Dynamic MR imaging of the skeletal muscle in young and senior volunteers during synchronized minimal neuromuscular electrical stimulation

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Abstract

Objective Neuromuscular electrical stimulation (NMES)-induced isometric contraction is feasible during MRI and can be combined with acquisition of volumetric dynamic MR data, in a synchronous and controlled way. Since NMES is a potent resource for rehabilitation, MRI synchronized with NMES presents a valuable validation tool. Our aim was to show how minimal NMES-induced muscle contraction characterization, as evaluated through phase-contrast MRI, differs between senior and young volunteers.

Materials and methods Simultaneous NMES of the quadriceps muscle and phase-contrast imaging were applied at 3 T to 11 senior (75 ± 3 years) and 12 young volunteers (29 ± 7 years). A current sufficient to induce muscle twitch without knee extension was applied to both groups.

Results Strain vectors were extracted from the velocity fields and strain datasets were compared with non-parametric tests and descriptive statistics. Strain values were noticeably different between both groups at both current intensities and significant differences were observed for similar current level.

Discussion In conclusion, NMES-synchronized MRI could be successfully applied in senior volunteers with strain results clearly different from the younger volunteers. Also, differences within the senior group were detected both in the magnitude of strain and in the position of maximum strain pixels.

Keywords Phase-contrast sequence · Age · Strain · Quadriceps muscle · Electrical muscle stimulation

Introduction

The combination of MRI and neuromuscular electrical stimulation (NMES) not only gives information about the magnitude of the muscle response, but also localized feedback about how each part of the muscle reacts [1, 2]. NMES involves the application of a series of intermittent stimuli to superficial skeletal muscles to trigger visible muscle contractions due to the activation of the intramuscular nerve branches [3]. It can be controlled by adjusting the waveform, frequency and amplitude of stimulation [3] and induce a synchronous activation of the motor units. In combination with imaging, this enables the direct assessment of muscle kinematics through MRI, by synchronizing the MR-data acquisition with NMES as recently presented [4]. This method offers single-slice three-directional velocity data and direct insights into the muscle contraction capabilities in a completely non-invasive way. It uses a low-cost, standard and
compact NMES device and is an easily applicable solution, whose results significantly depend on the applied stimulation current [4]. Although NMES responses have been investigated with MRI in the past [1, 2, 5], an extensive evaluation of what to expect as a baseline in the MR-based parameters (e.g., normal velocity, displacement maps, strain, strain rate) and how these parameters can change because of physiological and pathological processes is still missing. Other existing approaches offer data acquisition before and after the scan [2] or a synchronization process that comes from the sequence and not the stimulator [6]. In addition, these methods only focus on T2 mapping [2, 5] or 31P spectra acquisition [5, 6]. Yet, the contraction response of a muscle is important and complementary to characterize its mechanical/elastic capacities.

Comparably to existing approaches for voluntary exercise protocols [7, 8], the suggested method uses velocity information acquired with phase-contrast MRI (PC MRI) and provides dynamic muscle images in a similar way to cardiac imaging [9]. PC MRI is a variant of spoiled gradient echo imaging that employs bipolar gradients to get a direct measure of velocity in the direction of the applied gradient of the tissue contained in each voxel, encoded in the phase component of the MR signal. By applying bipolar gradients in the three principal spatial directions, time-resolved vectorial velocity maps are obtained at each point of the contraction cycle. Further quantitative evaluation of PC images yields displacement and strain maps [7, 10, 11]. While voluntary contraction follows the Henneman’s size principle (i.e., small motor units are recruited at lower force levels as compared to larger motor units) [12, 13], standard NMES induces a non-selective and mostly superficial random motor unit recruitment, allowing type II muscle fiber recruitment even at low force levels [3, 12, 14–16].

Age-related changes of the skeletal muscle tissue are associated with sarcopenia, which is a reduction of muscle mass due to a reduction of size and number of muscle fibers. In the elderly, muscle strengths decline faster than muscle volume [17–20]. It is well accepted that type II (fast-twitching) fibers are the most affected ones [18, 21, 22], which results in muscle fiber grouping, i.e., the reorganization of the remaining fibers in larger motor units [17, 22]. For these reasons, employing NMES as a tool to study muscle fiber alterations in aged muscle can be particularly interesting.

The aim of this study was to investigate velocity imaging in the quadriceps muscle through NMES-synchronized MRI and evaluate the potential differences between senior and young volunteers. While physiological differences are presumably expected between these two population groups [7], the sensitivity of the proposed method (i.e., type of stimulation and its visualization through imaging) to highlight such differences is not straightforward and is thus the primary end point of this study.

