Recovery of arm-hand function after stroke: developing neuromechanical biomarkers to optimize rehabilitation strategies.

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Chapter 5

Loss of selective wrist muscle activation in post-stroke patients

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ABSTRACT

Purpose

Loss of selective muscle activation after stroke contributes to impaired arm function, is difficult to quantify and is not systematically assessed yet. The aim of this study was to describe and validate a technique for quantification of selective muscle activation of wrist flexor and extensor muscles in a cohort of post-stroke patients. Patterns of selective muscle activation were compared to healthy volunteers and test-retest reliability was assessed.

Materials & Methods

Activation Ratios describe selective activation of a muscle during its expected optimal activation as agonist and antagonist. Activation Ratios were calculated from electromyography signals during an isometric maximal torque task in 31 post-stroke patients and 14 healthy volunteers. Participants with insufficient voluntary muscle activation (maximal electromyography signal < 3SD higher than baseline) were excluded.

Results

Activation Ratios at the wrist were reliably quantified (Intraclass correlation coefficients 0.77 – 0.78). Activation Ratios were significantly lower in post-stroke patients compared to healthy participants ($p < 0.05$).

Conclusion

Activation Ratios allow for muscle specific quantification of selective muscle activation at the wrist in post-stroke patients. Loss of selective muscle activation may be a relevant determinant in assigning and evaluating therapy to improve functional outcome.

INTRODUCTION

In post-stroke patients, impaired arm and hand function is determined by a complex interaction of primary neurological deficits and secondary changes in connective and contractile tissue [1-3]. Amidst these changes, loss of selective muscle activation plays a role [4-7]. The ability to voluntarily contract a muscle and to have selective control of antagonistic muscles predominantly defines the torque output a patient can generate during a task. Loss of selective muscle activation may result in energetically inefficient co-contraction and impaired dexterity in the affected limb [8-11]. Moreover, loss of selective muscle activation [12] may result in a lower torque output at joint level than expected by the level of paresis alone [13]. We expect clinical phenotypes to diverge from 1) patients with flaccid paresis, i.e. no selective muscle activation, to 2) patients with some loss of selective muscle activation, and 3) patients with normal selective muscle activation combined with either low or normal torque output. Addressing the role of selective muscle activation to loss of function is important in clinical decision making, e.g. to optimize patient selection and timing of costly or labor intensive therapies such as mCIMT or botulinum toxin.

Selective muscle activation is not yet assessed routinely in post-stroke patients. Current measures may have methodological drawbacks. For example, comparison of electromyography (EMG) signals of agonistic and antagonistic muscles is a frequently applied technique [14-18]. Yet the comparison of agonist and antagonist EMG-signals is for instance troubled by differences in volume of the muscles in an agonist-antagonist muscle pair [19,20] and complicated in case of spasticity [9], which makes quantification of selective muscle activation with this technique challenging. Furthermore, quantification of selective muscle activation by comparison of EMG-signals of the same muscle in the ipsilateral and contralateral sides [13,21] may be hampered, as muscle properties of the unaffected side should not be regarded as normal in post-stroke patients [22-26]. Moreover, proper address of selective muscle activation is of importance as morphological changes interfering with contractile behavior are already reported in the early phase after stroke [27].

In this study we describe selective muscle activation by comparing EMG-signals of wrist muscles during two isometric but antagonistic task conditions, using the normalized ratio of the EMG-signals per muscle group, also called Activation Ratio (AR) [28]. This method is methodologically advantageous because it describes the activation of both flexor and extensor muscles in relation to their expected agonistic and antagonistic function. AR may be applied to antagonist muscle pairs provided the axis of movement is controlled (limitation in degrees of freedom). Selective muscle activation around the wrist joint had our special interest because of its role in lasting impairment in arm-hand function after stroke, e.g. in case of flexion deformity. Muscle specific AR is assumed to assist in a better definition of clinical phenotypes in post-stroke patients. However, this method has not been evaluated in post-stroke patients yet. Our aim was to describe and validate this technique

for quantification of selective muscle activation of wrist flexor and extensor muscles in a cohort of post-stroke patients. Patterns of selective muscle activation were compared to healthy volunteers and test-retest reliability was assessed.

METHODS

Participants

The study cohort consisted of 31 stroke survivors and 14 healthy volunteers. Post-stroke patients were recruited from an outpatient rehabilitation department. Inclusion criteria were: first ischemic stroke between 1999 – 2009, age 18 – 80 years, a perceived persistent impairment of arm-hand function by the participant, being able to travel to the research laboratory, and being able to sit on a chair and follow instructions for one hour. Exclusion criteria were: previous orthopedic limitations of arm-hand function, a history of other neurologic impairments besides stroke. Participants were measured between November 2008 and January 2010 on two occasions within a month, under the assumption that clinical status would remain stable. Stroke onset was more than 6 months prior to assessment. Ethical approval for the study was received from the medical ethical committee at the Leiden University Medical Center and written informed consent was obtained from each participant prior to testing.

