Influence of neurorehabilitation on stroke-induced modifications of the quadriceps muscle in elderly subacute stroke patients with paresis

Irene Ciancarelli[a,b]
Franco Marinangeli[a,c]
Paolo Tonin[d]
Emilio Ciofani[b]
Maria Luisa Garo[a]
Maria Giuliana Tozzi Ciancarelli[c,a]

[a] Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[b] Nova Salus Nursing and Rehabilitation Center, Trasacco (L'Aquila), Italy
[c] Department of Anaesthesiology, Intensive Care and Pain Medicine, S. Salvatore Hospital, ASL n°1, L'Aquila, Italy
[d] S. Anna Institute and Research in Advanced Neurorehabilitation, Crotone, Italy

Correspondence to: Irene Ciancarelli, MD
E-mail: irene.ciancarelli@univaq.it

Summary

The influence of intensive multifunctional neurorehabilitation on post-stroke changes at the level of the paretic leg quadriceps muscle was examined in elderly subacute stroke patients. We assessed paretic leg muscle mass thickness and muscle fatty infiltration thickness, as well as clinical outcome measures (National Institutes of Health Stroke Scale, modified Ranking Scale, and Barthel Index) both before and after neurorehabilitation. Improved outcome measures ($p \leq 0.01$) and increased muscle mass thickness ($p = 0.005$) with decreased muscle fatty infiltration thickness ($p = 0.005$) were observed after neurorehabilitation. No correlations were found between clinical outcome measures and muscle parameters either before or after neurorehabilitation. The findings of this study suggest that neurorehabilitation has a positive influence on global functional recovery and on remodelling of the quadriceps muscle, even in elderly stroke patients, but they do not support the hypothesis that post-stroke muscle changes might have prognostic significance in terms of the severity of neurological deficit and disability, nor do they suggest that these changes can be regarded as a determinant of stroke severity.

KEY WORDS: ischaemic stroke, muscle wasting, neurorehabilitation.

Introduction

Post-stroke disability continues to place a heavy burden both on patients and on the socioeconomic system. The most widely recognised result of damage induced by brain ischaemia is motor impairment, which reduces the patient's mobility and independence in activities of daily living (ADL). Indeed, hemiparesis, paretic muscle atrophy and spasticity, together with frequent cognitive impairments, are decisive factors in the development of permanent disability in patients with stroke, leading to difficulty in achieving full reintegration into daily life (De Luca et al., 2018; Lundstrom et al., 2008; Sommerfeld et al., 2004; Wu et al., 2014). Adaptive responses in skeletal muscle tissue after stroke are of considerable interest in this context. Available studies underline that post-stroke skeletal muscle modifications, known as "stroke-related sarcopenia" (Scherbakov et al., 2013; Scherbakov et al., 2015), strongly contribute to disability, by impairing motility and motricity, and consequently compromise the patient's independence. Changes occurring immediately after cerebral ischaemia (i.e. changes in synaptic transmission and a decrease in the number of motor units) trigger skeletal muscle alterations in the affected limb, specifically a decrease in muscle mass, atrophy and a change in muscle fibre-type distribution towards an increase in fast-twitch fibres, which is a recognised predictor of motor deficit severity after stroke (De Deyne et al., 2004; Scherbakov et al., 2015). Later after brain injury, increased deposition of fat in/around the muscle fibres of paretic limbs is also observed, and this facilitates the development of muscle weakness and functional aerobic impairment (Ryan et al., 2002, 2011). The loss of skeletal muscle mass and muscle strength after stroke is likely a multifactorial and complex phenomenon driven by several various factors, including physical inactivity and the aging process (Evans, 2010; Hunnicutt and Gregory, 2017; Willey et al., 2017). Physical inactivity, frequent in frail older people, is associated with reduced muscle mass and impaired strength, whereas physical activity, due to its pleiotropic nature, may ameliorate muscle function and counteract the loss of skeletal muscle mass induced by both advancing age and a sedentary lifestyle (Marzetti et al., 2018; Montero-Fernandez and Serra-Rexach, 2013; Willey et al., 2017). Aging and a sedentary lifestyle are well-recognised risk factors for stroke. Stroke is indeed most frequent in those aged over 65 years, and the risk of a recurrent stroke doubles after the age of 55 years. It should, of course, be noted that aging per se contributes to a decline in physical activity and predisposes, in a sort of vicious circle, to a sedentary lifestyle (Vahlberg et al., 2016; Willey et al., 2017). The aims of subacute stroke care are to favour the patient's clinical stability and best possible functional recovery so as to ensure that, as far as possible, everyday life is manageable even in the absence of neurological recovery. Intensive multifunctional neurorehabilitation is an effective priority in subacute stroke and it aims to optimise residual abilities, particularly motor function, and to promote gait recovery (Ciancarelli et al., 2015). The possibility of performing routine diagnostic monitoring of the evolution of muscle changes occurring in paretic limbs both before and after a rehabilitation programme is an important issue, particularly in elderly patients. By acquiring data on thickness changes of skeletal muscle mass and muscle fatty infiltration of a paretic limb, clinicians might be better able to evaluate motor recovery in these patients and plan rehabilitation interventions specifically to maximise neuroplasticity. The quadriceps muscle is one of the most commonly measured skeletal muscles because of its relationship with mobility and its sensitivity to changes over time (Pardo et al., 2018).