**Material and methods**

The study was approved by the local ethics committee and written informed consent was obtained from all individual participants included in the study. Volunteers with a history of heart or kidney disease, cancer and muscle pathology or any operation on the examined lower extremity within the past 5 years were excluded. A total of 11 healthy senior (mean age: 74.9 ± 3.4 years, range 70–82; mean height: 170 ± 8 cm, mean weight: 72.0 ± 11.0 kg, 6 male, 5 female, BMI: 24.9 ± 3.3) and 12 healthy young volunteers [age: 29.3 ± 7.3 years (21–47), height: 174.3 ± 9.9 cm, weight: 69.8 ± 11.6, 6 male, 6 female. BMI: 22.9 ± 2.2] were included.

**Experimental setup**

An InTENSity Twin Stim III TENS and NMES Combo (Current Solutions LLC, Austin, TX, USA) was used for the stimulation of the quadriceps muscle and 5.1 × 8.9 cm² rectangular self-adhesive gel-based NMES electrodes (TENSUniTS) were attached to the muscle belly as described in [4]. The electrodes were placed at 15 cm distance from each other and 12 cm from the center of the knee joint on the vastus lateralis (VL). The young volunteers were scanned once with the stimulation level set to 18 mA, which was sufficient to achieve muscle twitching without knee extension [4]. For the senior volunteers, in case 18 mA did not suffice to induce a visible contraction, the stimulation was applied first at a minimum level to achieve this goal within their comfort levels and with the maximum limit set to 22 mA. For the younger volunteers, in case a visible contraction was achieved with less than 18 mA, the current was not increased further. Five minutes after the maximum applied level, an additional acquisition was obtained at 18 mA for comparison.

A monopolar square wave with frequency set to 150 pulses/s and pulse duration set to 0.3 ms was used for stimulation. The plateau of each contraction lasted 1 s (i.e., 1 s ramp time, 1 s plateau, 1 s ramp down, 2 s relaxation). A second waveform, generated at the beginning of every stimulation cycle, was used for triggering of the MRI acquisition.

**MR acquisition**

The acquisitions were performed on a 3 T clinical MRI scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany). The MRI protocol consisted of standard localizers and one or two single-slice phase-contrast datasets. The 2nd channel of the NMES device was used as an external trigger signal for the MRI acquisition [4]. The electrodes
were identified on the image localizers by means of glycerin capsules placed on each electrode. For the induced muscle contraction, the NMES device was used to periodically stimulate the quadriceps muscle and also triggered a single-slice three-directional gradient echo phase-contrast (PC) MRI acquisition [4]. A three-directional gradient echo PC velocity encoding sequence was performed on a parasagittal slice [through VL and vastus intermedius (VI) muscles] with a spatial resolution of $2.3 \times 2.3 \times 5 \text{ mm}^3$ and a temporal resolution of 42 ms (i.e., effective repetition time). The velocity encoding was $25 \text{ cm/s}$ [repetition time (TR)/echo time (TE) = 10.6/7.21 ms, bandwidth/pixel = 400 Hz/Px, flip angle = 10°, field-of-view = $225 \times 300 \text{ mm}^2$, 1 k-space line per segment, acquisition time 5 min] and 94 time frames were acquired. In total, during the whole image acquisition time, approximately 60 contractions were induced.

Since the data are acquired in a triggered mode, partial data corresponding to one time frame are aggregated over several contractions and repetitions, and then an image time series of 94 time frames and one contraction (ramp-up, plateau, ramp-down, dead time) can be reconstructed. Therefore, in this manuscript the data presented for one contraction are those collected partly for many contractions and reconstructed as the representation of one.

**Data processing**

The velocity images were elaborated off-line with Matlab (The Mathworks, Inc., Natick, MA, USA). Strain tensors were extracted from the velocity fields as described in [4, 7, 10, 23] and subsequently diagonalized to obtain the strain eigenvalues $e_1$. As the acquisition was limited to a single slice, only the in-plane strain tensors could be extracted from the velocity field.

The post-processing analysis was performed initially for the VL and VI and then four different regions of interest (ROI) were selected equidistantly covering both VL and VI muscles proximally to distally in respect to the knee. ROIs 2 and 3 were located approximately in between the two stimulation electrodes (see Fig. 1). For every time frame, the spatial median values were calculated (to account for the skewness of the statistical distribution of the values inside the ROIs). Temporal local maximum values were calculated for the strain over each ROI [4].

In addition to the magnitude of the deformation as described by the strain values, temporal information (i.e., the rate of reaching the maximum response) was also extracted from the datasets. This information was obtained in terms of “increase rate” of the strain following the onset of stimulus and was calculated through the fitting of a sigmoid curve to the rising slope of the contraction. The curve was described by the following equation:

$$ s(t) = a \frac{1}{1 + e^{-\frac{t-t_0}{\Delta t}}} + \text{offset.} $$

The ratio $a/\Delta t$ was defined as strain increase rate (see Fig. 1b) and it was descriptively evaluated through maps.

