Gait & Posture 59 (2018) 58–64

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Full length article

Towards an objective assessment of motor function in sub-acute stroke patients: Relationship between clinical rating scales and instrumental gait stability indexes

P. Tamburini[a,*], D. Mazzoli[b], R. Stagni[a]

[a] Department of Electrical, Electronic and Information Engineering "Guglielmo Marconi", University of Bologna, Viale Risorgimento 2, 40136, Bologna, Italy
[b] Gait & Motion Analysis Laboratory, Sol et Salus Hospital, Viale San Salvador, 204, Rimini, 47922, Italy

ARTICLE INFO

Keywords:
Stability indexes
Stroke
Walking deficits
Clinical scales
Wearable sensors

ABSTRACT

The assessment of walking function alterations is a key issue to design effective rehabilitative interventions in sub-acute stroke patients. Nevertheless, the objective quantification of these alterations remains a challenge.

Clinical rating scales are commonly used in clinical practice, but have been proven prone to errors associated to the evaluator subjective perception. On the other hand, instrumental measurement of trunk acceleration can be exploited for an objective quantitative characterization of gait function, but it is not applied in routine clinical practice, because the resulting quantitative indexes have not been related to the clinically information, conventionally provided by the rating scales. To overcome this limitation, the relationship between the indexes, in specific clinical conditions, and rating scale must be better investigated, to support their exploitability in the clinical practice as a fast and reliable screening tool.

Thirty-one sub-acute stroke patients (17 with and 14 without cane) participated in the study. All were assessed with 6 rating scales (MI, TCT, MRI, FAC, WHS, CIRS) and 2 functional tests (2MWT and TUG). Sample Entropy (SEN) and Recurrence Quantification Analysis (RQA) in AP, ML and V directions were calculated over 2MWT and walking section of TUG. The influence of assessment task and cane was analysed, as well as correlation of SEN and RQA indexes with clinical rating scales.

SEN and RQA on the medio-lateral plane resulted influenced by the use of the cane, while the correlations between indexes and clinical scales showed that SEN and RQA for antero-posterior direction correlate positively with WHS.

1. Introduction

Sub-acute stroke patients are often affected by residual alterations of gait associated to an increased risk of fall [1,2]. These patients are identified, according to Sullivan [3], as those in between the acute and the chronic phase, in the continuous timeline starting on the stroke onset until years post-stroke. Different symptoms (e.g. dystonia, spasticity, muscle weakness) may be observed during the evolution of the disease. Some of them (e.g. spasticity occurring in about 30% of patients [4]) have a highly variable onset and can occur in short-, medium- or long-term post-stroke period [5], interfering with the recovery of the ability to walk, to social participation and to autonomous living. The primary aim of the rehabilitation process is to restore and maintain the ability to perform activities of daily living, usually starting within the first days after the event and often continuing during the chronic stroke phase [6].

A recent review [7] has shown that, in the chronic stage, walk training resulted in increased walking speed and distance compared with no/placebo treatment. Hence, restoring gait ability is not only a primary objective during the sub-acute phase, but a feature to be extended to all post stroke recovery stages. Therefore, the assessment of walking functional alterations is crucial to design an effective rehabilitative project. Unfortunately, the objective quantification of these alterations remains a challenge, not allowing to eventually discriminate patients, who retain some functional reserve and consequently could benefit from additional specific rehabilitation.

In clinical practice, the assessment of motor function is usually performed using rating scales and/or motor functional tests. In the

Abbreviations: *NoCane*, Sub-acute stroke patents with the ability to walk without cane; *Cane*, Sub-acute stroke patents, who needed additional support for walking; 2MWT, 2-Minute Walk Test; d_2MWT, Travelled distance during 2MWT; TUG, Timed-Up and Go Test; t_TUG, Execution time of the TUG; MI, Motricity Index; TCT, Trunk Control Test

* Corresponding author.
E-mail address: p.tamburini@unibo.it (P. Tamburini).

http://dx.doi.org/10.1016/j.gaitpost.2017.09.033
Received 18 March 2016; Received in revised form 23 August 2017; Accepted 25 September 2017
0966-6362/

Nomenclature

Glossary

RMI	Rivermead Mobility Index
FAC	Functional Ambulation Category
WHS	Walking Handicap Scale
CIRS	Cumulative Illness Rating Scale
SI	Severity Index
CI	Co-morbidity Index
SEN	Sample Entropy
RQA	Recurrence Quantification Analysis
RR	Recurrence Rate
DET	Determinism
AvgL	Averaged diagonal line Length

perspective of a multi-dimensional rehabilitation process, these can assess patients through the International Classification of Functioning (ICF), which focuses on function, disability and contextual factors. Nevertheless, different clinical scales address different clinical aspects, can be time consuming and prone to inaccuracies and bias resulting from the subjective perception of the evaluator [8].

