FULL PAPER

Combined imaging of potassium and sodium in human skeletal muscle tissue at 7 T

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Purpose: To validate the feasibility of quantitative combined potassium (39K) and sodium (23Na) MRI in human calf muscle tissue, as well as to evaluate the reproducibility of the apparent tissue potassium concentration (aTPC) and apparent tissue sodium concentration (aTSC) determination in healthy muscle tissue.

Methods: Quantitative 23Na and 39K MRI acquisition protocols were implemented on a 7 T MR system. A double-resonant 23Na/39K birdcage RF coil was used. Measurements of human lower leg were performed in a total acquisition time of TANa = 10:54 min/TAK = 8:06 min and using a nominal spatial resolution of 2.5 × 2.5 × 15 mm3/7.5 × 7.5 × 30 mm3 for 23Na/39K MRI. Two aTSC and aTPC examinations in muscle tissue were performed during the same day on 10 healthy subjects.

Results: The proposed acquisition and postprocessing workflow for 23Na and 39K MRI data sets provided reproducible aTSC and aTPC measurements. In human calf muscle tissue, the coefficient of variation between scan and re-scan was 5.7% for both aTSC and aTPC determination. Overall, mean values of aTSC = (17 ± 1) mM and aTPC = (85 ± 5) mM were measured. Moreover, for 39K in calf muscle tissue, T2f components of T2f = (1.2 ± 0.2) ms and T2s = (7.9 ± 0.9) ms, as well as a residual quadrupolar interaction of ωq = (143 ± 17) Hz, were determined. The fraction of the fast component was f = (58 ± 4)%.

Conclusion: Using the presented measurement and postprocessing approach, a reproducible aTSC and aTPC determination using 23Na and 39K MRI at 7 T in human skeletal muscle tissue is feasible in clinically acceptable acquisition durations.
1 INTRODUCTION

Sodium (Na+) and potassium (K+) ions play a vital role in many cellular processes. In healthy tissue, Na+ exhibits an approximately eightfold to 10-fold higher concentration in the extracellular space than in the intracellular space. An inverse concentration gradient can be observed for 39K. For example, in human skeletal muscle cells, intracellular ion concentrations in the range of \([\text{Na}^{\text{+}}_{\text{int}}] = 10-25 \text{ mM}\) and \([\text{K}^{\text{+}}_{\text{int}}] = 150-165 \text{ mM}\) can be found,\(^2\) whereas the extracellular concentrations—measured as the serum Na+ and K+ concentrations—are normally in the range of \([\text{Na}^{\text{+}}_{\text{ext}}] = 130-145 \text{ mM}\) and \([\text{K}^{\text{+}}_{\text{ext}}] = 3.5-5.5 \text{ mM}\).\(^5\) This concentration gradient between the intra- and the extracellular space contributes to the cell membrane potential and is maintained by the Na+-K+-ATPase, often referred to as the Na+-K+-pump. In skeletal muscle cells, the ATPase activity and resulting maintenance of the Na+ and K+ concentration gradient are essential for the muscle contractility.\(^7\) Various diseases, such as diabetes and muscular dystrophies, as well as exercise have been reported to alter the ATPase activity and consequently the ion distribution in human skeletal muscle. Further, skeletal muscle cells are supposed to be an important storage site for Na+ and K+ to handle an overload or depletion of these ions.\(^8\)\(^,\)\(^9\) Thus, a noninvasive determination of the muscular Na+ and K+ tissue concentrations using 23Na and 39K MRI might help elucidate the physiological mechanisms underlying various pathologies.

Using 23Na MRI, it is possible to gain information about the tissue sodium concentration (TSC), which represents the mean of the intra- and extracellular sodium concentrations weighted by their respective volume fractions. Changed TSC in skeletal muscle tissue has been observed in the context of various diseases, for example, in muscular dystrophies,\(^10\)\(^,\)\(^11\) muscular channelopathies,\(^12\) hypertensive patients\(^13\) and patients with acute kidney injury.\(^14\) Additionally, efforts are made to enhance the sensitivity toward intracellular sodium by suppressing signal from the extracellular space, for example, using inversion recovery\(^12\) and multiple quantum filtration\(^15\) approaches. However, it is still an open question to what extent these techniques are able to differentiate between sodium ions within the intracellular and extracellular space.\(^16\) In particular for multiple quantum filtration, it has been shown that a significant amount of the detected signal arises from the extracellular space.\(^17\)\(^,\)\(^18\) Because K+ ions are mainly located in the intracellular space (around 98% of the total potassium content\(^19\)), a noninvasive determination of the tissue potassium concentration (TPC) using 39K MRI might help gaining deeper insights into pathological processes connected to the intracellular space.

In clinical practice, alterations of the K+ concentration in ion homeostasis are currently only analyzed in extracellular body fluids, for example, blood samples. However, increases in extracellular K+ concentrations are initially buffered by moving K+ into the intracellular space until it is excreted by the kidneys.\(^8\) Moreover, declines in extracellular K+ concentrations can be balanced by reducing the intracellular stores in skeletal muscle cells. This ensures that blood serum K+ concentrations are usually tightly regulated. In many diseases, however, either too low (hypokalemia) or too high (hyperkalemia) blood serum K+ concentrations lead to life-threatening conditions that are often associated with ventricular arrhythmias and sudden cardiac arrest. The underlying pathophysiological mechanisms can be depletion (in hypokalemia) or overload (in hyperkalemia) of the total body potassium and/or internal redistributions between extra- and intracellular space.\(^19\) A determination of the TPC might help to elucidate these underlying disease mechanisms. Because skeletal muscle is the most important storage of potassium within the human body, containing approximately 75% of the total potassium content,\(^2\) a noninvasive K+ concentration determination in human skeletal muscle tissue is desirable. However, because it has not yet been examined if the total potassium content in muscle tissue is MR visible and how the nonzero residual quadrupolar interaction of 39K ions in muscle tissue\(^20\) influences the signal intensity, we will use the term apparent tissue potassium concentration (aTPC)—and equivalently apparent tissue sodium concentration (aTSC)—instead, as suggested by Stobbe and Beaulieu.\(^21\)

