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Dispersion of helical axes during shoulder movements in young and elderly subjects

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ABSTRACT

The shoulder complex (SC) consists of joints with little congruence and its active and passive structures ensure its stability. Stability of the SC rotation centre during upper arm movements can be estimated through the analysis of Helical Axes (HAs) dispersion.

The aim of this study was to describe shoulder HAs dispersion during upper limb movements performed with dominant and non-dominant arms by young and elderly subjects. Forty subjects participated in the study (20 young: age 24.8 ± 2.8 years and 20 elderly: age 71.7 ± 6.3 years). Subjects were asked to perform four cycles of 15 rotations, flexions, elevations and abductions with one arm at a time at constant speed. Reflective markers were placed on participants' arms and trunk in order to detect movements and the HAs dispersion with an optoelectronic system. Mean Distance (MD) from the HAs barycenter and Mean Angle (MA) were used as HAs dispersion indexes. Young subjects showed significant lower MD compared to the elderly during all motion ranges of rotation, flexion and elevation ($p < 0.001$). Moreover, the MD was lower in the dominant arm compared to the contralateral for rotation ($p = 0.049$) and flexion ($p = 0.019$). The results may be due to joint degeneration described in elderly subjects and differences in neuromuscular control of SC stability.

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1. Introduction

Movement of human body segments can be described as instantaneous rotations around axes perpendicular to the planes of motion. These axes are not fixed, but vary in orientation and position due to the morphology of joint surfaces and the variability of muscle activation. The consequence is a continuous displacement of the joint rotation centre during the whole range of motion (Illyés and Kiss, 2007; Koo and Andriacchi, 2008). This phenomenon is particularly emphasized when movement is performed simultaneously by different joints as in the case of the shoulder complex (SC) (Illyés and Kiss, 2007). The SC is composed of glenohumeral, scapulothoracic, acromioclavicular and sternoclavicular joints, permits hand orientation in space during daily life activities and is the most mobile complex of joints in the human body (Amabile et al., 2016; Forte et al., 2009; Illyés and Kiss, 2007). Moreover, the SC anatomy is characterized by little congruence among joint surfaces, which have to rely on capsular structure, ligaments and muscles in order to ensure joint stability (Blaimont et al., 2005; Halder et al., 2000). This condition gives an important role to neuromuscular control, in order to minimize the displacement of the SC centre of rotation (CoR) during upper limb movements (Blaimont et al., 2005; Doorenbosch et al., 2001).

CoR displacement can be estimated through the analysis of Helical Axes (HAs) dispersion. HAs represent the whole of the actual rotation axes, independently from the contribution of joints involved in a movement (Woltring et al., 1985). They do not correspond to an anatomical landmark and represent all axes, variable in position and orientation, around which a rigid body has a rotational movement when it occurs around more than one CoR (Kettler et al., 2004; Woltring et al., 1985). HAs have been studied on the ankle, knee and cervical spine (Barbero et al., 2017; Graf and Stefanyshyn, 2012; Grip and Häger, 2013) and their dispersion can be described as an index of joint stability by specific kinematic quantitative parameters (Cescon et al., 2014). The analysis of joint stability by HAs dispersion could be particularly interesting in the SC, where instability is a frequent clinical condition, dependent on anatomical structural defects or wrong muscular coordination

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(Assi et al., 2016; Heuer, 2007; Kircher et al., 2014; Sachlikidis and Salter, 2007). This coordination relies predominantly on dynamic muscular control and successful rehabilitation treatment of SC instability depends upon the comprehension of abnormal kinematics and neuromuscular patterns (Jaggi and Alexander, 2017).

Against this background, no studies have investigated SC stability in vivo in terms of CoR displacement through the analysis of HAs dispersion. Prior to applying this approach as a means to studying SC clinical conditions it is necessary to set up data collection of healthy subjects. Studies have documented age-related joint defects in asymptomatic subjects, such as cartilage degradation and osteophytes formation (Bonsell et al., 2000; Loeser, 2010) and neuromuscular control has been demonstrated as more accurate when movements are performed with dominant upper limb (Sainburg and Kalakanis, 2000). The hypothesis of this study was that the different joint conditions between young and elderly subjects or the different neuromuscular control between dominant and non-dominant arms could modify the SC HAs dispersion. Therefore, the aim of the study was to describe the SC HAs dispersion during upper limb movements performed with dominant and non-dominant arms in young and elderly healthy subjects. Collected data could be used as reference in studies about SC clinical conditions or for measuring results of SC surgery or rehabilitative interventions.

