Quantitative assessment of the effects of 6 months of adapted physical activity on gait in people with multiple sclerosis: a randomized controlled trial

Massimiliano Pau[a], Federica Corona[a], Giancarlo Coghe[b], Elisabetta Marongiu[c], Andrea Loi[c], Antonio Crisafulli[c], Alberto Concu[c], Manuela Galli[d,e], Maria Giovanna Marrosu[b] and Eleonora Cocco[b]

[a]Department of Mechanical, Chemical and Materials Engineering, University of Cagliari, Cagliari, Italy; [b]Department of Medical Sciences and Public Health, Multiple Sclerosis Center, University of Cagliari, Cagliari, Italy; [c]Department of Medical Sciences and Public Health, Sports Physiology Lab, University of Cagliari, Cagliari, Italy; [d]Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy; [e]IRCCS San Raffaele Pisana, Rome, Italy

ABSTRACT

Purpose: The purpose of this study is to quantitatively assess the effect of 6 months of supervised adapted physical activity (APA i.e. physical activity designed for people with special needs) on spatio-tem-poral and kinematic parameters of gait in persons with Multiple Sclerosis (pwMS).

Methods: Twenty-two pwMS with Expanded Disability Status Scale scores ranging from 1.5 to 5.5 were randomly assigned either to the intervention group (APA, $n = 11$) or the control group (CG, $n = 11$). The former underwent 6 months of APA consisting of 3 weekly 60-min sessions of aerobic and strength train-ing, while CG participants were engaged in no structured PA program. Gait patterns were analyzed before and after the training using three-dimensional gait analysis by calculating spatio-temporal parameters and concise indexes of gait kinematics (Gait Profile Score – GPS and Gait Variable Score – GVS) as well as dynamic Range of Motion (ROM) of hip, knee, and ankle joints.

Results: The training originated significant improvements in stride length, gait speed and cadence in the APA group, while GPS and GVS scores remained practically unchanged. A trend of improvement was also observed as regard the dynamic ROM of hip, knee, and ankle joints. No significant changes were observed in the CG for any of the parameters considered.

Conclusions: The quantitative analysis of gait supplied mixed evidence about the actual impact of 6 months of APA on pwMS. Although some improvements have been observed, the substantial constancy of kinematic patterns of gait suggests that the full transferability of the administered training on the ambulation function may require more specific exercises.

KEYWORDS

Multiple sclerosis (MS); gait; Gait Profile Score (GPS); motion analysis; kinematics; adapted physical activity (APA)

Introduction

Adapted physical activity (APA, i.e. movement, physical activity, and sports in which special emphasis is placed on the interests and capabilities of individuals with limiting conditions, such as the disabled, health impaired, or aged [1]) has recently been proposed as a useful and effective approach to improving some of the most typical motor impairments due to multiple sclerosis (MS) and other neurological diseases.[2] Individuals with MS are thus often advised by their physicians to generically perform some kind of APA as a supplement to the pharmacologic treatments.

Many studies carried out in the last two decades appear to agree on the effectiveness of APA programs in improving cardio-respiratory fitness, muscle strength, mood, gait, and balance in people with MS, as well as overall quality of life.[3–7] It has also been hypothesized that APA has the potential to slow down the disease process, although the evidence supporting this is mixed and require further strengthening.[8,9] Nevertheless, the hetero-geneity of the approaches followed in administering APA (particu-larly as regard type, intensity, and duration of the exercises) and of the investigated outcomes has up to now made it difficult to define detailed guidelines having general validity.

In the spectrum of positive impacts possibly consequent to APA programs on people with MS, the improvement in walking abilities probably represents one of the most important and desired ones. In fact, people with MS perceive walking impairment as the most disruptive symptom with a high impact on social and working life.[10] Furthermore, gait impairment plays a relevant role in disability evaluation according to the Expanded Disability Status Score (EDSS [11]). As pointed out by the review of Snook and Motl, evidence suggests that exercise is associated with small

CONTACT Massimiliano Pau, Ph.D. massimiliano.pau@dimcm.unica.it Department of Mechanical, Chemical and Materials Engineering, University of Cagliari, Piazza d'Armi, 09123 Cagliari, Italy

(yet clinically meaningful) improvements in walking mobility, especially when the activity is supervised.[12]

