Residual limb volume changes in transfemoral amputees

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Abstract

This study constitute the first attempt to systematically quantify residual limb volume changes in transfemoral amputees. The study was carried out on 24 amputees to investigate changes due to prosthesis doffing, physical activity, and testing time. A proper experimental set-up was designed, including a 3D optical scanner, to improve precision and acceptability by amputees. The first test session aimed at measuring residual limb volume at 7 time-points, with 10 minute intervals, after prosthesis doffing. This allowed for evaluating the time required for volume stabilization after prosthesis removal, for each amputee. In subsequent sessions, 16 residual limb scans in a day for each amputee were captured to evaluate volume changes due to prosthesis removal and physical activity, in two times per day (morning and afternoon). These measurements were repeated in three different days, a week apart from each other, for a total of 48 scans for each amputee.

Volume changes overtime after prosthesis doffing showed a two-term decay exponential trend (R^2 = 0.97), with the highest change in the initial 10 minutes and an average stabilization time of 30 minutes. A statistically significant increasing effect of both prosthesis removal and physical activity was verified. No differences were observed between measures collected in the morning and in the afternoon.

1. Introduction

DESPITE the advancements in the prosthetic design and the enhancements concerning wearable robotic platforms [1], [2], most amputees still complain about discomforts related to the prosthetic physical human-machine interface (pHMI), *i.e.* the socket [3–6]. An optimal prosthetic socket must be comfortable for the user, while ensuring stable fitting and proper load transmission, especially in lower limb prostheses. These requirements are conditioned by residual limb volume fluctuations. In fact, residual limb volume changes can compromise the prosthesis fitting which can, in turn, cause relative socket-residual limb movements, alter the stress distribution on tissues, involve dermatological problems (*i.e.*, ulcers, irritations, vascular occlusions, dermatitis, blisters *etc*) and pain for the user [3], [7].

Such volume fluctuations are particularly relevant during acute and post-acute operative recovery periods (*i.e.*, 12–18 months after amputation) [8–10], albeit they occur in stabilized amputees (*i.e.*, + 18 months since amputation) as well [10]. Changes of the residual limb volume are mainly due to body weight increase and peripheral vascular diseases (*e.g.*, increased blood pooling in venous compartment, excessive arterial vasodilatation and changes in interstitial fluid volume) [10]. The prosthesis suspension system and the socket size can further exacerbate these phenomena. As matter of facts, earlier studies have documented an increased volume after prosthesis doffing when vacuum suspension systems are used; noticeably, the rate of variation depends on the applied vacuum pressure [10–13]. On the contrary, suspensions not based on vacuum, *e.g.*, pin locking systems, seem to mainly cause volume reductions after prosthesis removal [14]. Moreover, physical activity, diet, weather conditions, comorbidities, and several other factors can impact these changes [15]. All in all, these factors involve a rate of variation in volume ranging from − 11% to + 7% in transtibial amputees [16].

Despite the widely documented variation of residual limb volume in transtibial amputees, to the best of our knowledge, no reliable data pertaining to transfemoral amputees are available in literature (*see*TABLE S1*in supplementary material*). The skewed distribution of studies toward the population of below-knee amputees can be ascribed to different reasons such as the more straightforward measurement set-up and the more compelling need to reduce pain in bony regions. Specifically, an improper fitting of the prosthetic socket may involve high stresses on soft tissues more frequently in transtibial amputees than in transfemoral ones, because of the wide bony prominences at the residual limb-socket interface [3]. On the other hand, the larger volume of soft tissues in transfemoral residual limbs can be subjected to even larger fluctuations [17], highly affecting comfort and fitting of the prostheses. Accordingly, volume fluctuations in the residual limb of transfemoral amputees deserve to be in depth analyzed to provide suitable reference values for the design of novel prosthetic sockets.

