female) in a single axial slice positioned approximately five centimeter below the aortic arch. All scans were performed under an IRB-approved protocol and following written, informed consent. \(T_1\) and \(T_1^*\) times were calculated and manually drawn region of interests were used to determine mean values and standard deviations in the descending aorta. MOLLI \(T_1\) and \(T_1^*\) maps and MOLLIGRE \(T_1\) and \(T_1^*\) maps were acquired at various time
Figure 2. Measurement setup with the flow phantom. Setup of the flow phantom. A peristaltic pump (Watson-Marlow-Bredel, 300 Series Laboratory Tube Pumps) outside the magnetic safety region was used to pump a mixture of water and gadolinium from a reservoir through a pipe into a 30 cm long dialysis filter (at isocenter) back to the reservoir. The dialysis filter and a reference probe was put into the imaging slice.

points in systole and diastole within the cardiac cycle ranging from 250-800 ms after the R-wave. No SASHA measurements were performed in the aorta as no imaging could be performed during systole. For reference, VENC cine measurements were performed to calculate the blood flow velocity in the aorta throughout the cardiac cycle. Reference measurements of the left ventricular blood pool in a mid-ventricular short axis view (SHAX) were performed with all sequences.

3. Results

3.1. Simulations

Figure 3 demonstrates the effects of the previously described flow-induced phenomena studied in isolation with noise-free Bloch simulations for MOLLI and SASHA.

3.1.1. In-flow of non-prepared spins

The simulation results in figure 3 show that in-flow of 2% non-prepared spins per heartbeat (purple lines in figure 3) leads to faster recovery and shortened apparent relaxation times. This effect is studied in greater detail for various degrees of in-flow in figure 4. Both MOLLI and SASHA show underestimation, which is increasingly pronounced with higher in-flow. Simulations indicate that for in-flow of 10% non-prepared spins, $T_1$ time accuracy is compromised by more than 30% and 15% for MOLLI and SASHA, respectively.

3.1.2. Beat-to-beat exchange

Repeated application of imaging pulses leads to signal attenuation across heartbeats in stationary tissue (orange lines in figure 3). However, our results show that even slow flow velocities cause an exchange of the spins between heartbeats (beat-to-beat exchange), such that the imaging signal is just affected by a single set of imaging pulses for any given heartbeat (yellow lines in figure 3). Accordingly, the reduced signal attenuation from previous heartbeats leads to reduced underestimation of $T_1$ times compared with MOLLI values as commonly obtained in stationary tissue. Without Deichmann correction this leads to a major difference ($\Delta T_1 > 200$ ms), but was largely mitigated when using Deichmann correction ($\Delta T_1 < 60$ ms).

3.1.3. In-flow and out-flow during a readout

Flow during the imaging readout leads to further alteration of the magnetization signal as it leads to faster recovery during one imaging readout (i.e. between two imaging pulses, yellow lines in figure 3). This effect is studied in detail in figure 5 at various flow-velocities. Increased $T_1$ times are observed for SASHA 2P and increased $T_1^*$ times for MOLLI at slow flow up to 5 cm s$^{-1}$. However, the magnitude of this effect is small.
compared to the previously listed contributions (\(\sim 1\%\)). Furthermore, the effect is strongly mitigated by using MOLLI with Deichmann correction or SASHA with a 3-parameter fit model. Of note, the consistent offset in \(T_1\) observed with MOLLI is due to incomplete inversion efficiency caused by in-flowing spins. This is not due to its intrinsic well documented errors because we assume that all spins exchange from beat-to-beat and therefore no spins are affected by multiple readouts.

### 3.2. Phantom experiments

Figure 6 shows the \(T_1\) times measured in the flow phantom for various flow velocities. Negative flow direction for \(T_1\) measurements in the posterior slice and positive flow for the anterior slice, lead to in-flow of spins from the reservoir outside the scanner bore, into the imaging plane. For these regimes (blue shaded area, figures 6(a) and (b)) \(T_1\) times decrease by up to 125 ms with a decrease of 25 ms per 1 cm s\(^{-1}\) for SASHA/SASHA 2P and up to 250 ms with a decrease of 50 ms per 1 cm s\(^{-1}\) for MOLLI/MOLLIGRE with and without Deichmann correction. The highest deviation is observed at the largest velocity amplitude (\(v \sim 5\) cm s\(^{-1}\)).