The major challenge of 39K MRI is the low SNR due to low in vivo K+ concentrations and the low gyromagnetic ratio (\(\gamma_K = 1.99 \text{ MHz/T}\)). For similar Na+ and K+ concentrations as well as similar relaxation times, the SNR of 39K MRI is expected to be 34 to 126 times lower than the SNR of 23Na MRI, depending on the noise model (dominated either by inductive losses in the sample or by resistive losses in the coil).\(^22\)\(^,\)\(^23\) In addition, technical restrictions did not allow the application of 39K MRI on clinical MRI systems thus far. Therefore, in vivo 39K MRI was performed only on preclinical systems\(^24\)\(^,\)\(^25\) or using experimental, custom-built setups in humans.\(^20\)\(^,\)\(^26\)\(^,\)\(^27\) Recently, the first 39K images of human heart acquired at a clinical 7 T MR system were published.\(^28\) However, all previous studies using 39K

**KEYWORDS**

7 T, potassium MRI, sodium MRI, tissue potassium concentration, tissue sodium concentration, ultrahigh field strengths
MRI in humans did not examine the quantitative capability and especially not the reproducibility of $^{39}$K imaging. The aim of this work was to validate the feasibility of combined $^{23}$Na and $^{39}$K concentration quantification in skeletal muscle tissue using $^{23}$Na/$^{39}$K MRI on a clinical 7T MR system. In addition, the reproducibility of Na$^+$ and K$^+$ quantification in healthy skeletal muscle tissue was examined.

2 | METHODS

2.1 | Image acquisition

All measurements were performed on a whole-body 7T MR system (Magnetom Terra, Siemens Healthcare GmbH, Erlangen, Germany) using a dual-tuned, circular polarized $^{23}$Na/$^{39}$K calf coil with an inner diameter of 20 cm (Rapid Biomedical, Rimpar, Germany). A 5-compartment reference tube holder included in the coil design was used for quantification such that the leg can be positioned directly on the reference holder. The reference tubes were filled with different combinations of NaCl and K$_2$HPO$_4$ solution, resulting in Na$^+$ and K$^+$ concentrations of $[Na^+] / [K^+] = 10/240$, 20/210, 25/180, 30/150, and 40/120 mM. K$_2$HPO$_4$ solution possesses a lower electrical conductivity than KCl solution and is therefore expected to arise less image artifacts. Because the measurement setup does not contain a hydrogen (1H) channel, B$_0$ shimming was performed based on B$_0$ maps calculated from $^{23}$Na MRI data in combination with a constrained regularized algorithm.$^{29}$

$^{23}$Na and $^{39}$K images were acquired using a 3D acquisition-weighted density-adapted stack-of-stars scheme.$^{30-32}$ This acquisition scheme allows anisotropic sampling of the k-space, which is beneficial for muscle measurements due to possible higher in-plane resolution.$^{33}$ Moreover, it was found to provide a higher SNR compared with a density-adapted radial acquisition with cuboid k-space sampling scheme.$^{32}$ $^{23}$Na and $^{39}$K data sets were reconstructed offline using a custom-written MatLab tool (2017b, MathWorks, Natick, MA) and interpolated to the same matrix size ($240 \times 240 \times 120$), corresponding to an interpolated resolution of $1 \times 1 \times 2$ mm$^3$.

2.2 | Concentration determination

Na$^+$ and K$^+$ concentration calibration was performed by a linear regression of the signal intensities within the reference compartments to their nominal concentrations. The effect of different corrections on the $^{23}$Na and $^{39}$K signal intensities on the quantification accuracy was evaluated. The workflows for signal postprocessing and correction of in vivo data are illustrated in Figure 1.

2.2.1 | B$_0$ correction

Offresonances can cause signal blurring and therefore may induce quantification errors. This is of special importance if external references are used because the large susceptibility differences at the transition between reference tubes and muscle tissue might lead to strong B$_0$ inhomogeneities.$^{34}$ To correct for these inhomogeneities, offresonance maps were calculated using 2 echoes of both $^{23}$Na and $^{39}$K MR acquisitions according to

$$\Delta B_0 = \frac{\phi_{2,\text{unwrapped}} - \phi_{1,\text{unwrapped}}}{\gamma (TE_2 - TE_1)},$$

with the phase unwrapped phase images $\phi_{1,\text{unwrapped}}$ and $\phi_{2,\text{unwrapped}}$ the TEs of the double echo acquisition (TE$_1$ and TE$_2$), and the gyromagnetic ratios of $^{23}$Na and $^{39}$K, respectively ($\gamma_{^{23}Na} = 11.27$ MHz/T, $\gamma_{^{39}K} = 1.99$ MHz/T). B$_0$ correction was performed using a frequency-segmented approach,$^{35}$ in which the measured raw data are first multiplied by phases resulting from the offresonance frequencies found in the B$_0$ map. Then, these new k-space data are Fourier-transformed into the image space, and a voxel-wise combination is performed to create the B$_0$ corrected image. Because this B$_0$ correction approach does not require additional acquisition time, it was performed for all quantitative measurements in this work.

2.2.2 | Partial volume correction

For quantification in X-nuclei MRI, the signal intensities of the tissue and reference compartments are commonly determined within manually drawn regions of interest. However, especially for $^{39}$K MRI, the low nominal resolution in combination with fast T$_2^*$ relaxation lead to strong partial volume effects. These partial volume effects result in a strong dependence of the calculated tissue ion concentration on the positioning of the regions of interest. To enhance the reproducibility of the quantification approach while mitigating partial volume effects, a binary-mask based partial volume correction (PVC) as described by Niesporek et al.$^{36}$ was applied to the data. Using this approach, a constant ion concentration is calculated for each tissue compartment. The mask for the reference tube regions was calculated based on a high-resolution $^1$H image by thresholding. This mask was then coregistered onto the $^{23}$Na images using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Because coregistration of muscle tissue is challenging due to the varying positioning of the leg using different coil setups that would be necessary due to the lack of a $^1$H channel in the used $^{23}$Na/$^{39}$K calf coil, no $^1$H images were used for muscle mask calculation. Instead, the mask for the muscle area was calculated based on the $^{23}$Na images using a combination of manual segmentation and thresholding. For subjects exhibiting a significant subcutaneous fat
layer (thickness > approx. 5 mm), a binary mask for fat tissue also was extracted from the corresponding \(^{23}\)Na image. The central 20 slices (interpolated slice thickness = 2 mm) were evaluated both for phantom and in vivo measurements in the quantification process. After PVC, a corrected signal intensity is obtained for each compartment. Using these signal intensities in combination with the region-spread-functions describing the signal blurring of each individual compartment, an artificial partial volume corrected image was created.