**Statistical analysis**

Comparison with a significance level of 0.05 was performed between the independent groups of the results from the senior volunteers (SV) for 18 mA and 22 mA (SV18 and SV22) versus the results of the young volunteers (YV). The comparison was performed for all four ROIs. The internal control for distribution normality was performed with qualitative histogram visualization. Given the low number of participants, non-parametric statistics were applied; since the distributions were not all normal and the number of samples was small, two-sided Wilcoxon rank sum test was used. Statistical analysis was performed with Matlab (ranksum function). Due to the small number of volunteers, no statistical analysis between genders was performed.

**Results**

All but two YV were scanned successfully with the stimulation current set at 18 mA. Only in two female volunteers the current below 18 mA was already sufficient to achieve...
a standard visible contraction. Dynamic PC images were successfully acquired from SV at 18–22 mA. For the majority of SV (9 out of 11), a current amplitude of 22 mA had to be applied to achieve a similar muscle twitch as compared to 18 mA in the YV. Two SV were scanned at 20 mA instead of 22 mA, because the lower current already achieved sufficient muscle twitch. Since these were only two cases, the results from the scan at 20 mA of these two SV were not analyzed, but only the ones at 18 mA.

In general, the velocity averaged over, e.g., the VL as a function of time presents two pronounced peaks: one at the beginning of the contraction and one at the moment of the release of the muscle [4]. In Fig. 2, some exemplary velocity vector maps from the beginning of the contraction are presented. The three-dimensional colored velocity vectors from the VL were overlaid on an anatomical image of the thigh. In the senior volunteers, the contraction peak occasionally appeared at a later time frame than in the younger volunteers (i.e., around the 40th frame instead of the 30th frame).

The principal strain maps were calculated, and the temporal evolution of strain was analyzed for the VL and VI (see Fig. 3). As expected, we observed a response to the stimulation in both muscles, the VL and the VI, yet the response in the VL was stronger. When applying a lower current (i.e., 18 mA) to the senior volunteers, there was no discernible response in the VI. Moreover, for the younger volunteers, the strain reaches a maximum value faster than for senior volunteers (see Fig. 3).

The strain values in a wider ROI including both VL and VI were summarized for the four different ROIs (ROI1-4: proximal to distal) in Table 1. As expected, for the central ROIs 2 and 3 that are located approximately between the electrodes, the strain values had significantly lower values for the senior in comparison to the younger volunteers (Fig. 4).

Finally, the analysis of the spatial distribution of the strain increase rate showed different patterns. Figure 5 shows two young volunteers (Fig. 5a, b) compared with four seniors (Fig. 5c–f). In general, the young volunteers...
showed a distinct superficial region of high strain increase rate, whereas the seniors had a more homogeneous distribution and generally lower in magnitude.

Fig. 3 Temporal evolution of strain calculated for the vastus lateralis (VL, upper row) and vastus intermedius (VI, lower row) at every time frame given in arbitrary units (a.u.). Results are given for both young (YV: young volunteers) and senior volunteers (SV18: senior volunteers at 18 mA, SV22: senior volunteers at 22 mA). The mean strain curve is overlaid in red color.

Table 1 Strain values over a wider ROI including both vastus lateralis and intermedius, as well as sub-ROIs from proximal to distal: YV: young volunteers, SV-18 mA: senior volunteers during stimulation with 18 mA current, SV-22 mA: senior volunteers during stimulation with 22 mA current

| Median (1st, 3rd quartile) | ROI 1        | ROI 2        | ROI 3        | ROI 4        | ROI (1–4)    |
|----------------------------|--------------|--------------|--------------|--------------|--------------|
| YV                         | 0.119 (0.095, 0.145) | 0.135 (0.094, 0.205) | 0.1625 (0.114, 0.206) | 0.152 (0.104, 0.226) | 0.138 (0.121, 0.178) |
| SV-18 mA                   | 0.052 (0.041, 0.076) | 0.044 (0.035, 0.070) | 0.034 (0.026, 0.110) | 0.050 (0.031, 0.067) | 0.041 (0.030, 0.083) |
| SV-22 mA                   | 0.072 (0.053, 0.200) | 0.098 (0.036, 0.134) | 0.072 (0.046, 0.166) | 0.089 (0.035, 0.122) | 0.138 (0.052, 0.166) |

Fig. 4 Box plots of strain values of the young volunteers (YV, left box plot), and of the senior volunteers (SV) at 18 mA and 22 mA (SV-18 mA, central box plot and SV-22 mA, right box plot) averaged over four different ROIs of the vastus lateralis from proximal to distal (ROI1 to ROI4; see Fig. 1)

Statistical analysis

The results of the two-sided Wilcoxon rank sum test are presented in Table 2. The comparison was performed for
the four ROIs of both VL and VI. The differences between young and senior volunteers for contractions at 18 mA were all significant ($p < 0.05$). The differences of strain values from young volunteers and senior volunteers at 22 mA were not statistically significant (see Fig. 4).