This work aims at filling this gap in the state-of-the-art and to quantify the volume fluctuations occurring in the transfemoral amputee population. Volume changes due to prosthesis doffing and physical activity were investigated on 24 enrolled amputees, both in the morning and in the afternoon, resulting in 16 scans per day for each amputee. The protocol was repeated three times in three different days, a week apart from each other, resulting in 48 scans for each amputee. We envisage that the outcomes of this study will help in identifying the requirements for the design of smart adjustable sockets, similarly to what has been done for transtibial prostheses [18].

2. Methods

A. Subjects

This study was approved by the ethical committee "*Area Vasta Emilia Centro, Regione Emiglia-Romagna CE-AVEC*" (protocol ID: P-PPRAI1/2 − 01, CE protocol reference number: 105/2018/OSS/AUSLBO, date of registration: 11/05/2018; ClinicalTrials.gov ID: NCT04709367, date of registration: 12/01/2021) and carried out at the INAIL Prosthetic Center (Bologna, Italy). All experiments were performed in accordance with the World Medical Association's Code of Ethics and the Declaration of Helsinki. All recruited subjects signed an informed consent.

The inclusion criteria determined the involvement of stabilized (*i.e.*, time since amputation > 18 months) transfemoral amputees between 18 and 65 years old. Subjects with concurrent medical issues or unable to safely perform the physical tasks required in the experimental protocol were excluded.

To identify the target number of subjects needed to obtain a statistical power of 95%, a preliminary study was carried out on 6 transfemoral amputees, to measure residual limb volume fluctuations due to physical activity. Results of this preliminary study are reported in [19]. Then, using these data, the following equation was applied for the sample size estimation (paired t-test) [20]:

$$n = \left[\frac{\left(z_\alpha + z_\beta\right) \sigma}{\delta} \right]^2$$

1

where β is the type II error probability (0.05) for the desired statistical power of 95% (power = 1 - β), α the desired significance level (0.05), z_α and z_β the standard normal scores for confidence level α and β respectively, σ the population standard deviation (0.051 dm^3), and δ the expected difference (0.040 dm^3), both found in [19]. Thus, the target subjects number, n, resulted equal to 24.

B. Measurement systems for the assessment of residual limb volume

Residual limb volumes can be measured through many techniques, as we widely described in [10]. In this section, we will briefly recapitulate them in order to clarify the rationale undergoing the methodological approach used in this study.

The simplest measurement system for the assessment of residual limb volume consists in dipping the residual limb or its cast within a box filled with water, and measure the water displacement [21]. However, this technique is susceptible to errors due to subject's movements and surface tension at the limb-water interface, thus resulting in a low reliability [10].

Anthropometric models can be reconstructed by importing anatomical landmarks distances, measured by tapes or calipers, but these models are not accurate enough to guarantee reliable results [22], [23]. Furthermore, as all techniques involving contact with tissues, anthropometric measurements influence the residual limb shape during the evaluation [10].

Magnetic Resonance Imaging, ultrasound and spiral X-ray Computed Tomography can detect changes in volume and internal residual limb structures. Nevertheless, they are costly, invasive, and affected by errors due to subject's movements. In addition, they are time-consuming and not fast enough to allow for measurements of volume changes due to prosthesis doffing.

More recently, Sanders *et al.* [24–28] developed a bioimpedance device to measure the conductive tissue extracellular fluid (ECF) volume of transtibial residual limbs while donning the prosthesis. As a drawback, only ECF volume can be acquired, without including the one of bone and adipose tissues.