2.2.3 | \(B_1\) correction

Because the transmit-and-receive fields for both the \(^{23}\)Na and the \(^{39}\)K channel of the used calf coil were found to be not identical, no conventional \(B_1\) correction using flip angle (FA) maps and assuming \(B_1^- = B_1^+\) could be performed. Instead, constant \(B_1\) correction factors were determined for the reference compartments because \(B_1\) inhomogeneities were highest on the edges of the FOV (compare maps of effective FAs shown in Supporting Information Figure S1). Therefore, a phantom measurement was performed in which all compartments of the reference holder, as well as the phantom itself, were filled with the same solution (15 mM NaCl + 60 mM \(K_2HPO_4\)). After PVC, the signal intensities within all compartments and the phantom should be equal. The \(B_1\) correction factors for the reference compartments were therefore calculated as the inverse signal intensities within these compartments normalized to the phantom signal intensity.
TABLE 1 Parameters used for the simulation of $^{23}$Na and $^{39}$K MRI data of the phantom and lower leg muscles. Relaxation times and concentrations—except for $^{39}$K relaxation times in K$_2$HPO$_4$ solution and muscle tissue—were taken from literature. For $^{23}$Na ions in fatty tissue, the same relaxation properties as for muscle tissue were assumed due to a lack of references. Relaxation times were also used for PVC and relaxation correction of the measured data sets.$^{52}$

| Compartment | $^{23}$Na | $^{39}$K |
|-------------|----------|---------|
| Phantom     | 15       | 120     |
| Muscle      | 14-18$^b$ | 60      |
| Vessels     | 60       | 45      |
| Fat         | 8$^{11}$ | 0       |

$^{23}$Na, sodium; $^{39}$K, potassium; PVC, partial volume correction.

$^{b}$Gastrocnemius medialis/lateralis = 17 mM, tibialis anterior/posterior = 14 mM, soleus = 18 mM, fibularis = 16 mM

2.2.4 Relaxation correction

For quantitative MRI measurements, a short TE (<<$T_2^*$) and long TR (>5$T_1$) are needed. However, for in vivo measurements, a slight $T_1$ weighting by reducing TR was accepted to reduce measurement time and to increase SNR by increasing the number of averages for $^{39}$K MRI acquisitions. As the solutions used for the concentration calibration exhibit considerably longer relaxation times than muscle tissue (c.f. Table 1) a relaxation correction was performed. Assuming a homogeneous FA of 90°, the relaxation coefficients for solutions containing both contributions from $T_1$ and (monoeponential) $T_2^*$ can be calculated according to

$$c_{\text{relax, solution}} = \left(1 - \exp\left(-\frac{T R}{T_1}\right)\right) \exp\left(-\frac{T E}{T_2^*}\right).$$

(2)

For muscle tissue, the biexponential transverse relaxation has to be taken into account,$^{37,38}$ resulting in a relaxation correction coefficient of

$$c_{\text{relax, tissue}} = \left(1 - \exp\left(-\frac{T R}{T_1}\right)\right) \times \left(\exp\left(-\frac{T E}{T_2^*}\right) \cos \left(\omega_0 T E\right) + (1-f) \exp\left(-\frac{T E}{T_2^*}\right)\right).$$

(3)

Here, $f$ denotes the fraction of the fast component fraction of $T_2^*$, and $\omega_0$ describes the time-averaged, so-called residual, quadrupole interaction of the nuclei with their environment. For $^{39}$K, the individually measured relaxation behavior for each subject was used for relaxation correction (compare Section 2.4.2). For $^{23}$Na ions in muscle tissue, relaxation times as summarized in Table 1 were used. Further, $\omega_0 \approx 0$ was assumed for $^{23}$Na and $f$ was fixed to its theoretical value ($f = 0.6$) because sodium ions in healthy calf muscle tissue were reported to exhibit a fast component fraction close to 60%.$^{39}$ Finally, the signal was corrected by dividing the uncorrected signal by the relaxation coefficients.

2.3 Simulations

To evaluate the implemented quantification workflow, $^{23}$Na and $^{39}$K MRI data sets both of a phantom and a lower leg model were simulated (see Utzschneider et al$^{40}$ for detailed description of the simulation approach). The phantom was modeled as a cylinder with diameter 14 cm and height 12 cm. Two cylindrical tubes were included (diameter 2/4 cm) containing 0 mM ion concentration representing the tibia and fibula. For the muscle simulations, high-resolution $^1$H images of both a female and a male lower leg were manually segmented into 6 different muscle regions (gastrocnemius medialis/lateralis, soleus, tibialis anterior/posterior, fibularis), as well as subcutaneous fat tissue and vessels using the Medical Interaction Toolkit. Moreover, the reference compartments were extracted from a $^1$H image by thresholding and included into the simulation.

All phantom and muscle compartments were assigned specific Na$^+$ and K$^+$ concentrations (c.f. Table 1). The resulting simulation ground truth for $^{23}$Na and $^{39}$K MRI of lower leg can be found in Supporting Information Figure S2. They were then Fourier-transformed and regridded onto a radial trajectory by a nonuniform fast Fourier transform. The different compartments were added up to form the simulated k-space. Finally, Gaussian noise was added to yield a noise level close to actual measurements. Moreover, $T_2^*$ and $T_1$ decay was included into the simulated raw data of each compartment. For $^{23}$Na phantom and muscle simulations, relaxation times from literature were used (c.f. Table 1). For $^{39}$K muscle simulations, $T_2^*$ and $T_1$ relaxation times as determined in the phantom and volunteer measurements were used. Moreover, the same acquisition parameters as for the phantom/in vivo measurements were used for the simulations.