Protocol

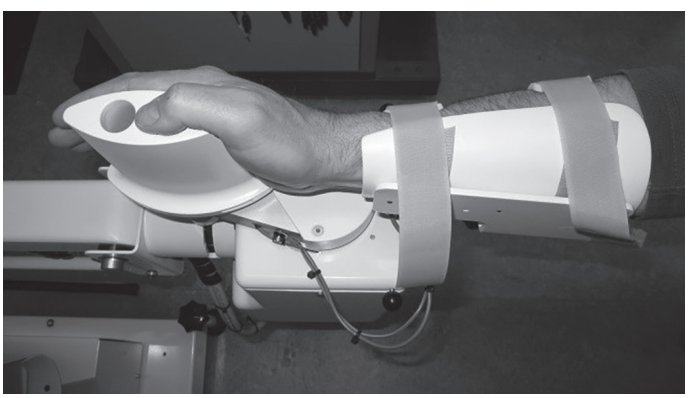
Participants were instructed to perform a voluntary isometric maximal flexion or extension torque, starting from a relaxed condition. The voluntary maximal isometric torque (MIT) had to be attained within a 15 second timeframe, followed by a minimum of 60 seconds rest. This procedure was performed twice for both flexion and extension. The position of the wrist during the test was a neutral angle where the average measured torque during a slow passive movement through the range of motion was 0 Nm (Rest Angle) [29]. For motivational purposes, visual feedback was provided on a computer screen. This feedback consisted of a vertical bar which showed both instantaneous and maximal attained torque.

Measurement set-up

Tests were performed on a haptic wrist manipulator (Wristalyzer®, Moog FCS, Nieuw Vennep, the Netherlands) [30], on which torque and wrist joint angle were recorded. Participants were comfortably seated on a chair in front of a video screen. The forearm of the participant was positioned horizontally with the elbow in 90° flexion. The hand was strapped to an ellipsoidal shaped handle (Figure 1) to prevent finger flexion and hand closure. The skin at the electrode positions was cleansed with alcohol and lightly abraded with skin preparation gel (SkinPure, Nihon Kohden, Japan). EMG activity of the m. flexor carpi radialis (FCR) and

m. extensor carpi radialis longus and brevis (together abbreviated as ECR) was recorded by bipolar parallel bar surface electrodes (Bagnoli® DE-2.1, Ag, single differential, inter electrode distance 10 mm; Bagnoli-8 amplifier, Delsys Inc., Boston, USA). FCR and ECR were chosen to reflect overall muscle activity of wrist flexor and extensors. Both muscles are the less pennate muscles of the lower arm, have good accessibility with surface EMG and are therefore likely to suffer less from measurement artefacts. Two bipolar electrodes were placed on each muscle group to ensure that a signal was available and to compensate for spatial alterations in the affected (atrophic) muscle after stroke [31]. Position, force and EMG were sampled at 2048Hz using a 16 bit analog-to-digital card (USB 6221, National Instruments, Austin, USA) [29].

Figure 1 | Photograph of Wristalyzer handle and arm-rest.
For a better view of the hand position, the hand straps are not shown.



Data processing

Data were processed with Matlab® (Mathworks, Natick, USA). Selective activation of FCR and ECR were computed by means of Activation Ratio (AR). This is an EMG-based method [28], which requires voluntary muscle activation. In patients with flaccid paresis, voluntary muscle activation is insufficient to distinguish between resting state and active conditions, and therefore insufficient to determine selective muscle activation. In this study, insufficient voluntary muscle activation was defined as EMG activity during the isometric maximal torque task of less than three times standard deviation above baseline EMG. When insufficient EMG activity was established for a trial, the trial was excluded from analysis.

AR was calculated per bipolar electrode according to equation 1 [28], where AIP is the in-phase muscle activation, i.e. activity during the agonistic task; and AOP is the out-of-phase muscle activation, i.e. activity during the antagonistic task of the muscle. An AR close to one indicates optimal in-phase (selective) muscle activation. If the AR equals zero, muscle activation is equal during flexion and extension. A negative AR indicates out-of-phase

muscle activation, i.e. the muscle is more active during its antagonistic task than during its agonistic task.

Equation 1

$$AR = \frac{(A^{IP} - A^{OP})}{(A^{IP} + A^{OP})} \qquad [-1 \leq AR \leq 1]$$

Raw EMG signals (online band pass filter 20-450 Hz) were rectified and smoothened by a 2Hz 3rd order Butterworth low pass filter [32]. Torque data were also smoothened with a 3rd order Butterworth low pass filter of 2 Hz. Smoothened torque data and corresponding EMG signals were sorted along torque magnitude with intervals of 0.01 Nm. Then AR were computed for each torque level using both flexor and extensor task data within the available torque range (containing matching torques from both flexion and extension task) per bipolar electrode. The average AR was then computed per bipolar electrode, resulting in two AR for FCR and two AR for ECR per trial.