On the other hand, instrumental assessment of walking can provide an objective quantitative evaluation. In particular, indexes proposed for the quantification of gait stability, calculated on trunk acceleration, raised great interest in recent years. They have been proposed to provide a synthetic and easy to use method for the objective quantitative characterization of gait function, and have shown promising results in the assessment of walking deficits and fall risk in healthy elderly subjects [2,9–11].

Differently from clinical rating scales, these indexes are fast and easy to use, requiring only a few minutes for the acquisition of trunk accelerations during gait, and are not affected by intra-rater variability. Thus, they could serve as an effective screening tool for the identification of those subjects potentially retaining some functional reserve, who could benefit of additional specific clinical assessment and rehabilitation.

Nevertheless, the possible exploitation of these indexes for clinical use requires, first of all, to establish their relationship with clinical scales, the current standard for clinical assessment.

On the other hand, from a methodological point of view, it is also essential to analyse relevant aspects associated to the specific experimental assessment conditions, since nonlinear time series analysis often showed contradictory results and non-monotonic relationships due to their intrinsic non-linear nature, even when applied in the same context [12,13]. Therefore, it is important to understand the specific conditions, in which the indexes are applied.

In particular, for the specific acquisition of trunk acceleration data during gait, different functional tests, already applied in clinical practice, could be instrumented. Different tests used to assess endurance (e.g. 2-min Walk Test (2MWT) [14,15]) or mobility (e.g. Timed-Up and Go Test (TUG) [16,17], Balance Evaluation Systems Test [18]) and others include a walking task. Among these, 2MWT is certainly the one offering the steady walking condition usually referred to for the calculation of gait stability indexes [19], while the walking section of TUG [16,17] is usually shorter and included between two transient conditions (standing from a chair and a U-turn), thus potentially different in the perspective of motor control assessment, for stroke patients in particular. Nevertheless, TUG has already been instrumented for clinical practice [17] and proposed for this type of assessment.

In addition to this, stability indexes have already been proposed and analysed for normal gait [11,19], while a large number of stroke patients cannot walk without the support of a cane, which modifies ground reaction forces and consequently can modify trunk accelerations. From the point of view of non-linear analysis, both these aspects (i.e. tasks and populations characteristics) should be taken into account to implement a reliable analysis.

Therefore, the aim of the present study was: a) from a methodological point of view, to evaluate how the stability indexes are affected by the task used for the acquisition of trunk acceleration during gait (i.e. 2MWT vs TUG) and by the use of a support (i.e. *NoCane* vs *Cane*) in the reference target population of sub-acute stroke patients; b) in the perspective of possible clinical exploitation, to assess the relationship between instrumental gait stability indexes calculated on 2MWT and TUG and some of the most used clinical scales for the assessment of sub-acute stroke subjects (*NoCane* and *Cane*).

2. Materials and methods

2.1. Study subjects

Thirty-one sub-acute stroke patients participated in the study, divided in two groups: *NoCane*, who were able to walk without a cane (53 ± 10 years, 70 ± 11 kg, 9 males and 8 females) and *Cane,* who required the support of a cane for walking (64 ± 11 years, 70 ± 15 kg, 9 males and 5 females).

Sub-acute stroke patients were selected based on clinical indication for the analysis, from 7 days following the stroke [3].

The inclusion criteria were: absence of cardiovascular, neurological, psychiatric diseases and severe visual/auditory impairments; absence of musculoskeletal pathologies influencing locomotion, with the exception of stroke; ability to stand up from a chair, walk along 6 m and sit down (TUG); resistance to fatigue allowing to walk for two minutes; ability to understand and follow instructions.

The Review Board Committee of the authors' institution approved the study, and informed consent was obtained from all participants.

