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THE USE OF MECHANICAL ACOUSTIC VIBRATIONS TO IMPROVE ABDOMINAL CONTOUR

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ORIGINAL ARTICLE

The Use of Mechanical Acoustic Vibrations to Improve Abdominal Contour

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Abstract Adaptive effects caused by mechanical acoustic vibrations on the neuromuscular system are widely described. These vibrations applied to the muscle belly cause the ''vibration tonic reflex'' characterized by an improvement in power contraction of the stimulated muscle. Mechanical acoustic vibrations of moderate strength placed on limited body areas produce a positive muscle activity without damage. A prospective study from January to September 2006 investigated 60 sedentary patients presenting with muscular hypotrophy associated or not associated with lipodystrophy of the abdominal region who desired a substantial contour improvement of such area without invasive procedures. Of these patients, 40 were subjected to a treatment protocol with mechanical acoustic vibrations applied to the abdomen, associated or not associated with physical aerobic exercise of moderate intensity. The remaining 20 patients engaged only in the physical training. The study aimed to evaluate whether the application of mechanical acoustic vibrations could improve body contour.

Keywords Abdominal contour · Mechanical acoustic vibrations

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Adaptive metabolic and mechanical responses of the human neuromuscular apparatus subjected to mechanical acoustic vibrations (MAV) are widely supported in the literature. These vibrations applied to muscle bellies and tendons cause the ''vibration tonic reflex'' characterized by an improvement in power contraction of the stimulated muscles [3, 4, 6, 9, 14].

Adaptations caused by the vibration tonic reflex involve particularly the superior motor centers of the neuromuscular apparatus [10]. These responses are char- acterized by an improvement in the neural stimulation that permits recruitment of a wider number of muscular fibers. Moreover, these vibrations cause hormonal adap- tive responses, probably due to the action of metabolic muscular receptors. In fact, an increase in testosterone and somatotropic hormone concentrations and a simulta- neous decrease in cortisol concentration have been documented [3].

In the literature, two main categories of studies on the effects of MAV applied to the human body are described [8]: the effects of MAV applied to the entire human body and the effects of MAV applied to limited body areas. The first group of studies shows the harmful effects on some body areas [8, 13], particularly the vertebras. The second group of studies analyzes low-intensity MAV applied to limited body areas such as single muscles or synergistic muscular groups. These low-intensity MAV produced positive effects without any body damage.

The improvements produced by high-frequency MAV seemed to be more suitable because they stimulated high-frequency contractions. These favorable effects have been used already in the rehabilitation of patients affected by a reduction in muscular tone caused by various diseases [7, 12]. Moreover, favorable aesthetic effects linked to significant muscular tone and power improvement comparable with those obtained using traditional isokinetic training have been noted.

Physical activity may provide a low-risk method of preventing weight gain and promoting maintenance of weight loss for overweight and obese women [11]. Exercise effectively reduces intraabdominal fat [5], a hidden risk factor for many chronic illnesses [1].

A prospective study investigated the effects on the abdominal contour of healthy sedentary patients caused by the machine called ''VISS'' (vibration sound system; Vissman, Rome, Italy), which emits high-frequency MAV. This study aimed to evaluate the cosmetic advantages of such treatment.

Materials and Methods

The prospective study, conducted in the Department of Plastic and Reconstructive Surgery of the University La Sapienza of Rome from January to December 2006, investigated 60 healthy patients (30 men and 30 women) ages 20 to 50 years (average, 35.8 years) who desired an improvement in the abdominal silhouette. The patients had a sedentary life (<60 min/week of moderate- and vigorous-intensity recreational activity and maximal oxygen consumption of <25 ml/kg/min) and a body mass index (BMI) of 21 to 25. They presented with moderate muscular hypotrophy of the anterior abdominal muscles associated or not associated with skin flaccidity and localized lipodystrophy.

The exclusion criteria for the study specified previous implantation of heart pacemakers or metal prosthesis, hormone replacement therapy, phlebopathy, arterial hypertension, neuropathy, diagnosis of diabetes, severe cardiopathy, infective or traumatic dermatitis, smoking, and pregnancy. Written informed consent was obtained from the patients.

The patients were randomly assigned to groups A, B, and C. Randomization was performed by random number generation, and group assignments were placed in sealed envelopes, which were opened by the study coordinator at the time of randomization. Randomization was stratified by sex and BMI (<23.5 vs ≥23.5) to ensure equal numbers of heavier and lighter patients in each study group. Each group consisted of 20 patients (10 men and 10 women).

Groups A and B were treated with MAV applied to the abdomen. During the 2 weeks of treatment with the VISS system and for the following month, group A performed physical aerobic exercises of moderate intensity; group B underwent only VISS stimulation without physical exercises; and group C performed the same physical exercises of moderate intensity as group A for 6 weeks without MAV application. Moderate-intensity physical activity refers to a level of effort at which a person should experience an increase in breathing or heart rate, a ''perceived exertion'' of 11 to 14 on the Borg scale [2], or the burning of 3.5 to 7 calories per minute (kcal/min).

The intervention included a 6-week exercise program intensively monitored by an exercise physiologist at a facility (University La Sapienza of Rome, Italy, and a commercial gym). The exercise intervention involved at least 45 min of moderate-intensity exercise 5 days per week for 6 weeks. The participants were required to attend three sessions per week at one of the study facilities and to exercise 2 days per week at home.

The training program began with a targeted maximal heart rate of 40% for 16 min per session and gradually increased to a rate of 60% to 75% for 45 min per session by week 6. The participants wore heart rate monitors (Polar Electro Inc., Woodbury, NY, USA) during their exercise sessions.

Facility sessions consisted of treadmill walking and stationary bicycling. Strength training comprising two sets of 10 repeated leg extensions, leg curls, leg press, chest press, and seated dumbbell row was recommended to decrease risk of injury and maintain joint stability but was not required. A variety of home exercises including walking, aerobics, and bicycling was suggested and encouraged. The participants were encouraged to wear their heart rate monitors when exercising at home.

For groups A and B, the treatment protocol involved two series of VISS applications. Each series comprised more sessions of MAV application. Four stimulators transmitting high-frequency MAV at a wave length of 100 or 300 Hz were laid on the abdomen and kept in contact with the skin by elastic compressive bands. These stimulators produced a negative pressure through a vacuum pump, which resulted in suitable adhesion to the patient's skin, and then transmitted high-frequency MAV. These should have stimulated the anterior abdominal muscles to improve power and tone. Each session was characterized by the emission of vibrations with a wave length of 100 Hz for 15 min combined with isometric contraction of the abdominal muscles. In fact, during this phase, patients were asked to contract the abdominal muscles voluntarily in an isometric manner every 5 min for 40 s. Then the session continued with vibrations at a wave length of 300 Hz for another 15 min, during which the abdominal muscles remained at rest.

The first cycle of treatment included three consecutive daily sessions, followed after 1 week by the second cycle composed of just two consecutive daily sessions. A hydrating lenitive cream was applied topically at the end of each treatment session to solve the light skin erythema caused by the vacuum pump. No results were related to any form of slimming diet or therapy during the study period.

Treatment efficacy was subjectively assessed using a patient questionnaire and by a panel of external physicians not involved in the study who analyzed pre- and post-treatment views. Objective evaluation also was performed using somatic measurements.

A questionnaire was submitted to the patients 1 month after treatment. Three questions were posed: (1) Did you note an improvement in the muscular power of the abdomen? (2) Did you note an improvement in the muscular resistance of the abdomen? (3) Did you note an improvement in the abdominal silhouette?

Objective measurements were executed before treatment began, at the end of VISS treatment (in groups A and B), and 1 month after VISS treatment (in groups A and B) or after the 6 weeks of physical training (in group C). The following parameters were evaluated: the sub- costal circumference (SC), and supra-iliac crest circumference (SICC). The skin and subcutaneous thick- ness (PL) in the periumbilical region were measured with a plicometer. Also, BMI was evaluated before the treat- ment and 1 month after the VISS treatment or physical training. Parameter modifications were statistically com- pared by using the Wilcoxon signed rank test for paired values.

Results

Subjective evaluation highlighted the following results (Table 1). In group A, 16 patients noted muscular power improvement, 16 patients noted muscular resistance improvement, and 17 patients noted silhouette improvement. In group B, 15 patients noted muscular power improvement, 15 patients noted muscular resistance improvement, and 15 patients noted silhouette improvement. In group C, 10 patients noted muscular power improvement, 11 patients noted muscular resistance improvement, and 9 patients noted silhouette improvement.

In group A, clinical examination and photographic documentation showed improvement in the abdominal contour of most patients 1 month after treatment (Figs. 1 and 2). Objective evaluation showed a statistically significant reduction in all the parameters evaluated (Table 2). In particular, the SC, SICC, and PL parameters were significantly decreased from baseline to the immediate post-treatment follow-up assessment (Table 2a) and to 1 month after treatment (Table 2b), and between treatment end and 1 month follow-up evaluation (Table 2c). Moreover, BMI showed a significant reduction from baseline to 1 month after treatment (Table 2b).

In group B, clinical examination and photographic documentation showed an improvement in the abdominal contour of most patients 1 month after treatment (Figs. 3 and 4). Objective evaluation showed a statistically significant reduction in all parameters evaluated (Table 3). In particular, the SC, SICC, and PL parameters were significantly decreased from baseline to the immediate post-treatment follow-up assessment and to 1 month after treatment (Table 3a and b), but no significant changes were highlighted between treatment end and 1 month follow-up evaluation (Table 3c). Moreover, BMI showed a significant reduction from baseline to 1 month after treatment (Table 3b).

In group C, clinical examination and photographic documentation showed no improvement of the abdominal contour in most patients after 6 weeks of training with exercises of moderate intensity (Figs. 5 and 6). Objective evaluation showed no statistically significant reduction in the parameters evaluated except for SC (Table 4).

The complications encountered were some local lesions at the site of stimulators applied to the abdomen. In particular, a transient erythema lasting for 48 to 72 h was noted in four patients and treated with topical antiinflam- matory-based cream. Superficial blisters developed in two patients, which were treated conservatively with saline solution, paraffin gauze, and sterile dressing (Fig. 7). No patient showed any lesion at the 1 month follow-up visit.

Discussion

The application of MAV to limited body areas allows improvement in motor ability through a proprioceptivity improvement in the neuromuscular plate [3, 4, 6, 9, 10, 14]. This focalized and circumscribed energy averts systemic damages to the body, gaining an effective advantage for circumscribed muscular groups [8].

Moreover, Saggini et al. [12] pointed out that the monolateral application of MAV produces a power improvement not only directly on the stimulated muscles, but also on the contralateral musculature due to adaptation of the neuromuscular plate. In our prospective study,

Table 1 Subjective results highlighted by patients' questionnaire

Questions	Group A		Group B		Group C	
	Yes	No	Yes	No	Yes	No
Did you note an improvement in the muscular power of the abdomen?	16	4	15	5	10	10
Did you note an improvement in the muscular resistance of the abdomen?	16	4	15	5	11	9
Did you note an improvement in the abdominal silhouette?	17	3	15	5	9	11

Fig. 1 Group A patient, frontal view. *Left:* Before treatment. *Right:* 1 month after vibration sound system (VISS) treatment

Fig. 2 Group A patient, lateral view. *Left:* Before treatment. *Right:* 1 month after vibration sound system (VISS) treatment

Table 2a Parameter modifications from baseline (t0) to immediately after treatment (t1) in group A

Parameter	t0 $M \pm SD$	t2 $M \pm SD$	p Value
BMI	22.6 ± 1.87	22.3 ± 1.79	↘0.01
SC	82.1 ± 12.74	79.8 ± 12.48	↘0.0001
SICC	87.1 ± 10.46	85.1 ± 10.17	↘0.0001
PL	3.19 ± 1.022	2.73 ± 0.955	↘0.0001

SC, subcostal circumference; SICC, supra-iliac crest circumference; PL, skin and subcutaneous thickness of the periumbilical region

Table 2b Parameter modifications from baseline (t0) to 1 month after treatment (t2) in group A

Parameter	t0 $M \pm SD$	t2 $M \pm SD$	p Value
BMI	22.6 ± 1.87	22.3 ± 1.79	↘0.01
SC	82.1 ± 12.74	78.8 ± 12.82	↘0.0001
SICC	87.1 ± 10.46	83.8 ± 9.59	↘0.0001
PL	3.19 ± 1.022	2.38 ± 0.973	↘0.0001

BMI, body mass index; SC, subcostal circumference; SICC, supra- iliac crest circumference; PL, skin and subcutaneous thickness of the periumbilical region

MAV, when locally applied, showed a subjective improvement in muscular tone and resistance, and an improvement in the body silhouette for most of the patients (Table 1). Pre- and post-treatment measurements objectively confirmed these observations (Tables 2 and 3).

Statistical analysis of parameter variations showed the significance of the results. Group A, which combined VISS treatment with physical aerobic exercises of moderate-intensity, showed a more significant reduction in the analyzed parameters than group B. This was evidenced by the statistical significance of parameter modifications between the immediate post-treatment measurements and those at the 1 month follow-up assessment. Furthermore, moderate-intensity exercises alone were not able to show evident improvements in the abdominal contour after 6 weeks of training.

Fig. 3 Group B patient, frontal view. *Left:* Before treatment. *Right:* 1 month after vibration sound system (VISS) treatment

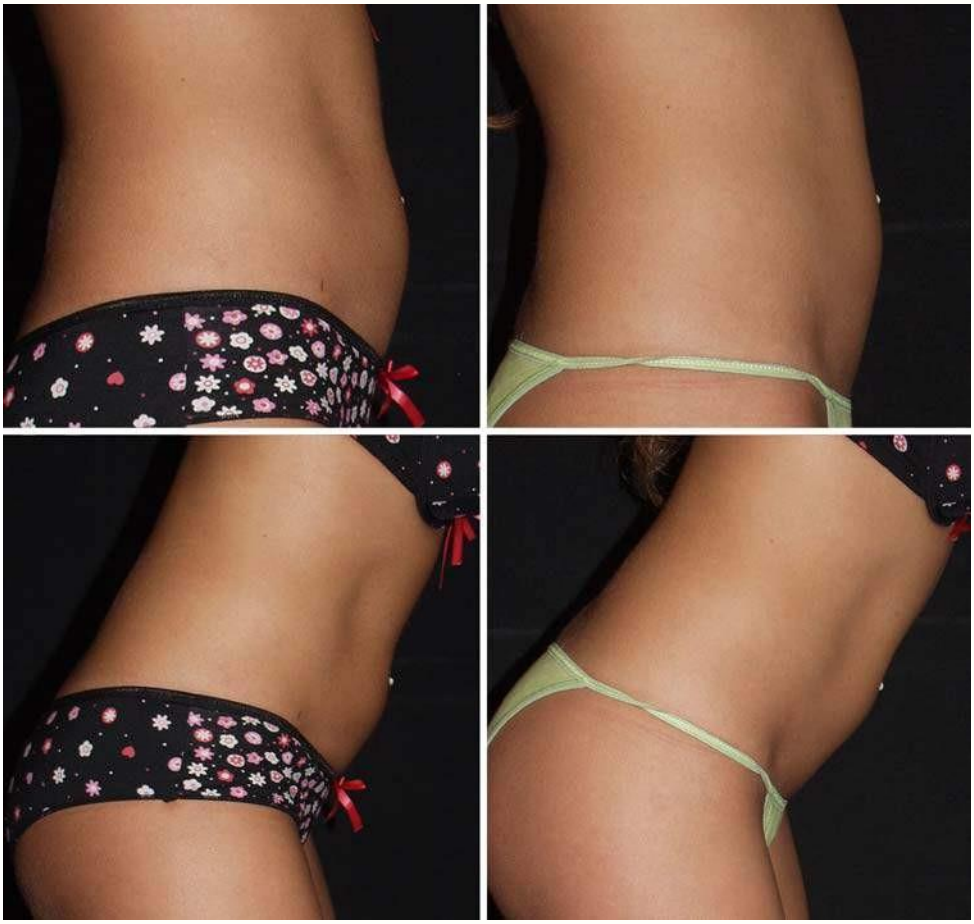

Fig. 4 Group B patient, lateral view. *Left:* Before treatment. *Right:* 1 month after vibration sound system (VISS) treatment

In addition, the results observed were not related to any form of slimming diet or therapy during the study period. The BMI decreased slightly in all the groups, but significantly only in groups A and B. The slight BMI reduction in groups A and B can be explained by the fact that the reduction in body fat was balanced by the

Fig. 5 Group C patient, frontal view. *Left:* Before physical training. *Right:* 6 weeks after training

Fig. 6 Group C patient, lateral view. *Left:* Before physical training. *Right:* 6 weeks after training

Table 2c Parameter modifications from immediately after treatment (t1) to 1 month after treatment (t2) in group A

Parameter	t1 *M* ± *SD*	t2 *M* ± *SD*	*p* Value
SC	79.8 ± 12.48	22.3 ± 1.79	<0.001
SICC	85.1 ± 10.17	78.8 ± 12.82	<0.001
PL	2.73 ± 0.955	2.38 ± 0.973	<0.0001

SC, subcostal circumference; SICC, supra-iliac crest circumference; PL, skin and subcutaneous thickness of the periumbilical region

Table 3a Parameter modifications from baseline (t0) to immediately after treatment (t1) in group B

Parameter	t0 *M* ± *SD*	t1 *M* ± *SD*	*p* Value
SC	82.05 ± 11.56	80 ± 10.83	<0.0001
SICC	88.2 ± 7.62	86.1 ± 7.25	<0.0001
PL	2.97 ± 0.715	2.3 ± 0.59	<0.0001

SC, subcostal circumference; SICC, supra-iliac crest circumference; PL, skin and subcutaneous thickness of the periumbilical region

abdominal muscle hypertrophy produced by MAV. Abdominal contour improvement can be correlated with a force and tone enhancement of regional muscles.

On the basis of our observations, we affirm that the VISS treatment combined with physical aerobic exercises of moderate intensity produces better aesthetic results than VISS treatment alone or physical aerobic exercises alone. It appears that VISS treatment alone can produce a significant improvement in capability of the muscles during the treatment protocol, whereas the following observation period does not show a similar trend of significant improvement. In contrast, physical aerobic exercises of moderate-intensity, when combined with MAV stimulation, appear capable of providing a further progressive increase in muscle force after facilitation of the

Table 3b Parameter modifications from baseline (t0) to 1month after treatment (t2) in group B

Parameter	t0 $M \pm SD$	t2 $M \pm SD$	p Value
BMI	22.7 ± 2.06	22.5 ± 2.01	≤0.05
SC	82.05 ± 11.56	79.84 ± 10.78	≤0.0001
SICC	88.2 ± 7.62	86.4 ± 7.31	≤0.0001
PL	2.97 ± 0.715	2.35 ± 0.653	≤0.0001

BMI, body mass index; SC, subcostal circumference; SICC, supra-iliac crest circumference; PL, subcutaneous thickness

Table 3c Parameter modifications from immediately after treatment (t1) to 1 month after treatment (t2) in group B

Parameter	t1 $M \pm SD$	t2 $M \pm SD$	p Value
SC	82 ± 10.83	79.84 ± 10.78	≥0.05
SICC	86.1 ± 72.5	86.4 ± 7.31	≥0.05
PL	2.3 ± 0.59	2.35 ± 0.653	≥0.05

SC, subcostal circumference; SICC, supra-iliac crest circumference; PL, skin and subcutaneous thickness of the periumbilical region

Table 4 Parameter modifications from baseline (t0) to 1 month after treatment (t2) in group C

Parameter	t0 $M \pm SD$	t2 $M \pm SD$	p Value
BMI	22.9 ± 1.54	22.8 ± 1.65	≥0.05
SC	82.0 ± 11.55	81.48 ± 11.33	≤0.05
SICC	87.8 ± 7.39	85.2 ± 12.02	≥0.05
PL	2.94 ± 0.730	2.89 ± 0.793	≥0.05

BMI, body mass index; SC, subcostal circumference; SICC, supra-iliac crest circumference; PL, skin and subcutaneous thickness of the periumbilical region

Fig. 7 Transient erythematic reaction caused by the vibration sound system (VISS) treatment

neuromuscular system due to mechanical acoustic vibrations realized by the VISS system.

Conclusions

Our study showed that VISS treatment may be used not only in the rehabilitative context to increase muscle capa- bility [12], but also for aesthetic purposes. It allows an improvement in the body silhouette through an enhancement of the muscle force and tone of a definite muscular group, particularly if combined with physical aerobic exercises of moderate intensity.

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HIGH FREQUENCY VIBRATION CONDITIONING STIMULATION CENTRALLY REDUCES MYOELECTRICAL MANIFESTATION OF FATIGUE IN HEALTHY SUBJECTS

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High frequency vibration conditioning stimulation centrally reduces myoelectrical manifestation of fatigue in healthy subjects

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Abstract

Objective: Vibration conditioning has been adopted as a tool to improve muscle force and reduce fatigue onset in various rehabili- tation settings. This study was designed to asses if high frequency vibration can induce some conditioning effects detectable in surface EMG (sEMG) signal; and whether these effects are central or peripheral in origin.

Design: 300 Hz vibration was applied for 30 min during 5 consecutive days, to the right biceps brachii muscle of 10 healthy males aged from 25 to 50 years. sEMG was recorded with a 16 electrode linear array placed on the skin overlying the vibrated muscle. The test protocol consisted of 30% and 60% maximal voluntary contraction (MVC) as well as involuntary (electrically elicited) contractions before and after treatment.

Results: No statistically significant differences were found between PRE and POST vibration conditioning when involuntary stimulus-evoked contraction and 30% MVC were used. Significant differences in the initial values and rates of change of muscle fibre conduction velocity were found only at 60% MVC.

Conclusions: 300 Hz vibration did not induce any peripheral changes as demonstrated by the lack of differences when fatigue was electrically induced. Differences were found only when the muscle was voluntarily fatigued at 60% MVC suggesting a modification in the centrally driven motor unit recruitment order, and interpreted as an adaptive response to the reiteration of the vibratory conditioning.

Keywords: Vibration; Muscle fatigue; sEMG; Rehabilitation

1. Introduction

Vibration has been studied and used in medicine for different purposes. It has been used to evoked the so called tonic vibratory reflex (TVR), in laboratories to study spinal reflex activity (Eklund and Hagbarth, 1966), as well as in pain medicine as a powerful pain control (Lundberg et al., 1984; Bongiovanni and Hagbarth, 1990). Although vibration was found to temporarily improve muscle functions since the late eighties (Bongiovanni and Hagbarth, 1990), only recently vibration has been put foreword as a tool to improve muscle force and reduce fatigue onset in sport medicine. Even more recently, from this area of application, the use of vibratory stimulations has shifted to a wide range of rehabilitation settings (Saggini et al., 2006; Gusi et al., 2006; Ahlborg et al., 2006; van Nes et al., 2006).

Two wide categories of vibrating devices are actually used in these fields: the so called whole-body vibration and vibration devices locally applied on a single muscle. Both types are based on a mechanical stimulation charac- terized by frequency (in Hz) and amplitude of the oscilla- tion induced (peak to peak displacement in mm).

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Vibration in this broad sense has been used with a wide range of frequencies and quite different settings (Cardinale and Lim, 2003). This gave rise to a large scatter of therapeutical treatments for patients, and protocols in healthy subjects whose results are not always comparable. Moreover, there are quite different results related to other technical as well as clinical parameters such as the duration of the vibratory stimulus and the onset of the clinically relevant effects. Particularly critical seems to be the application time as prolonged exposure to vibration seems to produce opposite effect, namely reducing muscle force and increasing fatigue onset (Bongiovanni et al., 1990; Mottram et al., 2006; Necking et al., 2003).

All these technical differences in the application of vibrations and the non uniform clinical as well as laboratory findings are mirrored by a lack of clear physiological basis of its efficacy (Cardinale and Bosco, 2003). In other words it is still not clear if vibration exerts its effect at muscle level or inducing more broad systemic responses at central level in the nervous system.

For these reasons our intention was to focus the present study to the evaluation of a single muscle high frequency vibration (VIB) in a group of healthy subjects with the aim to asses if VIB is able to induce any conditioning training visible in the surface EMG (sEMG) signal. Moreover, if such a modification occurs, we wish to assess where this conditioning occurs: a remodelling/shifting in muscle fibres functioning (peripheral effects) or a centrally mediated systemic adaptation.

2. Method and material

Vibratory threshold varies with age (Pearson, 1928; Goldberg and Lindblom, 1979; Verrillo, 1980) and gender (Roland and Nielsen, 1980). To limit the possible biases introduced by a wider range of age and by different gender, only males with an age between 25 and 50 years were screened for a possible enrolment in the study. Ten healthy males were then enrolled in the study. To further reduce measurements variability induced by substances acting on muscle contraction properties, subjects were asked not to smoke neither to drink tea or coffee (Kalmar, 2005) in the hours preceding the measurements as well as to empty the bladder to avoid any autonomic confounding factors. Moreover, as no reference values are available in the literature to estimate the expected change induced by the vibration conditioning it was decided not to use a control group (avoiding bias introduced by the differences between the subjects belonging to different groups) and thus to investigate the 300 Hz vibration conditioning for a paired comparison.

2.1. Ethical issue

The protocol followed the Helsinki recommendations on non-therapeutical biomedical research involving human subjects and was approved by the Ethical Committee. All the subjects had a careful explanation of the aim and methods used and agreed to participate in the study. Before their enrolment they gave a signed an informed consent. Subjects were free to stop the study at any time.

2.2. Vibration parameters

A pneumatic vibrator powered by compressed air formerly mainly utilized in physiology laboratory for research (Bongiovanni and Hagbarth, 1990) (VISS Circle San Pietro in Casale, Bologna, Italy) was chosen to avoid electrical artefacts in the EMG signal recordings and because its range of utilization spans between frequencies below 10 Hz to frequencies up to 300 Hz and more. A 300 Hz vibration so far produced was applied over the muscle belly of the right biceps brachii by means of a cup-shaped transducer with a contact surface of 2 cm^2 so that the amplitude of vibration was approximately 2 mm. The transducer was kept in place by a non elastic band wrapped around the arm with a constant contact force of 20–25 N. The arm was kept relaxed and extended along the body. Vibration sessions of 30 min each were made for five consecutive days approximately at the same time of the day (afternoon).

2.3. Surface EMG (sEMG)

sEMG was measured in basal condition, before vibration and two days after the end of the 5 day vibration sessions (Gantt diagram reported in Table 1).

2.3.1. Experimental protocol

Myoelectric signals were detected from the biceps brachii muscle of the dominant side. The subjects were asked to perform a brief (3–5 s) isometric flexion contraction that allowed the quality of the myoelectric signals to match the criteria described in detail by Rainoldi et al. (2004), and then performed three 3 s maximum voluntary contractions (MVCs) under isometric conditions, separated by intervals of 5 min. The contraction with the highest force value was selected as the reference MVC, thus allowing submaximal targets to be set on the visual feedback display.

After the MVC assessment, the motor points in the biceps brachii were identified and marked on the skin, and the motor point with the highest mechanical response and the lowest current intensity was chosen for the electrically elicited contraction session.

After placing an adhesive stimulation electrode (area = 9 cm^2, Spes Medica, Vignate, Milan, Italy) on the selected motor point, a rectangular current pulse with a time width of 0.3 ms and a frequency of 25 Hz was applied. The stimulation level was supramaximal (about 10% above the level generating the peak M-wave or the maximum level tolerated by the subject). Two electrically elicited 30 s contractions separated by a 10 min rest were performed in each experimental session.

After a further 5 min of rest, the subjects were asked to perform two voluntary contractions at 30% MVC and two at 60% MVC; these contractions lasted 30 s and were separated by 5 min rest period.

Table 1
Gantt diagram of experiment timetable

Day	1st	2nd	3rd	4th	5th	6th	7th	8th
Tests	sEMG							sEMG
Vibration sessions		V-1	V-2	V-3	V-4	V-5		

sEMG: surface electromyography; V-(1–5): vibration treatment (300 Hz for 30 min).

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2.3.2. Material

A linear array of 16 electrodes (silver contacts 10 mm apart, 1 mm diameter) was adopted for EMG signal recordings. Signals were passed through a 10–450 Hz bandwidth filter, amplified (EMG16-16 channel amplifier, LISiN Bioengineering Centre, Turin Polytechnic, Italy), sampled at 2048 Hz, digitized by a 12-bit A/D converter (DAQCARD-6024E National Instruments, Austin, Texas, USA), and stored on a personal computer.

Each subject laid on his back with the dominant arm hori- zontal and abducted at 90°. The forearm was at 120° with respect to the arm. The arm and forearm were placed in an isometric brace (MISO1, LISiN Bioengineering Centre, Turin Polytechnic, Italy), which was equipped with two torque transducers (one on each side of the arm) connected to a display that provided the subject with visual feedback concerning the produced level of torque.

2.3.3. Data analysis

The initial values and rate of change in mean spectral frequency (MNF), average rectified value (ARV) and conduction velocity (CV) were computed off-line by means of numerical algorithms using non-overlapping signal epochs of 0.5 s, thus generating 60 estimates of each variable during the 30 s contractions.

The correlation coefficient between the two adjacent double differential signals was used to ensure correct electrode positioning and the reliability of CV estimates.

Linear regression analysis was used to calculate the initial values and rate of change of MNF, ARV and CV during the voluntary and electrically elicited contractions. Due to the number of studied subjects a test for a Gaussian distribution should be inappropriate. A non-parametric Wilcoxon paired test for dependent samples was adopted to compare EMG parameters and MVC before and after vibration protocol administration. A p value of <0.05 was considered statistically significant.

3. Results

No statistically significant differences were found before and after the vibration treatment in voluntary contractions at 30% MVC and in electrically elicited contractions (Table 2).

In the signals recorded at 60% MVC significant differences before and after vibratory stimulation sessions were found for initial values (p = 0.009) and rate of change of CV (p = 0.04). Table 3 shows mean and standard deviation for each calculated variable and subject before and after the treatment in voluntary contractions at 60% MVC.