Measurement strategies comprising the use of a portable 3D scanner are among the most efficient solutions, as demonstrated by de Boer-Wilzing *et al.* [29]. Thanks to the recent developments in 3D scanning, these systems are nowadays reliable, safe, fast and portable. All these features are fundamental for clinical applications [15], [30]. Dickinson *et al.* [31] have evaluated the accuracy of three handheld 3D scanners: high reliability and accuracy for the VIUScan marker-assisted laser scanner and the Go!SCAN 3D optical scanner were demonstrated (both metrology-grade scanners of Creaform Inc; Canada). Moreover, the Go!SCAN50 scanner allows for a specific body-scanning option (namely *semi-rigid positioning*), consisting of an algorithm implementation within the acquisition software able to compensate small body tremors associated to the hand holding the scanner and to the scanned object. Furthermore, marker dots are not needed to be applied on the object to be scanned, thanks to the system ability to capture the object natural features. Thus, a 3D scanner based approach including the Go!SCAN50 was selected for the assessment of the volume fluctuations of transfemoral residual limbs in the framework of this study.

C. Experimental setup and Data acquisition

To yield the protocol reliable and acceptable for the enrolled amputees, a dedicated experimental set-up was developed (Fig. 1a). It included a mechanical support, adequately designed to help the enrolled amputees standing on the sound limb in a stable and comfortable way during scanning. A laser level and a laser meter were used to project two perpendicular lines on the anterior surface of the residual limb and a dot on the distal end, respectively. Such tools were positioned at the beginning of the protocol for each amputee and were kept in position until the end. The two lines and the dot, projected on the residual limb, were drawn before starting the tests, to identify the same limb orientation for all the scans. A mirror was placed in front of the amputee to allow for visual feedback, hence helping to maintain the same position. Before starting, four dots were drawn on the residual limb as anatomical landmarks to uniquely identify a scan cutting plane; they were used afterwards in the post-processing of the 3D image data. One dot was drawn on the ischial tuberosity, one on the external surface of the greater trochanter, and the two remaining dots were drawn on a horizontal axis, about 1 cm distally with respect to the great trochanter, and located about 5 cm anteriorly and 5 cm posteriorly on the skin (see Video 1*in supplementary material*). All dots were drawn by an expert prosthetist which identified the bony prominences by palpation. These body regions were selected since usually featured by minimal volume changes because of the presence of bony structures with a few soft tissues [10].

Scan files were acquired with the VXelements software (Creaform Inc; Canada), that allows for real-time visualization of the 3D image data (Fig. 1b, *see Video 1 in supplementary material*). Once the acquisition was completed, the mesh optimization was carried out (*i.e.*, filling holes, eliminating bad frames, performing data clean-up, smart decimation). Then, the meshes were imported in the VXmodel software (Creaform Inc; Canada) for post-processing. Three different options can be chosen in the software for aligning scans: (*i*) *Global registration*, (*ii*) *Surface Best-Fit alignment* and (*iii*) *N-Point alignment*. To select the best tool, 3 consecutive scans of a lower limb were performed on 4 not-amputated subjects, resulting in a total of 12 scans. Based on these data, the *Surface Best-Fit alignment* was selected (Table 1) since it involves the smallest volumetric error, as averaged across subjects.

The *Surface Best-Fit* tool aligns the meshes using their common surface when they are not in the same referential by considering one mesh fixed. Thanks to the *Pre-align* option of the tool, it was possible to select at least 3 points on the fixed mesh, and then the same points on the mobile one (Fig. 1c). Thus, the dots drawn on the residual limb as anatomical landmarks - visible in the acquired scan textures - were used (*see Video 1 in supplementary material*). Once the common points were selected, the *Surface Best-Fit alignment* was completed (Fig. 1d). Since the software allows for cutting meshes along planes, the point drawn on the ischial tuberosity, and the other two about 1 cm distally with respect to the great trochanter, were used to define the scan cutting planes (Fig. 1e). The resulted holes were filled in a planar way and the volume was computed by the software (Fig. 1f).

Table 1
Mean ± standard deviation of the volumetric error [%] of the 3 consecutive scans of a lower limb of 4 not-amputated subjects, for the three alignment tools of the VXmodel software.

Global registration	***Surface Best-Fit***	***N-Point***
0.338 ± 0.097	0.313 ± 0.072	0.315 ± 0.245

D. Experimental Protocol

Results reported in [19] highlighted that each amputee is featured by a specific time of stabilization in volume after doffing the prosthesis. Hence, the experimental protocol was constituted of four test days and defined as follows.