To the best of our knowledge, few studies have explored the influence of subacute stroke inpatient rehabilitation on adaptive responses in paretic limb skeletal muscles (Hafer-Macko et al., 2008; Scherbakov et al., 2016).

The purpose of this study was to examine the effects of an eight-week intensive multifunctional neurorehabilitation programme in a cohort of elderly subacute first-ever ischaemic stroke patients, evaluating quadriceps muscle mass thickness and muscle fatty infiltration thickness before and after a neurorehabilitation intervention. The study also examined whether post-stroke skeletal muscle changes might provide useful prognostic insight into functional outcome, and thus potentially serve as markers of recovery to be integrated with clinical evaluation of the neurological deficit and related disability.

Materials and methods

Study design and participants

Elderly patients with subacute first-ever ischaemic stroke (confirmed by brain computed tomography and/or magnetic resonance imaging) admitted to the Nova Salus Rehabilitation Centre between October 2017 and December 2018 to undergo in-hospital neurorehabilitation were screened within 14 days of stroke onset as potential participants in this observational clinical study. On the basis of evidence that multimorbidity and malnutrition are associated with many adverse consequences, including poor stroke rehabilitation outcome (Nelson et al., 2015) and progressive loss of muscle mass (Evans, 2010), the Adult Comorbidity Index-27 and Mini-Nutritional Assessment Short-Form (MNA®-SF; malnutrition indicator score, where scores of 24-30 points indicate a normal nutritional status and scores of less than 17 points indicate a state of malnutrition) were used to screen for multimorbidity and to assess nutritional status, respectively (Rubenstein et al., 1991; Kaiser et al., 2009). Stroke patients with a history of cardio- and cerebrovascular events before the index stroke, diabetes, evidence of peripheral artery disease, chronic inflammatory diseases, cancer, chronic renal failure, lower limb orthopaedic disorders, pain syndrome, psychiatric disorders, and malnutrition were excluded. Eligible patients were alert stroke survivors with right or left hemiparesis, preserved trunk control (i.e. able to remain in the sitting position for at least 10 seconds), with autonomous locomotion and without a state of malnutrition before the index stroke. Ten stroke patients (4 males and 6 females, aged 82.10 ± 4.3 years) fulfilled all the criteria and were enrolled in the study. As shown by their scores on the National Institutes of Health Stroke Scale (NIHSS) (9.7 ± 3.9) (Adams et al., 1999), modified Rankin Scale (mRS) (3.9±0.7) (Bonita and Beaglehole, 1998), and Barthel Index (BI) (43.5±28.0) (Mahoney and Barthel, 1965), these stroke patients were moderately disabled and required assistance in managing ADL. All the study parameters were measured before and at the end of the neurorehabilitation treatment. The study design, which was approved by the local ethics committee and complied with the Declaration of Helsinki of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/), was explained in advance to the stroke patients or their caregivers who gave their written informed consent to the study and to all the rehabilitation procedures.