As reported in those tables, the CV parameters were found lower after the treatment: initial values of CV reduced of 2.5% whereas CV rate of change (namely the fatigue index) reduced of 20%. A comparison among initial values and rates of change in 30% MVC, 60% MVC, and electrically elicited contractions are shown in Figs. 1 and 2.

Initial values of MNF changed after the treatment in the same direction of CV, although not in a significant way.

Torque values were found not different before and after the treatment. Their values are reported in Table 4.

4. Discussion

Due to technical limitation whole-body vibration devices have been used in clinical rehabilitation (Saggini et al., 2006; Ahlborg et al., 2006; van Nes et al., 2006) and sport applications (Cardinale and Lim, 2003; Cardi- nale and Bosco, 2003) with values not greater than 50– 60 Hz. However 100 Hz is the most widely used frequency especially in pain related papers (Ottoson et al., 1981; Lundeberg, 1983), and vibratory stimulus of 200 Hz or more, has been shown to be the most appropriate to elicit motor (Eklund, 1971) as well as analgesic (Bini et al., 1984) responses in man.

In this research vibration conditioning of 300 Hz was able to induce modifications in initial values of CV, i.e. in the recruited motor unit pool, and a greater alterations in the rate of fatigue only when voluntary contractions demanded more effort (60% MVC with respect to 30% MVC). These changes were not paralleled with modification in the mechanical performance and torque output. No modifications were also found in the electrically elicited contractions.

Since no peripheral changes (modifications in the fibre types) occurred after VIB, as demonstrated by the lack of any response differences when fatigue was induced by a peripheral electrical simulation, these findings suggest that the vibration conditioning acted at a central level generating a modification in the adopted strategies, optimizing the mechanical output and reducing the myoelectric manifestations of fatigue. Results in fact suggested that slower motor

Table 2
sEMG values (mean ± SD) before and after the vibration treatment in voluntary contractions at 30% MVC and in electrically elicited contractions

	MNF		ARV		CV	
	Initial value (Hz)	Rate of change (Hz/s)	Initial value (1V)	Rate of change (1V/s)	Initial value (m/s)	Rate of change (m/s^2)
Voluntary contraction (30% MVC)						
BEF	86.1 ± 13.6	—0.22 ± 0.16	67.9 ± 34.1	0.47 ± 0.85	4.7 ± 0.4	—0.005 ± 0.006
AFT	87.9 ± 13.1	—0.28 ± 0.21	88.6 ± 56.5	0.65 ± 0.98	4.6 ± 0.4	—0.005 ± 0.007
Electrically elicited contraction						
BEF	71 ± 39	—0.76 ± 20.12	28.9 ± 19.8	0.19 ± 2.19	4.4 ± 2.3	—0.019 ± 2.937
AFT	71 ± 41	—0.73 ± 18.31	29.8 ± 17.9	0.15 ± 2.22	4.4 ± 2.3	—0.019 ± 3.633

MNF: Mean Spectral Frequency; ARV: Averaged Rectified Value; CV: Conduction Velocity; BEF: before vibratory treatment; AFT: after vibratory treatment.

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Table 3
sEMG values in voluntary contractions at 60% MVC before and after the vibration conditioning treatment are reported for each subjects (N = 10) in the bottom lines mean and standard deviations (SD) are reported

Voluntary contraction (60% Maximal voluntary contraction)						
Subject code	MNF		ARV		CV	
	Initial value (Hz)	Rate of change (Hz/s)	Initial value (1V)	Rate of change (1V/s)	Initial value (m/s)	Rate of change (m/s^2)
Before treatment						
A	88.96	—1.08	364.27	7.23	4.82	—0.02
B	115.33	—1.51	651.42	5.68	5.17	—0.02
C	104.44	—1.04	306.58	3.49	4.97	—0.02
D	97.83	—1.16	372.93	2.49	5.68	—0.04
E	108.86	—0.62	270.03	5.77	5.08	—0.01
F	105.38	—1.22	398.7	6.14	4.45	—0.031
G	69.37	—0.62	208.49	4.1	5.2	—0.03
H	68.77	—0.65	194.98	4.72	4.51	—0.033
I	89.18	—0.28	102.59	—1.13	5.04	—0.01
L	48.32	—0.34	56.79	1.53	4.83	—0.02
Mean ± SD	89.6 ± 21.4	—0.85 ± 0.41	292.7 ± 170.2	4 ± 2.5	5.98 ± 0.36	—0.023 ± 0.01
After treatment						
A	81.55	—0.52	247.32	1.3	4.61	—0.01
B	94.93	—0.73	350.68	11.27	5.08	—0.02
C	103.16	—1.14	255.91	8.6	5.02	—0.02
D	85.26	—1.08	355.55	2.4	5.65	—0.04
E	99.67	—0.66	385.43	3.35	4.85	—0.01
F	111.6	—1.51	562.64	5.49	4.35	—0.03
G	63.51	—0.43	208.69	3.76	5.1	—0.02
H	70.23	—0.52	225.69	2.71	4.25	—0.02
I	88.28	—0.35	145.36	—3.7	4.95	—0.01
L	56.85	—0.68	102.39	1.93	4.7	—0.01
Mean ± SD	85.5 ± 16.9	—0.76 ± 0.35	284 ± 126.9	3.71 ± 3.89	4.86 ± 0.39	—0.019 ± 0.009

MNF: Mean spectral frequency; ARV: Averaged rectified value; CV: Conduction velocity.

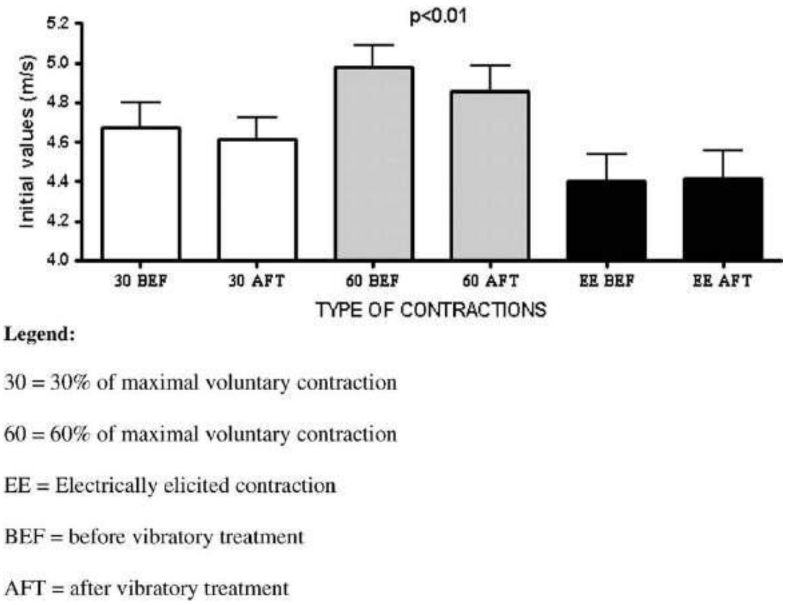
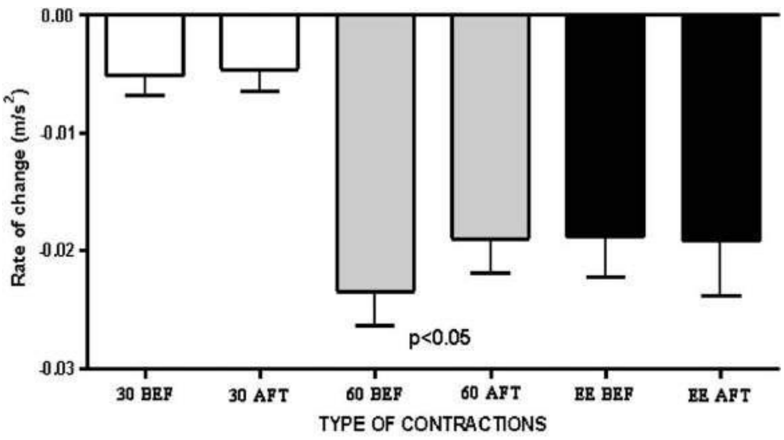


Fig. 1. Comparison of CV initial value in the three types of contraction before and after vibratory treatment.

units were able to provide the same force output with a reduced myoelectric manifestation of fatigue. Such a modification can be related, for instance, to the synchronization of the MUs, aimed to increase the force, without increasing the CV or to a different depth of the recruited MUs within the muscle. If slow MUs are recruited in a synchronized



Legend:

30 = 30% of maximal voluntary contraction

60 = 60% of maximal voluntary contraction

EE = Electrically elicited contraction

BEF = before vibratory treatment

AFT = after vibratory treatment

Fig. 2. Comparison of fatigue index (rate of change of CV) in the three types of contraction before and after vibratory treatment.

Table 4
Torque values in voluntary contractions at 60% MVC before and after the vibration conditioning treatment are reported for each subjects (N = 10) In the bottom lines mean and standard deviations (SD) are reported

Subject code	Force (Nm)	
	Before treatment	After treatment
A	79.4	73.4
B	62.6	64.6
C	65.6	72
D	82.6	82
E	58.8	55.4
F	57.2	63
G	66	63.4
H	75	66.2
I	43.8	46.4
L	52	62.8
Mean ± SD	62.62 ± 11.64	63.98 ± 9.87

manner at a more superficial level, their activity could be lower producing unaltered net signal amplitude at the recording site. In other words myoelectric manifestations of fatigue are reduced whereas torque and amplitude remain unchanged.

Moreover, the experimental protocol indicates a prolonged effect of 300 Hz vibration as the effects were found two days after the end of the vibration sessions. This duration is far more persistent than usually recorded in neurophysiological work using vibration as a conditioning stimulus (Eklund and Hagbarth, 1966; Lance et al., 1966; Delwade, 1973). The fact that VIB can induce different neurophysiological effects such as an initial inhibition of spinal monosynaptic reflex (Lance et al., 1966), a tonic prolonged contraction of the vibrated muscle (Tonic Vibratory Reflex-TVR) (Eklund and Hagbarth, 1966), and a post vibratory potentiation (Delwade, 1973), it is well known since the sixties. Indeed, all these effects are short lasting and with time of application of the vibratory stimulus and number of repetitions limited to a single application of few minutes. More recently, although with some differ- ences in the vibration parameters, VIB has been postulated to increase muscle force and extend fatigue limits. All these effects were observed for a considerable period of time in contrast with all the neurophysiological parameter above mentioned but in agreement with the present paper (Saggini et al., 2006; Bosco et al., 1999; Ribot-Ciscar et al., 2003; Bakhtiary et al., 2007).

As far as we know this is the first paper documenting, by means of sEMG, that VIB exerts its activity at a central level in the nervous system. This could be related to the abil- ity of the nervous system to modify its activity depending on the continuous inflow of relevant inputs (Elbert and Rockstroh, 2004) as in this research where we used a 300 Hz stimulation applied for 30 min, for five consecutive days.

It is well known that the brain maintains the capacity of reorganizing its neural network architecture following environmental changes (Sterr et al., 1998; Flor, 2003). In other term a congruous vibratory stimulus applied for a reasonable length of time and during several days seems able to induce plastic rearrangement in the sensory motor coupling.

It is worth noting that our data differ from those presented in the more recent literature since we did not find any improvement in mechanical output, but rather possibly a different motor unit recruitment strategies. We can speculate that such a different behaviour is probably due to the different sets of vibratory stimulation used (whole-body versus single muscle vibration; 30–60 Hz versus 300 Hz) and moreover due to the ability of the methodology herein used (i.e. multichannel sEMG), to disclose different pattern of muscle activation not detectable with classical bipolar EMG montage. Another possible source of different data interpretation is that in some papers vibration was superimposed to muscle voluntary contraction to further improve muscle force. Actually, also about the issue of force improvement, conflicting results are present in litera- ture: an enhancement of force differentiation has been observed only in fresh muscles after vibration treatment of 130–160 Hz whereas fatigued muscles did not show this effect (Caffarelli and Layton-Wood, 1986).

The importance of high frequency vibration versus lower frequency vibration is forwarded by laboratory acquisition showing that only when muscle spindle recep- tors are driven maximally by a high frequency vibration such as 300 Hz vibration, neurones in the motor cortex and in area 3A in monkeys are effectively activated (Lucier et al., 1975). This could indicate a supremacy in cortical activation of a 300 Hz frequency versus lower frequencies.

5. Conclusion

It is evident that the richness of different forms of utilization is, in the case of the vibratory stimulus, a great bias because of the huge amount of different vibration parameter and devices used. Our data point out that 300 Hz vibration is able to modify the motor unit centrally driven recruitment order and this could be considered a plastic changes induced by the reiteration of the stimulus. These changes are supported also by the presence of sEMG modifications at least two days after the treatment, and therefore not strictly related to the presence of an ongoing vibratory stimulus.

However, also in the light of the results herein obtained we believe in the need of future research aimed to understand the biological effects of vibration on muscle performance (Jordan et al., 2005; Cardinale and Bosco, 2003) and also to extend researches for instance to woman, to other age ranges, as well as to other categories such as ath- letes of different disciplines.

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EFFECTS OF LOCAL VIBRATIONS ON SKELETAL MUSCLE TROPHISM IN ELDERLY PEOPLE: MECHANICAL, CELLULAR, AND MOLECULAR EVENTS

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Effects of local vibrations on skeletal muscle trophism in elderly people: Mechanical, cellular, and molecular events

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Abstract. Several studies have examined the effects of vibrations on muscle mass and performance in young healthy people. We studied the effects of vibrations on muscles of elderly male and female volunteers (65-85 years of age) diagnosed with sarcopenia. We applied mechanical vibrations locally (local vibrational training) to the thigh muscles at 300 Hz for a period of 12 weeks, starting with a session of 15 min stimulation once a week and increasing to three sessions of 15 min per week. Treated muscles displayed enhanced maximal isometric strength and increased content of fast MyHC-2X myosin. Single muscle fiber analysis did not show any change in cross-sectional area or in specific tension. Analysis of transcriptional profiles by microarray revealed changes in gene expression after 12 weeks of local vibrational training. In particular, pathways related with energy metabolism, sarcomeric protein balance and oxidative stress response were affected. We conclude that vibration treatment is effective in counteracting the loss of muscular strength associated with sarcopenia and the mode of action of vibration is based on cellular and molecular changes which do not include increase in fiber or muscle size.

Introduction

Aging is associated with progressive loss of neuromuscular function. The term sarcopenia is commonly used to describe the loss of skeletal muscle mass and strength that occurs in connection with biological aging in the elderly. The onset of sarcopenia is generally assumed to occur around 60 years of age, with atrophy being an important symptom. The progression of sarcopenia is influenced by several factors, including genetic components, lifestyle, age-related diseases, decreases in the levels of hormones (GH, testosterone, IGF-1), loss of motor units, and decreased regenerative capacity of skeletal muscle stem cells (1,2). Atrophic conditions in the elderly are exacerbated when diseases force them to bed. The main countermeasure is regular and moderate exercise, but, besides general advice to stay active, there are no definitive indications for optimal training and/or treatment of sarcopenia (3,4).

In recent years, mechanical muscle vibration received considerable attention as a useful method of muscle stimulation in clinical therapy and sports training, but the results remain controversial. Only a few studies described specific vibrational training protocols, and this lack of information generates uncertainties regarding the most effective vibration intensities, frequencies, and application protocols. When frequency is considered, the main question is whether vibrations are applied to the whole body or to specific muscles. The body tolerates a vibration frequency in the range 20-50 Hz, whereas the level for local application to specific skeletal muscles is in the range of 300-500 Hz.

In view of the diversity of applied treatments, a precise comparison of results reported in scientific literature is difficult, and for this reason we report data on different vibrational protocols without extensive discussion. For instance, Bosco and coworkers showed positive effects of passive whole-body vibration under different conditions, reporting significant increases in muscle strength and power (5), elevations in plasma concentrations of testosterone and growth hormone (6,7), and improvement in neuromuscular properties (8). Another study showed that maximal isometric voluntary contraction increased (in young men) only when vibration was combined with squat training (7). De Ruiter and colleagues studied the effects on young men over a period of 11 weeks of whole-body vibration at 30 Hz and found that neither the strength nor the contractile properties of the knee extensor muscle improved (9). It is also worth remembering that negative effects of whole-body vibration on health were reported. Hand-arm vibration syndrome and

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Key words: vibrations, skeletal muscle, single fibers, gene expression

Table I. Anthropometric parameters of study participants.

	Age years	Height cm	Weight pre-training kg	Weight post-training kg	BMI pre-training kgm^{-2}	BMI post-training kgm^{-2}
Male	75.3±6.9	163.0±5.0	76.9±6.7	75.3± 6.2	29.1±3.5	29.0±3.3
Female	71.0±5.7	159.0±5.0	71.6±18.8	66.4 ±15	28.3±8.1	28.2±7.6

Data reported in the Table are the anthropometric measurements of male and female elderly volunteers. The values are means ±SD.

vascular disorders (10,11), low back pain (12) and spinal health risks (13), were reported in vibration-exposed workers.

The possible involvement of the nervous system in modifications of muscle performance induced by vibration has been the focus of several studies (14). It was hypothesized that mechanical stimuli are transmitted to sensory receptors of muscles, most likely the spindles, and that receptor activation results in the reflex stimulation of motor units, as seen in the tonic vibration reflex (15). However, the tonic vibration stretch reflex was originally described as the result of a brief exposure to high-frequency stimulation applied directly to a tendon (16,17). Any activation prolonged for tens of seconds could induce a reduction in muscle spindle firing frequency and, as a consequence, a decrease in muscle activation (15). Moreover, muscle spindle firing induced by vibration excites not only motor neurons but also interneurons in the spinal cord, which reciprocally inhibit the motor neurons of antagonist muscles (18). Brunetti and coworkers studied posture stability after vibratory stimulation following anterior cruciate ligament reconstruction. These authors concluded that vibration leads to a faster and more complete recovery of equilibrium, confirming a role for vibration in proprioceptive stimulation (19). In conclusion, it remains difficult to find a rationale that is logically used to design vibration treatment and to predict treatment outcomes.

In this study, we aimed to determine whether a training program of passive muscle stimulation, in which local mechanical vibrations at high frequency (300 Hz) were applied to the lower limbs in the absence of any voluntary muscle contraction, induces an increase in muscle mass and strength in elderly subjects showing signs of sarcopenia. Isometric strength developed in maximal voluntary contractions by knee extensor muscles, and thigh circumference, were the parameters selected to evaluate the impact of local muscle mechanical vibrations in elderly male and female volunteers, and thigh circumference was used as an indicator of structural modifications. Additionally, using small fragments of tissue from needle biopsies of the vastus lateralis muscle (pre- and post-training), some cellular features (fiber types, fiber cross-sectional area, single fiber tension development) and gene expression profiles were analyzed.

Materials and methods

Subjects. The study involved nine elderly people (four males and five females) with diagnoses of sarcopenia according to the criteria of the Centers for Disease Control and Prevention (CDCP). Anthropometric characteristics are summarized in Table I. The study was approved by the local ethics committee, and was performed in accordance with the 1964 Declaration of Helsinki. All individuals provided written informed consent before participating in the study.

The inclusion criteria were as follows: diagnosis of sarcopenia; normal ECG and blood pressure; and absence of bone/joint, metabolic, or cardiovascular diseases. Exclusion criteria were the presence of metabolic and/or cardiovascular diseases, evidence of hereditary or acquired muscular disease, or diagnosis of respiratory or psychiatric disorders. No subject was under treatment with testosterone or other pharmacological interventions known to influence muscle mass.

Training protocol and experimental design. The conditioning protocol consisted of application of local high-intensity vibrations on the lower limbs using the VISS apparatus. The VISS device (Vissman, Rome, Italy) is a tool capable of producing acoustic waves of different frequencies without affecting the set width. The device is not an acoustic wave generator, but rather a flux modulator, and has two components. These are a compressor delivering pressure in the range 0-400 millibar and a modulator producing an oscillatory air flux to create acoustic waves through a two-way rotating valve. The transducer develops a time-modulated sinusoidal wave (300 Hz). During application of vibration, subjects were invited to avoid isometric contractions of the treated muscle. The experimental protocol required that local mechano-acoustic vibratory stimulation was applied on the skin of the distal part of the quadriceps close to the tendon insertions of the intermedius femoris, rectus femoris, vastus medialis, and vastus lateralis muscles. The entire treatment lasted 12 weeks. The duration of each application was 15 min and the frequency chosen was 300 Hz. From weeks 1 to 8 the subjects received one application per week, whereas from weeks 9 to 12 they received three applications per week. We refer to this type of stimulation protocol as 'local high-intensity vibrational training'.

Two weeks before the training period, enrolled subjects were familiarized with the test session protocol. Isometric tests were performed a week before (pre-session) and a week after the conditioning period (post-session), to measure the bilateral maximal isometric strength of the lower limbs, the body mass index (BMI), and thigh circumference, assessed with a measuring tape at two levels on the dominant leg of each standing subject. The circumferences measured were the maximal circumference at one-third of the distance between the trochanter and the tibial-femoral joint space, and the minimum circumference above the knee. Skinfold measurements were next recorded at the anterior mid-thigh using a skinfold caliper.

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Sixteen weeks after the end of the conditioning period of local high-intensity vibrational training, the isometric test was repeated to monitor lower limb strength level.

Isometric strength measurement. Bilateral isometric torque developed by the knee extensor muscles was measured during maximal voluntary contractions using a Leg Extension machine (Panatta Sport; Apiro [MC], Italy) equipped with a load cell (Globus Italia, Codognè [TV], Italy). Participants were seated with the trunk-thigh and the knee joint angles at 90°. Subjects performed maximal voluntary isometric contractions of the knee extensors three times. Isometric contractions lasted for 5 sec, and were separated by 2 min rest intervals. The highest value of torque attained was taken as the isometric contraction strength. In each subject, the variation of knee extension isometric force was expressed as a percentage of the pre-training value.

Cellular and molecular analysis of muscle biopsies. Muscle biopsies were obtained using a semi-automatic needle (Precisa 13 Gauge; Hospital Service, Rome, Italy) from the vastus lateralis muscle at a level corresponding to one-third of the distance from the upper margin of the patella to the anterior superior iliac spine, after local anesthesia with lidocaine (0.5%, w/v). In each subject, several samples were collected from the same needle insertion and were divided into three groups: (i) samples immersed in skinning solution (see below) were used for dissection of single muscle fibers; (ii) samples immersed in Laemmli buffer (see below) were used for gel electrophoresis; and, (iii) samples immersed in Trizol reagent (Invitrogen, Paisley, UK) were used for extraction of RNA for analysis of transcriptional profiles.

Muscle fibers, mechanical characterization. Muscle biopsy fragments for single fiber dissection were immersed in ice-cold skinning solution with 50% (v/v) glycerol. Skinning solution is a high-potassium, high-EGTA solution which depolarizes membranes, removes calcium, and induces a rigor state, thus ensuring optimal conditions for fiber preservation. The fragments were stored at -20°C and analyzed within 2 weeks of sampling. On the day of the experiment, the skinning-glycerol mixture was washed off and replaced with ice-cold skinning solution containing ATP, to induce fiber relaxation. Single fibers were manually dissected under a stereo-microscope (x10-60 magnification). Following dissection, fibers were bathed for 30 min in skinning solution containing 1% (v/v) Triton X-100 to ensure complete membrane solubilization. Fiber segments 1-2 mm in length were cut, and light aluminum clips were applied at both ends. Skinning, relaxing, pre-activating, and activating solutions employed for single fiber experiments were prepared as described previously (20). Fiber segments were transferred to the experimental apparatus, and cross-sectional area and tension development during maximal calcium-activated isometric contractions at 12°C were measured according to a previously described procedure (21).

Electrophoretic separation and quantification of myosin heavy chain (MyHC) isoforms. MyHC isoform composition was determined in biopsy samples. Muscle biopsy fragments were stored in Laemmli solution (Tris 62.5 mM, Glycerol 10% [v/v], SDS 2.3% [w/v], ß-mercaptoethanol 5% [v/v], with E-64 0.1% [w/v] and leupeptin 0.1% [w/v] as anti-proteolytic factors; pH 6.8). After heating for 5 min at 80°C appropriate amounts of the protein suspension were loaded onto poly-acrylamide gels (~1 µg of total protein/lane). Separation of MyHC isoforms was achieved on 8% (w/v) gels (18 cm x 16 cm x 1 mm) at 70 V for 1.5 h and at 230 V for a further time according to the guidelines of Talmadge and Roy (22). After silver staining, three separate bands were detected in the 200-kDa region, corresponding to MyHC-1, -2A, and -2X, in order of migration from fastest to slowest. To quantify myosin isoform distribution, densitometric analyses of silver- stained bands were performed on at least two independent electrophoretic runs of each biopsy sample fragment. The mean values represent the measurements presented. Gel patterns were digitized with an EPSON 1650 scanner at a resolution of 1,200 dpi. Each band was characterized by a value of the Brightness-Area Product (BAP), using a constant threshold after black/white inversion employing Adobe Photoshop software. From each gel, BAP values for the bands identified as MyHC isoforms were summed and the BAP value for each isoform was expressed as a percentage of the total. The reproducibility of the procedure was confirmed by calculating isoform ratios of selected samples from gels loaded with different amounts of such samples.

Gene expression profile. A high-density oligonucleotide microarray technique was used to identify variations in gene expression induced by mechanical vibration. This technique involves RNA isolation, amplification, and labeling. The human oligonucleotide gene set consisting of 21,329 (70-mer) oligonucleotides (Operon version 2.0), designed on the basis of the Human Unigene clusters, was employed. Microarray co-hybridization involved simultaneous hybridization with pre- and post-training samples. Expression levels of all spot replicates were normalized (23). RNA was extracted from the biopsy samples of three different elderly subjects before and at the end of the vibrational training period. Very pure RNA samples from each subject were amplified and reverse-transcribed into cDNA, and dye-swap duplicated microarrays were analyzed for each subject. Arrays were scanned, and recorded fluorescence intensities were subjected to Lowess normalization. The expression of each gene was defined as the log base-2 of the ratio between the intensity of cyanine-coupled aaRNA from post-training samples and that of cyanine-coupled aaRNA from pre-training samples ($\log_2 I_{post\text{-}training}/I_{pre\text{-}training}$). Differentially expressed genes were selected using a permutation test procedure known as the 'Significance Analysis of Microarrays' (SAM), which defines genes with a computed score larger than the threshold value as showing significant variation. The false discovery rate (FDR) associated with the given threshold was additionally calculated from permutation data.

Statistical analysis. Data were expressed as means ±SE (Figs.) or SD (Tables). Statistical significance was set at $p<0.05$ and was calculated using the unpaired Student's t-test, with Welch's correction. Prism5 GraphPad software (Abacus Concepts GraphPad Software, San Diego, CA) was employed for statistical analyses. Gene expression analysis was based on SAM data and variations are expressed as means with SD.

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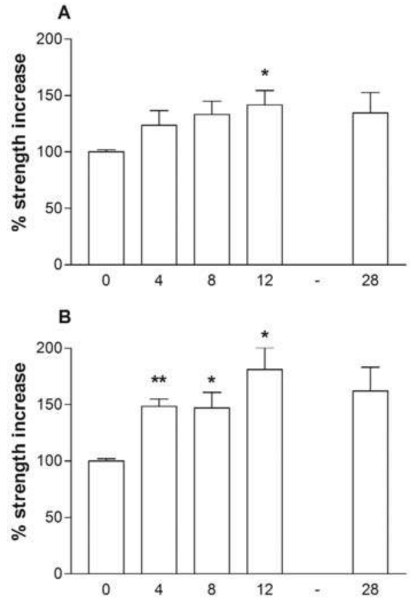

Figure 1. Variations in bilateral isometric strength of leg extensor muscles treated with local muscle vibration at 300 Hz in nine elderly male (A) and female (B) subjects. The histograms show the percentage increases in bilateral isometric strength, based on leg extension, at different times during the period of stimulation. 0 week, pre-training; 4, 8, and 12 weeks, intervals during the stimulation period when strength was measured. During the first 8 weeks, treatment was based on a single vibration application (300 Hz) of 15 min per week. From weeks 8 to 12, treatment was increased to three applications of 15 min per week (300 Hz). Treatment was interrupted after 12 weeks, and strength was measured again at week 28. Isometric strength measurements from the pre-training sessions are taken as 100%. Significant variations, $^{*}p<0.05$, $^{**}p<0.01$.

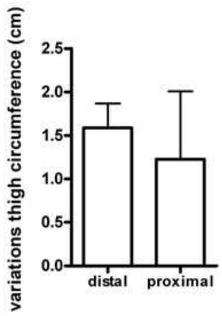

Figure 2. Variations in thigh circumference. Two thigh circumferences, one distal (just above the knee) and one proximal (at 2/3 of the knee-trochanter distance, to avoid the adductor muscles) were measured before the beginning of treatment (pre-training) and after 12 weeks of treatment (post- training). Changes are expressed in cm. As average, the distal and proximal circumferences showed small and insignificant increases after vibrational training in both male and female subjects.

Results

Maximal isometric strength of knee extensor muscles. Isometric strength of leg extensor muscles was measured before, and after 4, 8, and 12 weeks of vibrational training. The application of local vibration to the lower part of the thighs improved isometric strength (Fig. 1). In both male and female subjects (anthropometric characteristic in Table I), the increase was appreciable, beginning at 4 weeks (females) and 8 weeks (males) of vibration training. Importantly, during the first 8 weeks of the procedure, stimulation was scheduled only once a week. This increase in strength remained at a plateau upto week 12, even though training frequency was increased to three times per week from week 8 (see Training protocol). In general, the response was better in female than in male subjects. In male subjects, isometric strength increased by ~25% at weeks 4 and 8, with a significant increase at week 12 of training (141.7±12.7%, n=4, $p<0.05$). Follow-up measurements after 28 weeks revealed that the increase in strength was consistently maintained (134.5±18.0%) (Fig. 1A). In female subjects, the increase in bilateral isometric limb strength was higher than in males, commencing at week 4 (148.5±6.5%, n=5, $p\leq 0.001$), and remained significant until the end of the training period (181.2±19.3%, n=4, $p\leq 0.001$). The increase in strength at 12 weeks of stimulation was not significantly different between female and male subjects.