1st session: during this test session (Fig. 2 – Monday week 0), a resting period of 10 min was scheduled upon arriving in order to reach a homeostatic condition of the limb within the prosthesis. Then, the prosthesis was doffed, the amputee was helped to reach the mechanical support of the experimental set-up and 7 scans were acquired at intervals of 10 min in a standing position. This session allowed for the characterization, over time, of the residual limb volume changes due to prosthesis removal and for the identification of the time required to stabilize the residual limb volume for each amputee. More in detail, volume change was calculated starting from minute 20 and until it was lower than the error evaluated for the 3D body scanning method (*i.e.*, 0.313%; Table 1). By that time, volume was considered stabilized.

2nd session, 3rd session, 4th session: further three sessions of tests were performed in three different days, a week apart from each other (Fig. 2 – Tuesday week 0, Tuesday week 1, Tuesday week 2). Each session was featured by two testing times, one in the morning and one in the afternoon. During both (morning and afternoon), upon arrival, the amputee rested for 10 minutes with the prosthesis donned. Then, 2 consecutive scans were performed immediately after prosthesis doffing. Other 2 consecutive scans were carried out after the amputee's stabilization time (evaluated in the 1st session). Then, the amputee donned the prosthesis and 15 minutes of physical activity were performed (*i.e.*, walking at a self-selected speed on a treadmill) and the same scanning sequence (*i.e.*, 2 scans just after doffing the prosthesis and 2 scans after the residual limb volume stabilization) was repeated. This resulted in 48 scans for each amputee.

E. Statistical analyses

All statistical tests were carried out in IBM SPSS Statistics environment and the significance level was set equal to 0.05.

1st session: the normality of the volume data acquired in this test session was verified (Kolmogorov-Smirnov's test and Shapiro-Wilk's test), while the assumption of sphericity was violated (Mauchly's test) ($p = 0.05$). Accordingly, the 1-way ANOVA with repeated measures and the Greenhouse-Geisser correctional adjustment was used to investigate the effects of the factor *time* (7 levels; *i.e.*, time points at 10 min interval) on the measured volume (H_0: no difference among sample means at different time-points). Then, Bonferroni post-hoc comparisons were carried out.

The mean and the standard deviation of the post-doffing volume changes over time were calculated, using the first scan ($t = 0$, Fig. 2 – Monday week 0) as the reference. Then, the curve trend of the measured data was fitted in Matlab R2018a.

2nd session, 3rd session, 4th session: during each session, volumes were computed and averaged between the 2 consecutive scans resulting at each time-point (Fig. 2). This resulted in 8 volume values per day for each amputee. Afterward, these volume values were averaged over the three different test days, resulting in 8 values for each amputee at the specific time-points of the day. The normality (Kolmogorov-Smirnov's test and Shapiro-Wilk's test) and the sphericity (Mauchly's test) of data distribution were preliminarily verified. Then, the 3-way ANOVA with repeated measures was performed to investigate the effects of factors: *testing time* (2 levels: morning vs afternoon), *physical activity* (2 levels: before vs after physical activity), *prosthesis removal* (2 levels: immediately after prosthesis doffing vs after the stabilization time), and their interactions on measured volume.

3. Results

A. *Subjects and baseline condition (1st session)*

The general features of the enrolled amputees are summarized in Table 2. All subjects were traumatic amputees. Only one female took part in the study. The 20.8% of subjects reported a recent amputation (2–5 year) and the 79.2% was chronic (> 5 year). The majority of enrolled subjects wore a quadrilateral socket (54.2%) and a suction suspension system based on a unidirectional valve (91.7% in total: 50% without a liner and 41.7% with a Seal-In liner). The mean self-selected speed during walking on the treadmill resulted equal to 0.6 ± 0.1 m/s.