Statistical methods

SPSS 20 (IBM, New York, USA) was used for statistical analysis. For each participant, the average AR_{flex} for FCR and average AR_{ext} for ECR per visit was computed from the mean AR per bipolar electrode per trial (EMG was recorded by two bipolar electrodes per muscle group and participants had two trials per visit), after checking for systematic differences between the electrodes and trials using Wilcoxon rank sum test and scatter plots.

Test-retest reliability of AR was established by Intraclass correlation coefficient (ICC) between the two visits. ICC were calculated using the two-way mixed model for absolute agreement. Values above 0.75 were assumed to represent excellent reliability, values between 0.4 and 0.75 to represent fair to good reliability and values below 0.4 to represent poor reliability [33]. As ICC is a relative measure dependent on variance between measurements compared to total variance [34], Bland Altman plots were used to illustrate variability. Standard Error of Measurement (SEM) values were calculated to further substantiate ICC according to equation 2.

Equation 2

$$SEM = SD^{*}\sqrt{(1-ICC)}$$

At parameter level, normality of distribution was inspected with histograms and equality of variances between healthy volunteers and post-stroke patients was tested with Levene's test. Age was normally distributed, equal variances were assumed (Levene's test $p = 0.78$). The independent samples *t*-test was used to compare age between healthy volunteers and post-stroke patients. AR were not normally distributed within groups and variance was not equal between groups (Levene's test for AR_{flex} $p = 0.018$, and for AR_{ext} $p < 0.001$), hence median and range were used and the non-parametric Independent Samples Median Test

was used for comparison between post-stroke patients and healthy volunteers. The relation between AR_{flex} and AR_{ext} was tested with Spearman's rho correlation coefficient. Ratio of men to women within the two groups (post-stroke patients and healthy volunteers) was tested with the chi-square test.

RESULTS

Participants

All healthy volunteers completed all visits (100%) and 28 out of 31 patients completed all visits (90.3%). Reasons for dropping out were: unable to schedule the second visit (n = 2), patient was treated with botulinum toxin in period between first and scheduled second visit (n = 1). Demographics of the study population are summarized in table 1. Mean age in post-stroke patients was 59 years (SD 13 year) and 50 years (SD 15 year) in healthy participants (p = 0.04 when tested for difference in age between group; 95% confidence interval for the difference: -18 years to -0.2 years). However, further analysis showed that age did not have a significant correlation with either ARflex (Pearson correlation -0.079 with p = 0.62) or ARext (Pearson correlation -0.139 with p = 0.38), and in multivariate analysis, age was not a contributing factor. Therefore age was not corrected for in further analysis. The ratio of men to women was not statistically different in both categories (p = 0.14). Average time post-stroke was 3 years (SD 2.5 year). More information on limb dominance in the post-stroke patient group can be found in Supplementary Figure S1.

Table 1 | Demographics of the study population.
Data expressed as mean (SD) or number (%), n.a. = not applicable.

Population	Healthy volunteers (n = 14)	Chronic patients (n = 31)
Age (years) (SD)	49.4 (15.1)	58.5 (13.1)
Men (*n*)	9 (64%)	13 (42%)
Right side dominant (*n*)	13 (93%)	29 (94%)
Measured side dominant (*n*)	14 (100%)	14 (45%)
Rest Angle (degrees) (range)	-52 [-64; 1]	-35 [-72; -5]
Time between measurements (days) (SD)	27 (21)	22 (12)
Time after stroke (years) (SD)	n.a.	3.1 (2.6)
Age at moment of stroke (years) (SD)	n.a.	55.2 (13.8)
modified Ashworth Score = 0 (*n*)	n.a.	21
modified Ashworth Score ≥ 1 (*n*)	n.a.	10

Voluntary muscle activation

Three out of 172 trials were excluded because of recording errors. Insufficient voluntary muscle activation was observed in both FCR and ECR in three post-stroke patients, indicating flaccid paresis. The trials of these three patients were excluded from analysis. In two additional post-stroke patients, there was insufficient voluntary muscle activation in the ECR only. Therefore, all trials regarding the extensor muscles of these two patients were excluded from analysis.

Quantification of selective muscle activation

A typical recording of a healthy participant is illustrated in Figure 2. Voluntary maximal isometric torque (MIT) were 28.3 Nm (flexion) and 18.4 Nm (extension). EMG activity of the FCR during extension was low and EMG activity of the ECR during flexion was low, as expected. Resulting AR in this participant were therefore close to one (ARflex = 0.82, ARext = 0.81), indicating a high selectivity of FCR and ECR muscle activation.

Figure 2 | Wrist torque and EMG activity in a healthy volunteer with selective muscle activation.