For absolute flow velocities larger than \(1 - 1.5\) cm s\(^{-1}\) all spins from the imaging readout can be assumed to have left the imaging plane during one heartbeat (beat-to-beat exchange). However, for slow absolute flow velocities (\(-1.5\) cm s\(^{-1}\) to \(1.5\) cm s\(^{-1}\)) a varying degree of beat-to-beat exchange can affect the
Figure 4. Bloch simulations of non-prepared inflowing spins. \( T_1 \) time as a function of the amount of in-flowing non-prepared spins in percentage per heartbeat for SASHA (blue) and MOLLI \( T^*_1, T_1 \) (orange). Of note, the time for in-flow of non-prepared spins is substantially shorter for SASHA due to repeated magnetization saturation in every heartbeat.

Figure 5. Bloch simulations of partial saturation by imaging pulses. \( T_1 \) time for in-flowing and out-flowing spins during a single readout for SASHA (blue) and MOLLI \( T^*_1, T_1 \) (orange). Simulations were performed under the assumption that irrespective of the flow velocity, spins are fully exchanged from beat-to-beat.

\( T_1 \) times. In this regime (gray shaded area, figures 6(a) and (b)) MOLLIIs without Deichmann correction show a symmetrical peak for around \( v = 0 \) cm s\(^{-1}\), leading to \( T^*_1 \) deviation of more than 200 ms. This contribution is largely eliminated when using a Deichmann correction. SASHA shows only minor variation in this flow regime, which is expected as beat-to-beat exchange does not affect the SASHA signal due to the repeated saturation.

For large flow-velocities in the opposite flow direction, mostly prepared spins are flowing into the imaging plane. In this regime (white shaded area, figure 6(a) and (b)) varying amount of in-flow/out-flow during the readout is expected to be the dominant effect inducing flow susceptibility. MOLLI without Deichmann correction shows sensitivity to this flow effect, with increasing \( T^*_1 \) times for increasing flow magnitude. However, the effect is largely mitigated using Deichmann correction. No sensitivity to flow for SASHA or SASHA 2P can be discerned from the noise level in this regime. These findings are corroborated by the results of measurements with different slice thickness (figure 7), which also leads to difference in in-flow/out-flow during the readout. All \( T_1 \) methods yield excellent agreement for measurements at 4 mm and 8 mm slice thickness (absolute deviation less than 20 ms), except MOLLI without Deichmann correction. Substantial variation up to 80 ms is observed in the presence of flow, but excellent agreement is shown for the minimal flow case (deviation less than 26 ms).

In the reference probe \( T_1 \) maps of SASHA/SASHA 2P achieved good agreement with IR yielding deviations less than 6\% whereas MOLLI \( T_1/MOLLI T^*_1 \) underestimated the \( T_1 \) time of approximately 15\%. MOLLIGRE underestimated the \( T_1 \) time by almost 20\% and MOLLIGRE \( T^*_1 \) by 28\%. All measurements
resulted in standard deviations of less than 50 ms for SASHA, SASHA 2P, MOLLI, MOLLIGRE and less than 100 ms for MOLLI T∗ and MOLLIGRE T∗.

3.3. In vivo experiments
MOLLI T₁ maps were generated for an axial cross-section of the aorta at various time points throughout the cardiac cycle. Across all subjects, peak velocities up to 120 cm s⁻¹ were measured with an average peak velocity of 77 ± 24 cm s⁻¹. Figure 8 depicts the flow velocity and blood T₁ times as a function of time within the cardiac cycle of one healthy subject. A summary of T₁ times in the absence of flow and during peak velocity are given in table 1. T₁ times increased with decreasing velocity with differences up to 186 ms. Across all subjects MOLLI and MOLLIGRE measured during the diastole (slow flow) resulted in T₁ times comparable to the left ventricle in the SHAX measurement. Mean differences of T₁ times between peak flow and time point of minimal flow, and their corresponding standard deviations were 163 ± 57 ms for MOLLI, 115 ± 41 ms for MOLLIGRE, 424 ± 192 ms for MOLLI T∗ and 362 ± 181 ms for MOLLIGRE T∗. T₁ maps with Deichmann correction were more precise with standard deviations in the aorta of 107–252 ms over the cardiac cycle. Without Deichmann correction standard deviations vary from 203 ms for MOLLI up to 726 ms for MOLLIGRE respectively.
4. Discussion

In this study we performed flow-dependent $T_1$ measurements using MOLLI and SASHA to evaluate different contributions of flow effects with simulations, phantom and in vivo measurements. Three flow effects were studied to play a role in blood $T_1$ measurements:

- In-flow of non-prepared spins from outside the scanner bore increase the signal magnetization and induce a faster $T_1$ relaxation.
- Sufficiently fast spins flowing outside the imaging plane from heartbeat to heartbeat eliminate the in-plane saturation effect and can result in decreased underestimation of MOLLI $T_1$ times compared with stationary tissue. However, the effect is small when Deichmann correction is used.
- Spins which flow inside and outside the imaging plane during one readout increase the signal intensity. This leads to higher $T_1^*$ for MOLLI but was mitigated when using Deichmann correction and did not affect SASHA.