Variations of leg extensor muscle mass were evaluated from the measurements of two thigh circumferences, one distal (just above the knee), and one proximal (at 2/3 of the knee-trochanter distance), to avoid the influence of adductor muscles. After vibrational training the distal circumferences showed small and insignificant increases (0.5-3 cm) in both male and female subjects, whereas, with proximal circum-ferences, variations ranged from a slight decrease in two female subjects to an increase (0.5-6 cm) in other subjects (Fig. 2). Moreover, skinfold measurements at the end of the training period were not significantly different from those measured before training (data not shown). In conclusion, no significant variations in muscle mass accompanied increases in muscle strength.

Muscle fiber cross-sectional area and specific tension. Single muscle fibers were isolated from biopsy fragments of the vastus lateralis muscle obtained before and after vibrational training. From each biopsy, 8-9 fibers were analyzed, to yield data on a total of 80 fibers both before and after training. The average cross-sectional area (CSA) was 3667.0±310.7 μm^2 in pre-training samples, and 4238.0±357.4 μm^2 in post-training samples, thus, vibrational training did not significantly modify the CSA of single fibers (Fig. 3A). In specific tension measurements, the isometric strength per unit of fiber area was 177.0±14.6 mN/mm^2 in pre-training samples, and 164.0±17.4 mN/mm^2 in post-training specimens. These values were not significantly different (Fig. 3B).

Myosin isoform composition of biopsy samples. The fiber type composition of the vastus lateralis muscle was determined by analyzing the proportion of slow (MyHC-1) and fast(MyHC-2A and -2X) myosin heavy chain isoforms in biopsy samples taken before and after vibrational training. Myosin isoforms can be considered as molecular markers of fiber types (24). The average values for myosin isoform distribution in males (Fig. 4A) and females (Fig. 4B) are shown. In both groups, fast MyHC-2X levels were increased after vibration training, whereas slow MyHC-1 proportions were significantly lower in post-training compared to pre-training samples. The shift in myosin isoform expression might indicate either fiber

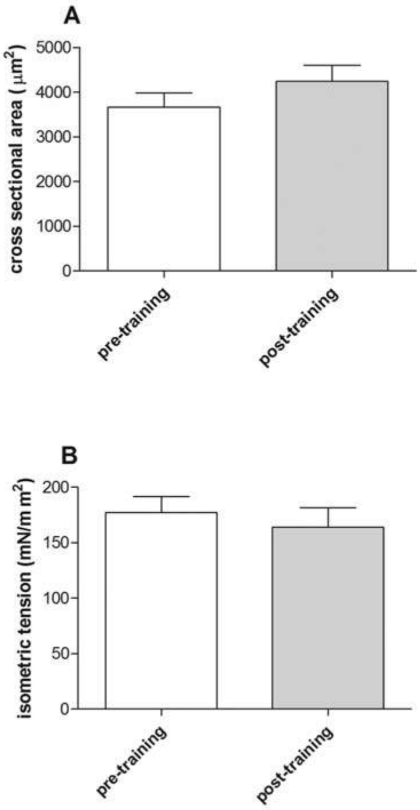

Figure 3. Single-fiber analysis, cross sectional area (A) and specific isometric tension (B). (A) Cross-sectional area (CSA) of single muscle fibers isolated from the biopsy samples from the vastus lateralis muscle before and after vibrational training of 12 weeks. (B) Measurements of specific isometric tension (force/CSA) developed in maximal calcium- activated contraction by the same fibers. In both cases, no significant difference was detected between pre- and post-training samples. For each measurement, a total of 80 fibers were analyzed.

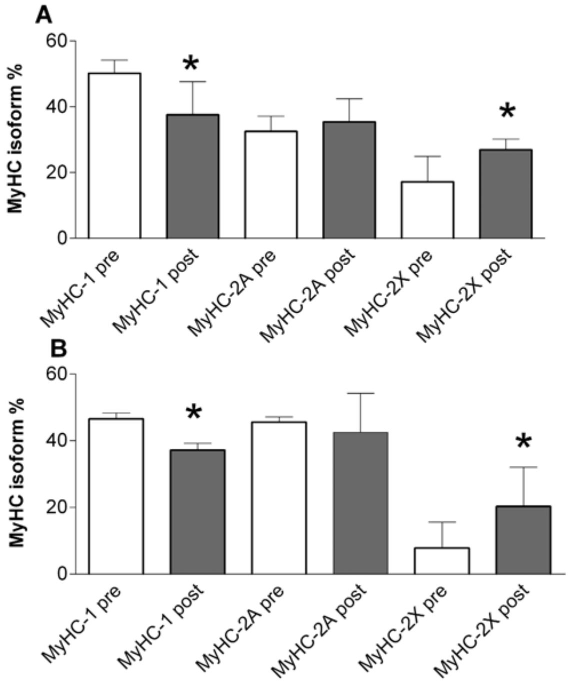

Figure 4. MyHC isoform distribution in biopsy samples collected before and after 12 weeks of vibrational training in nine elderly subjects. MyHC isoform distribution was determined by electrophoretic separation and densitometric analysis of proteins of biopsy samples from the vastus lateralis muscle. A and B show the percentage distributions of MyHC isoforms (1, 2A, and 2X) in male and female subjects, respectively. The grey columns represent the percentages of the MyHC isoform distribution post-training, and the white columns represent pre-training percentages. (A) The mean percentage of MyHC-1 decreased by 13%, whereas that of MyHC-2X increased by 12%, in elderly male subjects. (B) The mean percentage of MyHC-1 decreased by 11%, whereas that of MyHC-2X increased by 12%, in female subjects. $^{*}p\leq 0.05$.

transition (from slow to fast; 2X) or differential growth (a specific increase in the size of 2X fibers). The lack of any significant increase in fiber thickness after vibrational training (see Fig. 3) suggests that the change in myosin isoform distribution are caused by a fiber-type transition.

Gene expression profiles. Gene expression profiles from oligonucleotide microarrays were obtained from biopsy samples of three subjects before and after vibrational training. We listed the genes found significantly regulated after the vibrational training on each subject and we assessed possible changes in gene transcription analyzing these regulated genes. Genes that appeared to be significantly affected were further evaluated to elucidate the mechanisms by which vibration-trained muscles showed performance enhancement. Some genes with well-known muscle activities received particular attention, and were classified according to function. Such categories included, specifically, (i) genes of energy metabolism (Table II); (ii) genes involved in sarcomeric protein synthesis, protein degradation, and calcium homeostasis (Table III); and, (iii) genes dealing with oxidative stress (Table IV).

Genes involved in energy metabolism. Several enzymes involved in glucose and glycogen metabolism were upregulated after vibration therapy (Table II). We observed increased expression of the *phosphoinositide-3-kinase, regulatory subunit, polypeptide 3* (PIK3R3) gene that encodes a binding protein in the insulin-dependent pathway leading to inhibition of glycogen synthase kinase-3 (GSK-3), and that thus mediates net dephosphorylation of glycogen synthase (GS), with concomitant activation of the glycogen pathway (25). It is important to remember that PI3kinase functions upstream to Akt, a signaling factor very relevant to muscle hypertrophy mechanisms (26). Moreover, *protein phosphatase regulatory subunits 3A* and *3C* (PPP1R 3A and 3C), genes encoding key enzymes for glycogen conservation in muscle (25), were upregulated. Another gene showing enhanced expression was *dihydrolipoamide dehydrogenase, E3 complex of pyruvate dehydrogenase complex* (DLD), a protein of the pyruvate dehydrogenase complex that transforms pyruvate into acetyl-coenzyme A. In particular, the E3 component reduces NAD^{+} to NADH (27). Yet another up-regulated gene of interest was *fatty acid CoA ligase* that is important for fatty acid activation in the cytoplasm prior to ß-oxidation. *Glucan* (*1,4*-‑-), *branching enzyme 1* (*glycogen branching enzyme*, [relevant

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Table II. Changes in energy metabolism genes.

Subject	Gene name	Mean $\log_2 I_{post\text{-}training}/I_{pre\text{-}training}$ SD	GB accession	UniGene ID	Gene symbol
1	Phosphoinositide-3-kinase, regulatory subunit, polypeptide 3 (p55, Á)	0.86±0.39	NM_003629	88051	PIK3R3
2	Protein phosphatase 1, regulatory (inhibitor) subunit 3A (glycogen and sarcoplasmic reticulum binding	1.08±0.13	NM_002711	127614	PPP1R3A
2	Protein phosphatase 1, regulatory (inhibitor) subunit 3C	0.99±0.17	BC012625	303090	PPP1R3C
2	Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex)	0.85±0.16	NM_000108	74635	DLD
2	Fatty-acid-coenzyme A ligase, long-chain 2	0.91±0.09	NM_021122	154890	FACL2
1	Solute carrier family 16 (monocarboxylic acid transporters), member 4	0.84±0.32	NM_004696	23590	SLC16A4
1	Solute carrier family 21 (organic anion transporter), member 11	0.65±0.12	NM_013272	14805	SLC21A11
1	Solute carrier family 6 (neurotransmitter transporter), member 14	0.80±0.32	NM_007231	162211	SLC6A14
1	Ubiquinol-cytochrome c reductase core protein II	0.69±0.16	NM_003366	173554	UQCRC2
5	Glucan (1,4-alpha-), branching enzyme 1 (glycogen branching enzyme, Andersen disease, glycogen storage)	-1.16±0.15	NM_000158	1691	GBE1

The first column specifies in which of the three different elderly subjects (individuals 1, 2, or 5) the change in expression was detected. The second column lists the common names of the different genes up- or down-regulated in the vastus lateralis muscle, when post- and pre-training expression levels were compared. The third column reports changes in expression levels of genes as means of the log base-2 of the ratios ($\log_2 I_{post\text{-}training}/I_{pre\text{-}training}$), with SD. The fourth column lists Gene Bank Accession numbers, the fifth the UniGene Identification numbers, and the sixth specific gene symbols. Genes involved in energy metabolism were classified as upregulated (positive values) or downregulated (negative values).

to Andersen's disease and glycogen storage disease]) (GBE1), which participates in glycogen synthesis, was downregulated.

Expression of specific genes encoding several transporters was enhanced, including genes encoding *solute carrier family 16* (*monocarboxylic acid transporters*), *member 4* (SLC16A4) (28), a transport system implicated in both intracellular pH regulation during muscle contraction and lactate removal. The gene *solute carrier family 21* (*organic anion transporter*), *member 11* (SLC21A11), functioning in the transport of organic anions and thyroid hormones, and in modulation of glucose phosphorylation (29), was also upregulated. Moreover, the expression of *solute carrier family 6* (*neurotransmitter transporter*), *member 14* (SLC6A14), a gene encoding an amino acid transporter implicated in the utilization of non-glucidic substrates for plastic cellular reorganization and as an energy source (30), was increased. Notably, we observed elevated expression of *ubiquinol-cytochrome c reductase core protein II* (UQCRC2), encoding a cytochrome reductase of the mitochondrial complex III (31).

Genes involved in sarcomeric protein synthesis and degradation, and calcium homeostasis. Several genes encoding sarcomeric proteins were upregulated (Table III). These included *actin -2* (ACTA2), one of the six actin isoforms of thin filament proteins, *destrin* (DSTN), a key enzyme in actin polymerization (32), and *myosin, light polypeptide, regulatory, non-sarcomeric* (MLCB), together with *chaperonin ADP-ribosylation factor-like 5* (ARL5A), and *short coiled-coil protein* (SCOCO), linked to myosin folding and myofibrillogenesis (33). In the context of protein turnover, we observed upregulation of *ubiquitin-specific protease 15* (USP15), involved in the removal of damaged proteins, and downregulation of *ubiquitin-conjugating enzyme E2G 1* (UBE2G1), encoding a protease, and an enzyme that conjugates target proteins with ubiquitin, respectively. Moreover, expression of *calpain 3* (p94), specifically expressed in skeletal muscle, was enhanced. Calpain 3 mediates muscle remodeling by cleavage and release of myofibrillar proteins, targeting these proteins for ubiquitination and proteasomal degradation (34,35). The genes *-actinin-2-associated LIM protein* (ALP), and *Leman coiled-coil protein* or *angiomotin-like protein 2* (LCCP), encoding proteins important for sarcomeric structure (in particular, the Z line), and *Titin immunoglobulin domain protein* (TTID), encoding a big, elastic protein that stabilizes sarcomeric filaments (36-38), were additionally upregulated. Another interesting gene displaying increased expression was *Popeye protein 3* (POP3). POP genes are expressed in cardiac and skeletal muscles (39), and participate in the synthesis and stabilization of mRNA encoding tubulin (40). Genes encoding *ryanodine type 3* (RyR3), a receptor of the sarcoplasmic reticulum, and *calcium homeostasis endoplasmic reticulum protein* (CHERP), an intracellular calcium-mobilizing agent (41), were additionally upregulated.

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Table III. Genes encoding sarcomeric proteins.

Subject	Gene ID	Mean $\log_2 I_{post\text{-}training}/I_{pre\text{-}training}$ M2 VisS	GB accession	UniGene ID	Gene symbol
2	Actin, · 2, smooth muscle, aorta	1.29±0.37	NM_001613	195851	ACTA2
2	Destrin (actin depolymerizing factor)	0.83±0.13	NM_006870	82306	DSTN
1	Myosin, light polypeptide, regulatory, non-sarcomeric (20 kD)	0.80±0.32	NM_006471	233936	MLCB
2	ADP-ribosylation factor-like 5	1.09±0.20	NM_012097	342849	ARL5
2	Short coiled-coil protein	1.16±0.65	NM_032547	286013	HRIHFB2072
2	Titin immunoglobulin domain protein (myotilin)	1.07±0.26	NM_006790	84665	TTID
2	· -actinin-2-associated LIM protein	1.35±0.70	BC001017	135281	ALP
2	Leman coiled-coil protein	1.05±0.25	NM_016201	92186	LCCP
2	Ryanodine receptor 3	1.40±0.63	NM_001036	9349	RYR3
1	Calcium homeostasis endoplasmic reticulum protein	1.04±0.64	NM_006387	6430	CHERP
1	Popeye protein 3	0.89±0.18	AK055600	303154	POP3
2	Ubiquitin-specific protease 15	0.92±0.18	NM_006313	23168	USP15
5	Ubiquitin-conjugating enzyme E2G 1 (UBC7 homolog, C. elegans)	-2.23±0.41	NM_003342	78563	UBE2G1
1	Calpain 3, (p94)	0.84±0.22	NM_000070	40300	CAPN3

The first column specifies in which of the three different elderly subjects (individuals 1, 2, or 5) the change in expression was detected. The second column lists the common names of the different genes up- or down-regulated in the vastus lateralis muscle, when post- and pre-training expression levels were compared. The third column reports changes in expression levels of genes as means of the log base-2 of the ratios ($\log_2 I_{post\text{-}training}/I_{pre\text{-}training}$) with SD. The fourth column lists Gene Bank Accession numbers, the fifth lists the UniGene Identification numbers, and the sixth, specific gene symbols. Genes involved in energy metabolism were classified as upregulated (positive values) or downregulated (negative values).

Table IV. Genes involved in oxidative stress.

Subject	Gene ID	Mean $\log_2 I_{post\text{-}training}/I_{post\text{-}training}$ M2 VisS	GB accession	UniGene ID	Gene symbol
2	Nitric oxide synthase 1 (neuronal)	-1.18±0.53	NM_000620	46752	NOS1
2	DNA polymerase epsilon p12 subunit	-1.14±0.31	NM_019896	19980	P12
2	Peroxiredoxin 3	-1.12±0.35	NM_006793	75454	PRDX3
2	Thioredoxin	-1.11±0.47	NM_003329	76136	TXN
2	Methionine sulfoxide reductase A	-0.93±0.47	NM_014772	64096	MSRA

The first column specifies in which of the three different elderly subjects (individuals 1, 2, or 5) the change in expression was detected. The second column lists the common names of the different genes up- or downregulated in the vastus lateralis muscle, when post- and pre-training expression levels were compared. The third column reports changes in expression levels of genes as means of the log base-2 of the ratios ($\log_2 I_{post\text{-}training}/I_{post\text{-}training}$), with standard deviations (SDs). The fourth column lists Gene Bank Accession numbers, the fifth the UniGene Identification numbers, and the sixth specific gene symbols. Genes involved in energy metabolism were classified as upregulated (positive values) or downregulated (negative values).

Genes involved in oxidative stress. Oxidation of biological substrates, such as DNA, proteins, and lipids, in the elderly, is well-recognized, as oxidants are generated in the mitochondrial respiratory chain, and the deleterious function of such oxidants is particularly important in muscle fibers (1). Vibrational training caused down-regulation of the polymerase ε (P12) gene, encoding a low-affinity enzyme involved in DNA duplication and repair (42) and cell cycle control (Table IV). This enzyme, an important contributor to DNA repair, is involved in the rescue of oxidized DNA, although enzyme activity is less efficient than that of other polymerases. Furthermore, expression of the *peroxiredoxin* (PRDX3) gene was decreased. PRDX3 is a specific anti-oxidant enzyme able to remove endogenous cytokine-induced

H_2O_2 (43), using electrons donated by thioredoxin (TXN), the gene for which was also downregulated. *PRDX3* encodes a protein that acts as an antioxidant by facilitating the reduction of other proteins via cysteine thioldisulfide exchange. Another gene displaying diminished expression was methionine *sulfoxide reductase* (MSRA), the protein product of which repairs oxidized methionine (44), one of the most important targets of protein oxidation. Moreover, downregulation of the *constitutive nitric oxide synthase* (NOS1) was also observed. This gene encodes a constitutive form of the enzyme that synthesizes nitric oxide from L-arginine in the presence of NADPH and O_2, and downregulation may be linked to an altered nitric oxide signaling mechanism in aged skeletal muscle (45).

Discussion

Muscle isometric strength is defined as the maximum force exerted against resistance, and decreases significantly in humans with age (46). Healthy elderly subjects typically display diminished muscle mass, reduced movement velocity and skeletal muscle strength, combining to form the diagnostic characteristics of the condition termed sarcopenia (1).

In recent years, novel 'passive training' methods were proposed for clinical treatment of muscle atrophy and in sport training, consisting of mechanical vibrations applied to specific muscles or over the entire body. A number of investigators showed that such treatments enhance muscle strength and power (8,47), plasma concentrations of testosterone and growth hormone (5), and neuromuscular functions (6). Other studies, however, have drawn opposite conclusions, claiming that no improvement of muscle performance was obtained after vibration treatment (9). In addition, negative effects of whole-body vibration on health were documented. Workers exposed to daily vibration display vascular disorders (10), increased levels of lumbar prolapse, and lower back pain (12).

In this study, the measurements of knee extensor muscle isometric torque, obtained during pre-, during (weeks 4 and 8), and at the end of training, confirmed that local high-intensity vibration increases overall muscle strength in elderly male and female subjects. Specifically, isometric strength was elevated by the fourth week of stimulation, remained high during the training period, and also for at least several weeks after cessation of training. Indeed, follow-up measurements at 16 weeks after the end of training revealed consistently high values of muscle strength, similar to the levels recorded at the end of the vibrational protocol, for both female and male volunteers, although some inter-individual variability was noted.

The sustained increase in lower limb strength suggests modifications in the properties of skeletal muscle. Measurements of thigh circumferences and skinfolds showed that the force increase was not accompanied by an increase in muscle mass. We therefore examined the mechanical properties of single fibers to determine whether the changes can be explained at the cellular level. After 12 weeks of local high-intensity vibration, neither the cross-sectional area nor the specific tension of the vastus lateralis muscle fibers was changed, compared to pre-training data. Thus, the change in force of the whole extensor muscle group is not based on an alteration in the force-developing ability of single fibers. Previous studies have shown that muscle disuse in the elderly causes a decrease in specific tension (48), whereas resistance training in body builders is associated with increased specific tension (49). Apparently, the improved strength of leg extensor muscles after vibrational training is not related to an increase in muscle fiber-specific tension. Biopsy examination, however, yielded a valuable and unexpected result. The fiber phenotype distribution of the skeletal muscle was altered. The proportion of the fast MyHC-2X isoform was increased, and the proportion of the slow MyHC-1 isoform was significantly lower, in post-training biopsies compared to pre-training biopsies. This shift in myosin isoform expression is a clear indication of changes in fiber type distribution (49). Fiber type transition from slow to 2X, as suggested by the shift in myosin isoforms, should correspond to changes in the proportions of oxidative and glycolytic fibers, because, in human muscles, slow fibers are mainly oxidative whereas 2X fibers are principally glycolytic (24). Importantly, expression profile analysis validated this metabolic feature. In fact, indications for changes in fiber type distribution were seen in the transcriptional profile. In particular, changes in two of three functional categories (metabolic genes and those encoding sarcomeric proteins) of differentially regulated genes were identified in all screened elderly subjects. Glycolytic and glycogen-dependent metabolism appeared to be stimulated in trained subjects. In this study, personal transcriptional profiles, including data on specific differentially regulated genes, were generated for each of three subjects. Initially, the results appeared inconsistent, but, when the experimental plan was considered, and, particularly, when the long-term nature of the treatment was properly weighted, the transcriptional profiles of the three elderly subjects can be best regarded as specific temporal windows on genes functioning after consolidated or stabilized metabolic (in the wide sense) modifications. We employed a microarray technique to simultaneously screen all pathways activated at a given time-point, and we were able to detect compensatory pathways activated in the cells. Metabolic genes, either up- or down-regulated, were indeed distinct between subjects, but converged into enhancement of the glycogenosynthesis/glycolysis pathway. Glycogenosynthesis is considered as a compensator for increased glucose consumption during training. This hypothesis is consistent with the increased proportion of (specifically) fast MyHC-2X fibers as these fibers employ glycolytic metabolism.

The upregulation of genes, such as actin, destrin, titin and angiomotin, encoding sarcomeric proteins, is consistent with an increase in regeneration that recruits satellite cells to proliferate and fuse into new differentiated myotubes, that are comparable to *in vivo* primary fibers. We hypothesize that new fibers are generated during the first 4 weeks of local high-intensity vibrational stimulation, based on data showing that at week 4, the bilateral isometric strength of lower limbs was significantly increased. We used a biopsy fragment from one subject to collect and grow satellite cells (50), to study whether myogenesis properties *in vitro* are influenced by local high-intensity vibrational training. We induced the differentiation program in these cells, and, after 7 days of differentiation, we used an antibody MF20 against myosins

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to measure the proportion of myotubes expressing the myosin heavy chain proteins. The preliminary data reveal that, after vibrational training, the proportion of MF20-positive myotubes increased by 11.8% (from 41.3% pre-training to 53.1% post-training). These data further support the hypothesis that novel fibers stimulated by local high-intensity vibration are induced to differentiate into new, mature, fast MyHC-2X fibers.

Sarcopenic skeletal muscle shows reduced metabolic power because of several factors, such as decreased blood perfusion, increased fibrosis, and development of the atrophic state. Skeletal muscle tissue undergoes constant oxidation, and the main source of reactive oxygen species is the mitochondrion. A previous study by our group showed consistent oxidative damage in aged skeletal muscle tissue (1). Altered metabolism impairs the balance between oxidative stress and scavenger activity. In fact, several antioxidant genes were downregulated in the elderly, suggesting that ROS scavenger activity is insufficient. Peroxiredoxin is an important antioxidant enzyme that counteracts lipid per-oxidation, protecting cells by removing H_2O_2 (51). Thioredoxin plays a key role in oxidoreduction reactions (43). Methionine sulfoxide reductase A counteracts methionine oxidation of proteins (44), whereas polymerase ε is able to repair oxidized DNA, albeit at low efficiency (42). The downregulated constitutive NO synthase (NOS) could be responsible for lowered nitric oxide production and may disrupt nitric oxide signaling in skeletal muscle arterioles, thus impairing vasodilatation in old age (45). Also, in a study of atrophy induction by horizontal bed rest in young males, it was observed that sarcolemmal NOS1 immunofluorescence in the vastus lateralis muscle increased (52). These opposite effects may be explained by age-related variations in muscle conditioning. In fact, during aging, the bioavailability of substrates and cofactors important for NOS activity decreases (45), and this was not reversed by high intensity vibrational training applied to elderly subjects.

Only one elderly subject (subject 2, Table IV) showed downregulation of antioxidant genes mentioned above. This observation suggests that local high-intensity vibration exacerbate existing physiological and personal gene regulation conditions.

Overall, the results of our study indicate that vibrational training was accompanied by several changes at the muscle molecular level. However, the lack of correlation between marked increases in the force developed during maximal voluntary contraction on the one hand, and muscle mass, single fiber thickness, or specific tension, on the other, suggests that nervous control of contraction must also be considered as possibly influenced by our training protocol. Improved recruitment or better activation of motor units might also be invoked to explain the observed increases in muscle force. A recent study by Fattorini *et al* (14) provided evidence of long-lasting changes in proprioceptive motor control after vibrational training at 100 Hz, and such changes may be partly responsible for the improved contractile performance observed here.

In conclusion, our data validate the effectiveness of the VISS training procedure to counteract sarcopenia. The technique is easy to use, requires little patient commitment or time, and can be employed on patients with joint and/or neuro-muscular disorders.

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ACUTE AND CUMULATIVE EFFECTS OF FOCUSED HIGH-FREQUENCY VIBRATIONS ON THE ENDOCRINE SYSTEM AND MUSCLE STRENGTH

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ORIGINAL ARTICLE

Acute and cumulative effects of focused high-frequency vibrations on the endocrine system and muscle strength

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Glaugo Gialluca · Giorgio Fanò · Raoul Saggini

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Abstract The purpose of this study was to evaluate the acute and long-term effects of local high-intensity vibration (HLV, f = 300 Hz) on muscle performance and blood hormone concentrations in healthy young men. Totally 18 subjects (cV group) were studied in two sessions, either without (control) or with HLV treatment. The protocol was the same on both control and test days, except that, in the second session, subjects underwent HLV treatment. Counter-movement jumping (CMJ), maximal isometric voluntary contraction (MVC) test, and hormonal levels were measured before the procedure, immediately there- after, and 1 h later. To assess the long-term effects of HLV, the cV group was subjected to HLV on the leg muscles for 4 weeks, and a second group (cR group, n = 18) embarked upon a resistance training program. All subjects underwent an MVC test and an isokinetic (100 deg/s) test before training, 4 weeks after training, and 2 months after the end of training. The HLV protocol significantly increased the serum level of growth hormone (GH, P \ 0.05) and crea- tine phosphokinase (CPK, P \ 0.05), and decreased the level of cortisol (P \ 0.05). None of GH, CPK or testos- terone levels were altered in controls. There was a signif- icant improvement in MVC (P \ 0.05). After 4 weeks, both the cV and cR groups demonstrated significant improvement in MVC and isokinetic tests (P \ 0.05). This increase persisted for at least 2 months. Our results indicate that HLV influences the levels of particular hormones and improves neuromuscular performance. Our results indicate that HLV has a long-term beneficial effect comparable to that of resistance training.

Keywords High-intensity local vibration · Growth hormone · Testosterone · Muscle strength · Jumping performance

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Introduction

Vibrational stimulation (VS) can induce non-voluntary muscular contraction, and is often used in athletic training. Eklund and Hagbarth (1966) coined the term tonic vibra- tion reflex (TVR) to describe the phenomenon of non- voluntary contraction induced by VS.

VS can activate the proprioceptive sensory system, which is based on the excitation of Ia afferent signals from the neuromuscular spindle. This, in turn, activates large *a*-motoneurons and leads to recruitment of previously inac- tive muscle fibers (Matthews 1966a). Force enhancement in stretch-shortening cycle exercises is affected by reflexive facilitation of efferents influenced by Ia afferents (Ross et al. 2001). VS, in addition to activating neuromuscular spindles (which respond to variations in length), may also affect Golgi tendinous organs (GTO), which are sensitive to variation in tension (Issurin 2005). The adaptive response to VS in the neuromuscular apparatus involves an increase in the con- tractive force of stimulated (Bosco et al. 2000) and adjacent synergistic muscles (Seidel 1988). Vibrations stimulate spinal and supraspinal functions, leading to better nervous control of muscular fiber recruitment (Milner-Brown et al.

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1975). In addition, it is thought that VS inhibits the agonist–antagonist co-activation mediated by Ia-inhibitory neurons, and also decreases the protective forces around joints (Cardinale and Bosco 2003).

Two forms of VS are used in athletic training and medicine: whole-body vibration (WBV) and local vibration of a single muscle. Both VS types employ mechanical stimulation characterized by frequency (Hz) and amplitude (peak-to-peak displacement in mm). In recent years, many studies have investigated the effect of WBV on athletes and patients (Kvorning et al. 2006; Di Loreto et al. 2004), whereas local vibration treatment has received less attention. The effects of both types of VS on acute physiological responses and long term outcomes have been studied.

Acute effects may occur after a single WBV session, and include an increase in maximal muscle force, power output, and jump performance (Bosco et al. 1999, 2000; Issurin and Tenenbaum 1999; Torvinen et al. 2002a). However, Rittweger et al. (2000) found a decrease in jump performance and de Ruiter and associates (2003a) reported a decline of 7% in the maximal isometric voluntary contraction (MVC) of the knee extensor muscles 90 s after a single WBV training session. WBV has also been reported to have acute effects on the endocrine system, causing an increase in the serum concentrations of growth hormone (GH) and testosterone, and a decrease in cortisol (Bosco et al. 2000). However, these results are controversial. Di Loreto and co-workers (2004) confirmed that WBV activates the pituitary–adrenal–gonadal axis. Kvorning and colleagues (2006) found that MBV had no effect on testosterone levels, but, increased GH concentrations and decreased the levels of cortisol.

Similarly, studies on the long-term effects of VS have shown equivocal results. Some authors have reported significant improvement in muscle strength and performance (Issurin et al. 1994; Roelants et al. 2004), but others found no effect (Torvinen et al. 2002b; de Ruiter et al. 2003b). This discrepancy may be attributable to the use of vibrations of different frequency (f) and amplitude (A), and/or to distinct platform movements. Cardinale and Bosco (2003) suggested that the WBV effects on neuromuscular and hormonal systems are not caused by the vibrations per se, but rather by the increase in gravitational load caused by platform movement. Rittweger and colleagues (2001) emphasized the importance of both frequency and amplitude for development of long-term effects after VS.