Right arm measured. EMG FCR: EMG signal of m. flexor carpi radialis. EMG ECR: EMG signal of m. extensor carpi radialis longus and brevis.
Upper panel: red line represents flexion wrist torque. Blue line represents extension wrist torque.
Middle and Lower panel: red lines represent EMG activity during flexion. Blue lines represent EMG activity during extension.

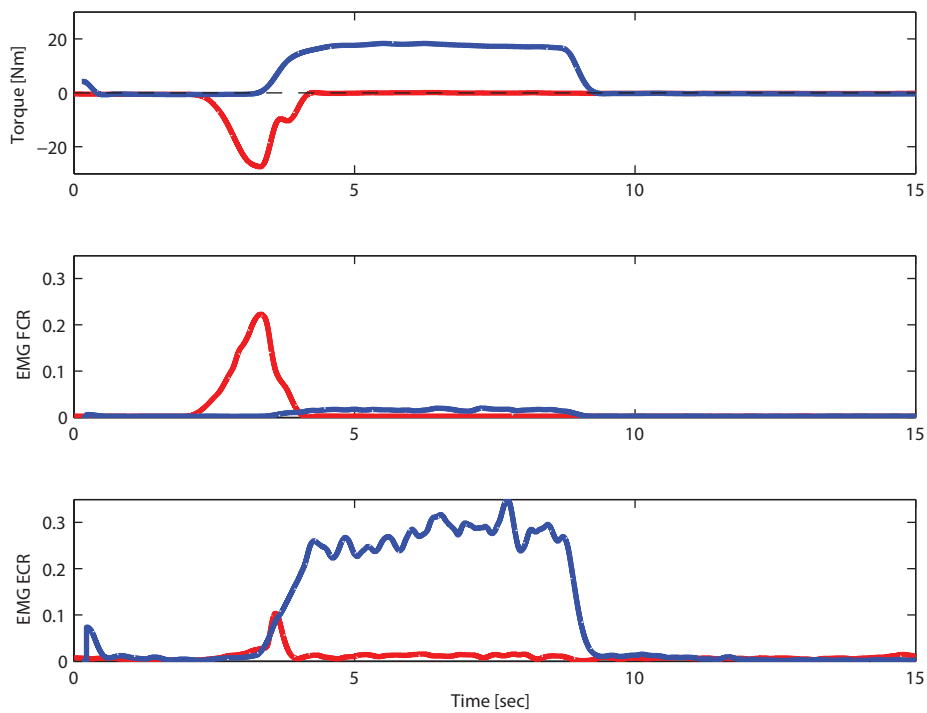
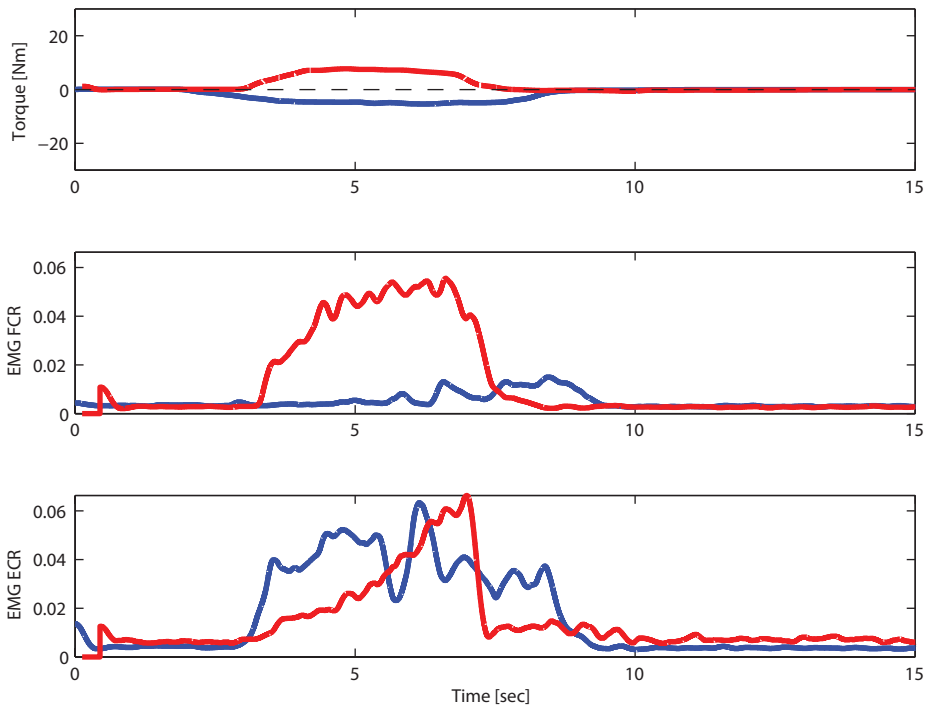


Figure 3 | Wrist torque and EMG activity in a post-stroke patient with loss of selective muscle activation.