2. Methods

2.1. Participants

The study was conducted between March and September 2017 at the Humanitas Research Hospital of Milan. Forty healthy right-handed volunteers were enrolled in the study. Twenty subjects, aged between 20 and 30 years old made up the "young" group (YG) and twenty, aged over 65, formed the "elderly" group (EG). Participants were enrolled from among Humanitas University students, Humanitas Hospital employees, and relatives of the aforementioned groups. Exclusion criteria were history of upper extremity disorders or shoulder pain and occurrence of traumatic injuries in the last year. Finally, in order to exclude subjects with trained upper limbs, participants could not have performed jobs involving load mobilization, or practised agonistic sportive activities requiring upper limb abilities. All participants provided written informed consent and the study was approved by the Ethical Committee for Human Investigations of Humanitas Research Hospital.

2.2. Procedures

Studied movements were performed with subjects seated on a chair without back support, with the flexion of hips and knees set at 90° through the use of a goniometer with the back kept in a physiological posture. They were asked to perform four tasks with dominant and non-dominant arms. The tasks were spaced by a resting period of 5 min. As shown in Fig. 1, the tasks were:

- Shoulder rotation – subjects started a cycle of rotations maintaining the upper arm horizontal on the frontal plane with the forearm in vertical position and the elbow flexed 90° by a thermoplastic splint (neutral position between pronation and supination). They were asked to perform a shoulder internal rotation until the forearm reached the horizontal plane.
- Shoulder flexion – subjects started a cycle of flexions with the upper arm relaxed along the side and the palm of the hand facing the body. They performed 180° of shoulder flexion on the sagittal plane, with the elbow extended.
- Shoulder elevation – subjects started a cycle of elevations in the same position as shoulder flexion and performed 180° of upper limb elevation along an imaginary plane placed 45° between the sagittal and the frontal plane, with the elbow extended.
- Shoulder abduction – subjects started a cycle of abductions in the same position as shoulder flexion and performed 180° of abduction on the frontal plane, with the elbow extended.

Each task was composed of a cycle of 15 movements, performed at a constant speed without rest and paced by an audio-signal of a metronome. Shoulder flexion, elevation and abduction were performed at a frequency of 0.5 Hz, while shoulder rotation at a frequency of 1 Hz. The increase in frequency of shoulder rotation was adopted to ensure the same angular velocity of the other tasks, in which the requested RoM was double (90° for shoulder rotation, while 180° for flexion, elevation and abduction). Standardized instructions were delivered to subjects and they were instructed to maintain a constant speed, minimize trunk movements, not to move their hips and knees from the initial position and to keep their elbow extended during shoulder flexion, elevation and abduction. The initial arm position was standardized, in particular, at the beginning of the rotation task the angle of arm abduction was set at 90° by the same operator with the use of a goniometer. Participants were also asked not to look at the arm during the movements and continue the movement on change of direction. Before each task, participants were instructed by a physiotherapist