However, it is noteworthy that only several studies have specifically investigated the impact of APA on gait features using objective quantitative measures (i.e. timed tests and quantitative human movement analysis), despite the fact that these are considered more sensitive than functional measures in capturing even slight changes in walking performance.[12–17] In a few of them,[13,15,16] gait parameters were calculated using a three-dimensional quantitative movement analysis, usually defined with the general term of "Gait Analysis" (GA). This technique is able to supply a very detailed and accurate representation of gait patterns through a combination of kinematic, kinetic, and electromyographic (EMG) data, and has been applied for more than 15 years in studies involving individuals with MS.[18–21] Moreover, the recent development of concise measures useful in summarizing the kinematic patterns of gait (and thus giving an idea of the degree of deviation from a physiological gait [22]) makes it possible to somehow reduce the complexity of a GA output and should make it easier for physicians to assess the patient's status in a short time. Recently, this approach has been successfully applied to characterize gait patterns of individuals with MS [23] and assess their alteration in presence of spasticity.[24]

On the basis of the aforementioned considerations, the aim of the present study is to quantitatively analyze possible changes in spatio-temporal and kinematic parameters of gait (described by means of synthetic indexes) consequent to a 6-month fully supervised APA program that integrates aerobic and strength training. Since in previous investigations, some improvements in gait parameters such as walking speed, step and stride length, stance, swing and double support phase duration were detected following several types of PA (i.e. resistance, strength and aerobic training [14,15]), our hypothesis is that individuals with MS who underwent the APA program would exhibit positive effects in terms of spatio-temporal parameters with respect to untreated patients, and that their gait kinematics would become more similar to physiological conditions.

Methods

Participants

In the period of March–April 2013, a convenience sample of 30 outpatients suffering from relapsing–remitting MS followed at the Regional Multiple Sclerosis Center of Cagliari (Sardinia, Italy) was informed about the study by the neurologists of the Center and assessed. Individuals who met the following criteria were considered eligible for the study:

1. diagnosis of MS according to the 2005 McDonald criteria [25];
2. age between 18 and 65 years;
3. EDSS in the range 1.5–5.5;
4. to be clinically stable and stable on treatment with disease modifying agents at least from 6 months;
5. absence of other associated medical conditions that would prevent participants from performing physical activity, such as cardiorespiratory and severe osteoarticular pathologies;
6. not to be engaged in any training or rehabilitative program in the 3 months prior to the beginning of the study.

The neurological examination was conducted by a neurologist expert in MS (EC, GC, MGM) and the degree of disability was quantified by the EDSS score. After the medical examination and an interview (to establish the motivation level of potential participants) 22 individuals were included and randomly assigned to either the APA or control group (CG) in a 1:1 fashion, using blocked randomization.[26] The flow of participants through the study is shown in Figure 1, and their main anthropometric features in Table 1. The study was carried out in compliance with the ethical principles for research involving human subjects expressed in the Declaration of Helsinki, and was approved by the Local Ethics Committee (approval no. 180, 17 October 2012). Written informed consent was obtained from all participants.

Design of the study and APA protocol

The study was a randomized controlled trial consisting of 24 weeks of training that started in January (T0) and ended in June 2014 (T6). The participants included in the APA group underwent a supervised training program, divided into three 60-min sessions per week, that included both aerobic and strength training. The typical session was as follows:

- 10-min warm-up on a electromagnetically controlled cycle ergometer (Bike Forma, Technogym, Forlì, Italy) carried out at 30% of the maximum workload previously calculated by means of a cardiopulmonary test (CPT) followed by stretching exercises for upper and lower limbs and trunk muscles.
- 20 min of aerobic training (cycling) at the work rate corresponding to 50% of the maximum value calculated for each participant on the basis of his/her CPT.[4] This value was progressively increased every week up to 80% of maximum work rate, and adjusted every 3 months taking into consideration the updated results obtained from the periodic CPT, which was performed with the same frequency. Participants then performed a gait training which included forward, sideways and backward walking, integrated with 90° and 180° turning and tandem gait.
- 20 min of strength training involving muscles of the upper limbs, lower limbs, and trunk. Initially, the participants performed one set of eight repetitions for each muscle group at a load corresponding to 15% of the one-maximum repetition (1-RM) load. Both loads and sets were then progressively increased up to performing three sets of 12 repetitions at a load corresponding to 30% of 1-RM. A suitable rest period (of approximately 2–3 min) was allowed between the sets.
- 10 min of cool-down with relaxation, postural control, and spine mobility exercises followed by post-stretching.