Left arm measured. EMG FCR: EMG signal of m. flexor carpi radialis. EMG ECR: EMG signal of m. extensor carpi radialis longus and brevis.

Upper panel: Red line represents flexion wrist torque. Blue line represents extension wrist torque.

Middle and lower panel: Red lines represent EMG activity during flexion. Blue lines represent EMG activity during extension.



An example of a post-stroke patient with loss of selective function of the ECR is shown in Figure 3. Voluntary MIT were 7.8 Nm (flexion) and 5.4 Nm (extension). There was an increased EMG activity of the ECR during flexion. This EMG activity was almost equal to the EMG activity of the ECR during extension. Therefore the AR_{ext} in this participant was close to zero (AR_{ext} = 0.01). The FCR showed more selective activation (AR_{flex} = 0.55).

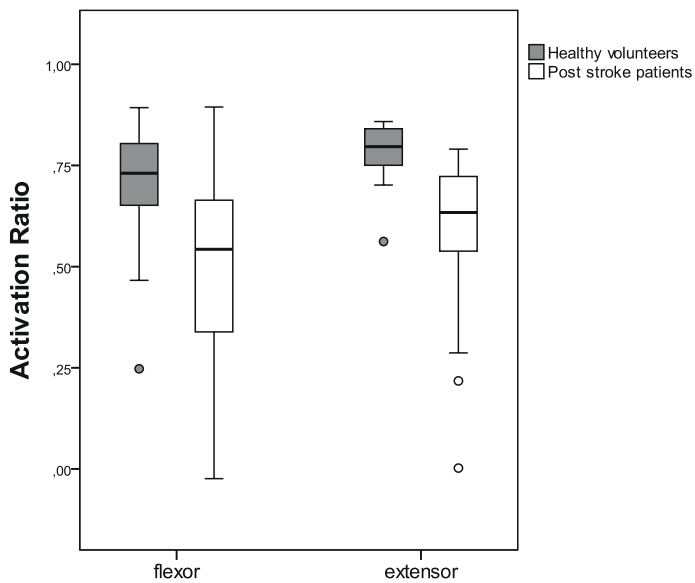
Activation Ratios in post-stroke patients and healthy volunteers

Median AR_{flex} was 0.62 and median AR_{ext} was 0.71 overall in all participants. Median and range of AR in post-stroke patients and healthy participants, as well as voluntary MIT per group are summarized in table 2. Median AR_{flex} and AR_{ext} in post-stroke patients were significantly lower than in healthy participants (p = 0.022 and p = 0.003 respectively), this is graphically represented in Figure 4. AR_{flex} and AR_{ext} were significantly correlated in post-stroke patients (Spearman's rho 0.486, p = 0.012), but not in healthy participants (Spearman's rho 0.262,

p = 0.366), which can be inferred from Figure 5. Test-retest reliability of AR_{flex} and AR_{ext} was excellent with ICC of 0.77 and 0.78 respectively. Bland Altman plots are shown in figure 6, depicting the mean of the two measurements (x-axis) compared to the difference between two measurements (y-axis). The values are scattered around the mean difference (solid line), which is close to zero, illustrating the absence of a systematic difference or learning effect between the two measurements. The 95% confidence interval of the difference between the measurements (dotted lines) illustrates measurement error. SEM values provide an indication of the dispersion of the measurement errors. SEM were 0.11 for AR_{flex} and 0.10 for AR_{ext}. More information on the influence of variance on ICC and SEM can be found in Supplementary Figure S2.

Figure 4 | Box plot for Activation Ratios of m. flexor carpi radialis (AR_{flex}) and m. extensor carpi radialis communis (AR_{ext}) in post-stroke patients and healthy volunteers.

Differences between post-stroke patients and healthy volunteers are significant as tested with Independent Samples Median Test. P-values: $p(AR_{flex}) = 0.022$, $p(AR_{ext}) = 0.003$.



Clinical Phenotypes

As introduced, clinical phenotypes were expected to diverge from 1) patients with flaccid paresis i.e. no selective muscle activation, to 2) patients with some loss of selective muscle activation combined with low torque output, and 3) patients with normal selective muscle activation combined with either low or normal torque output. To substantiate these phenotypes, combinations of AR and MIT can be used. In the first phenotype, voluntary muscle activation is insufficient to distinguish between resting state and active conditions, so AR cannot be quantified. In the second phenotype, combinations of low AR with both

high and low MIT are found. In the third phenotype, a high AR in combination with either a high MIT or a low MIT is expected. Patients of phenotype 2 and 3 are graphically represented in Figure 7, with the dotted line representing the lowest value in healthy volunteers (AR_{flex} 0.15 and AR_{ext} 0.56; MIT_{flex} 16.4 Nm and MIT_{ext} 4.6 Nm). High AR (representing high selective muscle activation) occurred within patients with both high and low MIT (right upper and lower quadrant in all panels), while low AR (representing low selective muscle activation) predominantly coincided with low MIT (left lower quadrant in all panels). The exception is low AR_{ext}, which coincided with both high and low MIT_{ext} (left upper and lower quadrant in lower right panel).