Neurorehabilitation protocol

As also described in previous papers (Ciancarelli et al., 2015, 2016), a multifunctional conventional intensive neurorehabilitation protocol was implemented. This was designed to promote recovery of post-stroke neurological deficits, such as paresis and impaired posture, balance, coordination and gait, and to restore functional abilities relevant to ADL and self-care management by promoting recovery of global motor control, dexterity, and fine motor skills (Ciancarelli et al., 2019). The rehabilitation treatment was carefully tailored to each patient, calibrating the complexity of the exercises after assessing each individual for strength, endurance, range of motion, gait pattern disorders, sensory deficits and related disability.

The inpatient neurorehabilitation intervention lasted 8 weeks and consisted of twice daily sessions, 6 days a week. Each rehabilitation session lasted about 45 minutes. Neurological deficits were documented using the NIHSS at baseline and at the end of the rehabilitation treatment; disability and independence in ADL management were evaluated using the mRS and BI, before and at the end of the rehabilitation treatment.

Quadriceps muscle measurements

Quadriceps muscle measurements were obtained, using a portable B-mode ultrasound unit (GE Healthcare, Solingen, Germany) with an 8-MHz linear array transducer, with patients in the supine position. A thin coating of water-soluble gel was applied to the contact surface of the probe. The ultrasound probe was positioned carefully to avoid muscle deformation and subcutaneous fat compression. Quadriceps muscle thickness was taken as a whole muscle group measurement. Muscle mass measurements were carried out by placing the ultrasound probe perpendicular to the long axis of the thigh on its anterior surface, at the two-thirds point and at the midpoint of the length between the anterior superior iliac spine and the upper border of the patella. After identifying the muscle tissue, the thickness of the quadriceps muscle was obtained by measuring the distance between the cortex of the femur and the most superficial muscular fascia (Pardo et al., 2018). Intramuscular fat content was evaluated as echo intensity (Akazawa et al., 2018).

Statistical analysis

Statistical analyses were performed using STATA for Windows, version 15 (Stata Corp, College Station, Texas, USA). All variables were tested for normal distribution using the Shapiro-Wilk test. Given the non-normal distribution of some variables, the Wilcoxon matched-pairs signed-rank test was used as appropriate to compare the mean NIHSS, mRS, and BI scores before and after neurorehabilitation treatment. Correlations between the variables of interest were tested using the Spearman rank correlation test. The association between quadriceps muscle parameters and positive outcomes, as measured using the mRS and BI, was tested by logistic regression analysis, including patient age as a covariate. The goodness of fit of the logistic regression was calculated with the Hosmer-Lemeshow statistic, setting a p-value higher than 0.05 for a good fit of the model. The assumptions of the logistic model were checked (independence of observation, no multicollinearity, linear relationship between continuous variables and the log transformation of the dependent variable, and no presence of significant outliers). All data are given as means ± standard deviation. A value of $p \leq 0.05$ was considered statistically significant for the Wilcoxon test.