Participants were instructed not to modify their usual daily activities and dietary habits and not to engage in any supplemental physical routine program for the entire duration of the training. They were also informed that a maximum of 3 d of absence, even not consecutive, was allowed before excluding them from the study. To ensure a proper instructor/participant ratio, the participants were divided into three subgroups (of 4, 4, and 3 components) and the training sessions were supervised by two accredited strength and conditioning coaches, constantly assisted by a physician. All training sessions took place in the University of Cagliari Sports Center Gym.

To avoid any confounding effect, the participants included in the CG were asked to abstain from any systematic rehabilitation or APA program, but they were allowed to perform occasional activities such as walking or swimming in the sea.

Kinematic data collection and processing

The acquisition of kinematic and spatio-temporal parameters of gait was performed using an optoelectronic system composed of eight cameras (Smart-D, BTS Bioengineering, Milano, Italy) set

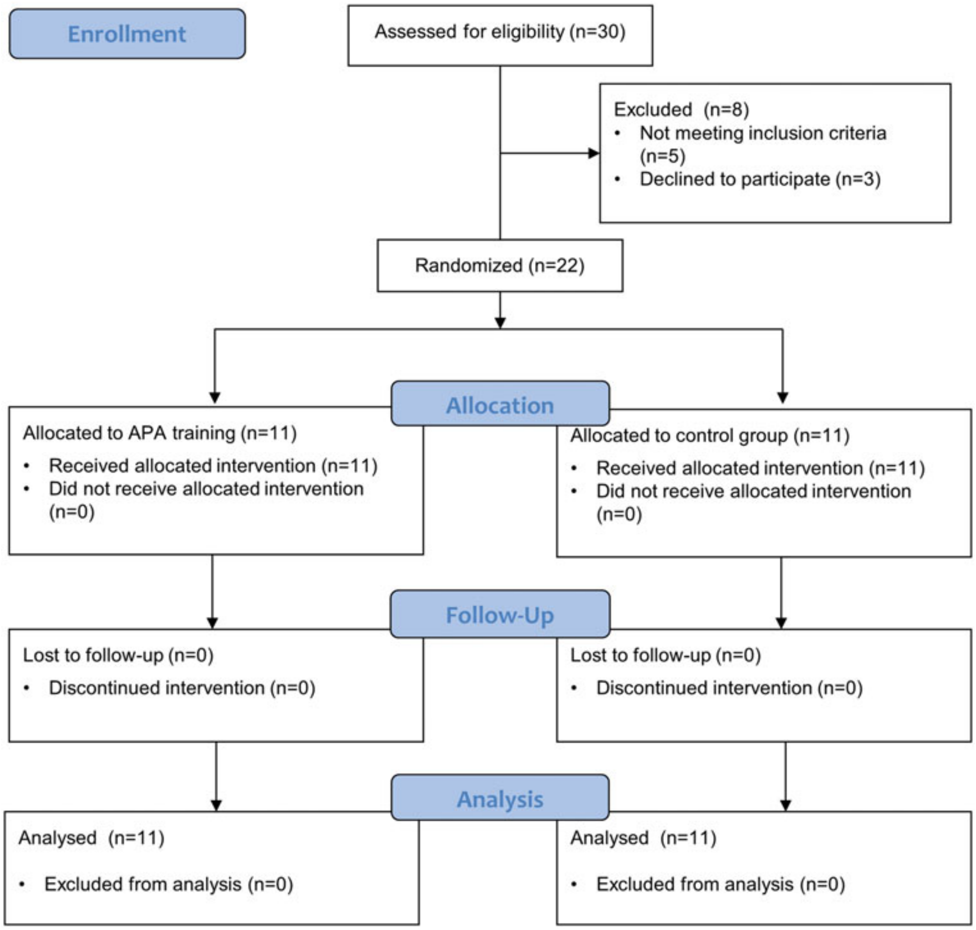

Figure 1. Flow of participants through the study.

Table 1. Anthropometric features of participants.