2.4 $T_2^*$ and $T_1$ mapping

The knowledge of the $T_2^*$ relaxation times is indispensable both for partial volume correction as well as for relaxation correction of the $^{39}$K signal intensities. Therefore, $^{39}$K $T_2^*$ maps were acquired for both phantom solutions and muscle tissue using a multi-echo acquisition-weighted density-adapted stack-of-stars scheme. Average signal intensities
within a region of interest were determined, and a fit of the theoretical signal decay was performed. For NaCl and K2HPO4 solution, a monoexponential $T_2^*$ decay was assumed

$$S = M_0 \exp \left( -\frac{TE}{T_2^*} \right). \quad (4)$$

For muscle tissue, a biexponential fit was performed $^{26,38}$

$$S = \sqrt{M_0^2 \left[ f \exp \left( -\frac{TE}{T_{2f}^*} \right) \cos (\varphi_{qTE}) + (1-f) \exp \left( -\frac{TE}{T_{2i}^*} \right) \right]^2 + n^2}, \quad (5)$$

with $n$ describing a noise factor. In a homogeneous environment possessing a constant quadrupolar interaction between the nuclei and the surrounding molecules, a fraction of $f = 0.6$ is observed. $^{37}$ However, in biological tissues such as muscle tissue, a distribution of quadrupolar interactions and consequently a varying relaxation behavior can be expected. $^{38}$

Thus, the fast component fraction was chosen as a free fit parameter. Because $^{39}$K ions in muscle tissue are expected to experience a residual quadrupolar interaction, $^{20}$ the time-averaged quadrupolar interaction $\overline{\sigma_q}$ was included in the fit.

Moreover, $^{39}$K $T_1$ maps were acquired using an inversion recovery acquisition-weighted density-adapted stack-of-stars scheme by varying the TI. Fitting was performed according to

$$S = \left| M_0 \left( 1 - 2 \exp \left( -\frac{TI}{T_1} \right) + \exp \left( -\frac{TR}{T_1} \right) \right) \right|. \quad (6)$$

### 2.5 Phantom measurements

To verify the quantification process under practical measurement conditions, a phantom representing the structure of the lower leg as described in the simulations section was used. It was filled with a solution containing 15 mM Na$^+$ and 120 mM K$^+$ (15 mM NaCl, 60 mM K$_2$HPO4). Both $T_1$ and $T_2^*$ times of $^{39}$K in K$_2$HPO4 solution were determined ($T_2^*$ mapping: TR = 150 ms, TE = 0.4-99 ms, 6 acquisitions with 3 echoes each, readout duration $T_{RO}$ = 3 ms, nominal spatial resolution $8 \times 8 \times 30$ mm$^3$, 6 averages, TA = 51:48 min, $T_1$ mapping: TR = 300 ms, TE = 0.4 ms, TI = 2-250 ms, 22 acquisitions, $T_{RO}$ = 3 ms, nominal spatial resolution $8 \times 8 \times 30$ mm$^3$, TA = 4 h 22 min). The measurement parameters for quantitative $^{23}$Na/$^{39}$K imaging were: TR = 120/40 ms, TE = 0.3/0.4 ms, $T_{RO}$ = 10/5 ms, FA = 90°, rectangular excitation pulse of 500 μs duration, nominal spatial resolution $\Delta x = 2.5 \times 2.5 \times 10/7.5 \times 7.5 \times 30$ mm$^3$, averages = 1/4, total acquisition time TA = 10:54/8:06 min. Quantification measurements for both ions were performed twice to assess the quantification accuracy of the implemented PVC approach. No relaxation correction was applied to the phantom data because the solutions within the phantom and the reference tubes were assumed to possess the same relaxation behavior.

### 2.6 In vivo measurements

$^{23}$Na and $^{39}$K images of the lower leg were acquired in 10 healthy volunteers (5 male, 5 female, age 27.4 ± 4.6 years). The study was approved by the local ethical review board, and all volunteers provided informed consent prior to the examination. Healthy subjects did not take any regular medication, did not suffer from any preexisting or acute illness, and had routine laboratory parameters (including blood pressure) within the normal range. For each volunteer, a $^{39}$K $T_2^*$ map was acquired (TR = 35 ms, TE = 0.4-20 ms, 15 acquisitions with 2 echoes each, $T_{RO}$ = 3 ms, nominal spatial resolution $8 \times 8 \times 30$ mm$^3$, 6 averages, TA = 32:15 min). The sequence parameters used for quantitative $^{23}$Na/$^{39}$K MRI were the same as those in the phantom measurements. Around 65% to 70% of the maximum admissible specific absorption rate in the normal operation mode was reached for $^{39}$K MRI using a 90° RF pulse of 500 μs duration and a TR of 40 ms. The minimum RF pulse duration was restricted by the maximum RF voltage of the MR system (339 V). To reduce motion effects during the acquisition, several cushions were used to fix the position of the leg in the RF coil.

Postprocessing of the data sets was performed as described in Figure 1. For PVC and relaxation correction of the $^{39}$K data sets, the individual $^{39}$K $T_2^*$ times were used. To assess the variation in the calculated ion concentrations, the $^{23}$Na and $^{39}$K quantification measurements were repeated for each subject after a short break (30-45 min). For comparison, Na$^+$ and K$^+$ concentrations in blood serum were determined. Moreover, $^{39}$K $T_1$ maps of muscle tissue were acquired for 2 male healthy subjects (TR = 100 ms, TE = 0.4 ms, $T_{1} = 2-40$ ms, 11 acquisitions, $T_{RO}$ = 3 ms, nominal spatial resolution $10 \times 10 \times 30$ mm$^3$, TA = 42:10 min).

### 2.7 Data analysis

A paired sample $t$ test was performed to compare the concentrations determined in the first and second measurement (M1 and M2) of the same subject. To assess the variability of the concentration determination, Bland-Altman graphs were created by plotting the difference between the aTSC and aTPC values of M1 and M2 against the mean values of the 2 measurements. Moreover, the coefficient of variation was calculated as the ratio of the SD to the mean concentration of the measurements, as well as the coefficient of repeatability.
as 1.96 multiplied by the SD of the differences between M1 and M2.\textsuperscript{41}

3 | RESULTS

3.1 | Simulations

Simulated $^{23}$Na and $^{39}$K data phantom sets, together with concentration calibration curves and resulting calculated Na\textsuperscript{+} and K\textsuperscript{+} concentration maps after PVC, are shown in Figure 2. Before correction, partial volume effects led to an underestimation of the signal intensity within the reference compartments, especially for the smaller reference compartments in the $^{39}$K acquisition. After PVC, calibration curves were in good accordance with the theoretical expectations both for $^{23}$Na and $^{39}$K. To determine the quantification variation due to random noise, data sets were simulated and evaluated 5 times each for phantom and muscle. For the simulated phantom, ion concentrations of $[\text{Na}^+] = (16.5 \pm 0.02) \text{ mM}$ and $[\text{K}^+] = (134.2 \pm 0.8) \text{ mM}$ before correction were determined. After PVC using the simulation ground truth as binary masks, concentrations of $[\text{Na}^+] = (15.2 \pm 0.02) \text{ mM}$ and $[\text{K}^+] = (120.0 \pm 0.7) \text{ mM}$ were determined. The deviation from the ground truth concentrations of $[\text{Na}^+] = 15 \text{ mM}$ and $[\text{K}^+] = 120 \text{ mM}$ were therefore reduced from $(10 \pm 1)\%$ to $(1 \pm 1)\%$ for Na\textsuperscript{+} and from $(12 \pm 1)\%$ to $(0 \pm 1)\%$ for K\textsuperscript{+} by applying a PVC.