2.2. Clinical evaluation

In agreement with clinicians, a selection of clinical scales was implemented in order to obtain a complete ICF description of stroke outcomes.

The selected clinical scales were:

- Motricity Index (MI): to assess limb motor function.
- Trunk Control Test (TCT): to evaluate trunk control.
- Rivermead Mobility Index (RMI): to assess different aspects of mobility in everyday life situations.
- Functional Ambulation Category (FAC): to evaluate patient's walking ability.
- Walking Handicap Scale (WHS): to evaluate the actual use of walking in daily life.
- Cumulative Illness Rating Scale (CIRS): to measure the patient's somatic health. It comprises Severity Index (SI) and Co-morbidity Index (CI).

Each subject also performed two clinical motor tests:

- 2MWT: endurance test that measures the travelled distance (d_2MWT) in 2 min of walking at self-selected speed in a corridor longer than 80 m.
- TUG: a simple test to measure mobility level as well as static and dynamic balance skills. It consists of rising from a chair, walking 6 m, turning around, walking back to the chair and siting down. The clinical outcome is the test execution time (t_TUG).

The same expert clinician performed all assessments to avoid inter-evaluator errors.

2.3. Experimental setup

One 3D-accelerometer (G-Walk, BTS Bioengineering, Italy; $f_s = 200$ Hz) was mounted on the lower trunk as close as possible to L5 to record approximately the acceleration of the center of mass.

2.4. Data analysis

The whole signal of 2MWT and the walking portions [17] of TUG were used for the calculation of stability indexes.

Among all the indexes proposed in the literature for the quantification of gait stability [11,19], Sample Entropy (SEN) and Recurrence Quantification Analysis (RQA) were chosen, because they did not require step segmentation [11], which can be critical in stroke patients due to the alteration of gait cycle; moreover these indexes could be quantified with acceptable reliability [19] for the limited duration of the walking section of TUG.

Multiscale Entropy [20] was calculated considering τ ranging from 1 to 6; m and r were fixed at 2 and 0.2, as suggested for biological time series [21,22].

For RQA, the analysed features were: recurrence rate (RR), determinism (DET) and averaged diagonal line length (AvgL) [23–25]. An embedding dimension of 5 and a time delay of 10 samples were used for state space reconstruction, based on previous literature [26].

All indexes were calculated for the antero-posterior (AP), medio-lateral (ML) and vertical (V) trunk acceleration direction.

Jarque-Bera test was performed to verify the normal distribution of the calculated indexes on the different groups (i.e. TUG, 2MWT, *NoCane*, *Cane*): since the normal distribution was not verified for all groups, median, 25- and 75-percentile values were calculated.

Kruskal-Wallis test with minimum level of significance at 5% was used to perform the paired comparison of the effect of TUG vs 2MWT and of *NoCane* vs *Cane* on SEN for all time scales and all RQA features in each direction.

Pearson correlation coefficients and the associated *p_value* were calculated per group (i.e. *NoCane* and *Cane*) and per task (i.e. TUG and 2MWT) between the log-transform of the indexes and the scores of clinical scales.

3. Results

For SEN:

- SENap and SENv showed higher values for all time scales during TUG than during 2MWT, in both *NoCane* and *Cane* group. In ML direction the opposite trend was found.
- NoCane and *Cane* groups showed similar values of SENap obtained for 2MWT; whereas, during the execution of TUG: *NoCane* had lower median values than *Cane* for $\tau = 1, 2$ and opposite trend for τ ranging from 3 to 6.
- SENv, calculated for 2MWT, showed lower values for *NoCane* subjects than for *Cane* ones for $\tau = 1, 2$ and the opposite trend was found with τ ranging form 3 to 6.
- For TUG instead, *NoCane* showed values lower than *Cane* with τ ranging from 1 to 5, and the opposite trend for $\tau = 6$.
- SENml showed higher values for *NoCane* than for *Cane* in both tasks.
- Kruskal–Wallis test on SENml ($\tau = 1,2$) showed a significant task effect for the *NoCane* group ($p = 0.01$ and $p = 0.03$), while SENv ($\tau = 1,2$) showed a significant supports effect during the execution of TUG ($p = 0.002$ and $p = 0.04$).