Local VS excludes any contribution from changes in gravitational load, but the optimal frequency of stimulation becomes more important. Some evidence suggests that muscle tension increases linearly with vibration frequency (Matthews 1966b). The primary endings of muscle spindles are stimulated with a one-to-one discharge rate up to 100 Hz (Roll et al. 1989), and some studies have suggested that a 30–50 Hz frequency is appropriate (Warman et al. 2002). This is identical to the discharge rate of motor units during maximal effort (Woodbury et al. 1968). The effects of high frequency VS ([200 Hz) on the neuromuscular and endocrine system are not well known. However, we recently demonstrated that high-frequency VS significantly increased muscle force, without signs of hypertrophy, in elderly subjects treated with HLV for 12 weeks (Pietrangelo et al. 2009).

The present study was designed to investigate the acute and cumulative effects of high-frequency local VS (HLV; $f = 300$ Hz, pressure/depression $p = 70$ mbar) in healthy young men. VS was applied to relaxed muscles when the subjects were prone. A group of subjects who engaged in a protocol of resistance training was used as a control.

Materials and methods

This study was approved by our local Ethics Committee, and performed in accordance with the ethical standards of the Declaration of Helsinki. Each subject gave written informed consent and was familiarized with the experimental procedure for 1 week prior to initiation of the study.

Thirty-six moderately trained (generally 1–2 sessions of physical activity per week) university students from Chieti, Italy, were enrolled (Table 1). No subject had musculoskeletal or other disorders that might affect motor ability, and all had body mass indices \30 kg/m^2.

Study design

Subjects were randomized to the cV group, which was given HLV, or the cR group, which received resistance training (Table 1; Fig. 1). Subjects in the cV group underwent control and vibration protocols at 3-day intervals. In both sessions, blood samples were drawn at 08:00 a.m., and, at 08:30 a.m., subjects performed a counter movement jump (CMJ) and a MVC tests of the leg extensor muscles. At 09:00 a.m., subjects in the control protocol remained in a prone position for 30 min, and subjects in the vibration protocol received HLV treatment (30 min at 300 Hz), in the same prone position. Next, a second blood sample was collected, and CMJ and MVC

Table 1 Anthropometric parameters of enrolled subjects before training (mean ± SD)

Group	Age (years)	Height (cm)	Body mass (kg)	Fat (%)
cV (n = 18)	21 (±1.4)	176.0 (±4.3)	78.3 (±4.5)	14.1 (±1.6)
cR (n = 18)	22 (±0.7)	172.0 (±3.8)	73.4 (±4.2)	12.5 (±1.1)

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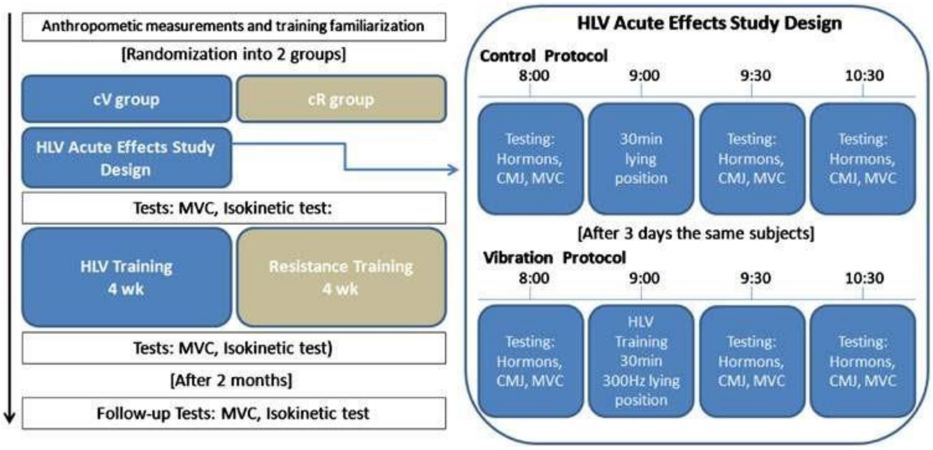

Fig. 1 Overall study design (*left*) and the protocol for the cV subjects (*right*)

tests were performed once more. One hour after the second blood sample was taken, a third sample was collected (Fig. 1). Subjects in the cV group were exposed to focused high-frequency vibration for 4 weeks, with three sessions in each week.

Subjects in the cR group underwent a resistance training protocol, which involved performance of leg extension exercises for 4 weeks, with three sessions in each week.

Before, immediately after, and 2 months after the end of the training program, all subjects performed an MVC test and an isokinetic test (100 deg/s) using knee flexing- extension movement exercises.

Vibratory stimulation

The HLV (mechano-acoustic perturbation) was applied via a device (VISSMAN, Rome, Italy) capable of producing acoustic waves of different frequencies and pressure/depression on the skin. The transducer can develop a time-modulated sinusoidal signal (f up to 300 Hz; p up to 70 mbar). During application of these sequences, subjects were not required to maintain isometric contraction of the treated muscle.

The experimental technique consisted of applying HLV over the base of the following muscles: vastus intermedius, rectus femoris, vastus lateralis, vastus medialis, gluteus maximus, biceps femoris, gastrocnemius, and tibialis anterior. The cup-shaped transducer had a contact surface of 2 cm^2, so that the amplitude of vibration was approxi- mately 2 mm.

Hormone determinations

Blood samples were collected from the antecubital vein at three different times (Fig. 1), with all subjects relaxed and seated. All subjects fasted overnight prior to testing. We used kits to measure the levels of GH (DRG instruments GmbH, Marburg, Germany), cortisol (Gamma Coat Cortisol, Incstar Corporation, Stillwater, MN), and free and total testosterone (Coat-A-Count Total Testosterone, Diagnostic Products Corporation, Los Angeles, CA), according to the manufacturers' instructions. Creatine phosphokinase (CPK) levels were measured using a CK-NAC-activated method in an Olympus AU2700 clinical chemical analyzer.

Counter movement jump

After warm-up, all subjects performed three maximal CMJs, the force of which was measured on a platform (Globus Italia; Codognè, TV, Italy). All subjects placed their hands on their hips and wore normal running shoes during the tests. A 2-min rest period was given between jump tests. The angular displacement of the knee was standardized with an electronic goniometer at approxi- mately 90°. Maximal performance was identified as max- imal jump height. Jump height was determined as the center of mass displacement calculated from force–time characteristics and body mass. Data were processed with software developed in-house using Microsoft Excel. All force (Fz) data were normalized to body weight (BW), and variables of interest were computed.

Long-term training protocol

All subjects completed two familiarization sessions to learn appropriate techniques and practice strength-testing protocols. The cR group returned to the laboratory 3 days after the second familiarization session for leg extension one-repetition maximum (1RM) assessments using established methods (Baechle et al. 2000). Data from 1RM tests with progressively increasing loads were gathered, with each attempt being separated by 120 s of rest. The 1RM was defined as the highest load lifted through a full range of motion. This test was repeated at the end of the 3rd week of training, to permit adjustment of the training protocol. Subjects warmed up on a cycle ergometer or treadmill for 5 min before each training session. The training protocol for the cR group was six sets of 10 (&80% 1RM) repeti- tions, with 2-min rest periods between sets.

Maximal voluntary isometric contractile force

Bilateral leg extension muscle strength was measured using a leg extension machine (Panatta Sport, Apiro, MC, Italy), with a transducer (Globus Italia) placed 23 cm from the knee joint. Participants were seated at a trunk–thigh angle at 90° and a knee joint angle of 90°. All subjects performed three maximal voluntary isometric contractions of the knee ex- tensors. Each isometric contraction lasted for 5 s, and 2-min rest periods were interposed between contractions. The MVC force was considered to be the highest value recorded.

Isokinetic evaluation

Quadriceps muscle torque was determined at 100 deg/s between 90° and 20° (0° = full knee extension) on an isokinetic dynamometer (Cybex International Inc., Med- way, MA) with subjects in seated position. Concentric and eccentric contractions were performed at 100 deg/s. The distal pad of the dynamometer arm was placed in the proximity of the malleoli. The axis of rotation of the Cybex dynamometer was adjusted so that the device was aligned with the joint margin of the knee. Fifteen warm- up trials and preconditioning of the testing device were performed prior to data sampling at 75% of subjective maximal effort. The three highest trials were used for analysis.

Statistical analysis

All data are given as means ± SEs. Differences between mean values before and after training period were tested for significance using Student's *t* test for paired observations. ANOVA with an interaction test was used to compare the responses to the training protocols in the two groups. Fischer's PLSD test was employed for post hoc analysis. The minimum level of statistical significance was set at *P* \ 0.05. GraphPad Prism (version 5) software (Abacus Concepts GraphPad Software, San Diego, CA) was used for statistical analysis.

Results

Acute effects of HLV stimulation

Figure 2 shows the acute hormonal responses to HLV in the cV group. There was no change in testosterone level either immediately after training (T1) or 1 h later (T2). An increase of ~200% in GH concentration was seen imme- diately after training (T1), and this persisted for 1 h (T2), although these changes were not significant because of a large degree of variation. A significant reduction in cortisol level was noted immediately after training (T1) and at 1 h after training (T2). The control group also exhibited some decrease in cortisol level, but this was not statistically sig- nificant. In the case of CPK, a significant increase was seen at both 1 (T1) and 2 h after training (T2) in the HLV group.

HLV training had no significant effect on jump height, mean force (F_{mean}), mean power (P_{mean}), or peak power (P_{peak}), produced during the concentric phase (Table 2).

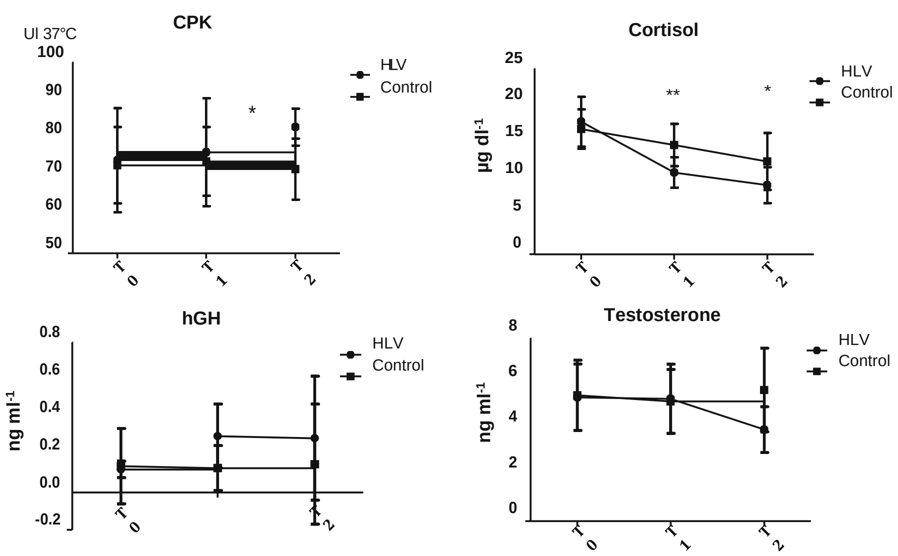

Fig. 2 Hormone concentrations before (*T0*), immediately after (*T1*), and 1 h after (*T2*) 30 min of HLV training at 300 Hz (*filled circles*), and without HLV training (*filled squares*). *P \ 0.05, **P \ 0.01): significant difference between groups; #P \ 0.05: significant time-related effect within a group

Table 2 Effect of HLV on counter jump height

	HLV		Control	
	Before	After	Before	After
Jump height (cm)	34.39 ± 0.47	34.14 ± 0.53	34.09 ± 0.38	34.79 ±0.71
P_{peak} (W kg^{-1})	47.64±1.39	47.23±2.42	46.34±2.21	47.83±1.82
P_{mean} (W kg^{-1})	27.63±0.92	26.72±0.83	26.37±1.06	27.28±0.82
F_{mean} (N kg^{-1})	20.45±0.63	20.22±0.86	20.14±0.72	21.02±0.53
T_{con}	305.6 ± 10.4	324.0±05.6*	296.2 ± 13.7	288.2 ±16.6

Values are means ± SDs for jump height, P_{peak} (peak power), P_{mean} (mean power), F_{mean} (mean force measured during the concentric phase), and T_{con} (time contact duration, defined as the time interval between the instant that the total vertical ground reaction force increased above 105% of body weight and the moment of takeoff). Measurements were taken before and 30 min after 300 Hz HLV stimulation (HLV group), or before and 30 min after lying in a prone position (control group)

* P \ 0.05

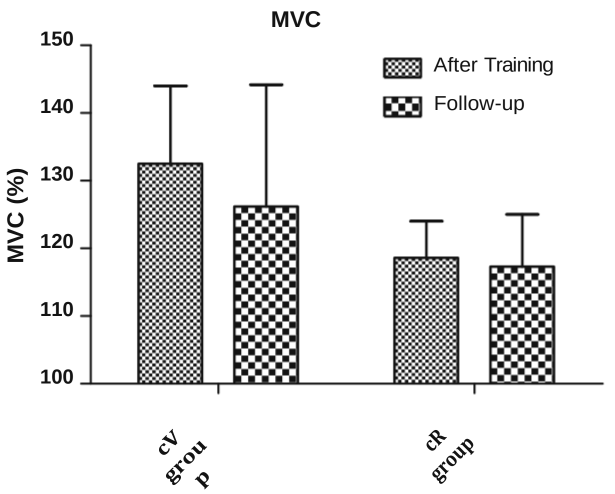

Fig. 3 Changes in bilateral isometric strength of leg extensor muscles. *Left*, treatment with local VS at 300 Hz (cV group, 132.5 ± 11.5%, n = 18, P \ 0.05 relative to performance before training). *Right*, treatment with a resistance program (cR group, 118.6 ± 5.4%, n = 18, P \ 0.05 relative to performance before training). Histograms show the percentage increases in bilateral isometric strength based on leg extension after 4 weeks of training, and at the 2-month follow-up. Isometric strength measurements from the pre-training sessions were set at 100%

However, there was a significant increase in contact time (T_{con}) after HLV (Table 2).

In the case of MVC, changes within each group were not significantly different either at 4 weeks (after training) or at 2 months in the one leg test (follow-up, Fig. 3). However, bilateral contraction showed a significant improvement (P \ 0.05) in the HLV group, from 107.0 (±17.0) to 115.7 (±15.3) kg. There were no significant changes in the control group.

Cumulative effects of HLV stimulation

After a 4-week training program, there was no significant difference between the two groups in MVC (Fig. 3).

Table 3 Effect of VS on leg extensor muscle torque

	Peak of force (N/m)					
	cV group			cR group		
	T0	T1	T2	T0	T1	T2
Right leg	79 ± 24	111 ± 19*	105 ± 3†	84 ± 22	115 ± 16*	109 ± 25†
Left leg	68 ± 12	102 ± 32*	93 ± 25†	75 ± 23	108 ± 16*	101 ±19†

Values represent means ± SDs. Pf (N/m), peak of force measured during an isokinetic test to 100 deg/s in right and left legs

T0 before training, *T1* four weeks after training, *T2* 2 months after the end of training

* P \ 0.05 T0 versus T1; † P \ 0.05 T0 versus T2

However, both groups registered an increase in bilateral MVC (32.5 ± 11.5% in the Cv group, 18.6 ± 5.4% in Cr group) relative to the initial MVC. The 2-month follow-up measurements indicated that both groups maintained this increase in strength.

Leg extensor muscle torque was measured before treatment, 4 weeks after treatment, and 2 months after the end of the training program. In this test, we compared the peak of force (Pf) of a single limb of the cV and cR groups. The isokinetic test to 100 deg/s indicates an increase in strength of the quadriceps muscle (P \ 0.05). As expected, subjects in the cV group experienced an increase of Pf of about 41% at T1 (P \ 0.05) and about 33% at T2 (P \ 0.05). Subjects in the cR group showed an increase in Pf of the dominant leg by about 37% (P \ 0.05) at T1 and about 30% at T2 (P \ 0.05) (Table 3).

Discussion

The purpose of this study was to describe the effects of high-frequency VS applied directly to the bases of muscle. Abundant, but controversial, data on the effects of low frequency VS, applied locally or to the whole body, are available, but no previous studies have examined the effect of local application of high-frequency VS. Our results showed significant improvement of muscle performance after several weeks of VS treatment, and we found that some hormonal responses and minor performance improvements were detectable after a single session. Below, we discuss the acute and long-term effects of HLV training.

Acute effects of HLV training

Our results indicated an increase in GH and a fall in cortisol levels after VS, in agreement with a previous study by Bosco and associates (2000), but we found significant changes in testosterone. Our results are in general agreement with those of Kvorning and colleagues (2006), who studied the effects of WBV training. Physical training has been shown to change serum levels of GH in association with improvements in muscle strength (Kanaley et al. 2001). Vibrational training seems to generate the same rapid endocrine activation that is triggered by collaterals of a central motor command to the hypothalamic neurosecretory and autonomic centers (Kjaer 1992). Di Loreto and co-workers (2004) suggested that part of the effects of vibration on GH levels was caused by other variables, such as pulsatile GH secretion and/or postural changes. In the present study, we observed no change in GH in the cV control group, possibly because our subjects remained prone during HLV treatment and for 1 h thereafter.

Previous studies have found that VS decreases serum levels of cortisol. Bosco et al. (2000) suggested that this was attributable to an inhibitory influence of exercise on hypothalamic neurosecretory centers, in agreement with the suggestion by Kvorning and colleagues (2006). Di Loreto and coauthors found a decrease in cortisol both after WBV and in the absence of VS. They concluded that the variation was related only to hormonal circadian rhythm and postural changes. In the present study, we also observed somewhat lower serum cortisol levels in both experimental situations. In the HLV group, the decrease was greater and we found a significant difference between the groups ($P \setminus 0.05$).

Our data on GH and cortisol disagree with those of Cardinale and Bosco (2003). The cited authors argued that an increase in gravitational load, generated mechanical aspects by the vibrating platform, was the real stimulus causing alterations in hormone levels. In the present study, we showed that VS-induced changes in GH and cortisol levels were not related to gravitational load or postural changes.

In the present study we observed no improvement in CMJ performance (P_{mean}, P_{peak}, F_{mean}, or jump height) after a single session of VS, in contrast with the results of Bosco and colleagues (2000). However, we did observe a significant increase in T_{con} ($P \setminus 0.05$). Usually, this occurred in the eccentric phase, with the concentric time remaining unchanged, show a change in motor strategy in the HLV group. This finding may be explained by a lower level of muscular activation following prolonged VS. Jackson and Turner (2003) showed that prolonged vibration (30 min at 30 Hz) significantly attenuated muscle strength and EMG activity. A decrease in muscular stiffness could alter muscle elasticity, which is the ability of muscles to store and then utilize elastic energy (Komi and Bosco 1978).

Our results showed an 8.1% increase in MVC after HLV stimulation, possibly related to the long contraction time. Isometric contraction was maintained for 5 s to increase synchronization of MUs, without increasing conduction velocity. Casale and colleagues (2008), using the same device as employed by us, showed that a vibration of 300 Hz induced modifications at the central level, changed adopted motoneuron recruitment strategies, optimized mechanical output, and reduced the myoelectric manifestation of fatigue. Thus, the MVC increase observed here may be related to the ability of our high-frequency (300 Hz) vibration stimulus to improve MU synchronization.

In conclusion, the present study showed that HLV training leads to modifications in serum hormone concentrations, and improvements in the neuromuscular system, but that these changes appear to be independent.

Long-term effects of HLV training

The most important result of our study was that 1 month of HLV treatment improved muscle force, in agreement with the data of Saggini and associates (2006). This improvement was evident at the end of treatment, and persisted for at least 2 months. This response may be attributable to a direct trophic action on the muscle or to an effect mediated by activation of the sensory nervous system. We exclude the former possibility, based on the rapid time course of the observed effects. Muscle mass cannot significantly increase after 1 or even 20 days (Ahtiainen et al. 2003). Also, the mechanical effects on muscle cross-bridges disappear immediately after vibration ends (Petit et al. 1990), and thus cannot explain our observations. It is well known that proprioceptive training can influence muscle strength and function (Lephart and Henry 1995; Liu-Ambrose et al. 2003), and it is possible that muscle torque increases before development of muscle hypertrophy (Moritani and DeVries 1979; Yue and Cole 1992; Dessy et al. 2008). Therefore, we ascribe the effect of vibration to a mechanism affording better central processing of afferent signals. Vibrations are powerfully stimulative of proprioceptors and cutaneous receptors. We believe that neuromuscular spindles may play an important role in the long-term effects observed.

Even though extensor muscle contraction may contribute to spreading of the vibration throughout the muscle, it is probable that vibrations below 300 Hz can reach spindles deep in the muscle. Other receptors are likely to be pri- marily activated, particularly in muscles close to the joint, including the Pacinian (120 Hz), Golgi (80 Hz), and types III and IV receptors (250–300 Hz). However, an indirect involvement of spindles cannot be excluded, because var- ious sensory signals can influence *a*-motoneuron activity and consequently alter spindle input (Yue and Cole 1992). In addition, a previous study has shown that the skin just above a contracting muscle (close to the tendon) is the cutaneous area responsible for modulation of monosynaptic reflexes and *a*-motoneuron activity (Gandevia 2001).

A final question to be addressed with respect to any specific vibratory protocol is induction of long-term effects on motor control. Previous studies indicated that the length of exposure stimulation is the most important factor for induction of long-term potentiation (Rosenkranz and Rothwell 2003, 2004; Ljubisavljevic et al. 1997). In our experimental protocol, 30 min/day may be adequate for development of long-term effects. We believe that our protocol may have enhanced spinal and supraspinal func- tions, given the high frequency of the vibratory stimulus and the ability of the mechano-acoustic waves to propa- gate. Moreover, isokinetic data showed remarkable increases in muscular strength, similar to that seen in the cR group. This improvement lasted for 2 months after the end of training, but decreased thereafter. Thus, the results are probably attributable to improvement in neuromuscular recruitment rather than hypertrophy. Our results are in agreement with the data of Pietrangelo and associates (2009), who found an isometric strength increase of ∼25% after 12 weeks of HLV stimulation in elderly subjects. The follow-up measurements (after 28 weeks) of the cited authors indicated that this increase in strength was main- tained. Muscle biopsy results suggested that the observed improvement in the strength of the leg extensor muscles after vibrational training was attributable to a phenotype of altered fiber distribution in skeletal muscle, and not to an increase in muscle fiber-specific tension.

In conclusion, we have shown that HLV treatment can increase muscle contractile force to the same extent as a resistance training regimen. The VS-mediated improve- ment lasted for at least 2 months.

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FLEXIBLE FLAT FOOT TREATMENT IN CHILDREN WITH MECHANICAL SOUND VIBRATION THERAPY

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FLEXIBLE FLATFOOT TREATMENT IN CHILDREN WITH MECHANICAL SOUND VIBRATION THERAPY

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The flat foot can be defined as a syndrome with multiple etiopathogenesis, characterized by an altered structure of the longitudinal arch of the plantar vault with its reduction in height. The plantar arch collapse can be counteracted by strengthening the muscles involved; for many years, specific physical exercises have been proposed with this purpose in physical and rehabilitation medicine. The aim of our work was to improve the plantar arch muscles' tone using high focal vibration therapy (300Hz) Methods. 10 children with a 4th degree flat foot (age: 8,7±2,2; height: 132±15cm; weight: 35,2±12,3Kg) underwent 10 sessions, 2days/wk, of 30 min of focused high vibratory therapy at a frequency of 300 Hz (Vissman, Italy). Before and after treatment stabilometry (StT), static and dynamic baropodometry tests were performed. Results. Evaluation of StT showed an improvement of stability, a decrease of sway area and ellipse area. Baropodometry tests showed a decrease in foot surface. Also dynamic tests showed a decrease in both foot surfaces. Discussion. The results lead us to consider this method as a method of first choice to a conservative approach in the rehabilitation of flat foot syndrome olso for the 4th grade in children.

Flatfoot is a common syndrome with multiple etiopathogenesis, that have long been associated with pain and disability, and very often worries parents for their children's health and mobility.

The generic term "flatfoot" describe any condition in which the longitudinal foot arch is abnormally low or absent (Evans 2011). It is characterized by an altered structure of the longitudinal arch of the plantar vault with its reduction in height and by heel eversion and talar prominence.

It is accepted that flatfeet are of different types. The most important classification considers two types, physiological flat foot and pathological flatfoot, with different prevalence and etiology (Evans 2011).

Pathological flatfoot has multiple etiologies and is associated with an underlying pathology (neurological, muscular, genetic, collagen, orthopedics or traumatic diseases) (Evans 2011), so its prevalence is closely related to the etiology (Pfeifer 2006).

Physiological flatfoot is considered developmental and is often seen in children. A recent prevalence research by Pfeiffer and coll. showed that 3 variables had a significant relationship to the prevalence of physiological flatfoot. The prevalence decreases significantly with age (prevalence: 3 year olds 54%, 6 year olds 24%), and is related to the gender (boys 52%, girls 36%) and to the weight, and, in addition, they observed that thirteen percent of the children were overweight or obese (Pfeiffer 2006). Physiological flatfoot is also correlated whit hypermobility and footwear use.

Although, many authors suggest that flexible flatfoot usually does not cause disability and that asymptomatic children should not be burdened with inserts, a considerable number of arch supports are prescribed unnecessarily (Garcia-Rodriguez, 1999).

Pediatric flatfoot can also be divided in flexible and rigid categories. Flexible flatfoot is characterized by a normal arch during non-weight bearing and a flattening

Key words: flat floot, vibration therapy, muscular strength

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of the arch on stance (Harris et al. 2004), rigid flatfoot is characterized by a stiff, flattened arch on and off weight bearing. Most rigid flatfeet are pathological.

The treatment of flexible flatfoot includes activity modification and orthoses. Usually the first step considers exercises that must be performed under physician or physical therapist supervision, as the plantar arch collapse can be counteracted by strengthening the muscles involved. Sometimes a treatment with NSAIDs is also necessary. Comorbidities such as obesity, ligamentous laxity, hypotonia, and proximal limb problems, must be treated (Harris, 2004).

Flatfeet have also been treated with arch supports or corrective shoes to improve the arch, whereas the effectiveness of these treatments are contrasting, and arch supports and corrective shoes are uncomfortable for the child.

Surgical intervention can be considered (Roye, 2000) but obviously a non invasive way to improve plantar arch is preferable.

An interesting and suggestive way to treat flatfoot with a conservative solution is to reduce structural alterations and symptoms increasing somatosensory input. The aim of the study was to improve the plantar arch proprioception information and muscles' tone using high focal vibration therapy (300Hz).

Mechanical muscle vibration is considered a useful method for clinical therapy and sports training.

The usefulness of this method in demonstrated in literature, Bosco and coll. showed a significant increase in muscle strength and power (Bosco et al., 1999). Recently, Fattorini and coll. observed the possible involvement of the nervous system in modifications of muscle performance induced by vibration (Fattorini et al, 2006). Pierangelo and coll. showed also that local vibrations increases muscle strength through an upregulation of genes for sarcomeric proteins, and by increasing the recruitment of satellite cells (Pierangelo et al., 2009).

We hypothesized that postural control would improve after this treatment ; in fact, somatosensory input from the lower limb has long been recognized as an important source of sensory information in controlling standing balance (Allum et al. 1998), and several evidences suggest a contributing role of cutaneous receptors from the foot in controlling standing balance (Kennedy et al. 2002). Moreover, Maurer and coll. demonstrated that mechanical stimulation of the plantar skin during quiet stance evokes postural sway that is highly correlated with the cutaneous stimuli. (Maurer et al. 2001).

Foot sole presents a characteristic distribution of cutaneous receptors, and it was analyzed by Perry and coll. (2000), Trussol (2001), and by Kennedy and coll. (2002). They demonstrated that the distribution of the receptors was preferential in the anterior lateral border and heel on the foot, that correspond to the critical regions that take up the majority of the body's weight in loaded conditions (Perry et al. 2000). They also observed that a large percentage of the skin receptors are fast adapting (FA) and have an elevated activation thresholds (if compared with the glabrous skin of the hand).

MATERIAL AND METHODS

This study was performed in accordance with the Helsinki Declaration. A parent of each subject gives written informed consent.

Subjects

Ten children (6 girls and 4 boys, mean age of 8,7±2,2 years, height: 132±15 cm and body weight of 35,2±12,3 Kg), right-handedness, were studied. All children presented a IV degree flatfoot. The diagnosis of flatfoot was based on clinical an instrumental evaluation. For the clinical diagnosis the children were observed while weight bearing, and we evaluated the presence of the longitudinal foot arch and the position of the heel (valgus or not). Instrumental exams consisted in a static and in a dynamic baropodometry with the evaluation of the total area of support for each foot.

Instrumental evaluation

Postural stability was evaluated with a pre-test (T0) before and a control test (T1) after the treatment using a Modular Electronic Baropodometer (Diasu, Italy) and elaborated with the software Milletrix. We made the following exams:

Static Baropodometry, to evaluate the total area of support and the body weight distribution, we analyzed: loading surface for right and left foot (expressed in cm^2); body weight distribution (expressed in percentage for the two sides).

Stabilometry, was used to quantify the sways of the body center of pressure (CoP). The CoP's movement was calculated by the software in both planes (anterior/posterior and lateral). We also analyzed 2 parameters: .

– Length of the path, which represents the linear length of the sway path in 52 seconds.

– Elliptic Area, an area that includes 95% of samples of statokinesigram, to evaluate CoP's sways (measured in mm^2).

This parameters, evaluated with eyes open (OE) or closed (CE), are indicative of energy expenditure on orthostasis.

The measurements took place in a room with uniform brightness, each patient had stood on the platform for 10 sec before underwent the tests. All test were made twice and we choose the second one. All patient looked at a light source during the test whit open eyes.