For the simulated muscle data sets, the effect of the relaxation correction and an imperfect binary mask extracted from the simulated $^{23}$Na data sets also were examined. Therefore, PVC was performed using both the simulation ground truth and a muscle/fat mask calculated based on the $^{23}$Na image for the simulated female calf (c.f. Figure 3; see Supporting Information Figure S2 for evaluation including all 3 tissue compartments). Before correction, Na\textsuperscript{+} and K\textsuperscript{+} concentrations were overestimated (deviation from ground truth concentrations > 10\%) (see Figure 4). For $^{23}$Na measurements, both PVC and relaxation correction reduced the deviation from the nominal concentrations (Figure 4A). In contrast, for $^{39}$K measurements the effect of relaxation weighting on the quantification accuracy was stronger such that both PVC and relaxation correction were needed to effectively reduce absolute quantification deviations (Figure 4B). Calculation of the segmentation mask based on the $^{23}$Na image led to an additional quantification error. Here, the total area of the calculated muscle mask showed a deviation of 9\% from the area of the ground truth mask in the evaluated slice range (deviation of fat mask: 20\%).

**FIGURE 2** Simulated $^{23}$Na (A) and $^{39}$K (B) phantom images, together with calculated Na\textsuperscript{+} and K\textsuperscript{+} concentration maps. Concentration maps were created based on the artificial images calculated using the RSF and corrected signal intensities for each compartment. The corresponding concentration calibration curves are shown on the right. Here, the signal intensities were normalized to the reference compartment containing the lowest ion concentration (compartment 5 for $^{23}$Na; compartment 1 for $^{39}$K). The calibration fit was performed before (red line) and after correction of partial volume effects (green line). The calibration curve after PVC for both ions is in good accordance with the theoretically expected relation for both nuclei (dashed line). K\textsuperscript{+}, potassium ion; Na\textsuperscript{+}, sodium ion
However, the concentration deviation from the ground truth increased only by approximately 2% after using the calculated segmentation mask. As for in vivo lower leg data sets with thin subcutaneous fat layer it is often difficult to extract a fat mask based on the $^{23}\text{Na}$ image, the simulated male calf images were evaluated. For the evaluation of $^{39}\text{K}$ images, only the muscle area was considered because a negligible $K^+$ concentration is expected in fatty tissue.

**FIGURE 3** Simulated $^{23}\text{Na}$ (A) and $^{39}\text{K}$ (B) images of human lower leg, together with $\text{Na}^+$ and $K^+$ concentration maps after PVC. Concentration maps were created based on the artificial images calculated using the RSF and corrected signal intensities for each compartment. As segmentation mask for PVC, both the simulation ground truth (middle column) and a muscle/fat mask calculated based on the $^{23}\text{Na}$ image (right column) were used to evaluate the influence of an imperfect binary mask as found in in vivo measurements.

**FIGURE 4** Deviation from ground truth concentrations of calculated ion concentrations for simulated muscle data sets before and after correction of partial volume effects and relaxation weighting. Moreover, the effect of an imperfect binary mask extracted from the simulated $^{23}\text{Na}$ muscle image overestimating the muscle area compared with the ground truth was examined. For $^{23}\text{Na}$, both concentrations in muscle and fat tissue were determined. Absolute deviations can be strongly reduced by applying both a PVC and relaxation correction. An evaluation including all simulated tissue types (muscle, fat, and blood vessels) can be found in Supporting Information Figure S2.

However, the concentration deviation from the ground truth increased only by approximately 2% after using the calculated segmentation mask.
additionally evaluated using only a muscle mask but no fat mask (see Supporting Information Figure S3). This muscle mask partially included the fatty tissue so that the area of the calculated muscle mask deviated from the area of the ground truth mask by 15%. In this case of strong overestimation of the segmentation mask, the concentration deviation increased by approximately 5% compared with the PVC based on the ground truth mask to a total deviation of −11% for K⁺ concentration determination.

3.2 | Phantom measurements

For K₂HPO₄ solution, ³⁹K relaxation times of $T_1 = (47.5 \pm 0.5)$ ms and $T_2^* = (43.2 \pm 0.7)$ ms were determined. Measured $^{23}$Na and $^{39}$K phantom images, together with concentration calibration curves before and after PVC as well as $B_1$ correction and resulting Na⁺ and K⁺ concentration maps, are shown in Figure 5. Mean ion concentrations of $[Na^+] = (13.9 \pm 0.1)$ mM and $[K^+] = (121.0 \pm 0.6)$ mM after corrections could be determined for the phantom. This corresponds to a deviation of $(−7.3 \pm 0.7)%$ for Na⁺ and $(0.8 \pm 0.5)%$ for K⁺ from the nominal concentrations of $[Na^+] = 15$ mM and $[K^+] = 120$ mM.

3.3 | In vivo measurements

Exemplary $^{39}$K $T_1$ and $T_2^*$ decay curves for human lower leg muscle tissue can be found in Figure 6. The resulting $T_2^*$ times for all volunteers, together with the measured Na⁺ and K⁺ concentrations in blood serum, are summarized in Table 2. Mean $T_2^*$ components of $T_{2f}^* = (1.2 \pm 0.2)$ ms and $T_{2s}^* = (7.9 \pm 0.9)$ ms, as well as a mean quadrupolar interaction of $\overline{\omega_q} = (143 \pm 17)$ Hz for $^{39}$K ions in muscle tissue, were determined. The fraction of the fast component was $f = 58 \pm 4\%$. Because this is close to the theoretically expected value ($f = 60\%$), the $T_2^*$ decay was additionally evaluated with a fixed fraction of 60% to enhance the fit stability. The resulting values were $T_{2f}^* = (1.2 \pm 0.1)$ ms, $T_{2s}^* = (8.1 \pm 0.2)$ ms, and $\overline{\omega_q} = (142 \pm 12)$ Hz. Moreover, a mean $T_1$ of $(8.8 \pm 1.3)$ ms for $^{39}$K in healthy lower leg muscle tissue was determined.