Results

Analysis of the results of the structured and validated questionnaires adopted in this study (Adult Comorbidity Index-27 and MNA®-SF), and of the pre-treatment anamnesis, showed that the stroke patients, before the ischaemic event, were suffering from moderate hypertension and dyslipidaemia (both of which were controlled pharmacologically and through appropriate nutrition) and were non-sedentary; their physical activity-induced energy expenditure was <4 metabolic equivalents of task (Fletcher et al., 2001). Table I shows the main clinical characteristics of the stroke patients evaluated in this study. All the patients completed the entire scheduled rehabilitation programme without the occurrence of significant events. As indicated in Table II, a significant improvement in outcome measures ($p \leq 0.01$) was observed after the 8-week neurorehabilitation treatment. Interestingly, at the end of the treatment, the percentage of patients with a BI score ≥ 60 points had significantly increased, from 18.5 to 70%; the percentage of patients with a mRS score ≤ 3 had also significantly increased, from 36.36 to 80%, and the percentage of patients with an NIHSS score ≤ 5 had risen from 9.1% to 30.91%. As shown in figure 1, increased muscle mass thickness ($\Delta = 2.41 \pm 0.37$mm, $p = 0.005$) and decreased muscle fatty infiltration thickness ($\Delta = -1.4 \pm 0.31$ mm, $p = 0.005$) were observed after neurorehabilitation. No significant correlations were found between any of the clinical outcome measures and the muscle parameter values, either before or after neurorehabilitation (Table III**)**. As shown by the multivariate logistic regression analysis (Table IV), the pre-rehabilitation measurements of thickness of muscle mass (OR = 1.36, 95% CI: 1.01-1.84, p = 0.04; Hosmer-Lemeshow test, p = 0.20) and muscle fatty infiltration (OR = 1.28, 95% CI: 1.00-1.65, p = 0.05; Hosmer-Lemeshow test, p = 0.40) both predicted an mRS score ≤ 3. The statistical significance of the independent variables included in the logistic regression was no longer detected after neurorehabilitation. No statistically significant OR was observed for the BI, either before or after neurorehabilitation.

Discussion

Phenotypic modifications in muscle mass occurring in the days immediately following a stroke are among the main factors involved in the onset of the long-term impairments that can afflict stroke patients. Despite the clinical implications of this evidence and the need for early prognosis of post-stroke functional outcome in order to schedule rehabilitation strategies designed to facilitate the physiological course of recovery, guidelines for the management of ischaemic stroke and rehabilitation-oriented recommendations do not yet include monitoring of muscle features as a main clinical end-point (Paolucci et al., 2000; Winstein et al., 2016; Zorowitz and Brainin, 2011). In the current study, the quadriceps muscle of the paretic leg was evaluated for thickness of muscle mass and of muscle fatty infiltration in a homogeneous cohort of elderly stroke patients before and at the end of an 8-week multifunctional intensive neurorehabilitation programme with the dual aim of assessing the potential significance of post-stroke modifications of the quadriceps muscle as a prognostic marker of global

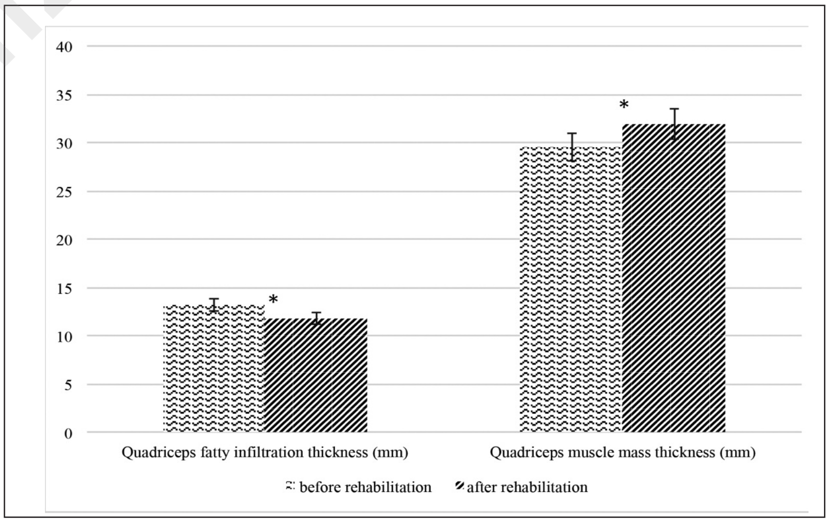

Figure 1 - Changes in quadriceps muscle features after intensive neurorehabilitation intervention. When compared with the pre-rehabilitation values, significantly decreased quadriceps fatty infiltration thickness (p = 0.005) and significantly increased muscle mass thickness (p = 0.005) values were observed after the neurorehabilitation intervention. Results are expressed as means ± standard deviation. * p< 0.05 *vs* before rehabilitation.

Table I - Subacute stroke patients' clinical characteristics on admission.