Dynamic Baropodometry, evaluating the Body Weight Distribution during the gait cycle, the Reaction Ground-foot and we assessed with particular attention the Toe-out angle, the Foot Contact Time, the Stride Width and the Loading Surface during walking cycle.

Rehabilitative Protocol

Rehabilitative protocol consisted in a mechano-acoustic stimuli applied with a device (VISSMAN, Rome, Italy) capable of producing acoustic waves of different frequencies. The transducer can develop a time-modulated sinusoidal signal (f up to 300 Hz; p up to 70 mbar). The experimental technique consisted of applying 10 session (2 days/week) of 30 min of focused high-intensity vibratory therapy at a frequency of 300 Hz on the skin of the feet.

Statistical Analysis

All data are given as mean ± SD. Differences between mean values before (T0) and after (T1) the rehabilitative protocol were tested for significance using Student's test for paired observations.

RESULTS

All subjects successfully completed the 10 sessions of therapy.

Static Baropodometry

Loading Surface of the Feet

Static Baropodometry shows a reduction of the loading surface of the feet after treatment. During the pre-test mean loading surface of both feet was 176,9 cm^2 (mean left foot surface was 91,9 cm^2, mean right foot surface was 85 cm^2). After the rehabilitation the total loading feet surface was 165,3 cm^2 (83,8 cm^2 and 81,3 cm^2 for left and right feet respectively) whit a reduction of 11,6 cm^2 (6.55%).

Static Body Weight Distribution

Graphic n°2 shows the percentage of body weight distribution on the feet before and after the treatment.

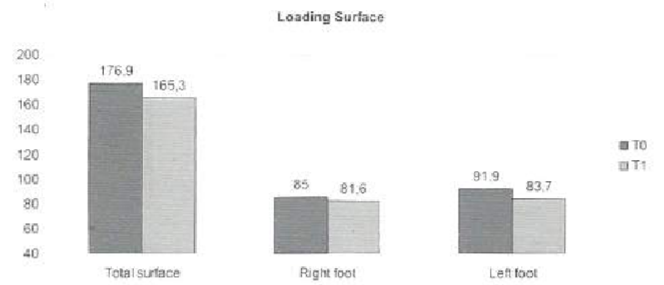
At the beginning of this work we observed a bad distribution of the static load. In fact 52,6% of the body weight was carried by the left foot and only the 47,4% by the right one (difference 5,2%). After the application of this rehabilitative protocol we observed a better distribution of the static load. In fact the difference between the load distribution on the feet was only of the 0,6% of the body weight, because the right foot carried the 50,4% of the body weight and the left the 49,6%.

Dynamic Body Weight Distribution

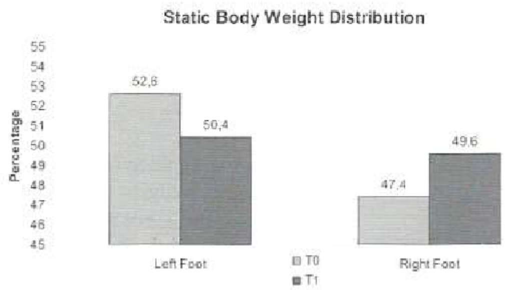
Regarding the Dynamic Body Weight Distribution there was no significant difference after the rehabilitative protocol. During the pre-test the dominant foot carried the 50.5% of the body weight (49,5% the nondominat foot), after the rehabilitation we observed a difference of 0,1% (50,4%, 49,6% on the dominant and nondominat respectively).

Stabilometry

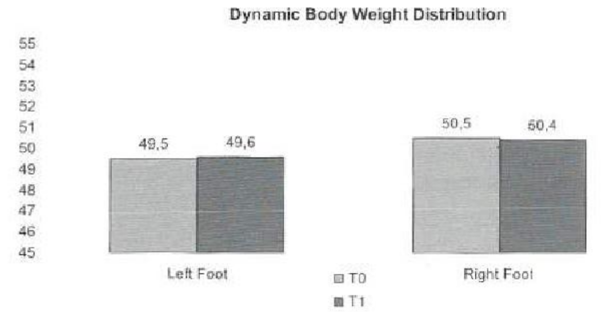
After the treatment the values of 4 stabilometric parameters (Elliptic Area and Length of the path, both with open and closed eyes) significantly reduced, thus also the magnitude of body sway was decreased. The reduction of Elliptic Area was observed in both conditions, with Open



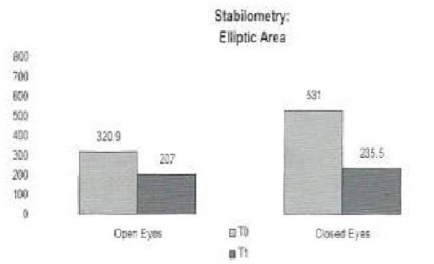
Graph. n° 1 *Values are reported as feet surface in cm²*



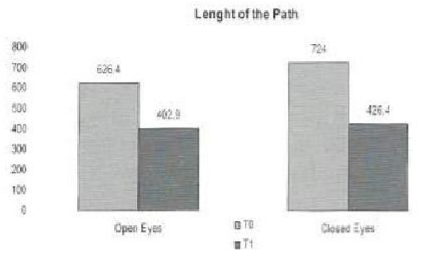
Graph. n°2 *Values are reported as a percentage related to the distribution of body weigh bearing on the latero-lateral axis.*



Graph. n°3 *Values are reported as a percentage related to the distribution of body weigh bearing on the latero-lateral axis during walking.*



Graph. n°4 *It shows the values for the Ellipse surface (mm2) with open eyes and closed eyes.*



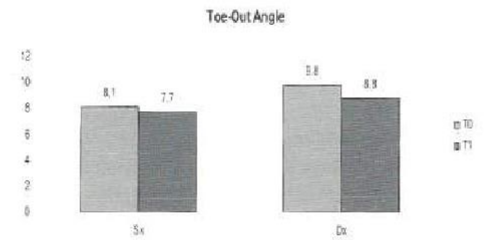
Graph. n°5 *It shows the values for the length of the path with open eyes and closed eyes.*

Eyes passed from 320,9 mm^2 to 207 mm^2 (reduction of 36%) and with Closed Eyes form 531 mm^2 to 235,5 mm^2 (reduction of 55,7%). The Length of the path passed from 626,4 mm to 402,9 mm with Open Eyes (reduction of 35,6%) and from 724 mm to 426,4 mm with Closed Eyes (reduction of 41,1%).

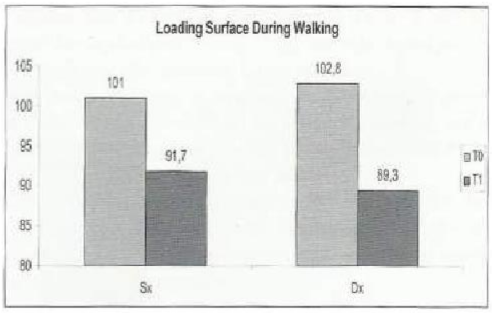
Gait Analysis

Toe-Out Angle

We observed a better mean Toe-out angle after the treatment. Before the treatment mean Toe-out Angle was



Graph. n°6 *It shows the values for the toe out angle.*

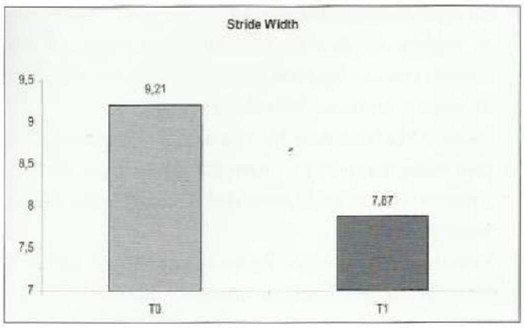


Graph. n°7 *It shows the values for the loading surface during walking.*

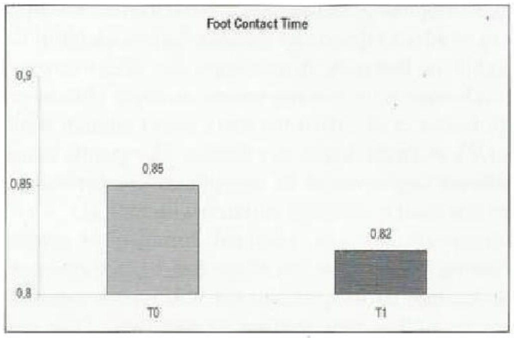
8,1° for the left foot and 9.8° for right foot. After the therapy mean angle was 7,7° for the left foot and 8,8° for the right foot showing a reduction of 4,9% and 10,2% respectively.

Loading Surface During Walking

Gait Analysis showed also an important reduction of loading surface of the feet during walking after the vibratory therapy. Left foot's surface passed from 101 cm^2 to 91,7 cm^2 (with a reduction of 9,2%) and right foot's surface passed from 102,8 cm^2 to 89,3 cm^2 (reduction 13,1 %).



Graph. n°8 *It shows the values for thestride width..*



Graph. n°9 *It shows the values for the foot contact time.*

		Before Rehabilitation Program (T0)	After Rehabilitation Program (T1)	Significance
Static Body Weight Distribution (%)	Left Foot	52,6	49,6	
	Right Foot	47,4	50,4	
Loading Surface (Cm^2)	Total Feet Surface	176,9	165,3	
	Left Foot	91,9	83,7	
	Right Foot	85	81,6	
Dynamic Body Weight Distribution (%)	Dominant Foot	50,5	50,4	
	Nondominat Foot	49,5	49,6	
Elliptic Area (Cm^2)	Open Eyes	320,9	207	
	Closed Eyes	531	235,5	
Length of the Path (Cm^2)	Open Eyes	626,4	402,9	
	Closed Eyes	724	426,3	
Toe-Out Angle (Degree)	Left Foot	8,1°	7,7°	
	Right Foot	9,8°	8,8°	
Loading Surface during Walking (Cm^2)	Left Foot	101	91,7	
	Right Foot	102,8	89,3	
Stride Width (Cm^2)		9,21	7,87	
Foot Contact Time (sec.)		0,85	0,82	

Stride Width

In the case of Stride width changes after therapy were evident, whit a mean reduction of about 14% from 9,21 cm at T0 to 7,87 cm at T1.

Foot Contact Time (FCT)

Figure 10 shows a reduction of foot contact time after rehabilitative protocol, at T0 mean FCT was 0,85 sec and after VISS application it became 0,82 sec with a reduction of 3,5 %.

DISCUSSION

The purpose of this study was to evaluate the effects of high frequency vibrations applied on the skin of the feet in children affected by flexible flatfoot. A lot of data available in literature demonstrate the effectiveness of this technique in increasing muscle strength (Bosco et al 2000; Iodice et al. 2010) but there aren't enough studies about VS and pathologies like flatfoot. Our results showed significant improvement in strength and performance in every test used to evaluate children with flatfeet.

Analyzing our data, obtained during quiet standing and during walking, we can affirm that VISS therapy may remit flexible flatfoot, in fact we observed a significant reduction of Loading Surface of the Feet. This result may depend on increase of muscle strength related to rehabilitative protocol in agreement with a study by Pierangelo et al. (2009). The increase in strength was also demonstrated by the reduction of Foot Contact time and of Stride Width (Saggini et al. 2006).

Brunetti et al. observed a faster and more complete recovery of equilibrium after vibratory stimulation following anterior cruciate ligament reconstruction. With the present study we can confirm these data, the improvement of equilibrium was evident analyzing our results about COP movement during quiet standing demonstrated by the significant reduction of the Elliptic Area and of the Length of the Path and by the better Body Weight Distribution after vibration therapy.

In our study we analyzed all children after the rehabilitative protocol but we haven't data about the long-term effects of VISS in flatfoot and we consider this lack the principal limit of this work.

In conclusion we can affirm that VISS therapy has an effectiveness in more than 90% of children with IV grade flexible flatfoot. The results lead us to consider this method as a first choice to a conservative approach in the proprioceptive and muscle tone rehabilitation of flatfoot syndrome also for the 4th grade in children but other data about long .term effects of Vibratory therapy are necessary.

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LONG TERM EFFECTIVENESS OF COMBINED MECHANOTRASDUCTION TREATMENT IN JUMPER'S KNEE

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SPECIAL ARTICLE

LONG-TERM EFFECTIVENESS OF COMBINED MECHANOTRANSDUCTION TREATMENT IN JUMPER'S KNEE

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The aim of the study was to show that the addition of extracorporeal shockwave therapy (ESWT) may significantly improve beneficial effects of eccentric training together with high efficiency focused acoustic waves for jumper's knee. We speculate that such an effect may be due to increased mechanotransduction effects on affected tissues. We assessed changes in pain and function in 42 male football players (aged 18-34 years) after a treatment protocol consisting of 1 session with focused ESWT per week combined with 3 physiotherapy sessions per week, for 3 consecutive weeks. While treatment protocol was administered, ordinary activities, but not playing football were permitted. Their condition was evaluated before treatment, at the end of the rehabilitation period (3 weeks) and at 2 months, 4 months and 6 months after the end of treatment by clinical examination, instrumental analysis and VAS for pain assessment. Functional ability related to symptoms was assessed with VISA score. At the end of 2005, 2006, 2007, 2008 and 2009 we carried out a telephone interview to investigate changes in pain and function and the efficacy of the treatment over time. Follow-up controls showed a reduction of average VAS score; after 6 months, tendons showed a structure closer to normal at ultrasonographic investigation. At the last telephone interview in 2009 many patients reported to consider ESWT as an effective treatment and described a significant improvement in their functional abilities, a significant reduction in drug consumption and 88% of subjects continued to play agonistic football. In conclusion, our results showed that, through the addition of ESWT, the effects of the classic vibration and eccentric training combination were improved compared to those found in our experience without ESWT. Although a control group was not included in the study (vibration and eccentric training without ESWT), results show a promising improvement and justify future prospective studies with a control group and more case series.

Patellar tendinopathy (jumper's knee) is an increasingly common condition characterized by overuse injury of the patellar tendon; jumper's knee is regarded as the consequence of failure of normal healing processes after the occurrence of chronic damage and inflammation of the tendon (1).

Affected patients often report a significant impairment in lower limb functions and daily activities, as well as sporting activities in the case of professional athletes (2, 3). Treatment strategy for patellar tendinopathy may include several conservative as well as non-conservative options, ranging from conventional anti-inflammatory treatment to surgery; recently, eccentric exercise

Key words: mechanotransduction, shock waves, eccentric training

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

regimens, alone or in combination with additional interventions such as high efficiency focused acoustic waves, have been shown to have a beneficial impact on disease course and patients' reported symptoms (4-6). However, jumper's knee is often unresponsive to the therapies employed; accordingly, there is a growing need for effective treatments in this field.

Extracorporeal shock wave therapy (ESWT) is a promising non-invasive option in the field of tendinopathies (7, 8). Shock waves are sound waves administered as single pulses with a wide frequency range, high-pressure amplitude, low tensile wave, small pulse width, and short rise time (9, 10). Biological effects of ESWT in treating chronic tendon diseases appear to be mainly due to high stress forces acting upon interfaces as well as tensile forces inducing cavities within treated tissues.

Recent evidence showing that ESWT may promote tendon healing prompted us to combine this intervention with conventional eccentric training aided by high efficiency focused acoustic waves in the treatment of patellar tendinopathy. In the present study, we show that the addition of ESWT may significantly improve beneficial effects of eccentric training together with high efficiency focused acoustic waves for jumper's knee. We speculate that such an effect may be due to increased mechanotransduction effects on affected tissues.

MATERIALS AND METHODS

This prospective, single-center study was approved by the local ethics committee, and was performed in accordance with the 1964 Declaration of Helsinki. All participants were professional football players from Italy and all of them provided written consent before taking part in the study.

The main inclusion criteria were: grade 2 to 3 patellar tendinopathy according to the Blazina classification; pain VAS (Visual Analogic Scale) score greater than 4 at the first evaluation, age over 18 years.

At baseline, demographic data, pain VAS, VISA (Victorian Institute of Sport Assessment) score were assessed. In addition, ultrasound (US) evaluation of the patellar tendon was performed; during US examination, subjects were supine with the knee at 30 degree of flexion, with probe being positioned so as to allow for entire visualization of the relevant tendon. US abnormalities were classified as: grade 1 (evidence of focal hypoecoic region in both longitudinal and axial scans), and grade 2 (evidence of focal or diffuse thickening combined with diffused hypoechogenity).

Study participants underwent a treatment protocol consisting of 1 session with focused ESWT per week combined with 3 physiotherapy sessions per week, for 3 consecutive weeks. While treatment protocol was administered, ordinary activities, but not playing football, were permitted.

For focused ESWT, Evotron Spark Gap Electrohydraulic equipment was used; focused ESWT probe had a 5 mm focal depth, and average energy of 0.132 mJ/mm^2. During each ESWT session 800 shots (240 sw/min) were administered, at a shot frequency of 4 Hz, and with an energy flow density of 0.10–0.14 mJ/mm^2; total absorbed energy per session was 3.30 mJ. Local anesthesia before ESWT sessions was never required.

Physiotherapy sessions consisted of eccentric training combined with simultaneous administration of high efficiency focused acoustic waves (VISS system). During each session, participants performed 2 types of exercise:

- half squat: flexion from the orthostatic position up to 90°, remaining for 8 seconds in eccentric phase (flexion) and for 2 seconds in concentric phase (extension – return to starting position);
- leg extension: while in sitting position and with the leg flexed at 90°, leg extension up to the level of the thigh.

Concomitantly with both the half squat and the leg extension exercises, high efficiency focused acoustic waves (VISS system) were applied for 14 minutes at a frequency of 300 Hz. Transductors for transmission of high efficiency acoustic waves were positioned on the following muscles:

- Biceps femoris
- Vastus lateralis
- Vastus medialis
- Rectus femoris
- Gastrocnemius
- Tibialis anterior

Clinical assessments to evaluate functional status and reported symptoms, including pain VAS and VISA score, were performed upon completion of the rehabilitation protocol as well as at 2, 4, and 6 months after the end of treatment. Furthermore, US evaluations as described above were repeated at 6 months after protocol completion.

Patients who had successfully completed the rehabilitation program as well as clinical and instrumental follow-up evaluations were took part in yearly telephone interviews. The latter were aimed at assessing long-term efficacy, by evaluating post-treatment course of functional status and reported pain; each interview included the following questions:

- Do you regard ESWT therapy as overall effective?

- Has knee pain recurred or worsened after completion of treatment protocol? If so, when did the knee pain recur or worsen?
- Do you feel that the recurrence or worsening of knee pain is clearly linked to an triggering cause (i.e., sport activity)?
- Are you feeling any pain today in the knee?
- What is the level of knee pain you are feeling today, measured from 0 (no pain) to 10 (pain preventing any joint movement)?
- After treatment protocol completion, have you ever received any additional medical or physical therapies for your knee pain?

At each interview, VISA score was measured to assess functional status.

All data are given as means ± SDs. Differences between mean values before and after the rehabilitation period were tested for significance using Student's *t*-test for paired observations.

Fischer's PLSD test was employed for post hoc analysis. The minimum level of statistical significance was set at $P<0.05$. GraphPad Prism (version 5) software (Abacus Concepts GraphPad Software, San Diego, CA) was used for statistical analysis.

RESULTS

Forty-nine patients (age range: 18-36 years; mean age: 27 years) were included in the study; of whom, 42 (age range: 18-34 years; mean age: 26 years) successfully completed the treatment protocol and underwent clinical and instrumental follow-up, as described in the Materials and Methods section; 7 patients did not complete the treatment protocol for logistic problems and withdrew from the study after the first session, consequently they were not included in the final evaluation.

Upon therapeutic protocol completion, significant improvement was recorded in both mean pain VAS and mean VISA score compared to baseline values (mean pain VASt0=7.7, mean pain VASweek3=2.3; mean VISA scoret0=27, mean VISA scoreweek3=57).

Follow-up controls after 2, 4 and 6 months confirmed the improvement in mean pain VAS (T0: 7.7 – T4: 2.5, $p<0.001$) and VISA score (T0: 27 – T4: 80) , as shown in Tables I and II.

Table I. *VAS results after protocol completion and at clinical follow-up.*

VAS	T0	T1 (3 weeks)	T2 (2 months)	T3 (4 months)	T4 (6 months)
	7.7	2.3	2.2	2.2	2.5

Results of the VAS, showing a reduction in pain at the end of treatment and at follow-up of 4 and 6 months.

Table II. *VISA score results after protocol completion and at clinical follow-up.*

VISA (score)	T0	T1 (3 weeks)	T2 (2 months)	T3 (4 months)	T4 (6 months)
	27	57	72	77	80

VISA score results before therapy, after 3 weeks and at clinical follow-up at 2, 4 and 6 months.

After the first ultrasonographic evaluation 18 subjects were classified level 1 and 24 subjects were classified level 2. After 6 months tendons showed a more normalised structure with reduction of their average thickness (T0: 5.3 mm, SD 1.5 – T1: 4.2 mm, SD 1) and reduction of hypoechoic areas in 15 subjects in group 1 and 20 subjects in group 2, as revealed by the last ultrasonographic investigation ($p<0.01$).

All patients who completed the treatment protocol were contacted by telephone at the end of 2005, 2006, 2007, 2008 and 2009 to assess the long- term efficacy. At the last telephone interview in 2009 it was found that:

- 79% of patients considered ESWT as an effective treatment and described a significant improvement in their functional abilities with further improvement in VISA score (T0: 27 – T9: 91 $p<0.001$).
- 74% of patients reported complete absence of pain ($p< 0.001$).
- the subjects reported also a significant reduction in drug consumption, especially during the first 3 years after treatment.
- 37 subjects (88% of patients) continued to play agonistic football.

Only two patients of those who had completed the rehabilitation program had need of surgery.

There was also a significant reduction in drug consumption ($p<0.001$), especially during first 3 years after treatment, as shown in Table VI (drugs that patients had been taking before starting the rehabilitation treatment).

The recurrence of pain was evaluated over a mean period of 22 months.

In summary, we evaluated athletes after treatment using ESWT associated with eccentric training and high efficiency focused acoustic waves (VISS system), during 5 years, and the therapy gave highly satisfying results for most patients (79%) and a

Table III. *Pain level before therapy and at follow-up, from 2005 to 2009.*

Pain level	T0	T5 1 year (2005)	T6 2 year (2006)	T7 3 years (2007)	T8 4 years (2008)	T9 5 years (2009)
	9	3	3	3	4	3

Pain level before therapy and at follow-up, from 2005 to 2009, controlled by interview questions.

Table IV. *Persistence of pain at each telephone interview.*

TREND OF PAIN (% of patients with pain)	T5 (1 year) 2005	T6 (2 years) 2006	T7 (3 years) 2007	T8 (4 years) 2008	T9 (5 years) 2009
	9%	13%	15%	19%	26%

Persistence of pain (% of patients with pain) at follow-up of 5 years, from 2005 to 2009.

Table V. *VISA score results at telephone interview.*

VISA (score)	T0	T5 (1 year)	T6 (2 years)	T7 (3 years)	T8 (4 years)	T9 (5 years)
	27	**77**	**87**	**85**	**85**	**91**

VISA score results at telephone interviews carried out at the end of each year, from 2005 to 2009.

Table VI. *Percentage of drug consumption reduction from 2005 to 2009.*

DRUGS CONSUMPTION REDUCTION (% of patients)	T5 (1year) 2005	**T6 (2years) 2006**	**T7 (3years) 2007**	**T8 (4years) 2008**	**T9 (5years) 2009**
	61.7%	**44.7%**	**32.5%**	**10.4%**	**8%**

The need for drugs from 2005 to 2009.

good outcome after 5 years (74% of patients refer a complete remission of symptoms and no functional restriction in sports and 88% of patients were continuing to play football at a competitive level at the follow-up at the fifth year).

DISCUSSION

Jumper's knee is an increasingly frequent condition caused by chronic repetitive loading exceeding the adaptive capacity of the patellar tendon; excessive mechanical stresses are thought to result in microscopic tears and ensuing tissue degeneration. According to updated epidemiological studies, tendon injuries may account for up to 50% of injuries occurring in sporting activities, and chronic problems caused by tendon overuse account for approximately 30% of all running-related injuries (11). In particular, incidence of patellar tendinopathy is reported to be as high as 32% and 45% in basketball and volleyball players, respectively (12); in these settings, average duration of pain and diminished function reaches 3 years, with up to 53% of patients reported quitting their sports career due to the impaired knee function in a 15-year follow-up study (13). A prolonged rehabilitation time is often necessary because of the slow tendon recovery; accordingly, patellar tendinopathy has a significantly negative impact on sporting careers of several athletes.

Interestingly, the presence of a lower patellar pole appears to play a role in the pathogenesis of this tendinopathy, as suggested by studies proving an association between a longer non-articular patellar surface and proneness to develop jumper's knee (14). Such pathologic finding is particularly frequent among athletes whose sporting activities involve running, jumping or kicking, likely due to significant increased patellar tendon torques (15). Furthermore, known risk factors for developing jumper's knee include training/playing for at least 12 hours per week, and/or weight training for at least 5 hours per week, and training/playing on hard surfaces (16, 17).

Several pathogenetic factors have been suspected to cause this disease by increasing the patellar tendon overload. It has been observed that chronic repetitive high load results in continuous, localized release of cytokines having autocrine and paracrine properties, leading to failure to adapt to continuous load, flogistic irritation, and ensuing intratendinous damage. Poor regenerative capacity of tendons, due to intrinsically insufficient blood flow, oxygenation and nutrition, is viewed as the basis for inadequate reaction to applied forces, warranting observed slow healing and difficulties in treating this chronic disease (13).

Among the multiple proposed treatments for this pathology (including US-guided polidocanol sclerosing of vessels, tendinous and peritendinous injections of aprotinin and autologous growth factors, and arthroscopic surgery) eccentric training appears to be particularly beneficial. Eccentric exercise has been experimented and studied for more than 80 years, with the first reported study comparing eccentric and concentric exercise dating back to 1938 (18). The multiple mechanisms leading to beneficial effects of eccentric exercise have been largely investigated in available literature. Traditionally, eccentric exercise has been employed as a component of the conventional strengthening regimens. In recent years eccentric exercise has become an increasingly popular option in rehabilitation management of a variety of pathological conditions. Available evidence supports the use of eccentric exercise in the rehabilitation of muscle contractures, damaged anterior cruciate ligament, and chronic tendinopathies; improvement in muscle strength induced by eccentric training appears to be very important for the recovery and maintenance of morphologic and structural characteristics of tendons (19). Several studies support the use of eccentric exercise in the treatment of tendon injuries in different body areas, including the patellar tendon. Wasielewsky et al. (20) and Kingma et al. (21) systematically reviewed the evidence regarding the effects of eccentric work in reducing pain and improving strength in patients with chronic tendinopathies of the lower limbs and tendinopathy of the Achilles tendon, respectively; their results revealed that eccentric exercise can reduce pain and improve endurance in patients with chronic tendinopathies, but failed to establish whether this type of exercise could be preferable to existing, conventional rehabilitation techniques. Jonsson and Alfredson (22) showed the benefits of eccentric work compared to concentric work in athletes with patellar tendinopathy employing a 12- week treatment regimen; after a 32-month follow- up period, athletes who had performed eccentric exercise were still satisfied with treatment results, even though the authors failed to specify whether these subjects had returned to sporting activity or not. In another study on professional volleyball players with patellar tendinopathy, Young et al. (23) found that subjects receiving a 12-week eccentric training- based protocol had significantly improved compared to baseline at the end of treatment, with benefits still lasting after 12 months. Lastly, Alfredson et al. (24) examined tendon structure through US gray scale in 26 patients with Achilles tendinopathy treated with eccentric exercise; importantly, after a 3.8-year follow-up period, 19 out of 26 treated tendons showed a structure closer to the normal, as evidenced by their thickness and by the reduction of hypoechoic areas by US evaluation.

It is currently thought that eccentric exercise may be beneficial in chronic tendinopathies by inducing mechanotransduction on myofascial structure, as indicated by Khan (25). Mechanotransduction is defined as a cascade of events that can be divided into 3 phases: 1) meccanocoupling (the action of a mechanical trigger or catalyst), 2) intercellular communication (leading to propagation of the load message through the tissue), and 3) effector response (the effector response at the cellular level which allows to produce and assemble the necessary materials in the correct order). Khan et al. showed that one of the major responses induced in tendons by load, both *in vivo* and *in vitro*, is the induction of IGF-1 production; the latter promotes cell proliferation as well as matrix remodeling within the tendon; further studies suggest that additional growth factors as well as cytokines, besides IGF-1, could play a role in such mechanisms.

Accordingly, it can be inferred that tendons respond positively to controlled load after damage, and load may be used therapeutically to stimulate tissue repair in tendons, as already demonstrated in muscle, cartilage and bone tissues. High intensity focused acoustic waves can also prompt mechanotransduction phenomena through focused vibration of muscles which, at the frequency of 300 Hz, has been shown to promote the increase in muscle tone as well as trophism through proprioceptive stimulation of neuromuscular spindles, Pacini corpuscles, Golgi tendon organs, and type III-IV muscle mechanoreceptors (26). Treatment with high-intensity focused acoustic waves is based on the action of vibrations, which allow, in selected muscle groups, to optimize muscular tone, increase muscle strength and endurance to repeated exercise, and improve coordination, producing a positive muscular activity without causing damage. Local high-intensity vibration may also improve muscular strength influencing the levels of particular hormones, and ameliorate neuromuscular performance; Saggini et al. (26) demonstrated the short- and long-term effects of high-intensity focused vibration, showing that focused vibration can influence the levels of specific substances, such as growth hormone, creatine phosphokinase, and cortisol, resulting in significant improvements in neuromuscular performance, comparable to that of endurance; local high-intensity vibration may also counteract the loss of muscle strength in both young patients and elderly subjects suffering from sarcopenia (27). The long-term beneficial effects of high-intensity focused acoustic waves have been shown to be particularly striking when local high-intensity vibration has been combined with eccentric training (28). Shock waves are acoustic waves characterized by a wide frequency range, high-pressure amplitude, low tensile wave, small pulse width, and a short rise time. It is well-known how shock waves are frequently produced in nature by explosive events (i.e., lightning strokes or the breaking of the sound barrier by airplanes). Shock waves are peculiar acoustic waves (or pulses) reaching high positive pick pressure amplitude in a short time compared to the ambient pressure; this energy can be transmitted over a long distance. Compared to US, shock waves have distinctive features due to large pressure amplitude and different nature of wave form; US are periodic oscillations with limited bandwidth, while shock waves are characterized by a single, mainly positive pick pressure, followed by a relative small tensive (negative) wave element, whose sequential transmission in living tissues is responsible for beneficial biological effects.