For RQA:

- DET and AvgL, in all directions, showed opposite trends both for groups and tasks. In particular: DET calculated for 2MWT showed higher values than for TUG. Moreover, DET showed higher values for *NoCane* subjects than for *Cane* ones.
- Kruskal-Wallis test showed support (*NoCane* vs *Cane*) effect on RRml ($p = 0.009$), DETv ($p = 0.002$) and in all directions for AvgL ($p < 0.05$) if calculated on 2MWT, while for RRap and DETv ($p = 0.01$) if calculated on TUG data. Task effect was found for *NoCane* group on RR, DET and AvgL in AP and ML directions ($p < 0.04$), while on RR and DET in V direction ($p = 0.03$) for *Cane* subjects.

Median values, 25th and 75th percentiles of SEN (for all τ) and RQA (all features) are shown in Figs. 1 and 2, respectively.

Regarding the correlation of indexes with clinical rating scales, in *NoCane* group:

- For both tasks, SENap and RQAap (all features) correlated significantly with WHS; moreover, RQAml (all features) correlated with t_TUG, d_2MWT and MI, while RQAv (all features) showed no correlation.
- SENml ($\tau = 2, 3$) correlated with WHS, during the execution of 2MWT, and with t_TUG ($\tau = 2\ldots6$) and d_2MWT ($\tau = 2\ldots4$) during TUG.
- SENv ($\tau = 2\ldots6$), calculated for 2MWT, correlated with t_TUG.
- No correlation was found for RQAv with clinical scales in both conditions.

In *Cane* Group:

- For both tasks, RQAap correlated with t_TUG and SENap showed no correlation.
- SENml ($\tau = 5, 6$), calculated on TUG, correlated with FAC.

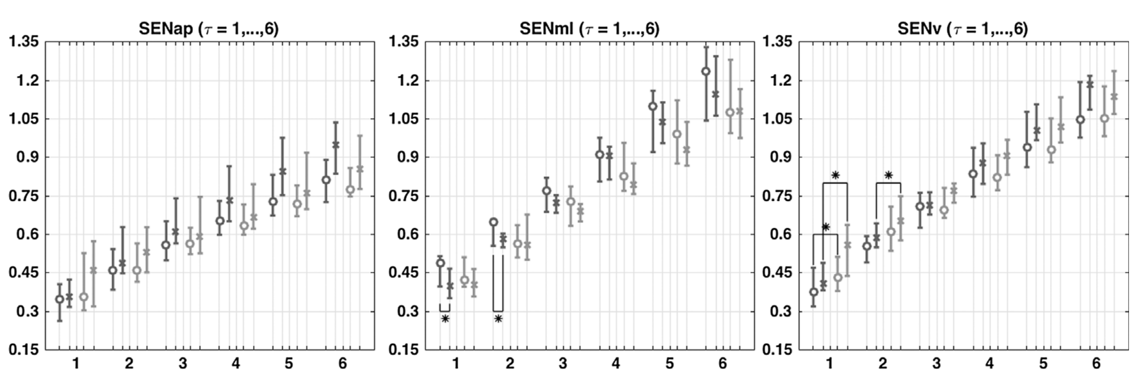

Fig. 1. Median values (and 25th and 75th percentiles) for SEN values. Groups are identified by color (*NoCane* light grey and *Cane* dark grey) and tasks by symbol (of median values) (o for 2MWT and x for TUG). Asterisks (*) represent statistically significant differences (*p_value* < 5%) between: tasks (same group), if above the bar plot, or groups (same task) if under the bar-plots.