Age (years)	82.10 ± 4.3
Sex, M/F	4/6
Time from stroke onset (days, range)	7-14
BMI (kg/m^2)	25.46 ± 2. 6
SBP (mmHg)	130 ± 1.6
DBP (mmHg)	80 ± 2.2
Glucose (mg/dl)	87 ± 28.5
Creatinine	1.2 ± 0.9
METs §	<4 METs
Diet (patients %)	100%
Antiaggregants (patients %)	70%
Statins (patients %)	40%
Total cholesterol (mg/dl)	220 ± 1.6
Triglycerides (mg/dl)	115.7 ± 0.3
C-reactive protein (mg/dl)	0.7 ± 0.6
Serum albumin (mg/dl)	3.5 ± 0.6
MNA®-SF score	24

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; METs: metabolic equivalents of task; MNA®-S F, Mini-Nutritional Assessment Short-Form. A malnutrition indicator score of less than 17 points indicates a state of malnutrition.

recovery and of verifying the effect of neurorehabilitation on muscle features and on neurological deficit and related disability, as assessed through the application of widely used stroke scales. Accordingly, the findings of this study provide evidence, in elderly stroke survivors, of a positive effect of intensive neurorehabilitation on global functional recovery, and of significant quadriceps muscle remodelling, but they do not support the hypothesis that post-stroke muscle changes might have prognostic significance in terms of the severity of neurological deficit and disability, nor do they suggest that these changes can be regarded as a determinant of stroke severity. Indeed, no statistically significant difference was observed between the scores recorded on the outcome scales used in this study and muscle parameters either before or after neurorehabilitation. In particular, the lack of significant correlations between NIHSS, mRS, and BI scores and quadriceps muscle features of the paretic leg suggests that neurological deficits and functional disability are not associated with the muscle modifications induced by ischaemic stroke. Interestingly, a positive functional outcome, corresponding to an mRS score ≤ 3 after neurorehabilitation, could occur either with an increase in muscle mass thickness, or with an increase in muscle fatty infiltration thickness. Therefore, as suggested by the binomial logistic regression analysis of our data, it is not possible to identify the different weight that increased thickness of muscle mass or muscle fatty infiltration might carry as a prognostic marker of recovery. Loss of skeletal muscle mass and fatty infiltration of muscle fibres are well known key features of the skeletal muscle atrophy characterising the paretic limbs of patients after stroke (English et al., 2010; Lang et al., 2010). Intramuscular fat deposition in the paretic limb, in particular, is recognised as predictor of limited mobility (Visser et al., 2005, Carin-Levy et al., 2006). In accordance with these studies, the changes in quadriceps muscle features of the paretic leg that we observed before rehabilitation intervention and within 14 days of stroke, could be an expression of a global modification of muscle tissue caused by the adverse impact of stroke rather than an expression of age-induced muscle modifications, given that the stroke patients enrolled in the current study were neither malnourished nor sedentary. Recent studies have indeed highlighted that lifestyle characteristics such as regular physical activity and satisfactory nutritional status may modify the aging process, promote successful aging, and positively prevent age-induced muscle tissue loss (Vahlberg et al., 2016, Strasser et al., 2018). It is worth noting that our results, in accordance with the findings of previous studies (Yang et al., 2006), suggest that the increased muscle mass thickness and decreased muscle fatty infiltration of the quadriceps muscle observed after neurorehabilitation may predispose to better global motor and functional recovery. These results also support recent evidence that the structural and functional characteristics of skeletal muscle fibres are not static (Zhang et al., 2018), but may undergo a remodelling that has the effect of limiting stroke-related loss of muscle mass, even in elderly patients with stroke, as we found in our study. Judging by the positive results observed in clinical outcome measures and in measures of the quadriceps muscle of the paretic leg at the end of the neurorehabilitation intervention, and also on the basis of previous studies (Yang et al., 2006; Ciancarelli et al., 2019), we suppose that the improvement of neurological deficits and functional recovery we observed may be ascribed to a combined effect of spontaneous and rehabilitation-induced motor learning which may favour remodelling of skeletal muscle on the paretic side, probably through re-

Table II - Evaluation of neurological deficits and related disability before and after 8-week multifunctional intensive neurorehabilitation.