Figure 5 | Scatter plot illustrating the correlation of Activation Ratio for m. flexor carpi radialis (AR_{flex}) and m. extensor carpi radialis communis (AR_{ext}).

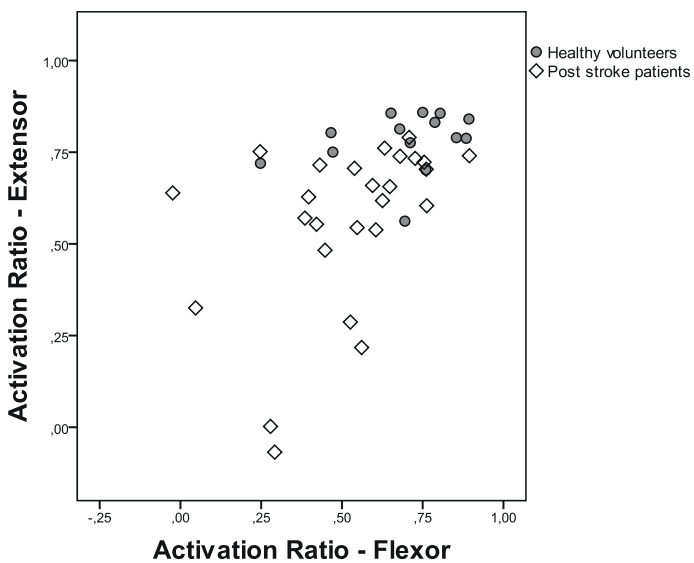


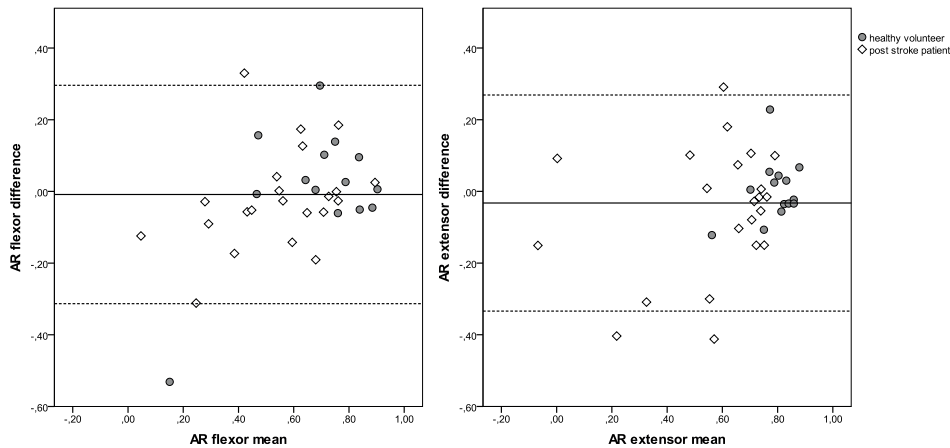
Table 2 | Median and range of Activation Ratio and voluntary Maximal Isometric Torque in post-stroke patients and healthy volunteers.

AR_{flex} = Activation Ratio for m. flexor carpi radialis; AR_{ext} = Activation Ratio for m. extensor carpi radialis communis; MITflex = Maximal Isometric Torque towards flexion (Nm); MIText = Maximal Isometric Torque towards extension (Nm).

	Post stroke Median [min;max]	Healthy Median [min;max]
AR_{flex}	0.54 [-0.02; 0.89]	0.73 [0.15; 0.90]
AR_{ext}	0.63 [-0.07; 0.79]	0.80 [0.56; 0.88]
MIT_{flex}	14.7 [0.9; 27.6]	25.2 [16.4; 28.7]
MIT_{ext}	8.8 [1.1; 18.9]	14.9 [4.6; 25.4]

Figure 6 | Bland Altman plots for Activation Ratio for m. flexor carpi radialis (ARflex) and m. extensor carpi radialis communis (ARext).

Solid line: mean of the difference between first and second visits. Dotted line: upper and lower limit of 95% confidence interval for difference between first and second visit.



DISCUSSION

Although essential, establishing selective muscle activation does not reflect the full potential for treatment of a patient yet. Inappropriate muscle activation, i.e. exaggerated stretch reflexes, and secondary biomechanical properties, such as increased stiffness should also be taken into account [29,35-39]. For example, loss of selective muscle activation might coincide with spasticity, for which botulinum toxin could be beneficial [40-42], while loss of selective muscle activation combined with structural shortening of a muscle unresponsive to physical therapy might benefit more from surgery [43,44]. In order to tailor treatment to patient characteristics, each clinical phenotype requires a different approach.