$^{23}$Na and $^{39}$K images of human lower leg acquired in measurement M1 and M2, as well as the corresponding aTSC and aTPC maps including all signal corrections, were found to be in good accordance (see Figure 7). The effect of the different correction steps on the aTSC and aTPC calculated for the first measurement in lower leg muscle tissue is shown in Figure 8A,B. For both $^{23}$Na and $^{39}$K measurements, $B_0$
correction did not result in an alteration of the measured ion concentrations. In future aTSC and aTPC measurements, a $B_0$ correction could therefore be omitted. PVC and $B_1$ correction reduced the measured Na$^+$ concentration, whereas they led to an increase in the measured K$^+$ concentration. The relaxation correction had a higher impact on the $^{39}$K data sets, resulting in a strong reduction of the measured ion concentration in muscle tissue.

Bland-Altman plots indicate a good agreement between the ion concentrations calculated from the corrected data sets of the 2 measurements performed for each subject (Figure 8C,D). Including all corrections, mean aTSC values for muscle and fat tissue of $\text{aTSC}_m = (16.9 \pm 1.0)$ mM and $\text{aTSC}_f = (7.0 \pm 1.3)$ mM in the first measurement (M1) and $\text{aTSC}_m = (17.0 \pm 1.1)$ mM and $\text{aTSC}_f = (6.7 \pm 1.2)$ mM in the second measurement (M2) were determined. For K$^+$, muscle concentrations of $\text{aTPC} = (83.4 \pm 6.1)$ mM in M1 and $\text{aTPC} = (87.2 \pm 4.9)$ mM in M2 were calculated. No significant differences between the apparent muscle tissue ion concentrations determined in M1 and M2 were observed ($P = .82$ for $^{23}$Na measurements and $P = .06$ for $^{39}$K measurements). Moreover, the coefficient of variation was similar for aTSC and aTPC (coefficient of variation = 5.7%). A coefficient of repeatability of 1.73 mM (10.2%) and 10.7 mM (12.6%) were determined for $^{23}$Na and $^{39}$K measurements, respectively. No correlations between the measured Na$^+$ and K$^+$ blood serum concentrations were observed.

### TABLE 2: Results of blood serum and muscle ion concentration measurements as well as determined $^{39}$K $T_2^*$ decay parameters for all 10 examined healthy subjects

| Subject | Sex | Age | K$^+$ (blood serum) [mM] | Na$^+$ (blood serum) [mM] | aTPC [mM] | aTSC [mM] | $^{39}$K $T_2^*$ [ms] | $T_1^*$ [ms] | $\overline{\alpha_q}$ [Hz] | f [%] |
|---------|-----|-----|--------------------------|---------------------------|-----------|-----------|-----------------------|-------------|-----------------|------|
| 1       | F   | 28  | 3.8                      | 137                       | 88.8 ± 1.7 | 17.09 ± 0.08 | 1.36 ± 0.20          | 7.4 ± 1.2   | 157 ± 13        | 56 ± 5 |
| 2       | M   | 40  | 4.1                      | 140                       | 81.3 ± 0.6 | 17.20 ± 0.39 | 1.43 ± 0.17          | 7.1 ± 0.8   | 150 ± 11        | 52 ± 4 |
| 3       | F   | 29  | 3.5                      | 139                       | 84.9 ± 4.6 | 15.79 ± 0.24 | 1.48 ± 0.13          | 7.2 ± 0.9   | 160 ± 9         | 58 ± 4 |
| 4       | M   | 24  | 3.8                      | 143                       | 80.7 ± 1.9 | 18.88 ± 0.03 | 1.24 ± 0.18          | 7.5 ± 1.0   | 139 ± 8         | 55 ± 4 |
| 5       | M   | 27  | 4.1                      | 141                       | 86.2 ± 5.2 | 16.66 ± 0.89 | 1.28 ± 0.18          | 6.6 ± 1.0   | 139 ± 8         | 54 ± 6 |
| 6       | F   | 24  | 4.3                      | 141                       | 93.4 ± 0.2 | 17.05 ± 0.15 | 1.09 ± 0.11          | 8.7 ± 0.8   | 168 ± 15        | 59 ± 3 |
| 7       | M   | 25  | 3.7                      | 140                       | 81.0 ± 4.3 | 17.49 ± 0.59 | 1.32 ± 0.15          | 7.7 ± 1.1   | 139 ± 13        | 58 ± 5 |
| 8       | F   | 24  | 4.1                      | 139                       | 78.6 ± 5.1 | 17.72 ± 0.27 | 1.36 ± 0.05          | 9.0 ± 1.3   | 127 ± 18        | 65 ± 3 |
| 9       | M   | 28  | 4.0                      | 141                       | 89.0 ± 1.3 | 15.52 ± 0.04 | 1.04 ± 0.21          | 7.7 ± 1.6   | 112 ± 19        | 58 ± 7 |
| 10      | F   | 25  | 3.6                      | 141                       | 89.4 ± 1.9 | 16.38 ± 0.57 | 0.86 ± 0.12          | 9.6 ± 1.9   | 123 ± 27        | 66 ± 4 |
| Mean    |     |     | 27.4 ± 4.6               | 3.9 ± 0.2                 | 140 ± 2   | 85.3 ± 4.8  | 17.0 ± 1.0           | 1.2 ± 0.2   | 7.9 ± 0.9       | 58 ± 4 |

aTPC and aTSC values are given as mean and SD of the 2 measurements per subject. Correlation plots between the ion concentration measures are shown in Supporting Information Figure S4.

$^{39}$K, potassium; aTPC, apparent tissue potassium concentration; aTSC, apparent tissue sodium concentration; f, female; m, male.
FIGURE 7  $^{23}$Na images obtained in measurement M1 and M2, together with resulting calculated aTSC maps (A) as well as corresponding $^{39}$K images and aTPC maps (B) of a healthy female subject. Concentration maps were created based on the artificial images calculated using the RSF and corrected signal intensities for each compartment. Images and concentration maps are in good accordance for the 2 measurements and both nuclei. aTPC, apparent tissue potassium concentration; aTSC, apparent tissue sodium concentration.