Clinical and functional outcome measures	Before rehabilitation	After rehabilitation	Δ scores	p
NIHSS	9.7 ± 3.9	6.8 ± 3.7	2.9 ± 1.5	0.006
mRS	3.9 ± 0.7	2.7 ± 1.2	1.2 ± 0.6	0.005
BI	43.5 ± 28.0	63.5 ± 32.1	20.0 ± 14.3	0.006

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel Index.

Table III - Correlations between functional outcome measures and thickness of muscle mass and of muscles fatty infiltration.

Clinical and functional outcome measures	Before rehabilitation muscle mass thickness	p	Before rehabilitation muscle fatty infiltration thickness	p	After rehabilitation muscle mass thickness	p	After rehabilitation muscle fatty infiltration thickness	p
NIHSS	- 0.24	0.27	-0.13	0.56	-0.49	0.15	-0.24	0.49
mRS	-0.47	0.03	0.33	0.13	-0.32	0.37	-0.06	0.86
BI	0.10	0.66	0.08	0.73	0.34	0.33	0.17	0.65

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel Index

Table IV - Multivariate analysis: association of thickness of quadriceps muscle mass and of muscle fatty infiltration with mRs (Panel A) and BI (Panel B).

Panel A

	Before rehabilitation			After rehabilitation		
	OR	95% CI	p	mRS	95% CI	p
Quadriceps fatty infiltration thickness	1.28	1.00 – 1.65	0.05	1.37	0.77 – 2.44	0.29
Age	0.89	0.76 – 1.04	0.14	1.59	0.67 – 3.81	0.30
Hosmer-Lemeshow (p-value)		0.20			0.33	
	OR	95% CI	p	mRS	95% CI	p
Quadriceps muscle mass thickness	1.36	1.01 – 1.84	0.04	0.54	0.15 – 1.99	0.36
Age	0.83	0.66 – 1.04	0.10	9.48	0.14 – 657.06	0.30
Hosmer-Lemeshow (p-value)		0.40			0.82	

Panel B

	Before rehabilitation			After rehabilitation		
	OR	95% CI	p	BI	95% CI	p
Quadriceps fatty infiltration thickness	1.09	0.85 – 1.38	0.50	1.32	0.81 – 2.15	0.27
Age	0.99	0.83 – 1.18	0.89	1.25	0.77 – 2.03	0.37
Hosmer-Lemeshow (p-value)		0.38			0.67	
	OR	95% CI	p	BI	95% CI	p
Quadriceps muscle mass thickness	0.99	0.86 – 1.15	0.94	1.05	0.80 – 1.37	0.73
Age	1.01	0.85 – 1.20	0.93	1.25	0.74 – 2.11	0.41
Hosmer-Lemeshow (p-value)		0.09			0.05	

Abbreviations: mRS, Modified Rankin Scale; BI, Barthel Index.

duction of the proinflammatory markers associated with post-stroke muscle mass loss (Coelho et al., 2016). Overall, the findings of the current study underline the positive effects of multifunctional intensive neurorehabilitation in counteracting or at least limiting the catabolic changes induced by stroke in skeletal muscles, and suggest that tracking muscle recovery in stroke patients receiving neurorehabilitation may provide useful information for clinical practice and targeted therapeutic strategies aimed at improving the quality of life of elderly stroke patients, who constitute a particularly frail stroke subgroup.

Limitations

The current study has a number of limitations that should be taken into account in assessing its results.

The main one is the size of the sample. This could, in fact, have reduced the power of the study and affected the OR significance values. Moreover, the selected exclusion criteria, aimed at increasing the sensitivity of the study, resulted in a small but very homogeneous cohort of patients, which could preclude generalisation of the results across all stroke patients.

Studies in larger samples of patients, including ones with a history of comorbidities and malnutrition and with more severe stroke disability, would therefore be needed to validate the results of the present study. There are two other aspects that, in our view, should be considered. First, this study examined only the quadriceps muscle, on the basis of the well-known evidence that this skeletal muscle is sensitive to changes over time (Pardo et al., 2018). Examining other muscles, as done by Ryan et al. (2011), might produce different results. The second limitation stems from the fact that we assessed quadriceps muscle changes only in the paretic leg, without monitoring muscle modifications in the non-paretic leg and without comparing them with leg muscle parameters of healthy subjects.