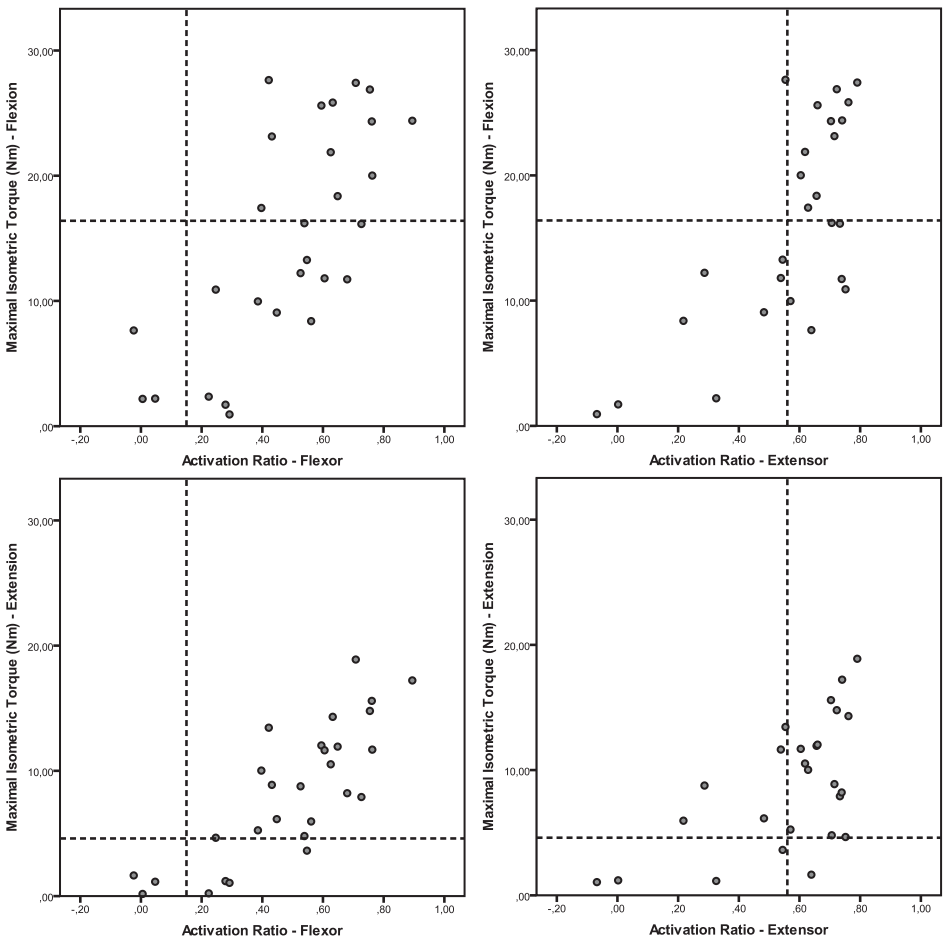
Strengths and limitations

The isotonic torque task preferred in earlier work [28] was modified to an isometric task during a maximal voluntary contraction. Voluntary maximal isometric torque is a widely used and easily applied clinimetric parameter that was already part of our test procedure. The necessary sorting technique to align EMG-signals along torque magnitude (that is not necessary in isotonic tasks) proved to be feasible. The current short task in a single torque direction also had the advantage of avoiding fatigue and signal modifications due to steering. The present measurement set-up allowed for standardization, however, further analysis of the dependence on orientation of the upper limb is required when test results are to be translated to functional task performance (i.e. reaching, grabbing). Visual feedback

might have supported any participants with diminished sensory functions, e.g. of the hand (visual feedback to compensate for lack of sensory feedback) or hemi-inattention or neglect (vertical bar), however, this was not tested. ICC might be different in a more homogenous population selected on stroke location or level of motor impairment. These data were not available in our population.

Figure 7 | Scatter plot of Activation Ratio versus Maximal Isometric Torque in post-stroke patients.

Dotted line: lowest values of AR and MIT in healthy volunteers (see minimum for healthy volunteers in Table 2). Patients with insufficient muscle activation are not represented in this figure. This figure illustrates the wide range of torque outputs for a given level of selective muscle activation. Lower torque in the agonist might indicate co-contraction of the antagonistic muscle, but only if it coincides with low selective muscle activation of that antagonist (lower left quadrant of upper right and lower left panel). Reversely, low torque combined with high selective muscle activation points more towards paresis of the agonist (lower right quadrant of upper left and lower right panel).



Bearing in mind that morphological changes (i.e. shortening of structures) may occur as early as four weeks post-stroke [45], the described neutral angle was chosen to minimize any influence of secondary biomechanical changes and to provide optimal conditions for the neural system in testing agonist and antagonist activity. Furthermore, an isometric task minimizes strain resulting from joint movement, allowing for isolated measurement of muscle activation.