	APA		CG		
	Mean values	Range	Mean values	Range	*p* Values
Participants # (M, F)	11 (6M, 5F)	–	11 (6M, 5F)	–	–
Age (years)	47.4 SD 10.8	26–62	44.5 SD 13.5	26–62	0.596
Height (cm)	167.6 SD 8.5	156–181	166.8 SD 9.2	151–192	0.831
Body Mass (kg)	69.7 SD 19.0	45–97	68.7 SD 8.2	49–81	0.876
EDSS Score	3.6 SD 0.9	2.5–4.5	3.4 SD 1.1	1.5–5	0.680

APA: adapted physical activity; CG: control group.

at a frequency of 120 Hz and two strain-gage based force platforms (P6000, BTS Bioengineering, Milano, Italy). Twenty-two spherical retro-reflective passive markers (14 mm diameter) were placed on the skin of individuals' lower limbs and trunk at specific landmarks following the protocol described by Davis et al. [27] Participants were then asked to walk barefoot at a self-selected speed in the most natural manner possible on a 10 m walkway, allowing suitable rest times between the trials. The trial was considered acceptable if at least one of the two feet correctly impacted one of the force platforms (i.e. no double contacts occurred). Three valid trials per limb were usually collected to obtain an overall number of six. The raw data were then processed with the dedicated Smart Analyzer (BTS Bioengineering, Milano, Italy) software to calculate data separately for each limb (where applicable):

- spatio-temporal parameters (gait speed and cadence, stride length, stance, swing and double support phase duration);
- kinematic parameters, namely pelvic tilt, rotation, and obliquity, hip flexion–extension, adduction–abduction and rotation, knee flexion–extension, ankle dorsiflexion, and foot progression;
- dynamic range of motion (ROM) for hip and knee flexion–extension and ankle dorsi–plantar–flexion calculated during the whole gait cycle as the difference between the maximum and the minimum value of each angle recorded during a trial.

Kinematic data were summarized using the Gait Variable Score (GVS) and the Gait Profile Score (GPS). These concise measures of gait quality were recently proposed by Baker et al. [28] and found effective in characterizing the gait alterations of individuals with MS [23]. In particular, the GVS represents the root mean square (RMS) of the difference, calculated on a point-by-point basis, between the curve associated with a certain movement (i.e. hip flexion–extension, ankle dorsi–plantar–flexion, etc.) and a reference curve representing the mean value of a population of

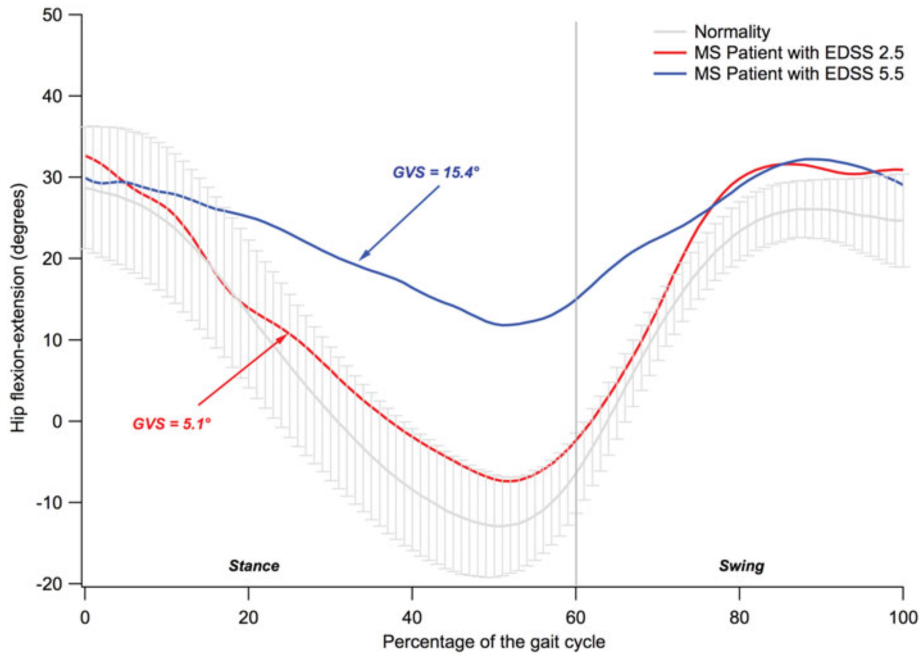

Figure 2. Hip flexion–extension angles during the gait cycle of two participants with MS characterized by low (red curve) and mild (blue curve) disability (see the online version for colour figure). The gray curve represents normality (mean ± SD).