This choice was essentially dictated by the purpose of this study, namely to verify the effectiveness of the intensive multifunctional neurorehabilitation in improving stroke-induced muscle modifications of the paretic leg, by evaluating the changes occurring before and after intensive rehabilitation.

In conclusion, overall, the findings of the current study confirm the positive effects of multifunctional intensive neurorehabilitation in promoting significant global functional recovery and in limiting the muscle changes induced by ischaemic brain damage in elderly patients. These results also suggest that monitoring muscle modifications as a routine screening measure in stroke patients receiving neurorehabilitation may provide clinical data useful for setting up a customised neurorehabilitation programme, and thus for improving the quality of life of very frail patients.

References

Adams HP Jr, Davis PH, Leira EC, et al (1999). Baseline NIH stroke score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 53: 126-131.

Akazawa N, Harada K, Okawa N, et al (2018). Relationships between muscle mass, intramuscular adipose and fibrous tissues of the quadriceps, and gait independence in chronic stroke survivors: a cross-sectional study. Physiotherapy 104: 438-445.

Bonita R, Beaglehole R (1988). Recovery of motor function after stroke. Stroke 19: 1497-1500.

Carin-Levy G, Greig C, Young A, et al (2006). Longitudinal changes in muscle strength and mass after acute stroke. Cerebrovasc Dis 21:201-220.

Ciancarelli I, Di Massimo C, De Amicis D, et al (2015). Uric acid and Cu/Zn superoxide dismutase: potential strategies and biomarkers in functional recovery of post-acute ischemic stroke patients after intensive neurorehabilitation. Curr Neurovasc Res 12: 120-127.

Ciancarelli I, De Amicis D, Di Massimo C, et al (2016). Mean platelet volume during ischemic stroke is a potential pro-inflammatory biomarker in the acute phase and during neurorehabilitation not directly linked to clinical outcome. Curr Neurovasc Res 13: 177-183.

Ciancarelli I, Tonin P, Garo ML, et al (2019). Effectiveness of intensive neurorehabilitation in obese subacute stroke patients. Funct Neurol 34:45-51.

Coelho Junior HJ, Gambassi BB, Diniz TA, et al (2016). Inflammatory mechanisms associated with skeletal muscle sequelae after stroke: role of physical exercise. Mediators Inflamm 2016: 3957958.

De Deyne PG, Hafer-Macko CE, Ivey FM, et al (2004). Muscle molecular phenotype after stroke is associated with gait speed. Muscle Nerve 30: 209-215.

De Luca R, Torrisi M, Piccolo A, et al (2018). Improving post-stroke cognitive and behavioral abnormalities by using virtual reality: A case report on a novel use of nirvana. Appl Neuropsychol Adult 25: 581-585.

Evans WJ (2010). Skeletal muscle loss: cachexia, sarcopenia, and inactivity. Am J Clin Nutr 91: 1123S-1227S.

English C, McLennan H, Thoirs K, et al (2010). Loss of skeletal muscle mass after stroke: a systematic review. Int J Stroke 5: 395-402.

Fletcher GF, Balady GJ, Amsterdam EA, et al (2001). Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 104: 1694-1740.

Hafer-Macko CE, Ryan AS, Ivey FM, et al (2008). Skeletal muscle changes after hemiparetic stroke and potential beneficial effects of exercise intervention strategies. J Rehabil Res Dev 45:261-272.

Hunnicutt JL, Gregory CM (2017). Skeletal muscle changes following stroke: a systematic review and comparison to healthy individuals. Top Stroke Rehabil 24: 463-471.

Kaiser MJ, Bauer JM, Ramsch C, et al (2009). Validation of the Mini Nutritional Assessment Short-Form (MNA®-SF): a practical tool for identification of nutritional status. J Nutr Health Aging 13: 782-788.

Lang T, Streeper T, Cawthon P, et al (2010). Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int 21: 543-559.