AR were specifically developed in view of potential problems with normalization when comparing different muscles [28]. Issues with variance in quality, quantity and control of muscles as outlined in the introduction, are avoided by relating the activity of the same muscles in different tasks. Other drawbacks of EMG based methods that researchers should take into account [8,46] are e.g. crosstalk and elevated background EMG activity. Crosstalk might be increased by using two electrodes per muscle group, but only if the EMG-signal is relatively silent [47]. A small amount of crosstalk from other flexors besides FCR during flexion or other extensors besides ECR during extension would have negligible consequences for the results. Elevated background EMG activity, i.e. muscle EMG-activity at rest in post-stroke patients [48] could theoretically lead to unjustified exclusion of patients with insufficient voluntary muscle activation and falsely low AR by mechanism of a lower ratio of activity (in-phase) to rest (out-phase) EMG. However, as elevated background EMG in post-stroke patients was quantified at around 3% of maximal EMG during a maximal voluntary contraction task [48], we assume that this had no influence on our definition of insufficient voluntary muscle activation and was of no clinical relevance for AR.

Future work

Objective and reproducible data such as AR support a more substantiated analysis of clinical phenotypes. In this light the next step is to gather longitudinal information on selective muscle activation to follow functional recovery of stroke patients over time [49] and to monitor results of treatment. Combining AR data and kinematic data could give a valuable insight into the connection between loss of selective muscle activation around a single joint (e.g. co-contraction or co-activation) and multi joint synergistic movements. Moreover, to help prevent under- or overtreatment and to ensure that not only the affected muscle but also the aims of the patient on activity and participation level are treated, knowledge on the relation between selective muscle activation and functional outcome is essential in the future design of treatment paradigms for post-stroke patients.

CONCLUSION

Activation Ratios allow for reliable muscle specific quantification of selective muscle activation in participants with sufficient voluntary muscle activity. We observed significantly lower Activation Ratios in the group of post-stroke patients compared to the group of healthy participants, which indicate loss of selective muscle activation in post-stroke patients. Information on loss of selective muscle activation will allow clinicians to improve clinical decision making, follow patients over time and monitor results of treatment.

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Declaration of Interest
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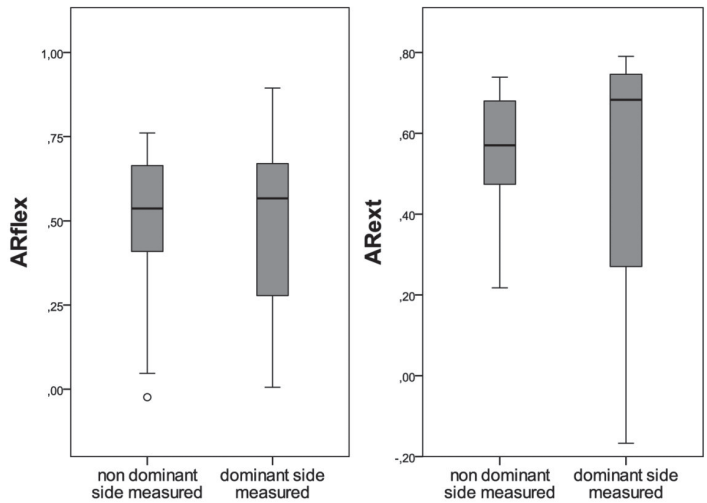
Supplementary Figure S1 | Limb dominance.

Boxplot for both AR_{flex} and AR_{ext} of post-stroke patients, separately depicting dominant and non-dominant side. Before this study, we had no data on the effect of dominance of the affected limb on selectivity of muscle activation. Our method allowed to test this: In our patient group, approximately half of the patients were affected (and measured) at the dominant side (Main text Table 1). A t-test showed that there was no significant difference in muscle selectivity (AR) between post-stroke patients measured at the dominant side, compared to the non-dominant side.



Supplementary Figure S2 | Influence of variance on ICC and SEM.

Group differences in reliability and heteroscedasticity were graphically represented in Bland Altman plots (Figure 6). The ICC for the stroke group may well be underestimated. Separate calculation of ICC and SEM per group (healthy vs stroke) would increase the ICC for post-stroke patients, as ICC are the between-measurements variance expressed as a proportion of the total variance. Variance in the stroke group is large (as can be seen in Figure 4), leading to higher ICC's. Variance in the healthy group is smaller, leading to lower ICC. SEM's are almost unchanged when separately calculated per group (i.e. lower ICC but also lower standard deviation).

ICC and SEM per group are represented in this table. As can be inferred from the 95%CI of the ICC's there is no significant difference between the ICC of the 2 groups per parameter.

	Healthy volunteers ICC (95%CI)	Healthy volunteers SEM	Post-stroke patients ICC (95%CI)	Post stroke patients SEM
AR_{flex}	0.67 (0.23 – 0.88)	0.12	0.80 (0.58 – 0.92)	0.11
AR_{ext}	0.58 (0.06 – 0.84)	0.05	0.74 (0.48 – 0.88)	0.13