FIGURE 8  Effect of different correction steps (compare Figure 1) on the resulting aTSC (A) and aTPC values (B) determined for the lower leg muscle tissue of 10 healthy subjects (results of measurement 1). Moreover, Bland-Altman plots show the difference in determined apparent ion concentrations after all corrections are performed between measurement M1 and M2 against the mean concentrations of the 2 measurements (C,D). The mean differences (blue line) as well as the coefficients of repeatability (red lines) are marked in the plots. A similar CV of 5.7% for the aTSC and aTPC measurements was calculated. CV, coefficient of variation.
concentrations and the mean aTSC and aTPC in muscle tissue were found for the healthy subjects (see Supporting Information Figure S4 for correlation plots between measured ion concentrations in muscle and blood serum, as well as hematocrit content).

4 | DISCUSSION

In this work, combined imaging of sodium and potassium in human skeletal muscle at 7T was performed for the first time using the same RF coil. Moreover, the repeatability of the quantification of Na+ and K+ concentrations using 23Na/39K MRI in muscle tissue was examined in 10 healthy subjects.

Mean apparent tissue concentrations of aTSC = (17 ± 1) mM and aTPC = (85 ± 5) mM for healthy lower leg tissue were determined in this study. For both apparent Na+ and K+ concentrations, we found a good agreement between the 2 measurements performed in the same subject. A low coefficient of variation (5.7% for both nuclei) was determined. Moreover, no significant differences between the mean measured ion concentrations in the 2 measurements were found.

Recent studies examined the reliability and repeatability of quantitative 23Na MRI in healthy calf muscle tissue at 3T.34,42 Both found a high degree of agreement between scan and re-scan, with a lower coefficient of repeatability (also referred to as smallest real difference) for measurements performed on the same day than for measurements performed within 1 to several weeks. Because measured Na+ concentrations in muscle tissue are highly sensitive to exercise and postural changes, a higher variation is expected when performing quantification measurements at different time points, and therefore under different physiological conditions. The results of our 23Na MRI measurements performed at 7T are in good accordance with these studies, even showing a slightly lower coefficient of repeatability (1.79 mM) than the same-day measurements performed by Dyke et al (1.71-5.89 mM, depending on the evaluated muscle area).42 This indicates a high reproducibility of our quantification approach. In contrast to the evaluations performed by Dyke et al42 and Gerhalter et al,34 the region-based quantification method proposed in this work does not depend on a manual positioning of the regions of interest, which we assume to be a reason for the observed higher degree of reproducibility.

The determined muscle aTSC values lie within the range of values that can be found in the literature for healthy calf muscle tissue (approx. 15-28 mM).11,14,43-45 Only 1 study measured the K+ content in thigh muscle tissue using 39K MRI so far, observing aTPC values significantly higher than the values observed in our study (aTPC between 112 and 125 mM for 3 healthy volunteers).26 However, this study corrected for neither partial volume effects nor inhomogeneities in the B1 or B0 field. From muscle biopsy, K+ concentrations in the range of 75 to 105 mmol per kg wet weight were derived.2 Assuming a muscle density of 1.056 kg/L,26 this corresponds to a range of 79 to 110 mmol/L. In our work, we measured a range of 74-94 mmol/L, which is close to the range observed in muscle biopsy. Overall, a direct comparison between muscle biopsy and MRI—as performed by Kopp et al for 23Na measurements of human calf growth—might be a promising approach to assess the deviation of the aTSC value from the real K+ concentration in skeletal muscle tissue.

Nevertheless, the aTSC values measured in our study might be slightly underestimated. For the simulated muscle data sets, we found an underestimation of the K+ concentration in muscle tissue of approximately 10% compared with the ground truth concentration in case of a strong overestimation of the muscle segmentation mask. In addition, 39K nuclei in muscular tissue experience a strong quadrupole interaction with a mean quadrupolar interaction frequency $\overline{\omega}_q \neq 0$.20 Over the entire lower leg muscle area, we found a mean quadrupolar interaction frequency of $\overline{\omega}_q = (143 ± 17)$ Hz using $T_2^*$ decay fits. Roesler et al even observed a quadrupolar splitting of up to $\overline{\omega}_q = 200$ Hz in unlocalized spectroscopic 39K measurements of human thigh and calf muscle.20 The so-called flip angle effect states that in case of large $\overline{\omega}_q$, only the central transition might be excited leading to an effective flip rate up to twice the value prescribed, and therefore a loss in measured signal intensity.48 Thus, in case $\overline{\omega}_q \neq 0$, it might be beneficial to use FAs lower than 90° to mitigate this effect.21 Kordzadeh et al recently observed a mild flip-angle effect in the head of the gastrocnemius muscle using 23Na MRI measurements of the knee.49 However, the examination of the flip-angle effect is challenging because the additional influences on the signal intensity corrected in this work—for example, caused by $T_1$ weighting—also vary with the effective FA. In addition, particularly for the 39K channel, an inhomogeneous distribution of the effective FA was found (compare Supporting Information Figure S1). These $B_1$ inhomogeneities would have a higher impact on the signal intensity at lower FAs.

Generally, $B_1$ correction of the 23Na and 39K MRI data sets was challenging because the transmit and receive profiles of the 23Na/39K calf coil were not identical. Thus, a 90° pulse—which is quite robust with respect to slightly deviating effective FAs—was chosen for quantitative 23Na and 39K MRI measurements to reduce the influence of $B_1$ inhomogeneities. Further, the applied $B_1$ correction approach is only valid in case the coil loading is the same for the quantitative in vivo measurements and the phantom measurements used to determine the $B_1$ correction factors. A different loading of the RF coil might result in a deviating $B_1^*/B_0^*$ profile and correspondingly varying $B_1$ correction factors. Although this condition was fulfilled for the 39K MR measurements, the coil loading was slightly lower in the phantom measurement than in the human lower leg measurements for 23Na MRI.
This might be a reason for the better agreement between the determined concentration calibration curves and the theoretical expectation for the $^{39}$K MRI data sets than for the $^{23}$Na MRI data sets.