Table 2
Subjects' general features, time required to stabilize the residual limb volume, t* [min], and self-selected speed on the treadmill, v [m/s].

	Age	t since amp.	K	Socket Design	Socket Susp.	t*	v
S1	42	14	K3	Cat-Cam	Seal-In	40	0.4
S2	63	33	K2	Ics	Suction	20	0.4
S3	58	5	K4	Sub-Isc	Seal-In	30	0.6
S4	59	13	K3	Ics	Seal-In	40	0.6
S5	44	15	K4	Ics	Suction	30	0.7
S6	48	12	K3	Mas	Suction	40	0.8
S7	62	44	K4	Quad	Suction	40	0.5
S8	59	42	K3	Quad	Seal-In	30	0.6
S9	46	22	K4	Quad	Suction	30	0.5
S10	51	11	K3	Quad	Suction	20	0.9
S11	58	10	K4	Quad	Seal-In	30	0.7
S12	47	2	K3	Quad	Pin- liner	50	0.7
S13	46	2	K4	Quad	Suction	20	0.8
S14	42	14	K3	Ics	Seal-In	20	0.7
S15	41	5	K4	Quad	Seal-In	20	0.7
S16	56	9	K3	Quad	Seal-In	20	0.8
S17	60	5	K2	Sub-Isc	Seal-In	30	0.5
S18	39	13	K3	Sub-Isc	Seal-In	40	0.6
S19	57	36	K2	Quad	Suction	50	0.7
S20	65	49	K3	Quad	Suction	60	0.4
S21	65	56	K4	Quad	Suction	30	0.5
S22	62	45	K5	Quad	Suction	20	0.7
S23	49	24	K3	Ics	Mechanic	20	0.5
S24	60	23	K3	Quad	Suction	30	0.7
M ± std	53.3 ± 8.4	21.1 ± 16.2				31.7 ± 11.3	0.6 ± 0.1

S: Subject; age and t since amputation in years; K: K level, rating system used to indicate the individual's potential functional ability; K2 = activities typical of limited community ambulator; K3 = activities typical of community ambulator; K4 = high-impact activities; Cat-Cam = Contoured Adducted Trochanteric-Controlled Alignment Method; Ics: Ischial Containment Socket; Sub-Isc: Sub-Ischial; Mas = Marlo Anatomical Socket; Quad: Quadrilateral; M: mean.

Among the recruited subjects, 22 completed the 1st test session, while 2 only performed 5 out of 7 scans (TABLE S2*in supplementary material*). Results revealed an increasing effect of the prosthesis doffing on the residual limb volume, with the highest change rate in the first 10 minutes (Fig. 3). In particular, the amputees' residual limbs required, on average, 30 min to stabilize in volume (see t* in Table 2 and Fig. 3).

The repeated measures 1-way ANOVA test with Bonferroni post-hoc comparisons confirmed these results, showing a significant differences for all time-points compared to t=0 (p < 0.05, TABLE 3).

TABLE 3. Results of repeated measures 1-way ANOVA test with Bonferroni post-hoc comparisons. LB: lower bound; UP: Upper bound

Test of within-subject effects							
Source		**Type III sum of squares**	**df**	**Mean square**	***F***	***P***	**Partial Eta square**
Time	GG	0.040	3.438	0.012	9.828	**0.000**	0.319

Result of Bonferroni post hoc comparisons						
(I)	**(J)**	**Mean (I-J)**	**Std. error**	***P***	**95% conf int diff**	
					LB	**UB**
t = 0	t = 10	-.031*	0.008	**0.023**	-0.060	-0.003
	t = 20	-.032*	0.007	**0.002**	-0.054	-0.009
	t = 30	-.040*	0.007	**0.000**	-0.064	-0.017
	t = 40	-.047*	0.008	**0.000**	-0.075	-0.019
	t = 50	-.044*	0.008	**0.001**	-0.073	-0.016
	t = 60	-.053*	0.010	**0.001**	-0.089	-0.017

As found in literature for transtibial amputees [15], [27,32,33], the following two-term exponential decay function was found and used to curve-fit mean volume changes versus time:

$$\Delta V_t = \Delta V_1 (1 - e^{-kt}) \qquad (2)$$

Results showed a good fit (R2 = 0.97) with ΔV_1 and k equal to 1.80% and 0.08 min-1, respectively.