The main biological effects of shock waves are due to high stress forces acting upon interfaces as well as tensile forces causing cavities. Specific parameters that need to be considered to correlate medical results with physical effects include pressure (measured as MPa – 1MPa=1bar), energy (mJ), energy flux density (EFD) (mJ/mm^2), and dimension of focal volume (fx, fy, fz at -6dB). In clinical practice, shock wave treatment protocols are classified based on the number of shots, energy levels, number of sessions, and time interval between them (9).

It has been shown that the main mechanism of action of focused shock waves does not involve mechanical disruption of living tissue cells, but rather the biological effects resulting from mechanotransduction, which have trophic and healing potential. The main biologic effects attributed to shock waves in available literature include antiflogistic action, neoangiogenesis, tissue specific healing and regeneration (bone, skin and heart), antibacterial action, stem cell stimulation (multiplication, migration and differentiation, analgesic effects, and resolution of spastic hypertone, contractures and similar conditions. In sum, shock waves appear as a valid therapeutic tool for the treatment of musculo-skeletal pathologies as well as several other pathological conditions related to tissue regeneration. In particular, the effects of shock waves on bone, soft tissues, and skin have been extensively studied in the literature. Effects on bone tissue include: trabecular sub-periosteal fractures with micro-hemorrhages and production of thrombi; increase of mitosis of CFU-O through BMP-2 and -4; proliferation of pro-osteoblasts and fibroblasts through TGF-b1; recruitment and differentiation of stem cells and angiogenesis through VEGF-A (29)*;* increased metabolism of osteoblasts through IGF-I and –II; osteogenic differentiation of mesenchymal cells through Wnt-family ligands; inhibition of osteoclastogenesis at the level of stromal cells through OPG; NO synthetase production with increase in

NO concentration and stimulation of angiogenesis and osteogenesis (30); activation of pERK and p38 pathways; changes in membrane permeability that cause the opening of K^+ and Ca^{+2} ion channels with increased osteoblastic metabolism; and modification of quantum energy levels of electrons with three-dimensional protein rearrangement. Effects on soft tissues have been described as an early response involving activation of the sympathetic nerve endings and opening of the capillary bed (wash-out effect), and a secondary response, ensuing during the following days, leading to angiogenesis and removal of inflammatory mediators. A significant result of shock waves applied on soft tissues is the analgesic effect, which is due to action on nervous conduction (31), increase of free radicals that change nociceptors excitability, degeneration of nerve fibers that originate from small ATF3+ neurons, rapid degeneration of intracutaneous nerve fibers, and release of substance P (32). Several studies demonstrated the effectiveness of shock waves in promoting wound healing through the stimulation of many growth factors, such as EGF, IGF-1, VEGFA, and NO, inducing angiogenesis (33). An antibacterial effect of shock waves mediated by the phenomenon of cavitation was also demonstrated (34-36).

With regard to tendon disorders, many authors described the therapeutic benefits of ESWT based on their bio-stimulating effects (9, 37). Shock waves appear to promote tendon healing by stimulating several biological effects, such as: increasing expression of lubricin, a glycoprotein that facilitates tendon gliding (38); promoting cell growth, proliferation, and collagen synthesis in tenocytes (39), thus promoting tissue repair; and decreasing the expression of several MMPs and interleukins in tendinopathy-affected tenocytes. Histological studies have demonstrated the effectiveness of ESWT in inducing neovascularisation (40), reorganization of collagen matrix with upregulation of gene expression for COL1 and MMP14 (41), increasing hydroxiproline levels, and exerting a condroprotective effect in damaged tendons (42, 43). Several studies have evaluated the short- and medium-term efficacy of shock waves in the treatment of osteomyofascial diseases, but only a few evaluated the long-term effectiveness of shock waves in the treatment of patellar tendinopathy (4).

Available evidence that ESWT can promote tendon healing by stimulating several biological effects led us to combine this therapy with eccentric exercise and high-intensity focused acoustic waves in order to boost the effects of mechanotransduction in rehabilitation of patellar tendinopathy.

Through the addition of ESWT, the effects of the classic vibration and eccentric training combination are improved compared to what we found in our experience without ESWT. Although a control group was not included in the study (vibration and eccentric training without ESWT), results show a promising improvement and justify future prospective studies with a control group and more case series.

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MUSCLE STRENGTH AND BALANCE TRAINING IN SARCOPENIC ELDERLY: A PILOT STUDY WITH RANDOMIZED CONTROLLED TRIAL

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MUSCLE STRENGTH AND BALANCE TRAINING IN SARCOPENIC ELDERLY: A PILOT STUDY WITH RANDOMIZED CONTROLLED TRIAL

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In aging, there is a gradual decrease in muscle mass (sarcopenia) and muscle strength which contributes to a decline in physical functions, increased disability, frailty, and loss of independence. Physical activity can reduce functional decline due to aging. Randomized controlled trials (RCT) are needed to determine the effectiveness of different exercise stimuli on muscle strength and balance in the sarcopenic elderly. Forty male volunteers diagnosed with sarcopenia (CDCP) (70.9±5.2yrs) were enrolled in this study. A randomized, controlled trial, with blind assessment, was designed to study the effect of global sensorimotor, high intensity focused vibrational (intensity: 300Hz) and resistance training (intensity: 60-80% of maximum theoretical force, 10-12 repetitions for 3 sets) stimuli on muscle strength and balance confidence. The subjects were randomly assigned to three different training programs or a control group which was encouraged to maintain their habitual activity level. The training was performed for 12 weeks in all groups: 2 sessions/week in Gsm and Ret groups; 1 session/week for the first 8 weeks and 3 sessions/week for the last 4 weeks in Vam group. The main outcome was maximal force contraction of the lower limbs, and secondary outcomes were static and dynamic balance confidence. All the training regimens increased isometric strength. Both the sensorimotor and the vibrational training increased stability with a reduction of sway area and of ellipse surface ($p<0.01$). Gait analysis showed a significant increase in the length of the half-step in all three groups (respectively 108%, $p <0.01$; 92% $p< 0.01$; 65% $p <0.05$). All the training programs implemented in the present investigation increase muscle strength. In addition, sensorimotor and vibrational training intervention aims to transfer these peripheral gains to the functional and more complex task of balance, in order to reduce the risk of falls.

Normal aging produces progressive loss of skeletal muscle mass and function, or sarcopenia starting between the ages of 30 and 40, and with faster loss after the age of 75. The loss of muscle mass and the lower efficiency of muscular enzymes result in a reduction both in the peak force during isoinertial motion and at high angular velocities. Maximal isometric voluntary contraction is still maintained at 45 years of age, but it decreases by 25% at age 65, and by 35% at the age of 70 years. In the following decades, this loss of strength is even more pronounced. Eventually, 40% of women between

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55-64, 45% between 65-74 and 65% between 75-84 years are no longer able to lift a 4.5 kg weight (1, 2).

The loss of muscle function in the elderly plays a major role in the weakness of elderly individuals (3). Sarcopenia is the leading cause of disability and weakness in the elderly (4), with unstable balance, inability to ascend and descend stairs, or take the shopping bags home, all contributing to impairment of quality of life. These features increase the risk of falls and their severity, and may worsen osteoporosis given the reduction of muscle tension on bone (4).

Resistance training reduces the effects of sarcopenia: age is not a limit to improve muscle mass and strength following resistance training, and the results of resistance training programmes are comparable to those obtained in healthy adults. Frontera et al. showed an increase of the transverse section (CSA) of thigh of 11.4% and an increase in muscle strength > 100% after 12 weeks of high intensity resistance training (2). Improvements in strength were also found in elderly women after such a training program. Increases of 3-9% of the CSA, of the muscle strength (> 100%), of the functional capabilities such as step speed and capability to ascend and descend stairs, were obtained in hospitalized patients after a period of progressive resistance training (4, 5). On the other hand, endurance training, such as walking, cycling or running, does not lead to significant improvements in muscle mass and muscle strength (6). The analysis of 41 randomized trials showed that resistance training produces a substantial increase in strength in the elderly at home and in nursing homes (7).

Hauer et al. (8) studied 28 elderly subjects (average age = 81 years) with a history of falls. They undertook 12 weeks of resistance training of the lower limbs at 70-90% one repetition maximum (1RM) and they obtained increases of 22-87% of the 1RM strength without health problems related to the training.

Vincent et al. (9) obtained different results with elderly people who participated in a 26-week resistance training program, performed at low intensity (50% 1RM) or at high intensity (80% 1RM). A moderate increase of the strength of the leg, which was slightly higher in the high-intensity group, was reported. Protocols with standard concentric exercises were used in most studies on the effects of resistance training in the elderly.

These training programs improved quality of life and prevented falls, disability and loss of independence among elderly patients (10). Focal vibration is an effective method to activate the proprioceptive sensory system. It consists in the excitation of the afferences coming from the neuromuscular spindle. This causes the activation of a large number of alpha-motor neurons, leading to the recruitment of muscle fibers, previously inactive, to contribute to muscle contraction (11).

The adaptive responses to vibration of the neuromuscular apparatus therefore cause an increase in contractility force of stimulated muscles and in the adjacent ones (12). The vibratory stimulus, in addition to acting on the neuromuscular spindles sensitive to changes in length, also exerts an action on Golgi tendon organs (13). The motor centers are therefore stimulated by vibration to produce a better performance of nervous commands responsible for muscle recruitment (14). In another study a long-term change in the perception of force was reported in the elderly (15).

Balance is significantly improved after 8 weeks of training (16) and an increase of muscle strength is correlated with balance training. A training program able to increase stability and strength may be used for intervention against sarcopenia and risk of falls. In the last few years, a multi-sensory approach has been proposed, whereby audio-visual stimuli provide the patient with feedback regarding body sensation and position, and has yielded excellent results (17).

The present study compared the effects of three different methods of training in the elderly on muscle strength, balance and walking.

MATERIALS AND METHODS

The study was approved by the local ethics committee, and was performed in accordance with the 1964 Declaration of Helsinki. Before taking part in the study subjects were informed about the procedures and purposes of the research and gave their written informed consent.

Eligible patients were male volunteers with diagnosis of sarcopenia according to criteria of the Centers for Disease Control and Prevention (sarcopenia was defined as a muscle mass index [muscle mass (kg)/height (m)2] less than two standard deviations below the mean of a young reference population) (18).

The inclusion criteria were as follows: diagnosis of sarcopenia; normal ECG and blood pressure; and absence of musculoskeletal, metabolic, or cardiovascular diseases. Exclusion criteria were the presence of metabolic and/or cardiovascular diseases, evidence of hereditary or acquired muscular disease, or diagnosis of respiratory or psychiatric disorders. No subject was under treatment with testosterone or other pharmacological interventions known to influence muscle mass (Fig. 1). Forty male volunteers aged between 64 and 80 (Table I) participated in the study.

The volunteers were randomly assigned to one of 4 groups with blind assessment, a control group and three training groups, which all followed a training period of 12 weeks as detailed below.

Global Sensorimotor Training (Gsm)

The subjects performed 2 sessions per week. A 5-minute cycle ergometer warm-up at an intensity equal to 60% of theoretical maximum heart rate (HR_{max}) (19), stretching exercises for the muscles of the lower limbs, and a 5-minute cool down were performed at each training session.

The subject also undertook 20-minute training using the multi-sensory protocol for balance and flexibility with the Imoove system (Allcare Innovations, 26120 Chabeuil, France), "Reboost" protocol program according to the manufacturer's parameters. The subjects were invited to perform postural exercises in isometric contractions on a motor platform with elliptic oscillatory movements. Visual feedback required different tasks.

Resistance Training (Ret)

The subject performed a resistance training for lower limbs using two isoinertial exercises, leg press and leg extension, 2 sessions for week. The load of the resistance training per each exercise was decided on the percentage of the maximum theoretical force (FMT). At the beginning of each training session, the subject carried out a warm-up on a stationary bicycle, pedaling for 10 minutes at an intensity equal to 60% of HR_{max} (29), and performed stretching exercises for the muscles of the lower limbs. The subjects performed 1 set of 15 repetitions with a load equal to 30% of FMT as specific warm-up, with the appropriate position on the machine.

In weeks 1 to 4, the subjects carried out resistance training on both machines performing 3 sets of 12 repetitions at 60-70% of the FMT, with a 2-minute rest between sets.

In weeks 5 to 8 weeks, the subjects carried out resistance training on both machines performing 3 sets of 10 repetitions at 75-80% of the FMT, with a rest between sets of 2 minutes.

In weeks 9 to 12, the subject undertook resistance training on both machines performing 3 sets of 6-8 repetitions at 80% to 85% of the FMT, with a 2-minute rest between sets.

Vibratory mechanical-acoustic focal therapy (Vma)

Subjects received a focused vibratory stimulation for 15 minutes (VISS, VISSMAN S.r.L., Roma, Italy). The transducer can develop a time-modulated sinusoidal signal f up to 300Hz and p up to 70 mbar. The size of the transducer was 23.7cm². The stimulation was applied on the vastus medialis, vastus lateralis and rectus femoris muscles. The subjects carried out training for 12 weeks: 8 weeks training with 1 session per week, and 3 sessions per week during the last 4 weeks.

Control group

The control group received a minimal intervention consisting of information bulletins with general information about the protocol study and test. All subjects were asked to keep the same daily habits concerning diet, social relations and physical activity.

Evaluations

Functional evaluation was performed before T0 and after T1 the training period using the following tests to investigate the muscular characteristics as detailed below.

- Maximal Isometric Test: the maximum isometric strength of each subject was tested on the leg extension machine [Panatta Sport, Apiro (MC), Italy] with a load cell [Real Power, Globus Italia, Codognè (TV), Italy]. After adjusting the position of the subject to have a 90°

Table I. *Physical characteristics of the study group, values are expressed as the average ± ds.*

n	Age, years	Weight, kg	Height, m	BMI
40	70.9±5.2	73.9±16.8	1.6±0.1	28.2±5.9

n, denotes the number of the subjects.

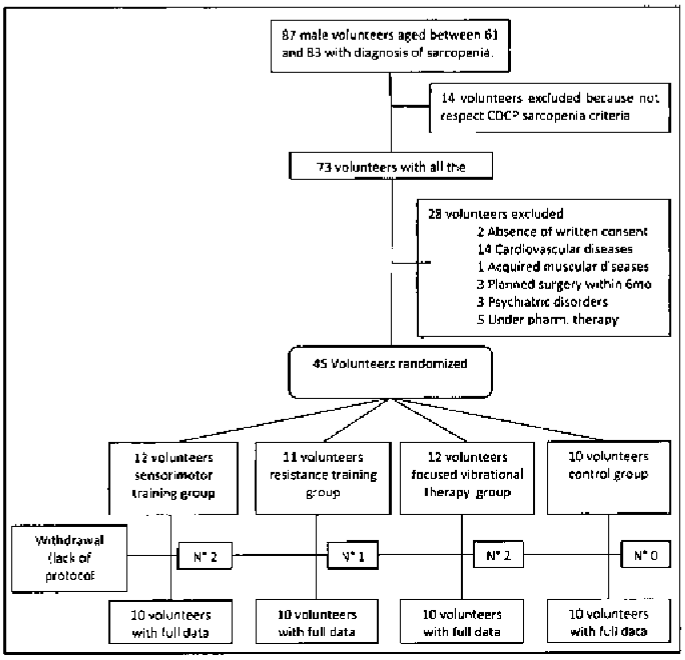

Fig. 1. *Flowchart of the study.*

knee angle and a 90° hip flexion angle, he was asked to perform a maximum contraction for 5 seconds. The measure was repeated three times with a two-minute rest between each test. The best result of three tests was considered the maximal isometric force (ISOmax).

- Gait analysis was performed at self-selected walking speed on a podobarographic platform 4 meters long (sampling rate= 50Hz) (Milletrix, Diagnostic Support, Italy). The length of half-step, width of the step and single leg time support were calculated. The stabilometric analysis was performed with the heels together and an angle of 30° between the feet, with the eyes first open and then closed. The analysis time was 52 sec. Any deflections in the center of pressure (COP) along the lateral and anterior/posterior axes were recorded (sampling rate =50 Hz) using a baropodometric platform (Milletrix, Diagnostic Support, Italy). The sway area (the area of body swinging during the stabilometric test) and the ellipse surface (the size of the ellipse in which is located the trajectory described by the COP during stabilometric analysis) encompassed by the COP were evaluated.

Statistical analysis

This study was designed to show the increase in muscle strength after the training period. Assuming that a clinically relevant increase in muscle strength following the training period would be 11 kg with a common standard deviation of 8 kg between two groups, 10 patients in each group were required for an 80% power and 0.05 significance.

All data are given as means ± SD. Differences between mean values before and after the training period were tested for significance using Student's t-test for paired observations. Analysis of variance (ANOVA) with an interaction test was used to compare the responses to the training protocols in the 4 groups. Fischer's PLSD test was employed for post hoc analysis. GraphPad Prism (version 5) software (Abacus Concepts GraphPad Software, San Diego, CA) was used for statistical analysis.

RESULTS

There was a highly significant increase in bilateral

Table II. *Maximal isometric force (kg) measured during leg extension exercise at 90°.*

Leg Extension 90° Isometric Test					
Test	Groups	T0	T1	%	p<
Right limb	Resistance (Ret)	22±8.9	33.2±3.3	51	0.01
	Motor-Sense (Gsm)	22.8±2.2	27.4±4.5	20.2	0.05
	Viss (Vam)	25±1.2	35.6±4	42.4	0.01
	Control	23±2.1	22.9±1.9	n.s.	n.s.
Bilateral	Resistance (Ret)	43.9±7.9	63.7±5.3	45.1	0.01
	Motor-Sense (Gsm)	47.7±7	54.6±15.5	14.5	0.05
	Viss(Vam)	48.5±6.6	69.1±8.4	42.5	0.01
	Control	44.3±4.3	46.1±7.3	n.s.	n.s.

Values represent means ± SDs. T0 before training, T1 after training. %: increase percentage T1 vs T0.

Table III. *Sway area (mm²) measured during stabilometric test for 52.2 s carried out with open and closed eyes.*

Sway Area								
	Open eyes				Closed eyes			
	T0	T1	%	P<	T0	T1	%	P<
Gsm	7287.8±2402.4	4436±1884.9	-39.1	0.01	9791±2438.2	6041.5±1405.4	-38.3	0.01
Ret	6962.4±1558.05	6761.2±2301.1	-2.9	n.s.	11096.9±2102	9858.4±1688.5	-11.2	n.s.
Vam	7100.2±2920.5	5927.4±2882.4	-16.5	0.05	9598.1±2951.9	7248.1±2270	-24.5	0.05
Control	6874.6±2351.3	6941.5±1899.5	-	n.s.	1006.5±2188.8	9214.71+3299.8	--	n.s

Values represent means ± SDs. T0 before training, T1 after training. %: decrease percentage T1 vs T0.

isometric strength of 45% for the Ret group and of 43% for Vma, and a significant increase of 15% for the Gsm group (Table II). There were no significant changes in the control group.

Our data showed a significant improvement in the sway area and in the ellipse surface with open and closed eyes in the Gsm and Vma group (respectively p <0.01 and p<0.05). There was no improvement in Ret and Control group (Tables III and IV).

Gait analysis showed a significant increase in the length of the half-step in all three intervention groups, with an increase of 108% in the Gsm group

Table IV. *Ellipse Surface (mm²) measured during stabilometric test for 52.2 s carried out with open and closed eyes.*

Ellipse Surface								
	Open eyes				Closed eyes			
	T0	T1	%	P<	T0	T1	%	P<
Gsm	28.5±14.4	12.6±6.3	-55.8	0.01	32.5±18.5	25±9.7	-23	0.01
Ret	22.4±10.05	20.3±8.1	-9.4	n.s.	34±10	34.4±11.6	1.2	n.s.
Vam	26.2±12.5	20±9.95	-23.7	0.05	38.5+16.1	30.8±17.2	-20	0.05
Control	28.6±11.8	27.6±20.2	-	n.s.	37.9±13.2	36.5±19.4	-	n.s.

Values represent means ± SDs. T0 before training. T1 after training. %: decrease percentage T1 vs T0.

Table V. *Length of the half-step (cm) measured during gait analysis test.*

Length of the half-step (cm)				
	T0	T1	%	P<
Gsm	22.4±9.6	46.5±12.9	107.6	0.001
Ret	22.8±8.8	37.6±14.2	65	0.05
Vam	20.3±9.1	38.9±15.1	91.6	0.01
Control	20.3±7.8	21.7±12.9	-	n.s.

Values represent means ± SDs. T0 before training. T1 after training. %: decrease percentage T1 vs T0.

($p < 0.001$), of 65% in the Ret group ($p < 0.05$), and 92% in Vma ($p < 0.01$) group; no changes were found in the control group (Table V). The width of the step showed a significant improvement in the Gsm group ($p < 0.01$). (Table VI).

The single leg time support decreased only in the Vma group ($p < 0.05$) (Table VII).

DISCUSSION

Taking part in regular training allows to reduce the functional decline associated with aging (20). As in the younger population, the adaptive response of elderly subjects to physical training (21) is specific for endurance and strength (1), and can contribute to substantial improvement in the quality of life in this age group. Many age-related physiological changes described in longitudinal studies, including the decline in aerobic capacity (22), muscle strength (4) and mass and bone density (23) are also favorably reversed by exercise in elderly subjects (17).

The present study confirmed the specificity of adaptation in older adults to different training stimuli. The measurement of maximal isometric force showed an increase of knee extensor strength in all groups. The improvement was most pronounced in the Ret and Vma groups, but was still significant in the Gsm group.

Table VI. *Width of the step (cm) measured during gait analysis test.*

Length of the half-step (cm)				
	T0	**T1**	**%**	**P<**
Gsm	22.4±9.6	46.5±12.9	107.6	0.001
Ret	22.8±8.8	37.6±14.2	65	0.05
Vam	20.3±9.1	38.9±15.1	91.6	0.01
Control	20.3±7.8	21.7±12.9	-	n.s.

Values represent means ± SDs. T0 before training, T1 after training, %: decrease percentage T1 vs T0.

Table VII. *Contact Time (s) measured during gait analysis test.*

Width of the step (cm)				
	T0	**T1**	**%**	**P<**
Gsm	13.3±2.1	7.6±1.8	-42.9	0.01
Ret	14.5±1.8	12.3±2.2	-15.2	n.s
Vam	12.9±1.4	9.8±2.3	-24	n.s.
Control	14.7±1.5	15.4±1.9	-	n.s.

Values represent means ± SDs. T0 before training, T1 after training. %: decrease percentage T1vsT0.

The results of resistance training are in line with previous reports: a recent systematic review substantiated that high-intensity resistance training is effective in increasing strength and muscle mass in older adult (24). Our data indicate that heavy resistance strength training (i.e., 80% of FMT) exerted little effects on the balance ability of our subjects.

The Vma group showed increases in strength similar to those found in the Ret group. Taken together, muscular power output can be increased by high intensity focused vibration exercise (15, 25, 26).

Recently, Pietrangelo et al. (27) hypothesized that new fibers are generated during the first 4 weeks of focal high intensity vibrational stimulation. Thus, a consistent up-regulation of genes encoding for sarcomeric proteins such as actin, destrin, titin and angiomotin has been reported together with an increase in regeneration that recruits satellite cells to proliferate and fuse into new differentiated myotubes.

Saggini et al. (15) attributes the increase in strength to the activation of the sensory nervous system. The effect of vibration therapy can be ascribed to an improved treatment of afferent signals of the central nervous system. These results may explain the unexpected increase in balance abilities of Vma group, so the ellipse surface decreases 23.7% (p <0.05). During walking, our data show an increase in the length of half-step (91.6%, p <0.05) and reduction of the width of the support (24.0%). The increased stability is associated with an increase in walking speed and a reduction of the single leg stance.

The Gsm group showed an increase of muscular strength (15%) after 12 weeks of reactive postural balance training. Lin and Woollacott have found a longer maintenance of postural muscle activation in responses to platform perturbations in older adults compared to young adults (28), and those results may correlate with the age-related changes in balance recovery mechanisms.

Several studies have recently investigated the effect of training protocols concerning postural balance in elderly subjects (29, 30). In line with these results, the Gsm group showed an improvement in the stabilometric test of the sway area of 39.1% ($p < 0.01$) and of the ellipse surface of 55.8% ($p < 0.01$) (29-31).

Lajoie (29) reported an improvement of reaction capability after 8 weeks of postural training with computerized feedback, but no changes in balancing capability. This difference with our own results can be ascribed to the different method of postural training which we employed. The Imoove system is equipped with a balancing platform with hemispheric movement, which requires continuous realignment of the surfaces and body and special subsystems to maintain an optimal posture to exercise a tensional force, involving a visual feedback in real time which allows the subject to monitor the obtained corrections. In short, a feedback is correlated with the request of muscular isometric-isotonic tension. This feedback is associated with the instability arising from the movements of the balancing platform, on which the person performs the motor task. Similar results were recently reported: Hue et al. (30) documented an improvement of static balance after a training program on the "foamy open cell" floor in comparison with that achieved on a hard floor. The proposed treatment with Imoove leads to increase both at vestibular and at basal motor levels.

The motor sense training program combines a motor task, correlated with a visual feedback, with a sense of instability of the supporting surface. This is in line with the multi-sensory approach of postural balance training in elderly subjects proposed by Hu et al. (31) and confirmed by Bellomo et al. (17).

The static balance improvement and the increase of the force of the lower limbs also produce benefits in dynamic balance. During walking, our data show an increase in the length of half-step in all three groups, especially in the Gsm group (107.6%; $p < 0.01$). The stability of the support is confirmed by the reduction of the width of the support during walking which is reduced especially in the Gsm group (42.9%, $p < 0.05$). The increased stability leads to an increase in walking speed and a reduction of the single leg stance phase.

All the training programs used in the present investigation produce improvements in muscle strength, as shown especially in the Ret and Vma groups. Given the specificity effects of a training program, there is a limited adaptive potential of traditional resistance training, restricted to strength alone. So resistance training alone may not produce great effects on functional performance and fall prevention. However, to produce a significant increase in postural stability requires a specific training able to stimulate muscle and central sensory receptors.

In conclusion, this pilot study has shown that global motor-sensory stimulation, produced by focused vibration and proprioceptive training, is an effective approach to improve strength and balance that could translate into increased quality of life in the elderly. Further adequately powered studies, with longer follow-up are necessary to assess the long-term effectiveness of these rehabilitative approaches in elderly subjects.

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TASK-ORIENTED PHYSICAL EXERCISE USING POSTURAL RE-ALIGNMENT WITH BODY WEIGHT SUPPORT IN CHRONIC STROKE

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TASK-ORIENTED PHYSICAL EXERCISE USING POSTURAL RE-ALIGNMENT WITH BODY WEIGHT SUPPORT IN CHRONIC STROKE

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The recovery of functional gait is the main target for subjects who have suffered a stroke. The methods designed to improve balance and gait appear to be essential for skills and autonomy and to reduce the costs of assistance. The aim of our study was to evaluate the improvement of stroke victims in the chronic phase through the rehabilitation of gait, balance and posture using postural re-alignment with specific body weight support. The study includes 20 subjects with residual hemiparetic gait after stroke. Evaluation with international rating scales, gait analysis and stabilometric test was carried out at the beginning and after the 1st and the 3rd month of therapy; a follow-up control was made 3 months after the end of the rehabilitation program. All subjects underwent the rehabilitation protocol with Dynamic Antigravity Postural System 2 times a week for 3 months and were also treated with high efficiency focused acoustic waves (ViSS) to increase strength and muscular endurance (300Hz) or to reduce spastic hypertonia (200-120 Hz). The study shows a significant improvement in gait and balance with the persistence of results at the follow-up 3 months after the end of treatment. The subjects showed an increase in walking speed, greater stability and a consequent reduction of sedentary lifestyle with less risk of complications or recurrence. In conclusion this rehabilitation program is efficient for posture and walking quality.