Table 2. Comparison between spatio-temporal parameters of gait for the two groups.

	APA		CG		p values		
	T0	T6	T0	T6	Time	Group	Time × group
Spatio-temporal gait parameters							
Stride length (m)	1.12 SD 0.20	**1.25 SD 0.25**[a,b]	1.15 SD 0.24	1.15 SD 0.26	0.039	0.740	0.038
Gait speed (m/s)	0.88 SD 0.21	**1.15 SD 0.29**[a,b]	0.89 SD 0.27	0.97 SD 0.32	<0.001	0.444	0.009
Cadence (steps/min)	101.97 SD 14.02	**133.65 SD 14.56**[a,b]	101.24 SD 9.42	103.94 SD 15.61	<0.001	0.360	0.012
Stance phase (% of the gait cycle)	64.53 SD 3.40	**62.44 SD 2.99**[a]	62.94 SD 3.18	61.66 SD 4.29	0.006	0.404	0.468
Swing phase (% of the gait cycle)	34.72 SD 2.78	37.26 SD 2.97	37.06 SD 3.18	36.82 SD 4.33	0.068	0.474	0.056
Double support (% of the gait cycle)	15.04 SD 2.97	**13.21 SD 3.57**[a]	12.93 SD 3.19	12.33 SD 3.46	0.039	0.264	0.275

APA: adapted physical activity; CG: control group; T0: Baseline; T6: after 6 months.
[a]Denotes a significant change with respect to T0.
[b]Denotes a significant difference with respect to CG.

healthy subjects. An example of hip flexion–extension curves and associated GVS values for the case of two participants characterized by mild and moderate disability (e.g. EDSS 2.5 and 5.5, respectively) is shown in Figure 2. Larger distances from a physiological trend imply higher GVS values,

The GPS, which is expressed by the following equation:

$$GPS = \sqrt{\frac{1}{N}\sum\nolimits_{i=1}^{N} GVS_i^2}, \quad (1)$$

combines the nine GVS values related to the nine relevant kinematic parameters in a single score, which indicates the degree of deviation from a hypothetical "normal" gait (i.e. the larger the GPS, the less physiological the gait pattern); values for healthy individuals lie in the range 5–6°.[23]

Statistical analysis

A preliminary independent sample *t*-test was carried out to assess possible differences between left and right limb, and no significant differences were found for any of the investigated parameters. Thus, the mean value calculated across the two limbs was considered representative of each participant.

Changes in spatio-temporal and kinematic gait variables induced by the APA training were assessed using two-way analyses of variance for repeated measures (ANOVA RM) performed using the IBM SPSS Statistics v.23 software (IBM, Armonk, NY). Data were preliminarily checked for normality (using the Shapiro–Wilk test), homogeneity of variances (Levene's test) and presence of outliers. The independent variables were the individual's status (belonging to the APA or the CG group) and time (T0, T6), and the dependent variables were the nine GVS scores plus the GPS index, the dynamic ROM of hip, knee, and ankle joints in the sagittal plane and the six spatio-temporal parameters previously listed. The level of significance was set at $p = 0.05$.

Results

All the participants completed the program and no relapses were reported during the period of training. Table 2 shows the results for the spatio-temporal parameters of gait, while Table 3 reports the GPS and GVS values calculated for the two groups.

ANOVA revealed a significant effect of time on stride length [$F(1,20) = 4.87$, $p = 0.039$], gait speed [$F(1,20) = 15.72$, $p < 0.001$], cadence [$F(1,20) = 19.63$, $p < 0.001$], stance phase duration

Table 3. Comparison between the GVS/GPS values for the two groups.