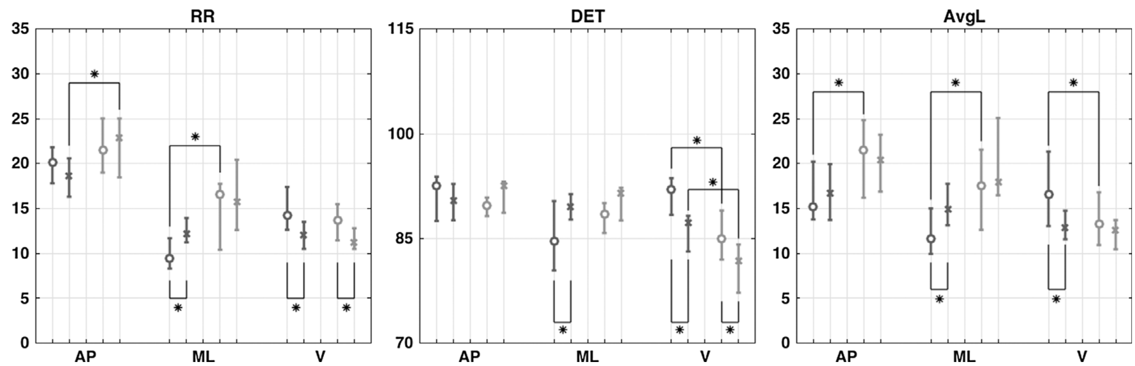

Fig. 2. Median values (and 25th and 75th percentiles) for RR, DET and AvgL values. Groups are identified by color (*NoCane* light grey and *Cane* dark grey) and tasks by symbol (of median values) (o for 2MWT and x for TUG). Asterisks (*) represent statistically significant differences (*p_value* < 5%) between: tasks (same group) if above the bar plot, or groups (same task) if under the bar-plots.

Table 1
Significant Pearson correlation coefficients (*p_value* < 5%) of *NoCane* subjects. White lines: (significant) correlations between indexes, obtained from 2MWT, and clinical scales. Grey lines: (significant) correlations between indexes, obtained from TUG, and clinical scales.

INDEXES		CLINICAL SCALES								
		t_TUG	MI	TCT	RMI	d_2MWT	FAC	WHS	SI	CI
SEN_ap1	2MWT				−0,48			−0,59		
	TUG	0,55				−0,63		−0,64		
SEN_ap2	2MWT							−0,59		
	TUG							−0,67		
SEN_ap3	2MWT							−0,55		
	TUG							−0,64		
SEN_ap4	2MWT							−0,58		
	TUG							−0,65		
SEN_ap5	2MWT							−0,53		
	TUG							−0,59		
SEN_ap6	2MWT							−0,52		
	TUG							−0,59		
SEN_ml1	2MWT									
	TUG									
SEN_ml2	2MWT									
	TUG	−0,69				0,57				
SEN_ml3	2MWT							−0,50		
	TUG	−0,56				0,58				
SEN_ml4	2MWT							−0,48		
	TUG	−0,49				0,50				
SEN_ml5	2MWT									
	TUG	−0,48								
SEN_ml6	2MWT									
	TUG	−0,50								
SEN_v1	2MWT			−0,53						
	TUG									
SEN_v2	2MWT	−0,53								
	TUG									
SEN_v3	2MWT	−0,54								
	TUG									
SEN_v4	2MWT	−0,55								
	TUG									
SEN_v5	2MWT	−0,57								
	TUG									
SEN_v6	2MWT	−0,52								
	TUG									
RR_ap	2MWT									
	TUG							0,55		
DET_ap	2MWT							0,51		
	TUG				0,72		0,69	0,89		
AVG_ap	2MWT							0,58		
	TUG							0,67		
RR_ml	2MWT	0,68				−0,63				
	TUG	0,84				−0,68				
DET_ml	2MWT	0,49	−0,49			−0,55				
	TUG	0,67	−0,48			−0,63				
AVG_ml	2MWT	0,66				−0,63				
	TUG	0,75	−0,58			−0,64				

Pearson correlation coefficients (*p_value* lower than 5%) between the indexes from the two tasks and the clinical scores are reported in Tables 1 and 2 for *NoCane* and *Cane* group, respectively.

4. Discussion

To analyse how stability indexes are affected by specific experimental conditions and correlate with all clinical rating scales, SEN and RQA were calculated for trunk acceleration data collected during 2MWT and TUG in two groups of sub-acute stroke subjects (*NoCane* and *Cane*). The same subjects were also assessed with clinical rating scales by the same expert evaluator.

Both SEN and RQA have been proposed as metrics for the quantification of motor stability, although they actually quantify different specific characteristics of the analysed signal. From the perspective of its mathematical implementation, SEN is a conditional probability measure that quantifies the likelihood of a sequence of m consecutive data points, matching another sequence of the same length, to still match the other sequence when their length is increased of one sample [22]. SEN provides a measure of unpredictability or irregularity of the time series that should not be always interpreted as complexity: a very periodic signal and a highly random one are both very low in complexity, but have different SEN values [27]. However, for the sake of the present study, SEN can be considered a measure of how much the acquired trunk acceleration deviates from the cyclic nature of gait and, therefore, in this context it is common practice to interpret SEN as a measure of complexity [20,22,28].