Stroke is a leading cause of acquired disability in adults. The increase in life expectancy, the control of risk factors and the improvement in health care have modified the incidence and prevalence of stroke as well as mortality. However, the increase in life expectancy is associated with a higher risk of stroke because of its higher incidence among elderly people. Moreover, the reduced mortality means an increase in the number of patients with residual disability after the acute event (1). The natural history of this disease states that most sensory-motor and cognitive recovery occurs in the first 3 months (2). The functional abilities can further improve, although with less intensity and speed over the following three months, and then reach a plateau within the year (3). Most of the recovery progress is achieved on average in the first 11 weeks, while the best recovery in self-care and of the ability in movement is obtained in 12.5 weeks (4). A specific rehabilitative program with multiple targets should be developed for each patient

Key words: chronic stroke, gait, balance, postural realignment, body weight support

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

in order to improve autonomy and thus quality of life. 90% of survivors have some functional disability; abnormal walking patterns and the lack of balance with the associated risk of falling are among the main deficits which contribute to limit the autonomy (5). Some individuals start with rehabilitation therapy in the acute and sub-acute phase, but rarely rehabilitation goes on over the first year after the event, since several studies have shown that after this period there is a plateau in functional recovery. Furthermore, we must also consider the lack in resources available for long-term treatment (6). Although between 65% to 85% of stroke survivors are able to walk again independently 6 months after the event, abnormalities of gait persist in the chronic phase. The low resistance to walk, as shown in the 6-Minute Walking Test (6MWT), is one of the most difficult problems to treat (7). The inability to walk independently leads to a greater need for hospitalization in nursing homes. It has been shown that resistance during walking, evaluated by 6MWT, is related to the possibility of reintegration of stroke patients in society. Moreover, the ability to walk has important implications for the health of the elderly population which is the most likely to experience stroke events (8). Newman et al. found that the ability and the time needed to walk for 400 meters was an important predictor of mortality, cardiovascular risk and disability in 3,075 older sedentary subjects (9). The disabling process linked to the lack of balance and abnormal gait after stroke leads to inactivity and new impairments, such as muscle atrophy, articular range reduction, decubitus ulcers, cardiovascular diseases, alterations in metabolism, decreased bone density. These comorbidities exacerbate the loss of functional capacity and lead to new disabilities and further reduction of social participation, thus increasing the risk for loss of autonomy and mortality. Motor relearning techniques are focused on the active collaboration of patients with the execution of motor tasks and their feedback to determine the relearning of the motor gesture (10). Robotic devices are increasingly accepted by the scientific community for the rehabilitation of functional impairments of both lower and upper limbs (11). The choice of using these tools is supported by the security and the possibility to perform intensive and task-oriented programs (12). As for the rehabilitation strategies of the gait cycle with robotic devices, many studies have shown that using such techniques leads to a better gait recovery than conventional techniques, in terms of symmetry, stride length, double stance time and balance (13). Robotic technologies for gait support are becoming increasingly widespread for rehabilitation treatment of neurological disorders. Many studies have demonstrated the effectiveness of training on a treadmill with Body Weight Support (BWS) in the rehabilitation of gait in patients with hemiplegia (14). The Dynamic Antigravity Postural System SPAD in particular, provides the partial degravitation of the "passenger" on the pelvis and the positioning of four proprioceptive stimulator blocks during the exercise, two on the anterior-superior iliac spines (ASIS), two on the acromion-clavicular joints and a third block at the level of the vertebra S1 and T6, to stabilize the subject when he starts to move and prevent possible twisting of the pelvis or shoulders during movement. Sometimes it is necessary to place an inflatable collar around the neck of the patient to align the subsystem cranio-mandibular joint. In this way it is possible to work on the subject in defined relief and in spatial alignment and to create homogeneous ground-foot reactions, with restoration of physiological and proprioceptive stimuli, resulting in the recovery of the motor pattern of the gait. The goals of therapy are simultaneously mechanical and proprioceptive.

The aim of our study was to evaluate the possibility of improving the quality of life of post-stroke patients and consequently increasing the level of autonomy, with this projected rehabilitative program (15).

MATERIALS AND METHODS

This prospective, single-center study was approved by the local ethics committee, and was performed in accordance with the 1964 Declaration of Helsinki. All participants were stroke patient with residual hemiparetic gait and all provided written consent before taking part in the study.

The main inclusion criteria were:

- Outcome of ischemic or hemorrhagic stroke with residual hemiparetic gait;
- Stroke at least 6 months previously;
- Age min 40 - max 80 years;
- Mini Mental State Examination score ≥ 24;

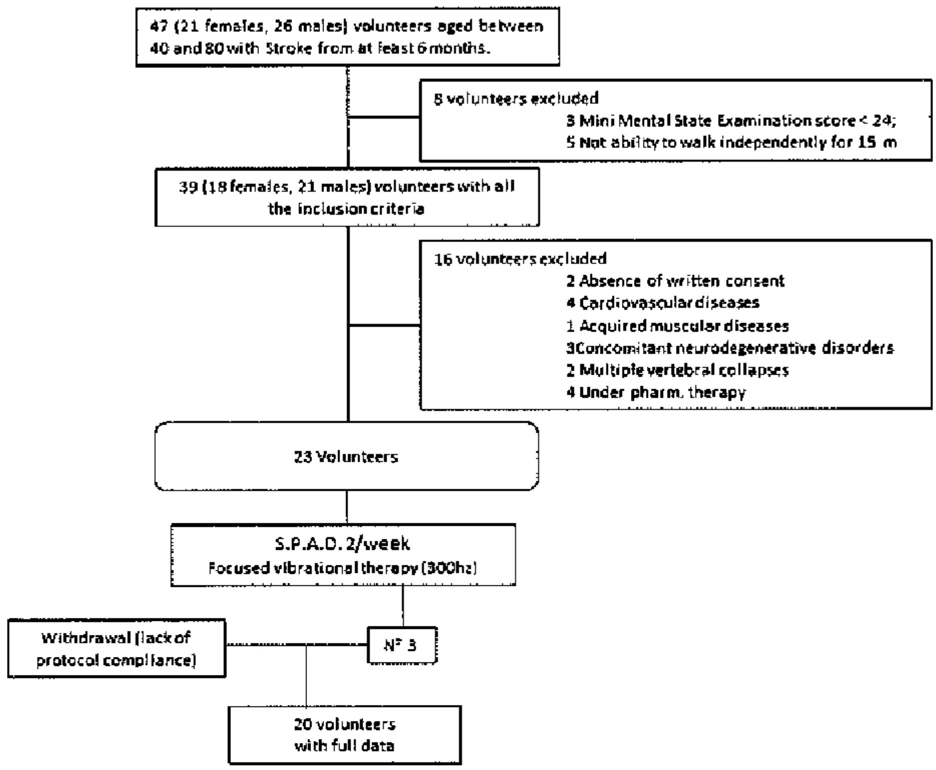

Fig. 1. *Flow chart of patients enrolled in the study.*

- Ability to walk independently for 15 meters.

Exclusion criteria were as follows:

- Recurrence of disease in the past 3 months;
- Concomitant neurodegenerative disorders;
- Peripheral arteriopathies of the lower limbs;
- Orthopedic disorders limiting activity;
- Multiple vertebral collapses (2 or more) in the last year;
- Femur fracture in the last 6 months;
- Not clinically compensated thyroid disregulation;
- Cardiovascular diseases (ischemic heart disease, congenital cardiomyopathies, syncope, heart failure of NYHA class III-IV, aortic aneurysm / indication for abdominal surgery Carotid Stenosis for surgical indication);
- Severe deterioration of cognitive status;
- Diseases that lead to a fatal prognosis at 6-12 months (cancer, etc.)
- Renal, pulmonary, and hematological diseases.

Twenty hemiplegic subjects (aged between 41 and 78 years, mean age 54 years, 11 females, 9 males), who respected the inclusion criteria, were included in the study between June 2011 and July 2012 (Fig. 1). All subjects followed the rehabilitation protocol with SPAD 2 times a week for 3 months; each session lasted 18-20 minutes and, if the patient's condition required it, the training time could be reduced and divided into several times spaced by appropriate breaks. De-gravitation of 50% of body weight was used. The SPAD system uses a support with a pneumatic mechanism able to follow the vertical displacement resulting in the opening of the legs, keeping constant the value of the BWS on high percentages. It is equipped with two alternative and complementary systems: a pneumatic system and a mechanical system consisting of split electric motors, which allow to work on the two hemisoma separately and manage the asymmetric adjustments of gait. All subjects were invited to walk on the treadmill, in front of a mirror, in an orderly and aligned manner with upright head and to make correct and long strides, laying on the ground consecutively heel-plant-toe. At the end of each session the operator gradually reduced the body relief down to 0% and then the speed of the treadmill down to 0 Km / h in order to accustom the patient to the gait without relief.

All subjects also underwent treatment with high efficiency focused acoustic waves (ViSS) to increase strength and muscular endurance (300Hz) or, in selected cases, to reduce spastic hypertonia (200-120 Hz) (16-19). The subjects were evaluated at baseline (T0) and after the 1st (T1) and the 3rd month of therapy (T2).

In detail, the evaluation and classification included: physiatric clinical examination and drafting of the medical record with: medical history, pharmacological history, diagnostic tests, neurological and musculoskeletal physical exam.

Administration of rating scales: Tinetti Balance Scale for the assessment of balance and gait (20); Functional Independence Measure (FIM) for disability measurement (21); Stroke Impact Scale to measure multifactorial outcomes, including strength and muscle function, activities of daily living (activities of daily living / instrumental activities of daily living ADL / IADL), mobility, communication, emotion, memory and cognitive status and participation in social life after stroke; Mini Mental State Examination (MMSE) which is a widely used tool to assess cognitive function during clinical visits. The 12-item scale tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30; a value of <23 is a positive screen for cognitive impairment. The test takes 5–10 minutes to administer and has been validated and extensively used in clinical practice and research (22). Hamilton Depression Scale, validated in 1960 as a measure of depressive symptoms both in children and adults; through this scale it is possible to investigate 21 areas crucial for the assessment of the depressive state of the subject: depressed mood, guilt, suicidal ideation, initial insomnia, middle insomnia, prolonged insomnia, work and interests, slowing of thought and words, agitation, anxiety of psychic origin, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, genital symptoms, hypochondriasis, introspection, weight loss, diurnal variation of symptoms, depersonalization, paranoid symptoms, obsessive symptoms (23). Motricity Index is used to measure muscle strength in upper and lower limbs in patients who had suffered a stroke, and consists of testing six limb movements with the patient sitting on a chair or on the edge of the bed, if required, it can also be tested from a supine position (24). Ashworth Score measures both peripheral and central spasticity; with this scale, each passive movement and the resistance perceived during movement of a joint are measured and assessed with a score from 1 (normal) to 4 (no movement) (25).

Administration of tests for speed and fatigue during movement

Six-minute walking test (6MWD) measures the distance that the subject can rapidly take on a flat and rigid surface in 6 minutes. It assesses global and integrated responses of all the systems involved in the exercise, including the pulmonary and cardiovascular system, the systemic circulation, peripheral circulation, blood, neuromuscular units, and muscular metabolism. It does not provide specific information on the function of each of the different organs and systems involved in the exercise or the mechanisms restricting the performance, because this is possible only with specific tests of cardiopulmonary stimulation. The 6MWT self-learning assesses the sub-maximal level of functional capacity. Most patients cannot reach the maximum capacity of exercise during the 6MWT, and they need to stop and rest during the test. The patient is asked to walk for 6 minutes at top speed, in order to cover as much distance as possible, which is recorded. At the end of the test the subject is required to express, using the Borg scale, the perceived level of fatigue (26).

Five repetitions Sit-to-Stand Test

The Sit-to-Stand Test was first introduced as a measure of functional outcome for muscle strength of the lower limbs1. The 5-repetition STS test has been used as a measurement of the physical performance to detect the possible correlation with the prediction of mortality and disability in weak elderly subjects and to differentiate among the elderly (aged 63-90) those with and without balance dysfunctions. It has also been used as a measure of outcome after total hip and knee replacement surgery, vibration therapy, for cross-sectional studies of correlation in subjects with osteoarthritis and vestibular dysfunction. The 5-repetition STS test was introduced as an outcome measure in studies investigating strength and functional performance in individuals with stroke in chronic phase as well as in cross-sectional studies evaluating the association of disability and falls in people with stroke. Despite the use of 5-repetition STS tests, test-retest reliability (ICC range, .890 –.960) is based on the evaluation of healthy elderly subjects and the elderly with osteoarthritis (ICC .960) but not of subjects with stroke. In addition, the muscle strength of the lower limbs and the ability to balance of the subject also may affect the performance of the test (27).

Ten-meter walking test

The 10-meter walking test assesses speed in covering a short distance. The subject has to walk without assistance for 10 meters and time is measured for each intermediate of 6 meters to allow acceleration and deceleration. The time starts when toes cross the limit of 2 meters and stops when toes cross the main limit of 8 meters. The use of assistive devices is allowed, but this fact should be documented and the procedures of implementation should be the same between testing sessions. If you need assistance in walking the test should not be carried out. The test can be carried out at a walking speed, preferential or otherwise, as quickly as possible. It is necessary to indicate the speed at which the test is performed (whether preferential or faster). The final result is represented by the mean of three consecutive trials (28).

Metabolic Holter was used for the measurement of the energy expenditure during exercise at the 1st, 9th and 24th sessions. It is made up by a multi-sensor monitor which is worn on the triceps of the right arm. It allows a continuous monitoring of physiological variables and data on physical activity, calculates the energy expenditure, the level of motor activity, detects the states of sleep and wakefulness and other parameters such as the number of steps, the outside temperature and that of the skin, and the electrical conductivity. These parameters are useful for the definition of the rhythm and the quality of life (29).

Gait analysis

Gait is characterized by a cyclic pattern of motor activity of the lower limbs and trunk which allows to transfer the body weight onto the supporting limb and to carry the contralateral limb forward. Studying gait may be useful in the diagnosis of diseases of one of the involved systems (nervous system, musculoskeletal) and can also provide information on the level of functional restriction resulting from the disease. It allows the planning of specific treatments and provides important elements for the evaluation of the effectiveness in rehabilitation treatments. The clinical evaluation of gait allows to carefully analyze the behavior of the various joints (from the toes to the ankle, knee, hip and pelvis and trunk) during the gait cycle, thus obtaining qualitative information which may be useful in identifying the main deviations of the gait. However, the low reliability and the absence of quantitative data represent an important limit; it is therefore fundamental to be able to use techniques which allow to describe, quantify and assess the movement in order to obtain detailed quantitative information able to characterize the gait of a pathological subject. The instrumental analysis of gait, made through the study of kinematics, dynamics and patterns of muscle activation, is a tool that can improve the ability of the clinician to describe, objectively and with sufficient precision, some features of the mechanisms at the basis of disability in walking, to identify the most appropriate treatment and to evaluate the outcome. The gait cycle is the functional unit of reference in gait analysis. It is defined by the interval between two successive initial contacts of the same foot (stride) and represents the temporal reference in which are described all other biomechanical events (30).

Stabilometric test

This test analyzes the postural strategy used by the patient in maintaining the position in a specific time frame. The subject is examined in the standing position for 51.2 seconds with the heels spaced about 1 cm and alignment plantar stance at 30°, with the eyes first open and then closed (OE-CE). With open eyes the subject is able to use all possible proprioceptive and exteroceptive information. When the eyes are closed there is no visual information and the subject has to rely exclusively on the proprioception. With this test it is possible to investigate how the subject controls his movements in order to have a correct balance. These swings physiologically should be found in front-rear direction according to the structural conformation of the lower limb. The indicators of this investigation are: the ellipse area, the sway path length, the Romberg index and the eccentricity index (31).

Each subject was classified according to the International Classification of Functioning, Disability and Health (ICF), which assesses the residual abilities of the individual replacing the concept of "function threshold" to that of "degree of disability". The ICF perspective is multidimensional, since it is not just limited to organic factors, defined as "functions" and "body structures" but also includes environmental and contextual factors acting on the individual within the categories of "environmental factors" and "activities and participation" (32).

All data are given as means ± SDs. Differences between mean values before and after the rehabilitation period were tested for significance using Student's t-test for paired observations. The minimum level of statistical significance was set at $p<0.05$.

RESULTS

Twenty-seven subjects (mean age 55 years, 14 females, 13 males) were included in the study, 20 of whom, (age range: 41-78 years; mean age: 54 years) successfully completed the treatment protocol and underwent clinical and instrumental follow-up, as described in the Materials and Methods section; 7 subjects did not complete the treatment protocol for logistic problems and withdrew from the study

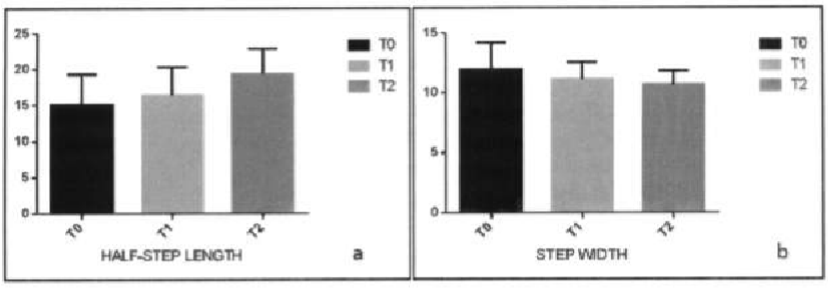

Fig. 2. ***a, b)*** *Increase of the amplitude of the half- step and the reduction of the width of the step at gait analysis.*

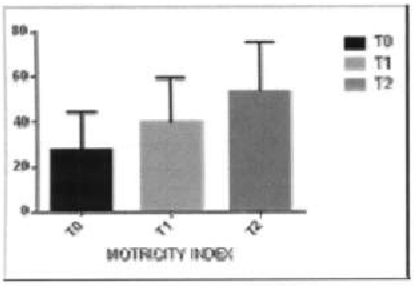

Fig. 3. *Improvement achieved in the scoring of Motricity Index.*

after the first session. As a consequence they were not included in the final evaluation.

On completion of the therapeutic protocol, significant improvement was recorded in gait performance and ability in daily activities compared to baseline values, as reported in the evaluation tests.

Follow-up control after 6 months showed the maintenance of the results. The results showed improvement in gait analysis with reduction in hemiparetic gait (average width step T0 11.9±2.29 cm/T1 11.1±1.45 cm/T2 10.6±1.19 cm, $p < 0.05$), prolonged half-step (mean T0 15±4.31 /T1 16.4±3.89 /T2 19.3±3.54 cm, $p<0.05$) as shown in Fig. 2. Even the score of Motricity Index had improved, as shown in Fig. 3 (T0 27.4±17.13 / T1 39.6±19.95 / T2 53.3±21.72, $p<0.01$).

The stabilometric test showed a reduction of the ellipse area both with open eyes (T0 240.9±97.78 / T1 229.4±96.18 / T2 210.4±92.64, $p<0.01$) and closed eyes (T0 262.4±119.82 / T1 256.5±117.20 / T2 247.9±118.17, $p<0.01$), a reduction in the sway path length both with open eyes (T0 357.4±52.85 / T1 340.6±58.84 / T2 327.9±56.77, $p<0.05$) and closed eyes (T0 349.8±84.66 / T1 339.2±77.57 / T2 328.4±64.82, $p<0.05$), an increase in balance with open eyes as shown by the trend of Romberg index (T0 108.9±35.52 / T1 11.8±35.78 / T2 117.8±32.86, $p<0.01$), as shown in Figs. 4, 5 and 6a; all the above results indicate a greater motor control of the hemiplegic side and then a gradual recovery of autonomy. An improvement in the score of the Tinetti Balance Scale was also recorded (T0 15.1±4.40 / T1 17.3±4.87/ T2 19.9±4.50, $p<0.01$) (Fig. 6b).

The average of the marks obtained in the rating scales showed a reduction of disability and the increase of independence in daily activities (FIM: T0 83±20.00 / T1 97±13.26 / T2 110±16.44, $p<0.05$ – Stroke Impact SCale: T0 164±23.47/ T1 173±23.57 / T2 187±26.16, $p<0.01$); an improvement was also found in mood evaluated through the Hamilton Depression Scale (T0 22.3±5.25 / T1 21.7±4.05 / T2 20.3±3.68, $p<0.05$). The Ashworth scale score (T0 3±0.94 / T1 2.6±1.05 / T2 2.3±0.94) highlighted a modulation of the muscular tone.

The walking speed at the 10-meter walking test (T0 23.3±6.01 sec / T1 21.1±5.04 sec / T2 19±4.30sec, $p<0.01$) increased, as well as the distance covered in the 6-minute walking test (T0 90±8.49 m / T1 107±7.11m / T2 132±10.86m, $p<0.01$); an improvement was also found in the physical performance at the 5 Repetitions Sit-to-Stand Test (T0: 23±2.50 / T1: 22±1.95 / T2: 21±2.64, $p<0.05$) and reduction of the average energy expenditure assessed by metabolic Holter (T0: 52± 3.81 kcal /

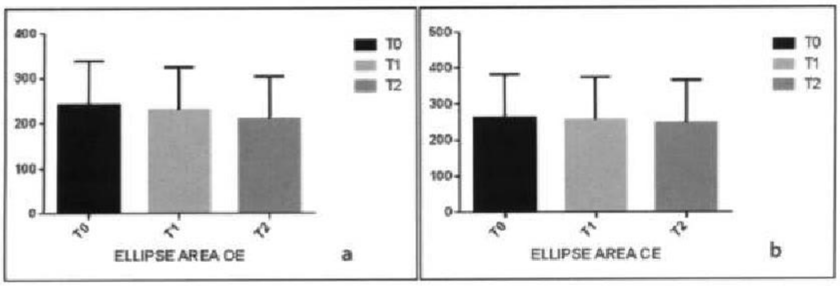

Fig. 4. ***a, b)*** *Trend of the ellipse area with open eyes and closed eyes at stabilometric test over time.*

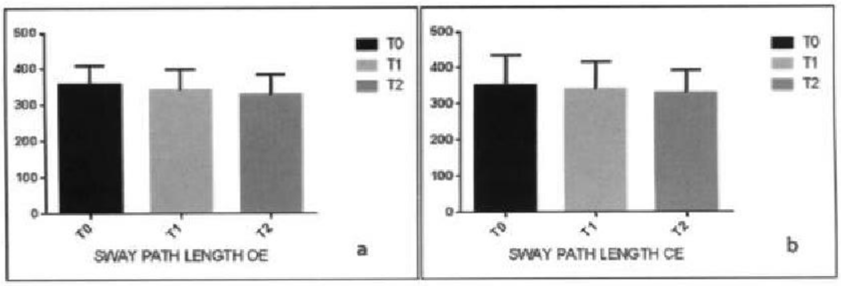

Fig. 5. a, b) *Numerical value of the sway path length with open eyes and closed eyes at stabilometric test.*

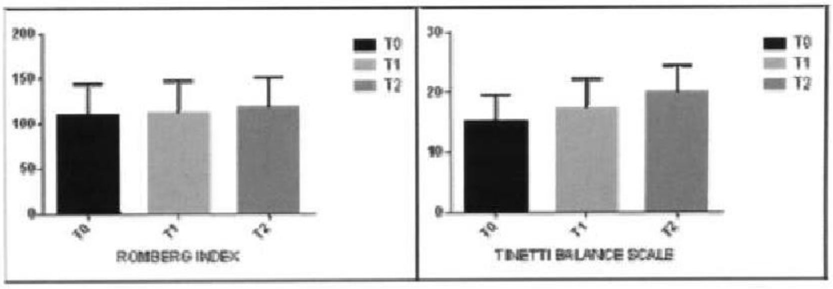

Fig. 6. ***a, b)*** *Trend of Romberg index and the improvement in balance and gait tested with Tinetti Balance Scale during the treatment period.*

T1: 51±3.93 kcal / T2: 47±3.35 kcal, $p<0.05$).

The follow-up carried out 60 days after the end of the treatment protocol showed a stabilization of the previously achieved results (Table I).

The results of our study show that the rehabilitation program was efficient on posture and on walking quality. The subjects showed an increase in walking speed, greater stability and a consequent reduction of sedentary lifestyle with less risk of complications or recurrence.

Table I. *Results achieved at follow up performed 3 months after the end of the treatment protocol.*

	T0	T1	T2	T3
Romberg	108.9	111.8	117.8	117.4
Ellipse area CE	262.361	256.503	247.928	249.324
Sway path length CE	349.759	339.2033	328.425	328.772
Ellipse area OE	240.914	229.436	210.426	211.37
Sway path length OE	357.354	340.665	327.867	329.734
Width of step	11.87	11.13	10.64	10.45
Length of half-step	15.02	16.41	19.35	18.97
Motricity Index	23.1	22.4	21.1	20.8
Tinetti Balance Scale	15.1	17.3	19.9	19.7
Ashworth Scale	3	2.7	2.3	2.4
FIM	82.95	96.6	110.3	111.4
Stroke Impact Scale	163.7	172.7	187.1	188.4
Hamilton Depression Scale	22.3	21.7	20.3	20.3
6-min Walk Test	90	107	132	134
10-met Walk Test	23.3	21.1	19	18.7
5-rep Sit-to-Stand Test	23	22	21	21
Energy consumption	51.85	50.58	46.77	47.19

DISCUSSION

The aim of our study was to create an effective rehabilitation program able to influence gait and balance in a positive way and consequently the quality of life of chronic stroke victims through the recovery of postural control, a more stable scheme of walking, a lower need of energy and the modulation of muscular tone.

The postural re-programming obtained by SPAD allowed the observation of evident improvement of the values of important parameters related to balance and gait.

The neurophysiologic rationale is summarized in the stimulation of the plasticity of the system of the neuro-motor control, through a repetition of a motor task, functionally corrected, in an intensive/extensive form.

The alternative loading/unloading of the leg and hip while walking is the main peripheral stimuli that activate the locomotor central generator patterns. The improvement of walking could hypothetically suggest a re-learning process and a plastic re-adaptation of a walking generator, which allows a more physiological and efficient gait cycle.

The stabilizing action on the body also causes beneficial effects on balance control through better synergy of anti-gravity muscles, a quicker response of the apparatus of support resulting in more rapid repositioning of the centers of gravity of the body subsystems, and of the barycenter (33); the trend of Romberg Index shows an improvement in balance with open eyes maybe due to the visual feedback implemented during training probably related to mirror therapy.

SPAD treatment has the ability to modify the asymmetric adaptations of gait, through a vertical movement of the center of gravity of the subject in correlation with the use of proprioceptive stabilizer bocks thus restoring the whole body's imbalances as well as improving gait.

In accordance with what is described in literature, our results showed that the SPAD system allows to work independently on the two hemisoma, manage asymmetric adaptations of gait and follow the center of gravity of the subject in his vertical movements, due to the opening of the compass in the lower limbs, reducing the load on the spine, through the degravitation on the pelvis, thus restoring proprioceptive stimuli with physiological recovery of the motor pattern of gait. Hemiplegic subjects should be treated with very high percentages of BWS, even over 50% and in these cases the combination to obtain the maximum outcome of therapy may provide the constant pneumatic traction realized with the sub-gluteal sling in hemiplegic subjects. In post-paresis, the possibility to work with a relief greater than or equal to 50% overcomes the positive features of water training without suffering the therapeutic and/or functional drawbacks related to deambulatory recovery. Moreover, with the need for such a high support, the possibility of following the vertical movements of the subject better respects the therapeutic request which is to coordinate the movements of lower limbs in a situation where the strength necessary to support the body weight becomes secondary in relation to the recovery of balance and coordination of the kinematic chains for walking (12).

The use of focused mechanic-sound vibrations (ViSS) showed an improvement in the quality of muscle tissue, which resulted in greater strength and security during the gait cycle and, when necessary, a reduction of muscular tone.

The results obtained in the rating scales attest that the synergy between SPA) and ViSS can represent a valid rehabilitative approach to improve the performance of the gait cycle and reduce disability in ADL in subjects with outcomes of stroke in the chronic phase.

In conclusion, the realignment of the body subsystems with proprioceptive information which is provided by the stabilizer blocks on the SPAD, have proved to be able to determine an increase in the knowledge of the motor action, further influencing the persistence of the obtained results probably related to the supposed cortical re-learning.

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THE TREATMENT OF CANCER: A COMPREHENSIVE THERAPEUTIC MODEL ENTAILING A COMPLEX OFINTERACTION MODALITIES

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Chapter 19

The Treatment of Cancer: A Comprehensive Therapeutic Model Entailing a Complex of Interaction Modalities

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Additional information is available at the end of the chapter

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1. Introduction

Although an overall rise in cancer incidence has been observed over the past 300 years concomitantly with the industrial revolution, a more prominent increase has been recorded since the '30s, with a further acceleration during the last 2 decades.

Genetic factors are thought to account for 5-10% of all malignant neoplasms, even though hereditary susceptibility will be variably relevant depending on histotype, anatomic site, and epidemiologic context; additionally, a key role is played by environmental factors. Socioeconomic improvements have resulted in an increase in food availability as well as significant changes in lifestyle habits; with new technologies allowing for automation of manual work, an overall physical activity reduction has been observed leading to unbalances between caloric intake and energy expenditure.

Cancer is no longer a rapidly lethal disease for an increasing number of patients. Knowledge of the main risk factors for cancer development is essential for establishing a comprehensive and integrated treatment plan (tab 1).

Cancer patients receiving treatment combinations of surgery, radiation therapy and chemotherapy are prone to developing several treatment-related diseases.

Pain, heightened risk of infection, neural deficits, lymphedema, fatigue, nausea and vomiting, loss of flexibility, myopathies, muscle weakness, cachexia, dehydration, emotional distress, shortness of breath are common side-effects capable of negatively affecting patients' lifestyle and physical activities. Any combination of surgical treatments, chemotherapy, and radiotherapy must be integrated within a global therapeutic plan aimed to reduce the above-

1.	Obesity and overweight
2.	Low fruit and vegetable intake
3.	Physical inactivity
4.	Smoking
5.	Alcohol consumption
6.	Unprotected sex
7.	Urban air pollution
8.	Indoor air pollution due to household use of solid fuels
9.	Spread of bacterial and viral infections through unsafe health care procedures

Table 1. The 9 modifiable risk factors responsible for a third of all cancer deaths in the world

mentioned negative effects that may become apparent immediately as well as after several months or years.

Mullan (1985) classified the life of cancer survivors into three stages: 1) Acute Stage, spanning from diagnosis to the first year after primary treatment; 2) Extended Stage, until the 5th year after primary treatment; 3) Permanent Stage, from the 5th year after primary treatment onwards.

The first year after primary treatment should be considered just as the "tip of the iceberg", and it is crucial that any approach to cancer treatment is holistic and comprehensive, based on the assumption that cancer is a chronic illness rather than an acute condition.

The aim of this chapter is not to describe the specifics of early management of patients diagnosed with cancer; however, the authors' view is that such approach should be as integrative and comprehensive as possible.

It is essential that physicians in the process of planning specific therapeutic interventions (either actions specifically aimed to the primary disease or supportive therapies) extensively profile patients according to their physical status in order to establish an individual patient-tailored strategy.

The integrative management approach relies on a number of basic interventions, including:

1. Therapeutic changes of lifestyle habits and daily diet;

2. Specific physical exercises and walking prescriptions;

3. Physical therapies coupled with psychophysical techniques.

2. Therapeutic changes of lifestyle habits and daily diet

2.1. What do you know?

Up to 30-40% of all malignant cancers could be prevented by interventions on diet, physical activities, and daily lifestyle.

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Calories intake directly correlates with risk of developing obesity as well as cancer.