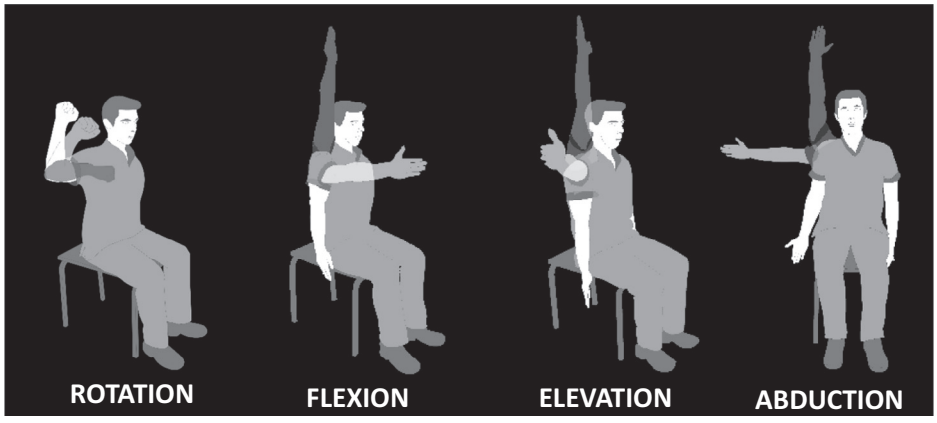

Fig. 1. The image shows the four tasks performed by subjects: each task is composed by a cycle of 15 movements, performed at a constant speed without rest.

on the movement to be executed, and were asked to perform it five times, in order to become familiar with the task and ensure a constant speed. The same physiotherapist randomized the order of the movements and the body side.

2.3. Data acquisition

Participants' movements were detected with an optical motion capture system (BTS SMART-DX, Italy) consisting of six infrared cameras located in standard points of a rectangular room. To identify the trunk, four retro-reflective markers (diameter 10 mm) were placed at the level of the incisura jugularis, xiphoid process, seventh cervical vertebra and eighth thoracic vertebra. To identify the arm, a cluster of five markers was placed on its lateral surface. The cluster was fixed through an inextensible band connected to Velcro straps fastened around the arm circumference, in order to avoid skin artefacts and to delete the between-group differences in term of soft tissues consistency (LaScalza et al., 2002). Two additional markers were placed on the angulus acromialis and on the ulnar styloid in order to facilitate the 3D reconstruction of the arm. Data acquisition was sampled at 100 Hz and an orthogonal dextral coordinate system was used with anterior, superior and right being positive. The tasks were also recorded with two optical cameras, in order to control the correct performance and posture of the subjects.

2.4. Data processing

The HA model accounts for the instantaneous relative movement of two rigid bodies, one respect to the other, as a composition of a rotation around an axis (defined as instantaneous Helical Axis) and a slide along the same axis (Söderkvist, 1990). In this study, the arm and the trunk were considered as two rigid bodies and their relative positions were calculated each time through a rotation matrix and a translation vector, which allowed for the direction vector, the rotation angle, the origin and the translation of each Helical Axis to be extracted (Söderkvist, 1990). In agreement with previous studies, HAs between arm and trunk were computed with an angle step of 10° (Cescon et al., 2014; Wesphal et al., 2013). The position of the trunk was normalized with respect to the arm and the first and the last movement of each cycle were removed in order to avoid artifacts or changes in angular velocity (Barbero et al., 2017). As shown in Figs. 2, HAs dispersion was assessed using Mean Distance (MD) and Mean Angle (MA) (Barbero et al., 2017).

Considering the plane crossed by the HAs and perpendicular to the Mean Axis (HA_0), where HAs dispersion is minimum, MD represents the mean distance between the HAs intersections and their barycentre. The distances from HAs barycentre are assumed to have a Rayleigh distribution and the expected value (MD) can be obtained with the equation:

$$\bullet\ MD = \frac{\sum_i^N d_i}{N} = \sigma\sqrt{\frac{\pi}{2}} = \sqrt{\sigma_x\sigma_z}\sqrt{\frac{\pi}{2}}$$

where d_i is the distance of each point from the barycentre and the $\sigma_x\sigma_z$ are the standard deviations of the distribution of the coordinates of each point in the plane ZX.

The MA represents the mean value of the angles between each HA and HA_0 and shows the ability to maintain the same plane of motion during a movement (Grip et al., 2008). The range of motion (RoM) of the upper arm with respect to the trunk was also measured for each movement using quaternions. In accordance with previous studies, the quaternions method was used to avoid singularities and to be as accurate as possible in arm motion representation over time (Herda et al., 2003; Phadke et al., 2011). Finally, each movement was also divided into portions of RoM and MD and MA were evaluated for each of them. In particular, the shoulder rotation was divided into two portions of 30° and a portion over 60°, while flexion, elevation and abduction movements were divided into three portions of 30° and a portion over 90°. Data were processed using Matlab Mathworks Inc, Natick MA, USA.

