NMR based biomarkers to study aging related changes in the human quadriceps

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Type of audience: researchers involved in muscle clinical protocols, tissue characterization, aging.

Introduction: Age-related sarcopenia has become a major health issue worldwide. To improve the quality of life of elderly persons, it is important to characterise and understand age-associated structural changes in the skeletal muscles such as fibrosis and inflammation. NMR based biomarkers are good candidate since they are quantitative and offer the major advantage to be non-invasive contrarily to the histological ones. In this work, our aim was to describe structural changes in the quadriceps muscle through a set of descriptors related to the distribution of the transverse relaxation time T2 with a focus on the heterogeneity within the tissue. In addition to age, we also investigated the impact of physical activity and gender on muscle NMR properties.

Materials and Methods Population description: this study was approved by local ethic comity and informed consent was obtained from each volunteer. We scanned a total of 96 subjects composed of 34 young adults aged between 19 and 27 years old (19 male and 15 female) and 63 older adults with age comprised between 69 and 80 years old (31 male and 32 female). For the elderly group, we considered two sub-groups, active (n=31) and sedentary (n=32). A subject was defined as active if he was performing activity sessions that lasts more than 30mn per session and three times or more per week. Data Acquisition For T2 determination, a standard multi-slice multi-echo (MSME) sequence was run with a TR = 3000 ms, a train of 17 echoes with TEs ranging from 9.5 ms to 161 ms. Field of view was equal to 224x448 mm², with a pixel size of 1.4 mm². We acquired 11 slices of 10 mm thickness. The transmit field spatial distribution (B1+) was calculated using an optimized version of the actual flip angle imaging (AFI) method [1] field of view was equal to 224x448x320 mm^3, with voxel size of 4x4x10 mm^3. For 3 point Dixon fat quantification [2], we acquired 3D gradient echo volumes with (TR=10ms, TE=2.75/3.95/5.15 ms, flip angle=3°) and with Field-of-view equal to 224x448x320 mm^3 and a voxel size of 1x1x5 mm^3. Data Analysis: First, all volumes were realigned and ROIs were drawn manually to identify the vastus medialis, the vastus lateralis, and the vastus intermedialis. In each ROI, we were interested in two features: water T2 values, and tissue heterogeneity indices. While the first one is straightforward using the tri-exponential model introduced in [3], the others can be affected by fatty infiltration. For the tissue heterogeneities within a ROI, there are several options: (i) the water T2 heterogeneities, (ii) the heterogeneities of the images obtained from MSME sequence. Knowing that for the TE we used, there is a difference between the fat and the water signals, the heterogeneities can be highly influenced by the degree of fat within the ROI which make it redundant with a measure of fat ratio. To overcome this issue, new images were synthesized, where pure fat pixel intensity was replaced by the intensity of the muscle water signal. It was defined for each TE as: $IM_{new}(TE) = IM(TE) + F_{dx}(Iref_w(TE) - Iref_F(TE))$ where: F_{dx} is the fat ratio and $Iref_w$ ($resp\ Iref_F$) is the reference signal of pure water (resp pure fat) in the MSME images (IM). For each TE, we attributed to $Iref_F$ the mean value of signal on the subcutaneous fat and to $Iref_w$ the mean value of the signal young volunteers muscles. The B1+ map served to discard pixels out of the [90%-120%] range of the prescribed flip angle. The measure of heterogeneity in a ROI for a given parameter is defined as the ratio between the standard deviation of the parameter and its mean value. To sum up for each muscle we computed the following: the mean value of the water T2, the heterogeneity of the water T2 (CvT2) and the heterogeneity of the synthesised images for the different echo times (CvTE1, CvTE2… CvTE17). Statistical analyses were done using NCSS software and we performed analysis of variance tests (ANOVA). The significance value was set to 0.05.

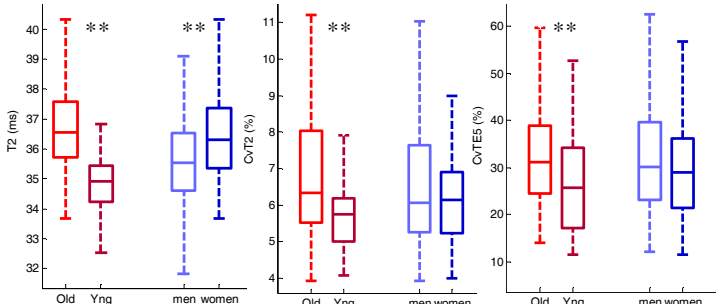

Figure 1: Box plot of water T2 and heterogeneity indices (CvT2, CvTE5). They showed age related differences. Only water T2 revealed a difference between men and women. (** for p<10e-3 and * for p<0.05).

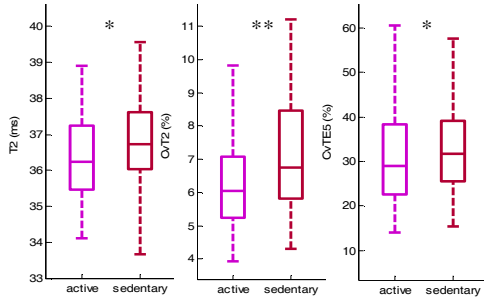

Figure 2: Box plot of water T2 and heterogeneity indices (CvT2 ,CvTE5). They reveal differences between active and sedentary within eldery group. (** for p<10e-3 and * for

Results & discussion: Results of statistical analyses are indicated on figure 1 and 2. They showed that water T2 values, are significantly higher in the elderly group and in the women group, as compared to the young and the men, respectively. Furthermore, a regular physical activity maintained lower muscle T2 values. Regarding the coefficient of variation of water T2, it was higher for the older group and also for sedentary when compared to the active ones. Finally, when considering the heterogeneity extracted from MSME images corrected for fat (CvTE1…CvTE17), we noticed that a significant difference existed between old and young as well as active and sedentary but only for echo times ranging from (TE4=38ms and TE12=114ms). The number of statistically significant differences related to age and physical activity was strikingly high. At the moment, data interpretation must be extremely cautious. It is tempting to relate the increase in T2 with age with the progressive atrophy and rarefaction of type II fibers and to the higher proportion of extracellular space in progressively predominant type I oxidative fibers [4]. The process might be slowed down by regular physical activity. It also would make sense to attribute increased image signal heterogeneities to some degree of tissue disorganisation, and more particularly to the development of interstitial fibrosis. It would be the case with aging, as indicated by higher heterogeneity indices in the elderly group. The phenomenon was partly prevented by physical activity.

Conclusion: In this work, we extracted from clinically available sequences several biomarkers that revealed age associated changes as well as the impact of physical activities on muscle structure. We also introduced new T2 related heterogeneity indices that may help reveal an interstitial fibrosis component not directly visible in the native NMR image.

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