Obesity *per se* is considered to be to blame for up to 14% and 20% of all men and women deaths.

Approximately 50% of all primary malignant cancers arise in tissues with a primary involvement in obesity physiopatology.

Cancer is responsible of approximately 25% of all deaths in the US.

According to recent predictions, by 2020 the global world population will have reached 7,5 billion, with a cancer incidence and disease-specific mortality of 15 million per year and 12 million per year, respectively.

At present the total US cancer survivors population is made of 5-y cancer survivors for up to 66%, and by 2020 it has been estimated that cancer survivors aged at least 65 years will have been increased by 42% compared to now.

The diet is responsible for approximately 30-35 % of total mortality in the US, with its impact on cancer development depending on histotype and anatomic location; nutrition may play a key role in up to 70% of colorectal cancer-related deaths.

Nowadays, men and women in Occidental countries are progressively increasing in body size, with average body-mass indexes (BMI, i.e. the ratio between weight and squared height) relentlessly soaring beyond the normal range (18.5-24.9); conversely, an increas- ing number of individuals is falling into the overweight range (25-29.9) as well as the overt obesity range (> 30).

Obesity is easily diagnosed by assessing the increase in horizontal body dimensions compared to height.

One method for measuring such imbalance is the BMI, i.e. the ratio between weight (kilograms) and squared height (centimeters^2). BMI ranges identifying malnutrition, normal weight, overweight and different obesity degrees (mild and severe) have been defined.

BMI, however, being frequently used in epidemiological studies to assess the effect of diet as a risk factor, may become a confounding factor; indeed, BMI is less reliable in elderly patients, with height being gradually reduced due to spinal degenerative processes. Likewise, children BMI measurements may be biased by different growth rates in different body areas. Additionally, BMI fail to provide any definite information regarding body composition, i.e. the percentage of lean body mass versus fat mass, bone mineralization status, and total body water, just to name a few examples.

The value of lean body mass is critical because it is the body component consuming higher energy values per weight unit, being therefore critical for any estimations of appropriate caloric intakes.

Any diet based on caloric restriction alone would be ineffective as well as potentially dangerous if no caloric intake assessment were to be calculated according to body composition and estimated energy requirements for performing daily physical activity (including walking, writing, or accomplishing ordinary housework actions).

Obesity plays a critical role in cancer promotion, progression, and therapy resistance; obesity oncogenic actions are thought to be mediated by dysregulation of hormonal networks (i.e., circulating insuline, IGF-1, testosterone, and estrogens levels) as well as through pro-inflammatory effects due to adipose tissues cytokines.

Increased BMI values correlate with circulating inflammatory cytokines levels, that appear to be related to insulin resistance.

A positive correlation between high BMI values (>30) and cancer risk is being observed in different areas worldwide, with significant increases in cancer risk being recorded for every 5 Kg/m^2-gain in BMI.

Obesity directly promotes tissue inflammation. Lipids intake should be proportional to that of other nutrients in order to reach an adequate energy balance; in this regard, it should be remembered that 1g of fat provides approximately 9 Kcal of energy, while 1g of carbohydrates or proteins only provides 4.5 Kcal. However, specific lipids significantly differ in their chemical structure and will result in different metabolic responses when given at equal calories levels. Increased amounts of fat per portion, a phenomenon commonly occurring in restaurant and cafèteria, leads to significant inflammatory response spikes, that can be quantified by assessing increases of circulating inflammatory factors; the latter are capable of inducing insulin resistance and free radicals production, resulting in oxidation of cell structures such as nucleic acids, proteins, and membrane lipids. Other lipids possess an anti-inflammatory activity. There is plenty of literature addressing the beneficial administration of omega-3 unsaturated lipids for lessening the inflammatory consequences of several chronic diseases. Omega-3 unsaturated lipids are available either as dedicated over-the-counter preparations or through several common foods, more prominently fish and dried fruit. Omega-3 lipids are unsaturated lipids, i.e. they are in liquid form at room temperature (oils); they can easily undergo oxidation if not protected by intrinsic animals antioxidant systems or by vitamin E addition in commercially available preparations. Their content in fish meat changes according to the species, the fishing site, temperature, type of feeding (algae or other kinds of food for livestock); these features make difficult to calculate the omega-3 unsaturated lipids daily dose. Many public health authorities have been encouraging increases in diet fish intake, but it is important to know diet fish origins because of the risk related to heavy metals; it is therefore necessary to avoid eating exceedingly large amounts fish. Of course, such details are hardly specified, if ever, in epidemiological studies assessing the effects of fish-based diets. Obesity results in a status of enduring subclinical inflammation within fat tissues. In obese individuals both visceral and subcutaneous adipose tissues are infiltrated by macrophages surrounding necrotic adipocytes forming the so-called crown-like structures (CLS). The infiltrating macrophages release inflammatory cytokines whose plasma levels in post-menopausal breast cancer patients were shown to correlate with cancer progression and disease-specific mortality. In both experimental animals and humans the CLS number is directly related to BMI values.

Diets with high concentration in saturated fatty acids (cafeteria food, sausages, dairy products, red meat) are becoming more and more frequent worldwide, leading to a global escalation in overnutrition-related diseases.

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Diets rich in saturated fatty acids closely correlate with metabolic syndrome and inflammation, especially inflammation of the white adipose tissue, which is not only a storage organ for lipids but also an endocrine organ.

It has been known since 1885 that hyperglycemia is more frequent among cancer patients than in the healthy population.

Warburg in 1930 highlighted the abnormal glucidic metabolism occurring in cancer cells, i.e. the so-called aerobic glycolysis, defined as the tendency of the cancer tissues to produce lactic acid even in the presence of sufficient oxygen to sustain Krebs cycle and mitochondrial membrane oxidation processes.

Glucose intolerance is an established risk factor for several cancers (including colorectal, breast, prostatic, pancreatic, and gastric cancer). Obesity and glucose intolerance are part of the metabolic syndrome, a condition characterized by increased insulin levels both during fasting and after glucose load. Metabolic syndrome, first described by Reaven in 1988, is defined by the presence of at least three of the following components: intra-abdominal or visceral obesity, glucose intolerance, hypertension, low HDL blood levels, and high triglyceride levels. In 2001, the National Cholesterol Education Program developed an alternative definition, which required the presence of at least 3 of the following 5 factors: increased waist circumference, hypertriglyceridemia, low HDL cholesterol, hypertension, and high levels of fasting glycemic levels. At the roots of metabolic syndrome there are increase in visceral fat, excessive caloric intake, and low physical activity.

The prevalence of metabolic syndrome is steadily increasing all over the world together with the increase in several types of cancer.

In subjects with glucose intolerance (IGT), both the levels of glycemia and fasting insulin are increased. The latter are coupled until glycemia reaches the concentration of 7-8 mM, a level beyond which insulin does not show further increases and may even begin to decline as a result of functional failure of pancreatic β-cells (De Fronzo 1992). This is paralleled by the gradual increase in glycemia, starting with postprandial glycemia.

Many people with newly diagnosed cancer are obese, with further changes in body structure being induced by chemotherapy, surgery, and therapy-related physical inactivity.

Chemotherapy often changes, even a year later, body composition, increasing fat mass and reducing muscle mass, creating a phenotype that could be defined as post-cancer sarcopenic obesity; the latter appears to correlate with a high risk of cancer recurrence.

Modifications in body composition in cancer patients imply that many studies conducted through questionnaires, perhaps using only one scale, were affected by significant biases. The reduction in caloric intake as a strategy to reduce obesity should be assessed on a case by case basis, followed over time, and maintained proportional with nutritional needs of the whole body in order to prevent secondary nutritional deficiencies.

The caloric intake, however, should be calibrated according to the composition of energy sources (carbohydrates, lipids, proteins); the latter, in a typical Mediterranean diet, should be in the ratio of 60%, 25%, 15%, respectively.

The American Cancer Society guidelines suggests that carbohydrates should be in the ratio of 40-65% of the energy pool, the same as for healthy population, lipids in the ratio of 20-35%, of which <10% saturated fats, and proteins should be 10-35%.

Daily protein intake should not be less than 0.8-1 grams per Kg of body weight.

Nutrition does not mean only caloric intake, but also replenishment of the very primary elements that the body uses to live. Nutritionists from different countries define the optimal daily replenishment levels of micronutrients depending on gender, age, and functional status (i.e., pregnancy, sporting activities, etc.). However, patients suffering from cancer will be almost always exhibiting to nutritional deficiencies.

Obesity itself is a malnutrition disease characterized by several deficiencies, including vitamin D deficiency. Many other deficits can be induced by specific therapies (i.e., those impairing renal tubular reabsorption through tubular damage, or intestinal absorption through mucositis, anorexia, and vomiting) and by treatments for related comorbidities (cholesterol-lowering agents, diuretics, anti-hypertensive drugs, etc...) resulting in minerals and antioxidants loss. These events may worsen the peroxidation phenomena of several biological structures, that will have been already compromised by metabolic syndrome and administration of chemotherapy.

Obesity is also associated with insulin resistance, i.e. the insulin inability, despite being available in physiological concentrations, of exerting its metabolic tasks in different body districts.

Insulin resistance assessment is performed in specialized centers, at times requiring expensive and complex methods. Such assessment could be easier by evaluation of blood glucose levels and fasting insulin levels according to the HOMA-IR algorithm, with values above 2.5 being indicative of insulin resistance.

Diet should not cause any further increase in insulin levels, either basal or food-induced.

The daily intake of carbohydrates (i.e., glycemic load) should be proportional with the body composition, the energy percentage (calculated in relation with other energy sources), and the degree of physical activity (including daily activities as well as activities planned by the rehabilitation system to reduce overweight and improve muscular function).

Carbohydrates intake should be progressively reduced throughout the day in light of the circadian increase in insulin resistance, more prominently observed during the last day hours.

Last but not least, it is necessary to avoid foods with high glycemic index (GI). The GI is determined by comparing the post prandial glycemic response of a food with the postprandial glycemic response to the same amount of available carbohydrate from a standard food in the same individual.

Baseline plasma levels of cytokines in obese people return to normal values after weight loss.

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3. Diet, caloric restriction and cooking: A therapeutic way

The nutritional sources of food themselves are different from those used by our ancestors. The production doesn't respect the proximity criteria (0 km), seasonality criteria, or crop rotation criteria, resulting in a loss of micro-elements in soil. Fruits and vegetables generally meet more the preservation criteria instead of those of maturation with the result of the unpredictability of their content in terms of micronutrients.

The taste for food has been gradually changing giving priority to a rapid food intake (fast food), high levels of fat, flour and refined sugar. The large use of sweetened drinks contributes to increase the excessive energy introduction.

As for oxygen free radicals (ROS) production, it is related to inflammation during oxidative stress.

In obese patients and in those with cancer the ROS problem has a special role; supplements or diets with high content of vegetables with antioxidant activity have been given. The use of fruits and vegetables showed positive results in reducing the risk for cancer and recurrences.

Data, however, are not univocal. Each vegetable contains many different compounds, their availability is not always in relation with their content (it is a typical example for Beta carotene of carrot), the contents of a type of antioxidant may differ for the production site, stage of maturation to collection, preservation, and preparation methods (tomato sauce contains more available lycopene than raw tomato). The availability of a substance may change in different individuals according to the integrity of the intestinal mucosa (often damaged by chemotherapy) or to the kind of intestinal flora (1-1,5 kg of bacteria). This condition can also modify the food chemical structure, producing harmful or healthy substances for our health as in the case of soy isoflavones transformed into the much more active Equol only in subjects with suitable bacteria. In our blood and urine there's a large amount of products of bacterial metabolism which may influence our health; it may differ depending on the breed, gender, functional states (pregnancy) and dietary habits: there's much more complexity in epidemiological studies with the use of the food or nutritional supplements than expected in the research protocol.

The real availability (absorption) of substances in food or in supplements has a good chance to be different from that hypothesized and calculated with questionnaires or bromatological tables.

Diet should not cause any further increase in insulin levels, either basal or food-induced.

The daily intake of carbohydrates (i.e., glycemic load) should be in proportional with the body composition, the energy percentage (calculated in relation with other energy sources), and the degree of physical activity (including daily activities as well as activities planned by the rehabilitation system to reduce overweight and improve muscular function).

Carbohydrates intake should be progressively reduced throughout the day according to the circadian increase in insulin resistance, more prominently observed during the last day hours.

Last but not least, it is necessary to avoid foods with high glycemic index (GI). The GI is determined by comparing the postprandial glycemic response of a food with the postprandial glycemic response to the same amount of available carbohydrate from a standard food in the same individual.

Often using fruit we take more attention to the amount (5 servings a day) and to the concentration in antioxidants rather than the sugar content, which brings us back to the problem of calories and metabolic syndrome (fructose plugged to lead to a lower insulin response, is indeed much more dangerous than glucose for the pathogenesis of metabolic syndrome).

Diet is often unbalanced, not respecting the right proportions between carbohydrates (60%), lipids (25%) and proteins (15%).

The use of processed foods induces a higher salt intake, with effects on blood pressure and 10 on the integrity of structures such as the gastric mucosa with possible susceptibility to cancer.

The use of sweetened drinks and refined flour, without fibers, which are characteristics of white bread and pasta, causes a rapid absorption of carbohydrates and a rapid elevation of blood glucose, followed by a massive insulin response. Insulin is a hormone with multiple activities involved in the regulation of blood glucose, the transport of amino acids, the mobilization of fat from their deposits, the monitoring of urine output and of cell proliferation.

Persistent high levels of insulin indicate a loss of activity of the hormone (insulin resistance) that goes together with obesity, dyslipidemia (low HDL cholesterol, high triglycerides), high blood pressure and, according to data, even the cancer.

Fast food diets, also known with the term “Cafeteria Diet”, are often characterized by an excessive fat content, often saturated, (those who melt at higher temperatures) contained in marbled meat, so defined because at a thin shear it shows impregnation of lipids within the muscle structure, typical of those animals kept under movement restriction.

A high-fatty acids diet an altered ratio between saturated and unsaturated fats, an alteration in the ratio of unsaturated omega-6 (those that have a double bond in position 6 from terminal COOH) and omega-3 (those that have the double bond in position 3, typical of fish, nuts, etc.) causes increase in blood inflammatory markers. In a state of inflammation it leads to resistance to insulin receptors, which is the first step for obesity and metabolic syndrome.

Foods with sugar and refined flour should be reduced or abolished. Bread and pasta should be made with whole grain flours, that give them a distinctive dark color, rice should be strictly integral.

As for pasta it should be investigated whether the product is integral outset or if fibers have been added to starch in a second time. The difference is huge because the slow release of the starch in an originally integral flour can give an IG <40% than the refined flour = 75%. Rice and pasta should never be overcooked.

It is absolutely necessary to avoid using fructose as an alternative to sucrose.

Salt is an important part in the preparation and storage of food. It is blamed for stomach cancer, but may be also critical for its action on blood pressure and, indirectly, on the metabolic and inflammatory situation. Very often it is not calculated in nutritional epidemiological studies in oncology.

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During the cooking process an improper use of heat can turn food into a non-profit element, even dangerous for health. The use of high temperatures for long periods can produce carcinogenic substances. The use of cooking helps the extraction of carotenoids from tomatoes and carrots, but degrades the antioxidants in cruciferous vegetables, often investigated for their anticancer properties. The problem regarding the cooking should be extended to the used instruments types (oven, microwave, fry, steam, etc.).

All food should be cooked with adequate methods, tools and cooking times. A typical example may be that of the french fries, for which the interest in compositional characteristics of nutritional caused a controversy about their potential toxicity, related to frying due to the formation of acrylamide.

4. Caloric restriction

Caloric restriction is an integral part of religion requirements in several countries (Islamic Ramadan, Orthodox Church abstinence during Christmas, Easter, Assumption, the Jewish tradition of Daniel's fasting, etc.).

Over the past 30 years there have been more and more studies addressing health benefits related to caloric intake reduction in animal models and in humans.

Data seem to show that maximum benefits may be achieved by applying the highest possible calory reduction without resulting in overt malnutrition, and by prolonging this status as long as possible.

In animal models, caloric reduction of not more than 10-40% of the normal calories intake exerts an anticancer effect which is directly related to its duration.

Caloric restriction induces changes in metabolic and hormonal status in a similar way among animals and humans.

Caloric restriction improves sensitivity to insulin and improves glucose metabolism.

Caloric restriction can reduce oxidative stress.

Caloric restriction can increase life expectancy in animals; however, the restriction of carbohydrates or lipids alone does not seem to influence this result, which instead appears to be related to the reduction in methionine intake by lowering consumption of animal proteins. One year-long caloric restriction alone, even without physical activity, can reduce several markers of inflammation in obese postmenopausal women, including C-reactive protein, serum amyloid, and IL-6.

Accordingly, the excess of caloric intake induces obesity and represents a risk factor for cancer.

From rodents to primates, including humans, caloric restriction has been shown to be one of the most powerful tools in the prevention of carcinogenesis.

However, epidemiological data deriving from forced restrictions during the events of II World War showed conflicting results.

Conversely, Norwegians with a mean caloric intake reduction of about 50%, maintaining a balanced diet, showed a reduction in the incidence of breast cancer compared to controls.

In the Netherlands, a caloric intake reduction (70% in adults, 50% children) was paralleled by an increase in breast cancer but not in other forms of cancer.

The survivors of German and Russian concentration camps showed a sharp increase in all forms of cancer.

This apparent inconsistency of results can be due, in our opinion, to the distinction between caloric restriction and forced malnutrition characterized by the presence of other factors such as emotional stress, infections, etc.

5. Physical exercise and walking prescriptions

5.1. What do you know?

About the component of physical exercise, the American Cancer Society recommends the exercise like part of a continuum of cancer survival care.

The physical exercise is able to reduce the risk to develop the breast cancer and colon on 25% and pulmonary cancer on 30%, uterine cancer and ovary cancer about on 20% and on 9% about the prostate cancer.

After the diagnosis and the treatment there is a reduction from 26 to 40% of recruitment of Brest cancer and of colon cancer with daily physical exercise and also good quality of life.

Also during the prostate cancer the aerobic and endurance physical activity can reduce the fatigue and improve the life's quality.

During the hematological cancer especially in non-Hodgkin lymphoma and multiple myeloma, the physical exercise can improve the quality of life with reduction of fatigue and also the aerobic capability in bone marrow transplantation.

The general benefits of physical exercise in cancer treatment are numerous and include: improved cardiac output, increased ventilation, improved flexibility and range of motion; increased muscular strength and endurance; decreased resting heart rate; improved stroke volume, vasodilatation, perfusion; improved metabolic efficiency; improved blood counts; improved psychological attitude to resist to the cancer disease. The cancer-specific benefits are related to cancer treatment toxicity especially to muscular degeneration with 1) fatigue and weakness, 2) neurotoxicity, 3) cardiotoxicity, 4) pulmonary toxicity.

Our therapeutic approach using the physical exercise and walking prescriptions is divided in 3 phases to: 1) recovery of residual capacity; 2) sensory-motor and functional recovery capacity; 3) the quality of life improvement.

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The recovery of residual capacity is designed to recovery joint mobility and to increase the uninjured muscle tone after reprogram of flexibility.

In the cancer patient there is usually a marked reduction of the flexibility.

Flexibility is one of the physiological parameters involved in almost all forms of the human movement and is similar to aerobic capacity, strength, and neuromuscular endurance in being a trainable fitness parameter.

Flexibility has been defined as mobility compliance and, alternatively, as the reciprocal counterpart of stiffness. Most of the authors define flexibility either as range of motion at or about a joint. Another definition represents flexibility like the ability of a joint to move throughout its potential range of motion. Those definitions confuse the property of flexibility with the criterion able to measure the range of motion and using hardly synonymous; since potential range of motion is a variable factor among others in deterring flexibility, flexibility cannot be understood simple as relative to it.

We define flexibility like the disposition of body tissues to allow, without injury, excursions at a joint or set of joints. This property is measured by, but not equivalent to, range of motion. Both joint tissues and the surrounding soft tissues contribute to flexibility, although only the latter should be modified in order to enhance flexibility.

To increase this capability is possible to use yoga, slow / static and dynamic stretching techniques, Pilates method; in our experience we prefer anyway Elispheric Imoove method (fig. 5) and exercises deriving from proprioceptive neuromuscular facilitation (PNF). This last technique is designed as a manual, partner-assisted stretching; a partner is needed to provide the fixed resistance against which the lengthened agonist isometrical contracted at or near maximum (to use spindle facilitation).

Some factors that affect flexibility are modifiable, subject to voluntary control to some or large extent, others are not modifiable.

Flexibility decreases with age. In cancer patients, it suggests that regular activities, in order to maintain elasticity, or to do specific stretching programs, are important for aging.

Gender is another factor that influences flexibility. Females are generally more flexible than males especially during the same stretching program; probably women have a larger percentage of elastin in their miofascia.

Flexibility varies during the course of the day. There is greater flexibility of cervical spine during the late afternoon and evening hours and about the lower lumbar spine data show an improvement during daytime later hours.

About the anatomical constraints, the excessive fatty tissue limits range of motion related to the tightness of soft tissue structures. This problem is connected with some conditions of diseases like arthritis, diabetes mellitus, hemophilia and finally the cancer but also is correlated to bad posture in orthostasis or with seated flexed posture.

Other ways to improve flexibility: massage, warm-up and stretching are three basic techniques used to increase flexibility but neither massage or warm-up is as efficient as a proper stretching regimen in increasing flexibility.

The best method to realize stretching involves a series of less than maximal isometric contractions of the agonist muscles in a pre-lengthened state (to set up the stretch), followed by concentric contractions of the antagonist muscle group (to lengthen the agonist) in conjunction with light pressure from a partner when needed and with an instrumentation like sensorized postural bench system (TecnoBody, Italy).Though this mode the objectives are to alleviate muscle tension, to facilitate healing by increasing blood flow, to decrease muscle pain by reducing vasoconstriction. This work is to applied day by day using at the cancer patients home a specific personalized postural bench like Fleximat postural bench (fig. 1 DeltaDue, Italy).

Figure 1. Fleximat

When it is not possible to get a flexibility increase in cancer treatment: there are specific contraindications, due to time and circumstances, where stretching should not be performed to get flexibility improvement. Especially when there are reduced joint receptor and pain sensation, when mobilization of tissue is not possible, for example in post-acute cancer surgical treatment or when stretching or tension in tissue elicits pain.

After the recovery the joint mobility with the flexibility replanning, the improvement of the uninjured muscle tone and strength should be possible using before focused vibratory acoustic

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stimulation at high intensity with Vissone (fig. 4 Vissman, Italy) and after anaerobic work with TRX system. Vibrations are able to induce muscular adaptions to the recovery of muscle tone at the 300 Hz, of frequency and to stimulate the upper motors centers in order to obtain a better performance of controls, responsible for the muscle recruitment. Is noted that so is possible to 1) activate the aerobic metabolism; 2) determine an analgesic effect; 3) increase local circulation and bone density; 4) finally increase the contractile capacity and elasticity of the muscle treated.

6. Walking prescriptions

To elicit the sensory-motor and functional recovery we need to get acceptable walking.

Human movement usually is defined by the walk and is not limited to bipedal locomotion; however, such locomotion is a fundamental part of daily life and is a prominent focus of public health physical activity guidelines.

The human gait is more complex; going one step forward, although it can start from the hip flexors of the Deep Frontal Line, especially the psoas and iliacus, afterwards, it involves the hip flexion, the knee extension, and the ankle dorsiflexion necessary to step forward, thanks to the myofascia of the Superficial Frontal Line. As the leg travels forward, the entire myofascia prepares to receive the weight of the body and the ground reaction.

Once the heel places on the ground and the step begins, the Superficial Back Line takes over as the back of leg engages into hip extension and plantar flexion. The abductors of Lateral Line, Ischio-Tibial-Tract, and the lateral compartment of the lower leg provide stability that prevents the hip adduction, while the adductor group and the other tissues of the Deep Frontal Line assist the flexion- extension motions and provide stability to the inner arch of the foot and up the inside of the leg. In the upper body, the common contralateral walking pattern involves the Functional Lines bringing the right shoulder forward to counterbalance the left leg when it swings forward and vice versa. Therefore the gist of walking capability is to improve the miofascial flexibility.

The walking objective monitoring evolution, using pedometer and accelerometer technology, offers an opportunity to perform guidelines, including recommendations for cancer patients.

All the studies in literature have used a variety of objective parameters using instruments that have been previously validated. The Yamax pedometer is considered a criterion research quality pedometer (Schneider et al., 2004), the Lifecorder's validity is well documented (Crouter et al., 2003; Schneider et al., 2004), and the ActiGraph has been adopted by national surveillance strategies (Troiano et al., 2008) and is probably the most utilized accelerometer in research today.

Therefore is possible to define with the pedometer the sedentary level into < 2,500 steps/ day (basally active) and into < 2,500 to 4,999 steps/day (limited activity); but using an established step-defined physical activity scale is possible to establish a level one for sedentary < 5,000 steps/day ; a level two >5,000 <7,499 steps/day for low active; a level three >7,500 <9,999 steps/day for somewhat active ; a level four >10,000 <12,499 steps/day for active; and a level five ≥ 12,500 steps/day for highly active.

We also noticed that healthy adults can perform between approximately 4,000 and 18,000 steps/day, and, in our opinion, also 7,500-9,9990 steps / day, resulting in between 50/ 85 steps /minute. That would be a reasonable target for the cancer patients in the first Mullan phase.

In order to get a better walking performance in the first phase of Mullan, and also in the second phase, we adopt two integrate procedures: 1) normalization of the foot-ground reaction forces using a personalized viscoelastic insoles to control vertical and shear forces on the foot during the stance phase without the obligatory use of athletic shoes; 2) use of the microgravitary system S.P.A.D (fig. 2) that determine the sensory-motor and functional recovery of the posture during the walking in combination to the development of proprioceptive information from the periphery to the cortical central system.

Figure 2. SPAD

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7. Physical therapies connected with psychophysical techniques

During the first year after the cancer treatment the immune system shows some specific changes in patient with cancer especially in some specific T-cell populations.

There is no scientific evidence that physical therapies, like magnetic fields, are effective in the treatment of cancer itself. Global physics community perfectly knows what the extreme low frequencies and intensity of magnetic fields are. They also know how they provoke the resonance of ions (Ion Cyclotron Resonance), with the exact frequency in order to remove an ion from its orbit of rotation in order to escape.

Only in the last decades the studies in biophysics have shown that with the ion cyclotron resonance is possible to stimulate the passage of ions through the membranes of the cells of the living beings changing their permeability and therefore improving the ion exchange on both sides of the membrane itself. The increase of the bioavailability of the essential ions, makes better the efficiency of the cell itself to achieve its correct metabolism.

The role of electromagnetic fields for control of cancer pain and chemotherapy nausea-induced symptoms remains controversial but this theory is to be correlate to water coherence domains' theory (G. Preparata, E. Del Giudice, G. Talpo 1999).

The activities and the exchanges of the molecules in the body doesn't happen by chance, but they follow an "order" dictated by the magnetic field produced by the water, where all the elements fluctuate in phase in the those regions called coherence domains.

Only the molecules which react to the frequency of this magnetic field, interact with each other, starting in ordered way the correct chemical reactions necessary for life of the cell and the organism. An imbalance of this 'order' jeopardizes the functioning of the cell, with the consequence of the manifestations of the diseases.

The 40% of the water is coherent and it can receive and deliver electromagnetic information, while the remaining 60% is not coherent, equally essential for life; it represents the solvent of the ions and of the fundamental elements to the cellular economy.

Also Montagnier L. in 2009 has recognized the validity of the coherence domains, stating how the water is not an inert substance, but may take special configurations emitting electromagnetic waves that can become an not pharmacological instrument of the therapy and the adjustment, but always deeply medical care.

The cells' DNA emits extremely low frequency waves, from zero to a few hundred of Hertz. The studies were published on the unbalance of this "range" that disturbs the harmony of the cell, with the onset of the manifestations of diseases. Some chronic diseases such as Alzheimer's, Parkinson's, multiple sclerosis, rheumatoid arthritis, and the viral diseases such as HIV -AIDS, influenza A and hepatitis C, "inform" the water of our body (biological water) of their presence issuing a special electromagnetic signals that can then be "read and decoded".

With Ion Cyclotron Resonance we have the possibility to intervene in a not invasive, natural and precise adjustment mechanisms of the body's homeostasis, where the only pharmacological support can be not complete.

Therefore you get the possibility:

1. To rebalance subjective metabolism
2. To adjust the enzyme functions, the ion channels and the body pH
3. To strengthen the immune system
4. To encourage the bioavailability and absorption of nutrients for cell metabolism
5. To treat neuralgia, headaches and migraines
6. To stimulate healing in all kinds of wounds, even after surgery.
7. To balance the water retention
8. To enhance the effect of drugs and supplements
9. To detoxify and to allow antioxidant function against free radicals, metabolites, toxins
10. To stimulate a pain-killer function (acute and chronic)
11. To get muscle relaxation, from anxiety and stress
12. To improve the homeostasis recovery under stress (physiological micro trauma and muscle protein catabolism)
13. To improve the quality of life for cancer patients.

In a preliminary observational study of 43 cancer patient group, they were divided into 3 groups of 14 patients, using also the Ion Cyclotron Resonance with QUEC PHISIS QPS1 (fig. 3) we observed the initial and final values of d-ROMs Test.

The first group only used the QUEC PHISIS QPS1

The second group used the QUEC PHISIS QPS1 and the antioxidants.

The third group only used the antioxidants.

The study shows a significant improvement after 90 minutes before the beginning of the first treatment. The values are improved and consolidated in the time after a month about the end of the cycle of treatments with the values well below average.

Figure 3. Qps 1

Figure 4. Viss

Figure 5. Imoove

8. Conclusion

The integration between the pharmacology, the biochemistry, the biophysics and the lifestyle with energetic modulation using therapeutic diet through the use of the information and the signals, probably will be able to restore a robust immune response in the tumor-bearing host or to promote by adoptive transfer of activated effector cells or tumor-specific antibodies into the tumor-bearing host.

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