2.5. Statistical analysis

All measurements were checked for normality through the Kolmogorov-Smirnov test. Parametric and non-parametric variables were described as mean and standard deviation or median and range respectively. Two tails T-test and Mann-Whitney test were used to compare YG and EG and dominant and non-dominant arms. One-way Analysis of Variance (ANOVA) and the

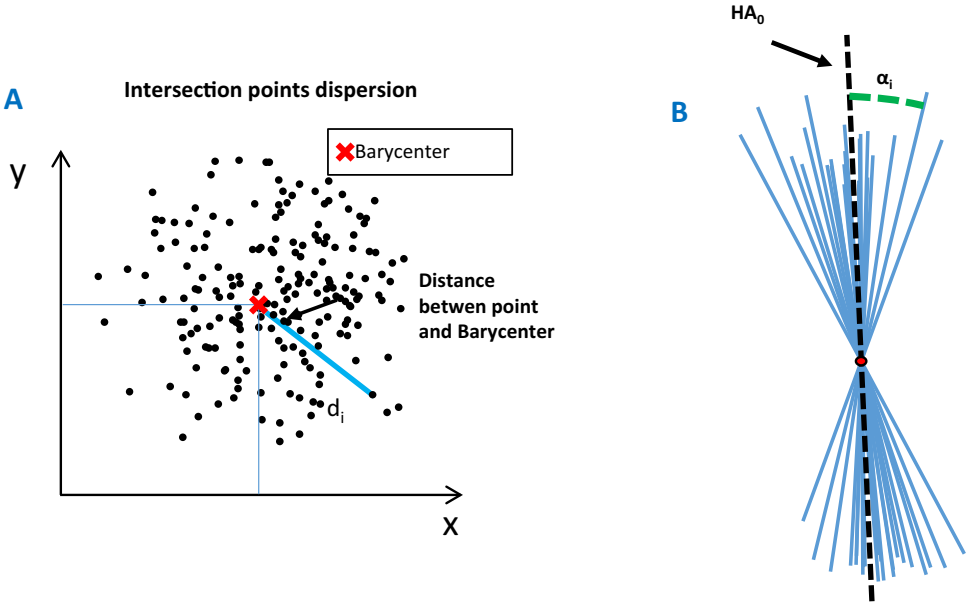

Fig. 2. (a) Representation of the HAs Mean Distance (MD) count, corresponding to the average distance between the intersection points and their barycenter. (b) Representation of the HAs Mean Angle (MA), corresponding to the average of the angles (αi) between each helical axis and the mean axis (HA0).

Kruskal Wallis test with Bonferroni adjustment for multiple comparison were used to compare MD and MA values among the portions of RoM. Statistical level of significance was set at $\alpha = 0.05$. Data were analyzed using SPSS Statistics 20.0 for Windows.

3. Results

All 20 participants of YG (mean age 24.8 ± 2.8 years; mean height 171 ± 6 cm; mean weight 77.2 ± 4.3 kg) and the 20 participants of EG (mean age 71.7 ± 6.3 years; mean height 167 ± 5 cm; weight 75.8 ± 4.1 kg) completed the evaluation correctly.

3.1. Young versus elderly group

This comparison was achieved by gathering data of dominant and non-dominant arms. Table 1 shows the results.

- Shoulder rotation movements revealed lower MD and MA ($p < 0.001$) and greater RoM (YG: 81.5° ± 3.5°, EG: 79.2° ± 4.7° $p = 0.014$) in YG. The division of RoM in portions maintained this difference for MD ($p < 0.001$) and MA ($p = 0.027$ for 0-30°, $p = 0.001$ for 30–60°, $p < 0.001$ over 60°).
- Shoulder flexion movements revealed lower MD and a greater RoM (YG: 154° ± 10.7°, EG: 143.2° ± 14.4° $p < 0.001$) in YG. The division of RoM in portions maintained this difference for MD ($p < 0.001$).
- Shoulder elevation movements revealed lower MD and a greater RoM (YG: 151.8° ± 7.7°, EG: 136.7° ± 16° $p < 0.001$) in YG. The division of RoM in portions maintained this difference for MD ($p = 0.013$ for 0–30°, $p = 0.001$ for 30–60°, $p < 0.001$ for 60–90° and over 90°).
- Shoulder abduction movements revealed a greater MA ($p < 0.001$) and RoM (YG:154.2° ± 6.7°, EG: 132.9° ± 17.7° $p < 0.001$) in YG. The division of RoM in portions maintained the difference in MA ($p = 0.009$) only in the portion over 90°.