Simulations and phantom measurements indicate that in-flow of non-prepared spins is the dominant flow effect. Our results show that this can lead to substantial deviations in the $T_1$ time, especially for large fractions of in-flowing non-prepared spins. The effect on SASHA $T_1$ times was substantially smaller.
The amount of non-prepared spins in blood $T_1$ times plays a role in the calculation of ECV. However, our results indicate that the flow effects are more pronounced for longer $T_1$ times. The ECV calculation is more susceptible to changes in the post-contrast $T_1$ times, and thus shows stronger resilience to flow induced variations. Given the simulated effects from figure 4, errors about 5% can be expected for ECV. However, the synthetic Hct is inversely proportional to the native blood $T_1$ times. Thus, decreasing blood $T_1$ times increases the Hct. With flow induced $T_1$ deviations of up to 20% synthetic Hct may vary by up to 17%. Hence, when using synthetic Hct for ECV calculation this error propagates to the ECV value linearly.

In vivo measurements confirm the flow effect of decreasing $T_1$ times by increasing flow velocity in the descending aorta. Due to the relatively high standard deviation in vivo, in-flow and out-flow of spins during a readout as observed in phantom can be assumed to be negligible. Flow susceptibility due to varying degrees of beat-to-beat exchange can also be assumed to be negligible due to the high ejection fraction in the aorta.

### Table 1. Tabular of all in vivo blood $T_1$ values.

| subject, gender | Sequence | Deichmann correction | speed $[cm \cdot s^{-1}]$ | min. flow $T_1$ $[ms]$ | peak flow $T_1$ $[ms]$ | diff. $T_1$ $[ms]$ |
|----------------|----------|----------------------|--------------------------|------------------------|------------------------|----------------------|
| 1, f           | MOLLI    | on                   | 76                       | 1917±107               | 1759±66                | 158                  |
|                |          | off                  | 2126±384                 | 1806±231               | 319                    |
|                | MOLLIGRE | on                   | 1838±375                 | 1664±170               | 174                    |
|                |          | off                  | 2456±825                 | 2041±649               | 415                    |
| 2, m           | MOLLI    | on                   | 64                       | 1809±252               | 1751±121               | 58                   |
|                |          | off                  | 1898±726                 | 1965±386               | 67                     |
|                | MOLLIGRE | on                   | 1757±186                 | 1737±133               | 20                     |
|                |          | off                  | 2056±843                 | 1853±656               | 203                    |
| 3, m           | MOLLI    | on                   | 63                       | 1868±123               | 1681±209               | 186                  |
|                |          | off                  | 1839±366                 | 1159±785               | 680                    |
|                | MOLLIGRE | on                   | 1757±186                 | 1737±133               | 20                     |
|                |          | off                  | 2056±843                 | 1853±656               | 203                    |
| 4, f           | MOLLI    | on                   | 54                       | 1973±222               | 1817±424               | 156                  |
|                |          | off                  | 1921±562                 | 1430±951               | 490                    |
|                | MOLLIGRE | on                   | 1930±99                  | 1844±204               | 86                     |
|                |          | off                  | 2150±330                 | 1846±675               | 304                    |
| 5, m           | MOLLI    | on                   | 87                       | 1662±162               | 1580±410               | 82                   |
|                |          | off                  | 1607±207                 | 1039±725               | 568                    |
|                | MOLLIGRE | on                   | 1639±123                 | 1552±185               | 87                     |
|                |          | off                  | 1731±457                 | 1382±627               | 349                    |
| 6, m           | MOLLI    | on                   | 120                      | 1792±174               | 1650±301               | 142                  |
|                |          | off                  | 1638±203                 | 1297±631               | 342                    |
|                | MOLLIGRE | on                   | 1734±213                 | 1650±294               | 84                     |
|                |          | off                  | 1663±452                 | 1445±671               | 218                    |
Accordingly, our in vivo results in the aorta suggest a strong impact of in-flow of non-prepared spins on the $T_1$ time, indicating potential in vivo contribution of the dominant effect observed in phantom and simulations.