Lundstrom E, Terent A, Borg J (2008). Prevalence of disabling spasticity 1 year after first-ever stroke. Eur J Neurol 15: 533-539.

Mahoney FI, Barthel DW (1965). Functional evaluation: the Barthel Index. Md State Med J 14:61-65.

Marzetti E, Hwang AC, Tosato M, et al (2018). Age-related changes of skeletal muscle mass and strength among Italian and Taiwanese older people: results from the Milan EXPO 2015 survey and the I-Lan Longitudinal Aging Study. Exp Gerontol 102:76-80.

Montero-Fernández N, Serra-Rexach JA (2013). Role of exercise on sarcopenia in the elderly. Eur J Phys Rehabil Med 49:131-143.

Nelson ML, Kelloway L, Dawson D, et al (2015). Stroke rehabilitation and patients with multimorbidity: a scoping review protocol. J Comorbidity 1:1-10.

Pardo E, El Behi H, Boizeau P, et al (2018). Reliability of ultrasound measurements of quadriceps muscle thickness in critically ill patients. BMC Anesthesiol 18: 205.

Paolucci S, Antonucci G, Grasso MG, et al (2000). Early versus delayed inpatient stroke rehabilitation: a

matched comparison conducted in Italy. Arch Phys Med Rehabil 81: 695-700.
Rubenstein LZ, Stuck AE, Siu AL, et al (1991). Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. J Am Geriatr Soc 39: 8S-16S.
Ryan AS, Dobrovolny CL, Smith GV, et al (2002). Hemiparetic muscle atrophy and increased intramuscular fat in stroke patients. Arch Phys Med Rehabil 83: 1703-1707.
Ryan AS, Buscemi A, Forrester L, et al (2011). Atrophy and intramuscular fat in specific muscles of the thigh: associated weakness and hyperinsulinemia in stroke survivors. Neurorehabil Neural Repair 25: 865-872.
Scherbakov N, von Haehling S, Anker SD, et al (2013). Stroke induced sarcopenia: Muscle wasting and disability after stroke. Int J Cardiol 170: 89-94.
Scherbakov N, Sandek A, Doehner W (2015). Stroke-related sarcopenia: specific characteristics. J Am Med Dir Assoc 16: 272-276.
Scherbakov N, Knops M, Ebner N, et al (2016). Evaluation of C-terminal Agrin Fragment as a marker of muscle wasting in patients after acute stroke during early rehabilitation. J Cachexia Sarcopenia Muscle 7:60-67.
Sommerfeld DK, Eek EU, Svensson AK, et al (2004). Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. Stroke 35: 134-139.
Strasser B, Volaklis K, Fuchs D, et al (2018). Role of dietary protein and muscular fitness on longevity and aging. Aging Dis 9: 119-132.
Vahlberg B, Zetterberg L, Lindmark B, et al (2016). Functional performance, nutritional status, and body composition in ambulant community-dwelling individuals 1–3 years after suffering from a cerebral infarction or intracerebral bleeding. BMC Geriatr 16: 48
Visser M, Goodpaster BH, Kritchevsky SB, et al (2005). Muscle Mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 60: 324-333.
Willey JZ, Moon YP, Sacco RL, et al (2017). Physical inactivity is a strong risk factor for stroke in the oldest old: findings from a multi-ethnic population (the Northern Manhattan Study). Int J Stroke 12: 197-200.
Winstein CJ, Stein J, Arena R, et al (2016). Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 47: e98-e169.
Wu S, Barugh A, Macleod M, et al (2014). Psychological associations of post-stroke fatigue: a systematic review and meta-analysis. Stroke 45: 1778-1783.
Yang YR, Wang RY, Lin KH, et al (2006). Task-oriented progressive resistance strength training improves muscle strength and functional performance in individuals with stroke. Clin Rehabil 20: 860-870.
Zhang S, Chen M, Gao L, et al (2018). Investigating muscle function after stroke rehabilitation with 31P-MRS: a preliminary study. Med Sci Monit 24: 2841-2848.
Zorowitz R, Brainin M (2011). Advances in brain recovery and rehabilitation 2010. Stroke 42: 294-297.