	Kinematic gait parameters						
	APA		CG		*p* values		
	T0	T6	T0	T6	Time	Group	Time × group
GPS (°)	8.98 SD 1.55	8.65 SD 2.51	8.80 SD 1.72	8.44 SD 2.16	0.413	0.804	0.969
GVS (°)							
Pelvic tilt	4.94 SD 3.32	5.71 SD 3.70	8.25 SD 5.70	6.72 SD 4.38	0.720	0.175	0.284
Pelvic rotation	4.42 SD 2.08	4.07 SD 1.30	4.71 SD 1.36	**3.41 SD 0.99**[a]	0.003	0.759	0.068
Pelvic obliquity	2.77 SD 0.69	2.60 SD 0.60	2.70 SD 0.81	2.59 SD 0.77	0.257	0.880	0.841
Hip flexion–extension	13.83 SD 4.84	13.37 SD 7.57	12.11 SD 6.82	13.04 SD 7.72	0.882	0.683	0.660
Hip abduction–adduction	4.91 SD 3.83	4.36 SD 0.73	4.29 SD 1.17	3.80 SD 1.40	0.395	0.410	0.645
Hip rotation	11.53 SD 5.70	10.67 SD 3.80	11.83 SD 3.79	10.55 SD 3.33	0.428	0.944	0.961
Knee flexion–extension	12.42 SD 2.91	12.07 SD 4.96	9.42 SD 2.88	10.06 SD 3.97	0.844	0.094	0.517
Ankle dorsi–plantar–flexion	6.04 SD 1.58	5.30 SD 1.61	7.84 SD 2.57	6.76 SD 2.59	0.056	0.062	0.678
Foot progression	7.19 SD 3.41	**6.61 SD 3.51**[a]	6.41 SD 1.24	6.26 SD 1.53	0.020	0.621	0.156

APA: adapted physical activity; CG: control group; T0: baseline; T6: after 6 months.
[a]Denotes a significant change with respect to T0.

Table 4. Comparison between the dynamic ROM values for the two groups calculated during the gait cycle.

	Dynamic range of motion						
	APA		CG		*p* values		
	T0	T6	T0	T6	Time	Group	Time × group
Hip flexion–extension (°)	42.70 SD 9.61	**47.04 SD 10.13**[a]	42.71 SD 6.00	43.54 SD 3.88	0.029	0.585	0.125
Knee flexion–extension (°)	52.88 SD 9.60	**57.71 SD 10.06**[a]	50.75 SD 14.46	51.91 SD 12.98	0.047	0.427	0.210
Ankle dorsi–plantar–flexion (°)	23.60 SD 5.81	**26.08 SD 6.53**[a]	25.06 SD 10.14	25.17 SD 8.17	0.043	0.934	0.062

APA: adapted physical activity; CG: control group; T0: baseline; T6: after 6 months.

[a]Denotes a significant change with respect to T0.

[$F(1,20) = 9.38$, $p = 0.006$], and double support phase duration [$F(1,20) = 4.90$, $p = 0.038$]. Significant time × status interactions were found as regard stride length [$F(1,20) = 4.93$, $p = 0.038$], gait speed [$F(1,20) = 8.51$, $p = 0.009$], and cadence [$F(1,20) = 7.64$, $p = 0.012$].

As regard the kinematic parameters, the main effect of time was found only for the GVS associated with foot progression [$F(1,20) = 6.35$, $p = 0.02$] and pelvic rotation [$F(1,20) = 11.07$, $p = 0.003$]. No significant time × status interactions were found.

Finally, the values of the dynamic ROM during the gait cycle are shown in Table 4. Significant main effects of time were found as regard the ROM of hip [$F(1,20) = 5.53$, $p = 0.029$], knee [$F(1,20) = 4.48$, $p = 0.047$], and ankle [$F(1,20) = 4.67$, $p = 0.043$]. Even in this case, no significant time × status interactions were found.

The mean values of the joint angles in the sagittal plane calculated before and after the training period for the APA groups are given in Figure 3.

Discussion

The purpose of the present randomized study was to verify the effect of 6 months of APA on individuals affected by MS with a specific focus on gait, which represents one of the functions most affected by this disease. Consistent with previous studies, it was found that the training program induced a positive effect on spatio-temporal parameters of gait, particularly as regards stride length, speed and cadence. In particular, gait speed, which is the outcome measure most commonly used to assess the effectiveness of APA, was found to have increased by 0.27 m/s (23.4%). Such change is on the same order of magnitude (or higher) as in similar studies, despite the different kind of training performed [14–17,29] and can be considered clinically meaningful.[30,31]