### Discussion

The aim of this study was to investigate velocity imaging in the quadriceps muscle through NMES-synchronized MRI and evaluate the potential differences between senior and young volunteers. Significant differences in skeletal muscle contraction parameters (i.e., principal strain) were assessed with PC MRI between healthy young (average: 29 years old) and senior (average: 75 years old) volunteers. It was also shown that the differences of strain values between the young and senior volunteers, at the same stimulation current, were significant.

The significant difference in strain values between the two age groups is in agreement with Sinha et al., who showed differences not in strain, but in strain rate maps calculated from PC images in senior and younger volunteers (78 years vs 28 years) during voluntary contractions [7]. While this agreement seems straightforward, the results presented in this work could not be simply deduced from similar data acquired during voluntary contraction, since the two types of exercise are fundamentally different. In our case, the difference between the two populations could be attributed to stiffer muscle elasticity with increasing age [17, 18, 24]. A reduced number and size of mainly type II muscle fibers in the seniors might contribute to a difference in strain values between young and senior...
individuals as well, since NMES allows type II muscle fiber recruitment even at low force levels [17, 18, 21].

In addition, the spatial distribution of the parameter of the strain curve, defined here as “strain increase rate”, was examined. This parameter intimately relates to the strain rate, determined as the temporal derivative of strain, but it still depends on the reference state. For linearly increasing strain curves, the two parameters should be approximately alike. However, the muscle response to electrical stimulation is not linear (i.e., the force, the magnitude of stretching, etc.) and often not monotonic and thus this assumption is typically not valid. This was the case especially in the senior volunteers, who overall proved to be less responsive to the same stimulation current.

In the present study, we observed a faster response of higher amplitude that “activated” a larger area of the most superficial muscles in younger compared to the senior volunteers. This observation can be used as a potential marker to show the efficacy and improvement of NMES training protocols in the aged muscle. Furthermore, within the SV group some responses were similar to the ones of the YV group. A next step would be to investigate whether this fact depends on the special characteristics of one’s physical status, which has to be characterized with other parameters such as external force measurements. Simultaneous measurements of the induced force could be performed during the simultaneous EMS and MRI acquisition [25]. These parameters in combination with clinical markers (i.e., biopsy data showing fiber composition) could potentially offer a comprehensive description of the muscle condition. Additional data might be obtained through other noninvasive imaging methods, namely magnetization transfer imaging [26] or T1ρ imaging [27]; however, these methods are currently too unspecific to offer meaningful discriminating power [28]. MR elastography [29] might provide additional insight into the muscle characteristics; however, this is not easily implementable as it requires specialized hardware and dedicated reconstruction algorithms.

Clinical applications of the presented method include a variety of pathological muscle conditions sensitive to fiber type II atrophy such as chronic obstructive pulmonary disease [30], or chronic steroid myopathy [3, 31], and age-related diseases such as sarcopenia [32]. It can also be applied to competitive or elderly people who need to train fast fibers with low effort [15, 16].

Due to the limited number of volunteers in this study, the group of senior volunteers was considered as one single group. However, there was a variability in the physical condition of the subjects, since some of the senior volunteers performed vigorous training on a regular basis. For better differentiation, the volunteers would have to be grouped more strictly according to their physical condition and training habits, which can be the subject of future investigation.

Finally, one technical restriction of the current study is that there was no comparison of the calculated strain with the force output. In part, this was due to the lack of a suitable measurement equipment at our institution. Yet, the choice of using a stimulation current that only generates a visible twitch of the muscle without noticeable knee extension was dictated by the strong discomfort associated with NMES at higher force outputs [3], which makes the detectability of physiological differences at minimal stimulation intensity very relevant for the compliance and comfort of a potential patient. Nevertheless, it would be interesting to compare strain for the same force output in future investigations.

In conclusion, strain measurements with MRI of NMES-induced muscle contraction show age-related differences between healthy volunteers. The differences were more significant when the same stimulation current was used for young and senior subjects. Moreover, there were prominent differences not only in the strain magnitude, but also in the temporal rate of strain and variable for different muscle regions. Despite these physiological inter-individual differences, the data shown here may be used as a preliminary data baseline for a more accurate and detailed assessment of muscle function disturbances.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study was approved by the local ethics committee and written informed consent was obtained from all individual participants included in the study.

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