Skeletal muscle tissue characterization by ^{23}Na NMRS under different vascular filling conditions

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Target audience: To clinicians and researchers involved in seeking new biomarkers of sodium distribution in normal and diseased skeletal muscle

Introduction

The sodium ion (Na^+) is involved in a vast number of functions at the cellular level. In healthy tissues, the intracellular volume fraction is about 80% with a Na^+ concentration of 10-15 mM, and the extracellular volume fraction (including the vascular compartment) is around 20%, with a Na^+ concentration of 140-150 mM[1]. Changes in sodium intracellular concentration or volume fraction are associated with disorders that alter cell function/integrity or that are responsible for metabolic changes. Several NMR methods have been previously proposed to discriminate intra- and extracellular Na^+ signals, the most popular of which are inversion-recovery methods[2] and triple quantum filtration (TQF) experiments[3]. Here, we proposed a ^{23}Na protocol to characterize skeletal muscle tissues in acquisition times compatible with clinical studies. We evaluated the sensitivity of different parameters (FID signal, TQF signal, TQF/FID ratio, T1 value, short T2* fraction) to differentiate various intracellular volume fractions conditions.

Materials & Methods

Twenty one healthy volunteers were scanned on a 3T whole-body scanner (Tim Trio, Siemens Healthcare). Experiments were performed on their right calf, and a home-made volumic ^{23}Na coil was used for magnetization excitation and signal reception. Ten subjects were scanned at rest, and for the other eleven, data were acquired under different vascular filling conditions expected to modify the extracellular volume exclusively. Vascular draining was obtained by a manual compression of the calf from toes to thigh with a medical compression band, a cuff wrapped around the thigh was then inflated to 250 mmHg to completely block both arterial inflow and venous outflow, and finally, the medical compression band was released while keeping the cuff inflated. Next, vascular filling was produced by decreasing cuff pressure from 250 to 60 mmHg to block the venous outflow only and to fill up the capacitance vessels. Normal conditions used for control were finally reached by a complete release of the cuff. Total sodium content and short T2* fraction were derived from an FID sequence acquired with the following parameters: acquisition delay = 350µs, TR = 300ms, 400 NEX, FA = 90°, BW = 2000Hz, resolution = 256pts, T_{acq} = 2min. Slowly tumbling Na^+ signal was estimated by TQF experiments using a classical 6-steps phase cycling sequence[4] with main parameters: τ_1 = 11ms, τ_2 = 500µs, τ_3 = 350µs, TR = 100ms, 3000 NEX, FA = 90°, BW = 2000Hz, resolution = 256pts, T_{acq} = 5min. T1 relaxation times were quantified with an inversion-recovery Look-Locker sequence using the following parameters: 75 inversion times (from 5 to 375ms), FA = 3°, TR = 1000ms, 950 NEX, T_{acq} = 7min. ANOVA with repeated measures were performed in SPSS 22 to evaluate variable differences between the 3 groups. Bonferoni post-hoc tests were then carried out for pairwise comparisons.

Results

As depicted by figure 1, FID, TQF and T1 recovery signals acquired on the same subject were modified by varying extracellular volume. Repeated measures ANOVA revealed significant variations of FID signals, TQF signals, TQF/FID ratios, T1 values and short T2* fractions between the 3 conditions ($p<0.01$). Figure 2 shows that FID signals and T1 values were significantly increased with vascular filling ($p<0.01$) and slightly decreased with vascular draining (not significant) as compared with control conditions. On the contrary, short T2* fraction as well as TQF/FID ratio were significantly increased with vascular draining ($p<0.01$) and significantly decreased with vascular filling ($p<0.01$) as compared with normal conditions. TQF signal significantly increased with vascular draining ($p<0.01$) and slightly decreased with vascular filling (not significant). Figures 3-a and -b respectively shows that there were significant correlations between T1 and TQF/FID ratio and between short T2* fraction and TQF/FID ratio on the entire subjects cohort (R^2 = 0.46 and 0.63 respectively).