Finally, in each of the four tasks in both YG and EG, MD and MA did not differ among the RoM portions.

3.2. Dominant versus non-dominant side

This comparison was made by gathering data of young and elderly people. Table 2 shows the results.

- Shoulder rotation movements revealed a lower MD ($p = 0.049$) and MA ($p < 0.001$) on dominant side. No difference was found in RoM (YG: 80° ± 4.5°, EG: 80.7° ± 4°). On dividing RoM in portions this difference remained for MA ($p = 0.009$ for 0–30°, $p = 0.001$ for 30–60°, $p = 0.005$ over 60°).
- Shoulder flexion movements showed lower MD ($p = 0.019$) on dominant side. No difference was found in MA and RoM (YG: 147.8° ± 14.7°, EG: 149.3° ± 12.8°). On dividing RoM in portions this difference remained for MD over 90° ($p = 0.032$).
- Shoulder elevation and abduction movements showed no difference in MD, MA and RoM (YG: 145.4° ± 12.7°, EG: 143° ± 16.8° for shoulder elevation, YG: 144.3° ± 13.9°, EG: 142.8° ± 19.9° for shoulder abduction) between dominant and non-dominant side.

Finally, in each of the four tasks on both dominant and non-dominant sides, MD and MA did not differ among the RoM portions.

3.3. Discussion

The aim of this study was to evaluate HAs dispersion in dominant and non-dominant arms of young and elderly healthy subjects during upper limbs movements. The main finding is that young subjects showed significant lower HAs dispersion in all the studied tasks, independently of the considered portion of RoM. Moreover, HAs dispersion resulted lower in the dominant arm with respect to the contralateral arm. These results could be discussed considering two aspects: joint degeneration and decrease of motor control.

Concerning joint degeneration, Grip et al. accounted the irregularities of joints structures as a cause of increased CoR displacement (Grip et al., 2008). Degenerative changes have been found in several structures involved in shoulder stabilization of asymptomatic older adults (Prescher, 2000; Roldan-Jimenez and

Table 1
Comparison between young and elderly group for Mean Distance (MD) and Mean Angle (MA). Data are shown as mean and standard deviation for MD and as median and range for MA. * $p < 0.05$ for MD ** $p < 0.001$ for MD § $p < 0.05$ for MA §§ $p < 0.001$ for MA.

		MD (cm)		MA (°)	
Movement type	RoM portion	Young	Elderly	Young	Elderly
Rotation	Total RoM** §§	0.87 ± 0.22	1.4 ± 0.65	3.6 (1.8–17)	8.4 (2.1–23.6)
	0-30° ** §	0.86 ± 0.22	1.43 ± 0.87	3.9 (1.7–23.8)	5.5 (1.2–25.5)
	30-60° ** §§	0.86 ± 0.21	1.41 ± 0.71	3.3 (1.9–24.3)	5.8 (1.7–23.7)
	Over 60° ** §§	0.88 ± 0.26	1.51 ± 0.95	3.1 (1.5–20.5)	6.3 (2.2–18.9)
Flexion	Total RoM**	1.29 ± 0.29	1.75 ± 0.46	6.2 (4–11)	6.4 (4.1–12.6)
	0–30° **	1.38 ± 0.39	1.81 ± 0.62	4.6 (2.2–14.8)	5.3 (2.9–17)
	30–60° **	1.32 ± 0.29	1.81 ± 0.61	5.1 (2–20)	4.7 (2.8–23.5)
	60–90° **	1.36 ± 0.32	1.83 ± 0.62	5 (2.2–22)	5.4 (2.4–22.2)
	Over 90° **	1.25 ± 0.26	1.76 ± 0.48	5.8 (1.8–12.3)	6 (3.3–12.5)
Elevation	Total RoM**	1.59 ± 0.39	2.11 ± 0.74	5.1 (3.3–8.8)	5 (3.2–14.3)
	0–30° *	1.71 ± 0.62	2.09 ± 0.72	4.4 (2.3–29.3)	4 (2.5–19.7)
	30–60° **	1.63 ± 0.43	2.11 ± 0.72	4 (1.7–27.3)	4.1 (1.9–25.9)
	60–90° **	1.63 ± 0.42	2.14 ± 0.75	3.9 (1.5–31.6)	4 (1.5–28)
	Over 90° **	1.55 ± 0.37	2.07 ± 0.65	4.5 (2.6–15.8)	5 (2.8–26.6)
Abduction	Total RoM§§	2.09 ± 0.72	2.19 ± 0.53	8.8 (4.6–13.3)	6.7 (3.5–12.2)
	0–30°	2.13 ± 0.73	2.16 ± 0.62	5 (1.3–32)	4.7 (2.3–16.2)
	30–60°	2.06 ± 0.71	2.3 ± 0.77	5.5 (2.1–35.3)	4.8 (2.3–21.8)
	60–90°	2.08 ± 0.75	2.27 ± 0.7	7.9 (2–27.6)	5.7 (2.2–23.3)
	Over 90° §	2.16 ± 0.89	2.15 ± 0.5	7.6 (3–13)	5.3 (2.6–12.9)