The quantification accuracy in this work was mainly limited by the segmentation approach based on $^{23}$Na data sets. For example, the determination of Na$^+$ concentrations in muscle tissue could be improved by including the vessels in the PVC process due to the high Na$^+$ concentration in blood. An inclusion of the vessels into the muscle mask—as it was done in this work—leads to an overestimation of the muscle Na$^+$ concentration (compare Supporting Information Figure S2). However, the segmentation of vessels as well as determination of muscle-specific aTSC and aTPC values that would be interesting in the context of muscle specific pathologies would require high-resolution $^1$H images, which could not be acquired using the given coil setup. Thus, to improve the quantification accuracy, dual-tuned $^1$H/$^{23}$Na or $^1$H/$^{39}$K RF coils might be advantageous compared with the used dual-tuned $^{23}$Na/$^{39}$K RF coil. However, this would require a repositioning of the subjects and thus would complicate translation into clinical studies. In addition, further examinations—for example, using the proposed simulation approach—would be required to evaluate if a muscle-specific aTPC determination might even result in reasonable values given the low nominal spatial resolution of the $^{39}$K acquisitions.

In this work, PVC of $^{39}$K data sets were performed using individually determined $T_2^*$ relaxation times for each subject. Mean $T_2^*$ components of $T_2^*$ = (1.2 ± 0.2) ms and $T_2^*$ = (7.9 ± 0.9) ms were determined. Furthermore, the fraction of the fast component was close to the theoretical expectation (f = 58 ± 4%). The measured $T_2^*$ times are in good accordance with the values reported by Umathum et al.\textsuperscript{26} and Roesler et al.\textsuperscript{20} for human thigh and calf muscle tissue. Because the variation in determined fast and slow components of $T_2^*$ in healthy lower leg tissue between the 10 volunteers examined in this work was quite small, a PVC based on the mean relaxation time values instead of the individual values in future work is supposed to be reasonable. In patients, altered $T_2^*$ might be found due to edema or fatty infiltration, resulting in quantification errors. Therefore, relaxation times should also be measured in pathological muscle tissue before applying the PVC workflow, as described in this work to patient data. However, because $T_2^*$ mapping is highly time consuming (~30 min), a general inclusion in clinical studies might not be feasible.

Overall, the noninvasive determination of tissue potassium concentrations using $^{39}$K MRI offers a great potential for the application in various diseases. Due to the high reproducibility of the aTPC determination in healthy muscle tissue, this technique should be able to detect alteration in the ion concentration, for example, in patients with renal impairment or muscular channelopathies. Moreover, a higher variation can be expected in the measured muscle aTPC values than in the blood K$^+$ concentrations, which are tightly regulated. Therefore, quantitative $^{39}$K MRI could help gaining additional insights into the underlying physiological processes of various diseases.

5 | CONCLUSION

We showed that using the presented measurement setup and image postprocessing approach, a reproducible aTSC and aTPC determination using $^{23}$Na and $^{39}$K MRI at 7T in human skeletal muscle tissue is feasible in clinically acceptable acquisition times.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

**FIGURE S1** Map of effective flip angles of the 23Na and 39K channel relative to the nominal flip angle of 90° measured in the calf phantom and the reference compartments. Within the phantom area, which corresponds to the lower leg region in human examinations, effective flip angles were close to the nominal value. However, for the 23Na channel, a slight gradient between the left and the right site on the coil was found, which was particularly strong within the reference compartments. For the 39K channel, the effective flip angle was strongly enhanced within the reference compartments close to the rungs of the birdcage coil. As the receive field was not identical to the excitation field for both coils and the deviation of the effective from the nominal flip angle was strongest within the references, constant B1 correction factors were calculated for the reference compartments to mitigate the influence of the inhomogeneous B1 field.

**FIGURE S2** Deviation of the determined ion concentrations from the ground truth concentrations in simulated female lower leg depending on the compartments included in the partial volume correction. For 23Na MRI (A), the data sets were evaluated using the ground truth masks for all three simulated tissue types (orange bars), using the masks for muscle and fat (yellow bars) or using only the muscle mask (purple bars). The deviation from the ground truth concentration of the resulting Na+ concentration in muscle tissue and subcutaneous fat was lowest using all three compartments in the PVC. However, even if only the muscle mask was used for the evaluation, the deviation from the ground truth concentration in muscle tissue still was below 5%. For 39K MRI (B), the data sets were evaluated using the ground truth masks for muscle and vessels (orange bars) and using only the muscle mask (yellow bars). The K+ concentration of subcutaneous fat tissue was assumed to be zero. The inclusion of the blood vessel compartment in the PVC did not yield an improvement of the resulting K+ concentration in muscle tissue. Moreover, the determined K+ concentrations in the blood vessels strongly deviated from the ground truth concentration, even after PVC with the ground truth masks. The simulation ground truth data for 23Na and 39K MRI are shown in (C). Overall, only larger blood vessels—that can also be depicted by 23Na MRI—were included in the simulation.

**FIGURE S3** Evaluation of simulated 23Na (A) and 39K (B) male lower leg images. The PVC was performed based on the ground truth segmentation masks, as well as muscle and fat masks extracted from the 23Na MRI data set and only a muscle mask extracted from the 23Na MRI data set partially including fatty tissue. The deviations of the calculated mask areas from the ground truth mask areas were 10/37% (muscle/fat) for the evaluation including both muscle and fat tissue and 15% (muscle) for the evaluation including only the muscle mask. The resulting calculated ion concentration deviations from the ground truth concentrations are shown in (C) and (D). Using the calculated, strongly deviating muscle mask for the PVC, the deviation of the determined muscle ion concentration from the ground truth concentration increased by approximately 5% compared with the evaluation using the ground truth masks for both muscle and fat to a total of approximately −11% for 39K.

**FIGURE S4** Correlation plots for measured tissue ion concentrations in healthy calf muscle tissue and corresponding blood serum values: Apparent tissue potassium concentration (aTPC) vs. K+ blood serum concentration (A) and hematocrit content (B), apparent tissue sodium concentration (aTSC) vs. Na+ blood serum concentration (C) and hematocrit content (C), as well as aTSC vs. aTPC (E). Shown are the Pearson’s correlation coefficients (R), as well as the P-values for the hypothesis of no correlation between the two measures. There was no significant correlation (P < .05) found for any of the examined measures.

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