Discussion & Conclusion

Here, we proposed a method based on ^{23}Na NMRS to characterize skeletal muscle under different vascular filling conditions in less than 15 minutes. Results revealed that FID signal variations reflected changes in total sodium content when filling or draining the vascular compartment. Interestingly, TQF signal was not largely affected by changes in vascular content (7% increased with vascular draining, and 2% decreased with vascular filling). This observation tends to confirm the hypothesis that most of TQF signal should arise from intracellular compartment which was not modified by our experiments. Nevertheless, significant increase of TQF signal was observed under vascular draining as compared with vascular filling condition. This difference probably comes from sodium ions in interstitial space that were in closer interactions with macromolecules when extracellular volume is drained. This statement is confirmed by looking at short T2* fractions that were also significantly higher during vascular draining. T1 values were significantly increased during vascular filling but this parameter did not allow differentiating between the two other conditions (filling and control). Finally, the TQF/FID ratio was the most robust and sensitive index to discriminate between the three conditions. In conclusion, ^{23}Na NMR spectroscopy indices sensitive to changes in sodium biodistribution and interaction with macromolecules can be acquired in human skeletal muscles with acquisition times compatible with investigation of patients in a clinical research setting.

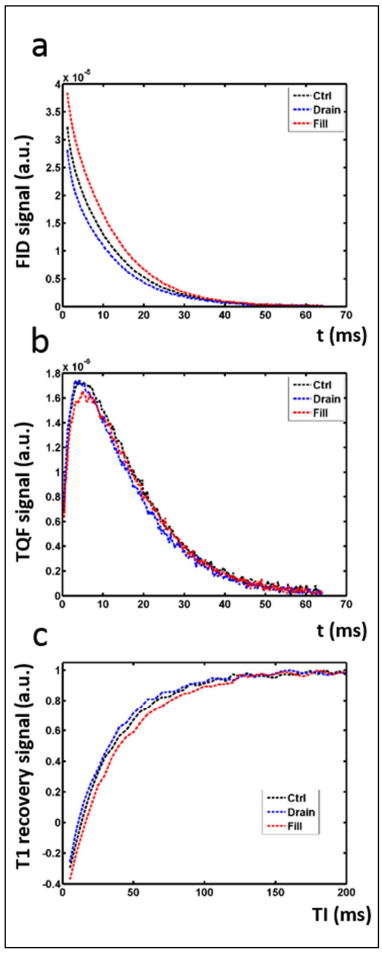

Figure 1: FID signal (a), TQF signal (b) and T1 recovery signal (c) acquired on one volunteer under different vascular filling conditions

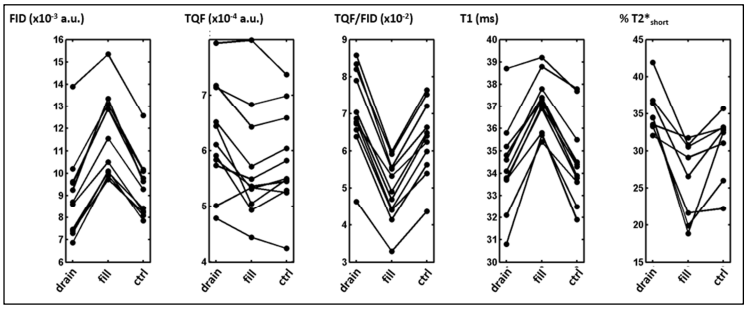

Figure 2: Evolution of the different ^{23}Na parameters for each volunteer under the three different vascular filling conditions

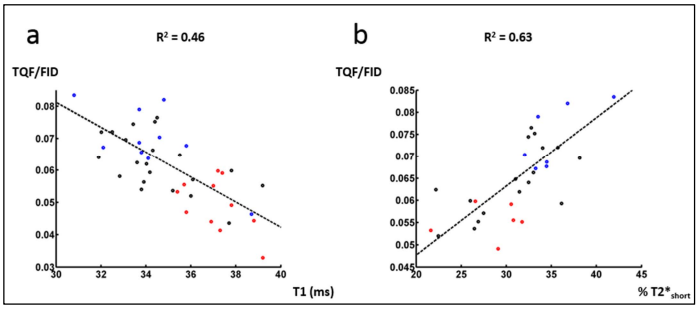

Figure 3: Correlations between TQF/FID ratio and T1 value (a) and short T2* fraction (b) (blue circles: vascular draining, red circles: vascular draining, black circles: control)

References

[1] Madelin et al., JMRI, 2013 ; [2] Nagel et al., Invest. Radiol., 2011 ; [3] Benkhedah et al., MRM, 2012 ; [4] Wimperis et al., JMR, 1992