Comparing SEN values, obtained for the two tasks in both groups, they were found higher during 2MWT than during TUG in both AP and V directions, while the opposite trend was observed in ML direction. TUG can be considered to require higher cognitive (i.e. programming the next movement) and biomechanical (i.e. adapting gait pattern to the task constrains) efforts than 2MWT to correctly complete the task. In this perspective, these results are in agreement with those previously reported by Lamoth et al. [29], who reported higher values of SEN in AP direction, but not in ML (V was not analysed), analysing elderly subjects performing dual task, and interpreted this result as an indicator that changes in cognitive functions result in changes in gait complexity and automaticity. Accordingly, these results suggest that gait during 2MWT is perceived as less complex/more automatic than that during TUG.

The support effect on SEN was found mainly in V direction and for low τ values. Even if the results were not all statistically significant, a trend could be observed: in ML direction, for both tasks, *NoCane* subjects showed higher SEN values than *Cane* ones. SEN results can be related to the level of automaticity in the control of gait, therefore small SEN values can be associated to high automaticity [28]. In this perspective, these results suggest that *NoCane* subjects exhibit a more complex (less automatic) gait pattern than *Cane* ones in ML direction, highlighting the dominant constraint of the cane in this direction.

In AP and V directions, SEN changes for increasing τ. For τ from 1 to 3, *Cane* subjects showed higher SEN than *NoCane* ones, *vice versa* for higher τ. τ values lower than 3 (i.e. frequency components higher than 33 Hz) were characterized by high complexity for *Cane* subjects, while τ higher than 4 (namely frequency below 25 Hz) for *NoCane* ones. In general, this suggests that *Cane* subjects are characterized by high complexity at high frequencies (low τ), *vice versa* for *NoCane* ones. This could be explained taking into account muscular stiffness, a characteristic symptom of stroke patient, magnified by the use of supports.

From the perspective of their mathematical implementation, RQA features quantify the structure in the recurrence plot. In particular, DET relates to how often the trajectory re-visits similar state space locations ("shape"), the higher DET the more regular is the dynamic structure of the data [25]; AvgL is the average length of all the found diagonal structures [11,25] (i.e. how long the repeated trajectory "lasts"), this can be interpreted as the duration of the most repeated "shape". It is

Table 2
Significant Pearson correlation coefficients (*p_value* < 5%) of *Cane* subjects. White lines: (significant) correlations between indexes, obtained from 2MWT, and clinical scales. Grey lines: (significant) correlations between indexes, obtained from TUG, and clinical scales.

INDEXES		CLINICAL SCALES								
		t_TUG	MI	TCT	RMI	d_2MWT	FAC	WHS	SI	CI
SEN_ml1	2MWT									0,42
	TUG									
SEN_ml2	2MWT									
	TUG									
SEN_ml3	2MWT									
	TUG									
SEN_ml4	2MWT									
	TUG									
SEN_ml5	2MWT									
	TUG						−0,55			
SEN_ml6	2MWT									
	TUG						−0,63			
SEN_v1	2MWT					−0,61				
	TUG	0,56						−0,64		
SEN_v2	2MWT					−0,63				
	TUG							−0,65		
SEN_v3	2MWT					−0,58				
	TUG							−0,56		
RR_ap	2MWT									
	TUG					−0,57	−0,55			
DET_ap	2MWT									
	TUG					−0,54				
AVG_ap	2MWT									
	TUG									
RR_ml	2MWT	0,69						−0,57		
	TUG	0,72								
DET_ml	2MWT	0,55						−0,62		
	TUG	0,57								
AVG_ml	2MWT	0,55								
	TUG	0,67								

related to the velocity in the execution of the test (i.e. higher AvgL is expected for slower gait), but this duration is not independent from the regularity of the pattern (i.e. the gait is slower because each stride on average is slower). Therefore, results suggest that: i) all groups had a more regular dynamic structure of gait during 2MWT than during TUG, confirming TUG gait more challenging/less automatic; ii) *NoCane* group repeated the same "shapes" more than *Cane*, in agreement with Labini et al. [23]. On the other hand, AvgL results can be explained by its intrinsic time dependent nature: *NoCane* subjects were, in general, faster than *Cane* ones, thus *NoCane* repeated shapes were shorter than *Cane* ones. Moreover, during 2MWT all subjects walked faster than during TUG, thus the repeated trajectories were shorter in TUG than in 2MWT.