MOLLI $T_1$ mapping is well known to be susceptible to variations in prescribed or actual flip-angles (Cooper et al 2014, Kellman et al 2013). In-flow of spins during the readout, also impacts the amount of signal attenuation in tissue, although with different underlying principles. Therefore, we studied the contribution of flow to MOLLI $T_1$ times. Simulations suggested that the Deichmann correction is highly effective in mitigating the effects of variable signal saturation in the presence of flow. To further confirm this result, phantom experiments were conducted in a slow flow regime. In these experiments, in-flow during the readout is expected to affect $T_1$ times independent of the flow direction thus constituting a symmetrical peak. While this effect was observed the relative contribution compared with in-flow of non-prepared spins was almost negligible after Deichmann correction. This was further confirmed in scans with decreased slice thickness, which leads to increased in-flow/out-flow during the readout for a given flow velocity. As shown in our simulations, theoretically there is no need for correcting with Deichmann for sufficient fast flow. Nevertheless, our phantom measurements resulted in decreased $T_1$ times with higher standard deviations compared with using the Deichmann correction.

SASHA $T_1$ mapping showed substantially lower susceptibility to flow effects. However, residual changes in $T_1$ times were induced, primarily due to the in-flow of non-prepared spins. In simulations and phantom experiments, constant flow velocities were simulated throughout the heartbeat. However, in vivo in-flow of non-prepared spins is largely restricted to the systolic phase, potentially leading to even smaller flow susceptibility in the $T_1$ measurement. However, no SASHA imaging could be performed to study the flow effect in the aorta directly, as SASHA is incompatible with a variable readout timing with respect to the cardiac cycle.

Overall, our results demonstrate that under controlled conditions the $T_1$ times of moving fluids can be strongly dependent on flow velocities. These results are obtained in simplified and well controlled conditions. However, a multitude of factors likely determines the effect size on left ventricular blood $T_1$ as commonly performed. While this limits the feasibility, our results confirm the literature postulation that in-flow of non-saturated spins is a potential confounder in blood $T_1$ measurement. The total in-flow and the flow velocity depends on a number of physiological parameters. The total stroke volume determines how much potentially non-prepared spins can flow in from the periphery. The patient size can affect the amount of blood in the periphery that is potentially not completely prepared. Ejection fraction can also be a confounding factor for blood $T_1$ measurements as this can variably affect the amount of beat-to-beat exchange. Hence, our results suggest that the use of blood $T_1$ as an independent parameter warrants careful consideration. Thorough control for flow determining physiology might potentially help to reduce variability (Becker et al 2019, Collis et al 2001, Barone-Rochette et al 2013). Due to the important role of blood $T_1$ in ECV mapping and due to its recent use in synthetic Hct numerous clinical studies evaluated cardiomyopathies based on blood $T_1$ based quantities (Haaf et al 2016, Kellman et al 2012, Ugander et al 2012, Ntusi et al 2014, Cameron et al 2018, Messroghli et al 2017, Moon et al 2013). As the effects observed in quantitative myocardial tissue characterization are often small it is paramount to understand potential confounders. Our results indicate that measurements in patients with largely varying flow-determining physiology could lead to increased variability in blood $T_1$ based biomarkers. This can potentially hamper the identification of pathological changes.

This study has several limitations. A number of simplifications had to be made in order to systematically analyze the impact of flow on myocardial $T_1$ mapping. These simplification limit the direct feasibility of the results to the measurements of blood $T_1$ times in the left ventricle. Firstly, the phantom setup was a simplified approach to measure the effects of different flow patterns in isolation. The reservoir was put outside the bore to create an environment where non-prepared spins flow into the imaging plane. However, the fraction of spins that is poorly polarized is likely smaller in vivo than as in this setting. Imaging of the descending aorta was performed as an in vivo model with controllable instantaneous flow velocities. However, different and more variable flow patterns are characteristic for the left ventricle potentially giving rise to different flow response of the $T_1$ time. A difference in local flow-patterns can potentially have minor impact on the effects of in-/out-flow during the readout. In our simulations we assumed 100% inversion efficiency with a rectangular slice profile without taking the distribution of flip angles into account. However, in-plane saturation only demonstrated minor effects on blood $T_1$ times. For this reason we suspect that a distribution of flip angles as a result of the slice profile will only play a minor role. However, given our results indicate overall negligible contribution of this flow effect a detailed analysis of turbulent flow in dedicated phantoms or the ventricles might not be required.
5. Conclusion

$T_1$ times in moving fluids such as blood obtained with commonly used $T_1$ mapping techniques can be susceptible to flow-effects. In our simplified model analysis, we found the most significant flow effect due to in-flow of non-prepared spins. Other flow-induced effects showed minor impact and were well compensated for using either a Deichmann correction for MOLLI or SASHA. Overall, SASHA proved to be less prone to flow effects as the magnetization is saturated in every heartbeat compared with MOLLI, where a single inversion pulse spans up to five heartbeats. These results are suggestive that in-flow of non saturated spins could potentially be detrimental to blood $T_1$ measurements with potential implications for analysis of ECV and synthetic Hct, but thorough clinical investigation of the impact is warranted.

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