Notably, the maximum measured volume change among all subjects was found equal to +5.92%.

B. Volume changes within a day: 2ndsession, 3rdsession, 4th session

Among the 24 recruited amputees, 1 dropped out of the study after the 1st test day, resulting in 23 amputees. Results of the 3-way ANOVA with repeated measures showed no statistical differences for testing time ($p > 0.05$), and a significant effect of both prosthesis removal ($p < 0.005$) and physical activity ($p < 0.005$) (TABLE 4 and Fig. 4). Specifically, after removing the prosthesis, and after the physical activity, the residual limb volume increased, on average, of 0.50% and 0.46%, respectively.

A significant effect was also observed for the interaction among all the three within-subjects factors (i.e., testing time * physical activity * prosthesis removal) ($p < 0.05$, TABLE 4). Specifically, results revealed that the residual limb volume increased during the day, in particular after physical activity and prosthesis removal.

TABLE 4. Results of repeated measures 3-way ANOVA test. Within-subject factors: 1) *testing time*: morning or afternoon; 2) *physical activity*: before or after; 3) *prosthesis removal*: immediately after prosthesis removal or after stabilization time.

Test of within-subject effects		
	F(2, 22)	*P*
Testing time (1)	1.195	0.286
Physical activity (2)	10.862	**0.003**
Prosthesis removal (3)	10.862	**0.003**
1 * 2	0.314	0.581
1 * 3	4.263	0.051
2 * 3	1.705	0.205
1 * 2 * 3	6.024	**0.022**

Notably, the maximum volume changes due to the prosthesis removal as a percentage of the value immediately after the prosthesis doffing, across all subjects, ranged between -4.18% and 2.65%. Noticeably, the maximum volume reductions were always verified for subject 12, which is the only recruited amputee with a pin locking suspension system (TABLE 2). Also, the volume change due to the physical activity was evaluated for each subject as a percentage of the value before activity, resulting in a total change range equals to -1.43% ÷ 3.19%.

4. Discussion

This study focused on the volume fluctuations affecting the residual limbs of transfemoral amputees. At first, the volume changes after the prosthesis doffing was characterized overtime. Then, the effect of the prosthesis removal and the physical activity was investigated within a day – comparing morning and afternoon results – and repeating the tests during three different sessions, one week apart from each other.

A specific experimental set up was realized, including a portable metrology-grade 3D scanner, namely the Go!SCAN50, that was identified as the most suitable solution for the study. A mechanical support for amputees in standing position was designed to increase the protocol acceptability and improve the measurements precision. The final volumetric error of the 3D body scanning method was found equal to 0.3%. This value ensures a high reliability of the obtained results if compared to other measurement approaches described in the literature. Indeed, the water displacement method showed a measurement error between 2.1% and 3.7% when directly applied on residual limbs [34]. The error is improved to 1% when residual limb casts are measured [35] but they cannot perfectly replicate the residual limb volume. Anthropometric measurements resulted in an error between 2.4% and 5.7% [10], while contact probes 3.7% on average [36–38] and spiral X-ray Computed Tomography ≈1% [39], [40]. Better results were reported when using custom optical scanners (0.6% ÷ 0.8%) [41] or laser scanners (0.5% ÷ 0.4% on residual limb casts) [42], [43].

The study included 24 amputees, a number guaranteeing a statistical power of 95% with an α-value of 0.05 by using preliminary data [19]. However, only 22 subjects completed the required scans of the 1st test session, while 1 subject dropped out the subsequent ones. This resulted in a statistical power of 93% and 94%, respectively (α = 0.05).