To the knowledge of the authors, the correlation between stability indexes and the scores of clinical scales in sub-acute stroke subjects was not assessed previously.

In *NoCane*, WHS correlated positively with RQAap and negatively with SENap in both tasks, this suggests that subjects with a good use of walking in daily life exhibit slow gait pattern (i.e. high AvgL), high regularity (i.e. high RR and DET), and low complexity/high automaticity (i.e. low SEN) [28] of gait in AP direction.

High regularity (i.e. high RR and DET) and a slow pattern (i.e. high AvgL) in AP direction also correlated positively with t_TUG, commonly associated to low functional performance, but in these subjects correlated positively with WHS, due to the concurrent high regularity (i.e. high RR and DET), and low complexity/high automaticity (i.e. low SEN) of the gait pattern. Moreover, SENml and SENv also correlated negatively with t_TUG. This result confirms that a gait pattern with an increased t_TUG, but regular and slow in AP direction and with low complexity/high automaticity in AP, and ML or V directions, although slow is similar to that of an healthy subject [23,28,30], still providing a good functional outcome (i.e. higher WHS values). This seems to suggest that TUG outcomes could be analysed and interpreted in more detail using non-linear indexes, and related to other functional scales, providing insight in the actual effective use of gait in daily life.

The negative correlation between WHS and SENv for *Cane* and *NoCane* subjects confirms an efficient walking related to low complexity/high automaticity, and seems to suggest that the use of the cane constraints the gait pattern not only in ML but also AP direction.

As for *NoCane*, t_TUG correlates positively with RQAml also in *Cane*, supporting the idea that a high t_TUG is not necessarily related to a reduced gait performance, and a decreased speed can still be associated to a functional gait pattern in daily life.

Of course, these results require further investigation, due to the very specific analysed population and the limited number of subjects, which could be a possible limitation of the study. Nevertheless, the coherence of the results of the statistics in the different conditions, and the accordance with existing literature, support these preliminary results for future investigations.

No correlation was found with CIRS, but, considering the specific population analysed in the present study, this is not surprising, since stroke outcome is likely to be predominant over all other possible pathologies. Minor, but promising, correlations were found between RQAml and MI and between SENml and FAC, suggesting that RQAml and SENml could identify changes in motor abilities in limbs and in walking, respectively. Nevertheless, these results require further investigations, due to the small number of subjects analysed and to the moderate and sparse values of the obtained Pearson coefficient.

One possible limitation of this preliminary study is the limited number strides (few more than 10) in the analysed gait section for TUG. Nevertheless, Riva et al. [19] showed that 10 strides are sufficient to reach a steady value and a quite high reliability (at least 20%) for SEN and RQA. Moreover, time series from TUG included a number of data points between 2800 and 8000, and SEN is largely independent on the time series length when the total number of data points is larger than 750 [20,31].

In conclusion, this preliminary study suggests that: i) both complexity (SEN) and repeatability (RQA) of gait pattern are influenced by the use of supports in ML direction; ii) TUG gait is a more challenging than 2MWT; iii) non-linear stability indexes SEN and RQA show promising correlations with clinical scales, potentially providing a better insight in the functional analysis of gait pattern. In particular, a regular (i.e. high RR and DET) gait pattern with low complexity (i.e. low SEN) and slow pattern (i.e. high AvgL) in AP direction can be related to an efficient use of walking in daily life (WHS), although an overall slow speed associated to high values of t_TUG.

Clearly, for an effective exploitation in clinical practice, further efforts are required to establish reference values for indexes and correlated clinical scales. Future researches will focus on the inclusion of a higher number of participants per group and on the assessment of different populations. These improvements will allow to strengthen and to further understand these preliminary conclusions.

Conflict of interest

We confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Acknowledgments

The authors thank laboratory staff of Sol et Salus Hospital for the subject recruitment and data acquisition. This work was supported by the project "Fall risk estimation and prevention in the elderly using a quantitative multifactorial approach" (project ID number 2010R277FT) managed by the Italian Ministry of Education, University and Research.

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