In contrast, mixed evidence was found for gait kinematics as no significant time × group interaction was detected for overall GPS or single GVS values. After the training, however, a trend of improvement for the dynamic ROM during walking of hip, knee, and ankle was observed, more marked as regard ankle dorsi–plantar–flexion. The absence of changes in GPS indicates that from a kinematic point of view, the APA was unable to make the walking closer to a physiological condition. Even though very few studies have specifically analyzed this aspect,[13,15,16] it is noteworthy that in none of them were significant improvements of kinematics ever found following APA protocols. We think that a possible explanation of such a lack of effectiveness lies first of all in the different degree of transferability to ambulation functions that can be achieved with different training equipment and methods. Damiano et al. [32] investigated the existence of possible kinematic similarities in four different locomotor tasks, namely overground walking, treadmill walking, elliptical training and stationary cycling. They found that since the treadmill is characterized by the best degree of similarity with level walking, this might be the most appropriate training technique for gait training purposes, while cycling appears to be the less similar, and thus probably less effective. Of course, this analysis could not have considered a number of indirect effects that are still able to influence walking performance such as increases in strength and flexibility. From this point of view, cycling can in any case still be considered a useful training tool for people with MS because it increases lower limb strength, a parameter that was found directly correlated with walking speed.[14]

Another possible reason for the lack of kinematic effects of the training involves the initial level of disability of the participants enrolled in the present study which was mild to moderate (EDSS range 2.5–4.5) with GPS values at baseline of approximately 9° (values for healthy subjects are in the 5–6° range). It can be

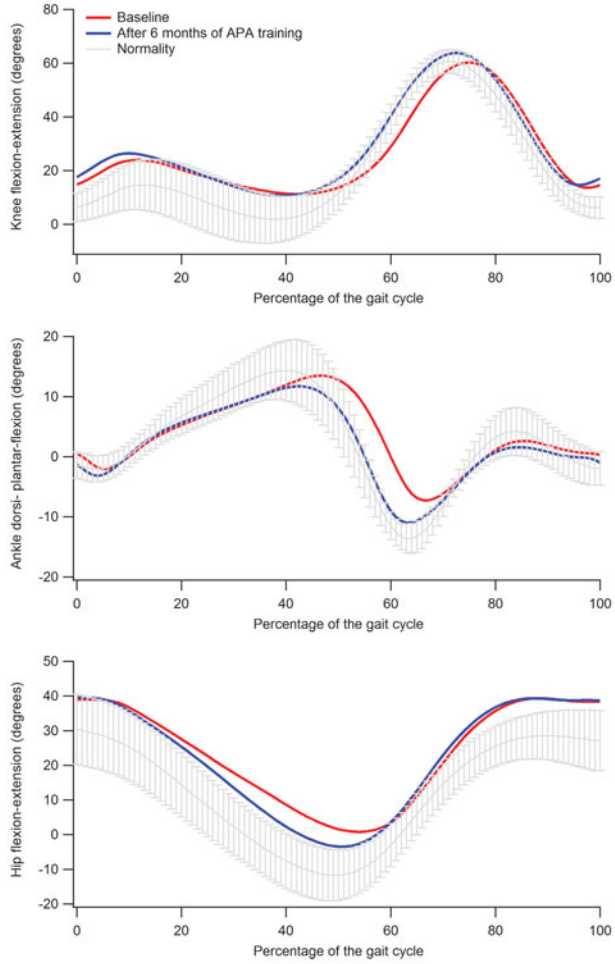

Figure 3. Mean value of hip, knee flexion–extension, and ankle dorsi–plantar–flexion before and after the APA program. The blue curve represents the baseline condition, the red curve after 6 months of APA and the gray curve normality (mean ± SD) (see the online version for colour figure).

hypothesized that possible improvements in kinematic of gait patterns cannot be captured by the GPS/GVS approach when the difference from normality is not very large with respect to cases involving individuals in which walking is more severely impaired. It is noteworthy that as observed by Snook and Motl, the majority of studies involve individuals with mild to moderate disability (e.g. EDSS <4.5) rather than those with most serious walking problems who might possibly receive superior benefits from exercise because they are unresponsive to current disease-modifying therapies and thus rehabilitation is one of the few approaches that might alleviate their symptoms.[12] Moreover, a similar effect was observed by Kalron et al. [17] who analyzed the effect of an intensive AFA program on gait in individuals with MS categorized according to their disability level and concluded that after the training both moderate and severe groups (EDSS 4.5–6.5) improved considerably compared with the mild (EDSS <4.5) gait disability group.