Table 2
Comparison between dominant and non-dominant arm for Mean Distance (MD) and Mean Angle (MA). Data are shown as mean and standard deviation for MD and as median and range for MA.* $p < 0.05$ for MD ** $p < 0.001$ for MD § $p < 0.05$ for MA §§ $p < 0.001$ for MA.

		MD (cm)		MA (°)	
Movement type	RoM portion	Dominant	Non-dominant	Dominant	Non-dominant
Rotation	Total RoM* §§	1.01 ± 0.47	1.26 ± 0.6	3.7 (1.8–23)	8.6 (2.3–23.6)
	0–30° §	1.07 ± 0.62	1.22 ± 0.55	4 (1.2–23.8)	6.6 (1.9–25.5)
	30–60° §§	1.02 ± 0.5	1.25 ± 0.65	3.3 (1.7–19.1)	5.7 (1.9–24.3)
	Over 60° §	1.03 ± 0.5	1.36 ± 0.94	3.5 (1.5–18.9)	6 (2.1–20.5)
Flexion	Total RoM*	1.4 ± 0.38	1.64 ± 0.48	6.4 (4–11)	6.5 (4.2–12.6)
	0–30°	1.52 ± 0.51	1.67 ± 0.61	4.5 (2.2–16.6)	5.4 (3.2–17)
	30–60°	1.46 ± 0.46	1.67 ± 0.58	4.7 (2–23.5)	5.5 (2.8–21.1)
	60–90°	1.48 ± 0.45	1.71 ± 0.61	5 (2.2–22)	5.5 (2.4–22.2)
	Over 90° *	1.4 ± 0.41	1.62 ± 0.49	6.3 (3.4–12.3)	5.7 (1.8–12.5)
Elevation	Total RoM	1.87 ± 0.69	1.84 ± 0.6	5.2 (3.3–12.4)	4.7 (3.2–14.3)
	0–30°	1.88 ± 0.66	1.93 ± 0.74	4 (2.3–29.3)	4.2 (2.7–7.5)
	30–60°	1.88 ± 0.66	1.86 ± 0.61	3.8 (1.7–27.3)	4.1 (1.9–23.1)
	60–90°	1.89 ± 0.69	1.88 ± 0.63	3.6 (1.5–31.6)	4.2 (1.9–25.5)
	Over 90°	1.8 ± 0.57	1.82 ± 0.61	4.5 (2.6–15.8)	5 (2.8–26.6)
Abduction	Total RoM	2.18 ± 0.68	2.11 ± 0.57	7.3 (3.5–13.2)	8 (3.8–13.2)
	0–30°	2.27 ± 0.77	2.02 ± 0.54	4.9 (2.3–32)	4.6 (1.3–20.3)
	30–60°	2.26 ± 0.8	2.1 ± 0.68	5.7 (2.4–35.3)	4.6 (2.1–27.4)
	60–90°	2.22 ± 0.8	2.13 ± 0.66	6.6 (2–27.6)	6.4 (2.2–25.9)
	Over 90°	2.19 ± 0.79	2.12 ± 0.65	5.6 (2.6–13)	7.5 (2.7–12.9)

Cuesta-Vargas, 2016). In particular, these degenerative processes mainly affect the glenohumeral joint surfaces, the ligaments and the glenoid labrum, leading to a decrease in congruence between the humeral head and the glenoid cavity (Pfahler et al., 2003; Prescher, 2000). The acromioclavicular joint is also affected by deformation as is the case of the rotator cuff muscles and the tendons, which often appear atrophic and damaged in elderly asymptomatic subjects (Bonsell et al., 2000; Roldan-Jimenez and Cuesta-Vargas, 2016).

As for the decrease of motor control, several studies have shown age-associated impairments in neuromuscular control, able to influence motor dexterity during upper limbs movements (Enoka et al., 2003; Shinohara et al., 2011). Moreover, low accuracy and increased variability in motor performance were described in the elderly during upper limb movements. This phenomenon seems to be linked to age-related sensory alterations, which influence the mechanical stability of the involved joints (Krampe, 2002; Kwon et al., 2014; Shadmehr et al., 2010).

In the present study, shoulder abduction showed the greatest MD with no differences between the RoM potions, independently of age and upper arm side. This finding could highlight the importance of sensory control for shoulder stability, since movements in frontal plane are less controlled by sight. Moreover, it is worth noting that shoulder abduction is in an infrequent movement during the activities of daily living (Aizawa et al., 2010; Magermans et al., 2005).

MA variability means that the movement is performed moving from the correct plane of movement and a decreased ability to maintain a constant plane of motion mainly emerged during the rotation movements performed by both the EG and the non-dominant side. During this task, participants were asked to keep their arm actively abducted at 90° and their difficulty may have arisen from the need to control two planes of movement (frontal and horizontal) differently on flexion, elevation and abduction movements (Ketcham et al., 2004; Scholz et al., 2001; Seidler et al., 2002). On the contrary, MA in abduction over 90° was lower in EG, probably for the less RoM expressed by this group.

Literature data described several inter-limbs differences in motor control during upper limb movements, suggesting the employment of specific mechanisms of neural control (Sainburg and Kalakanis, 2000; Schaffer and Sainburg, 2017; Zuoza et al., 2009). In particular, the dominant upper limb showed a more accurate motor control in movements requiring great shoulder excursion, as in the case of the present study (Sainburg et al., 2000). Moreover, similarly to what was already hypothesized, also the greater motor expertise and practice of dominant arm could be one reason for some results. (Carson et al., 1992; Mieschke et al., 2001). Finally, the differences in MD were more pronounced in the comparison made between YG and EG, when the decrease of motor control is likely associated to anatomical degenerations. Some limits of this study need to be underlined. First, we cannot to be sure that differences in skin artifact between young and elderly groups have not influenced the presented results. However, the inextensible band placed on the arm should have limited this possibility. Moreover, despite the instructions to follow the rhythm imposed by the metronome, we cannot exclude variability in maintaining the fixed speed during the execution of the tests. Finally, any differences in tendency towards fatigue between groups may have also influenced the results. This point could be particularly relevant in the rotation task, as fatigue could have affected the ability to maintain the upper arm at a steady level of elevation, thus increasing HAs dispersion irrespective of motor control. However, the visual assessment permitted by the optical cameras did not show any evident unwanted movements of the upper limbs. Nevertheless, fatigue itself could have influenced HAs dispersion, as it has been shown to alter muscle timing, coordination and kinematics, representing a variable able to decrease motor control (Cowley et al., 2014; Ebaugh et al., 2005).

In conclusion, presented results showed a lower shoulder complex CoR displacement in young healthy adults as well as in the dominant upper arm, mainly for a better neuromuscular control of shoulder complex stability. The results could be used as reference in further studies addressed at investigating shoulder complex CoR displacement after rehabilitation or shoulder surgery.

4. Conflict of interest statement

The authors have no conflict of interest related to the manuscript.

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