In contrast, it is noticeable that some positive effects in terms of joint kinematics were originated by the training, as the dynamic ROM of hip, knee, and ankle resulted increased by similar amounts (+9%) in all joints. In particular, after the APA program the hip ROM appeared in line with those of healthy individuals [20,33] and in the ankle the value approached normality (26° versus 30°), while the difference from a physiologic condition remains still relevant as regard the knee (57° versus 68°). It can be hypothesized that such results are due to a combination of factors associated with the increase in speed and the presence of cycling training in the APA program. The first effect was observed in previous studies, which established a positive correlation between lower limb joint kinematics and gait speed.[34,35] At the same time, even stationary cycling was recognized as capable of affecting the functional ROM of the lower limbs during walking in people affected by neurological diseases [36] as it originates magnitudes of ROM quite similar (or even superior) to that of level walking, although characterized by higher degrees of flexion.[37] However, even though cycling shares a similar kinematic pattern with walking, as the two activities are cyclical and involve flexion and extension of hip, knee, and ankle, the overall results of the present study suggest that including a relevant amount of cycling (one-third of the overall time) as aerobic exercise in a training session designed for people with MS has no clearly identifiable effect on gait because, although the ROM increases, the overall kinematics trends still remain quite distant from the physiological condition.

Some limitations of this study are to be acknowledged: first of all, although the number of tested subjects is in line with similar previous studies [12] limited statistical power due to the reduced sample size may have played a role in limiting the significance of some of the statistical comparisons carried out. Thus it would be desirable to extend the analysis to larger cohorts, possibly stratified in relation to different initial conditions of the participants. Second, owing to geographic reasons, the warm climate that characterizes the city where the study was performed may have affected the performance of the participants by exacerbating fatigue phenomena, especially in the last months of training.[38] The third limitation is that the results may have been partly influenced by the fact that the gait analysis was performed under barefoot conditions, as previous studies detected significant differences in gait speed and step length when participants walked barefoot or shod.[39,40] Finally, a follow-up measurement, not performed in this study, would be necessary to establish the actual duration of the training effects. However, our study has the important strength of being randomized and thus, as includes a fully comparable control group is characterized by a superior robustness of the results. It is also noteworthy that an excellent adherence of participants to the study was achieved, as none of them reached the maximum number of sessions missed leading to exclusion. This was probably due to the fact that this was the first program specifically designed for pwMS in the city of Cagliari area, and thus the participants, even though the policy for the study was quite strict and the period of training quite long (usually most APA programs for MS last no more than 3 months), were highly motivated. Participants appeared quite satisfied with the training and verbally reported to coaches a reduced fatigue level in everyday activities and a generally improved quality of life.

Conclusions

The overall results of the present study suggest that 6 months of APA produce beneficial effects on gait in individuals with MS, even though mostly in spatio-temporal parameters, while kinematic effects appear restricted to increases in dynamic ROM. The absence of significant improvements in terms of GPS/GVS may indicate a scarce degree of transferability of the training program to the ambulation function but, at the same time, the mild to moderate level of disability of the participants may have masked some potential positive effects, which are possibly detectable in more severely impaired individuals.

Further studies are needed to clarify some critical issues such as what kind of training is most suitable to achieve a real improvement in the ambulation function and if the APA activity, which is time- and resource-consuming, both for people with MS and the national health system, can be effectively integrated with home-based activity that patients could perform with remote supervision by therapists.

Disclosure statement

The authors report that they have no conflicts of interest.

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ORCiD

Massimiliano Pau http://orcid.org/0000-0001-9835-3629
Federica Corona http://orcid.org/0000-0002-4928-5129
Giancarlo Coghe http://orcid.org/0000-0002-3796-3279
Elisabetta Marongiu http://orcid.org/0000-0002-0954-2901
Andrea Loi http://orcid.org/0000-0003-2037-2445
Antonio Crisafulli http://orcid.org/0000-0003-1933-2841
Alberto Concu http://orcid.org/0000-0002-1813-0845
Manuela Galli http://orcid.org/0000-0003-2772-4837
MariaGiovanna Marrosu http://orcid.org/0000-0003-2334-2081
Eleonora Cocco http://orcid.org/0000-0002-3878-8820

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