The homogeneous features of the recruited population (TABLE 2) can be easily attributed to the recruiting prosthetic center, that is a national rehabilitation facility for work-related disabilities (INAIL, Italian National Institute for Insurance against Accidents at Work). This prosthetic center mostly deals with traumatic amputations due to work-related accidents; thus, it introduced a bias in the recruitment, as also described for other clinical studies [44], and may likewise have contributed to the predominance of male amputees. Indeed, only one female subject was enrolled and all subjects reported a traumatic amputation.

The protocol consisted of four test sessions in four different days for an overall duration of 3 weeks. During the 1st session, amputees' residual limb volume was measured 7 times at intervals of 10 minutes after the prosthesis removal. As reported in literature on transtibial amputees [15], [27,32,33], a two terms exponential decay function demonstrated to curve-fit well the data (R^2 = 0.97). Generally, residual limbs increased in volume after doffing the prosthesis (maximum measured value across all subjects equals to +5.9%). The greatest volume change was found in the initial 10 minute (Fig. 3 and TABLE 3). Then, values stabilized after 30 minutes, on average. This could be due to the effect of the negative pressures applied on residual limb tissues by the prosthesis suspension system. Indeed, 22 among 24 enrolled amputees used a vacuum suspension (*i.e.,* suction by unidirectional valve with or without a Seal-In liner). Negative pressures on tissues mainly draw in body fluids, differently from the drawing out effect of positive pressures [27]. As a consequence, the residual limb increased in volume when the prosthesis was removed. In addition, the socket doffing probably caused a reduction in the interstitial fluid pressure. Thus, an increment of the amount of fluid from arterial vessels into the interstitial space may occur, as well as a reduction from the interstitial space into the venous vessels [28].

The increment in volume due to the prosthesis doffing was also confirmed by the results obtained in the following three test days. In particular, during these sessions, the residual limb volume was measured immediately after the prosthesis doffing and after the amputee's stabilization time, before and after 15-min of walking on a treadmill, both in the morning and in the afternoon. The adopted stabilization time resulted from the 1st test day for each amputee. After averaging the corresponding volumes of the three test days, the data were analyzed by a repeated measured 3-way ANOVA test, featured by three within-subjects factors with two levels: (1) *testing time* (morning vs afternoon), (2) *physical activity* (before vs after physical activity), (3) *prosthesis removal* (immediately after the prosthesis doffing and after the stabilization time). Significance differences were found for factors 2 and 3 and the interaction of all the three factors (TABLE 4). Both *prosthesis removal* and *physical activity* showed a mean increasing effect on the residual limb volume (Fig. 4). Also for *physical activity*, this could be due to the pressure distributions applied on the residual limb tissues by the prosthesis socket and suspension system. Indeed, it is known that cyclic changes of pressures at the prosthetic pHMI continuously occur during walking - negative pressures in the swing phase and positive pressures in the stance phase [21]. Furthermore, the application of vacuum due to the suspension system causes an increment of the negative pressures during the swing phase and a reduction of the positive pressures during the stance phase [7]. This influences the blood circulation and the drawing in/ out body fluids, suggesting an increment in volume.

In addition, volume changes within a day, albeit not statistically significant, were also observed, resulting in an overall range across subjects of -4.2% ÷ +2.6% due to the prosthesis removal and -1.4% ÷ +3.2% due to the physical activity. However, it needs to be stated that high volume reductions were verified only in subject 12, which used a pin locking suspension system for the prosthesis. Then, the positive pressures applied on the residual limb tissues might have caused a drawing out effect of the body fluids, when doffing the prosthesis.

These data point out the critical need for an optimal pHMI interface for transfemoral prostheses, able to adapt comfortably and effectively to the residual limb. Indeed, these volume increments are enough to generate severe discomforts for amputees and, in the worst cases, impediments in donning the prosthesis [13]. On the other hand, the residual limb volume reductions can compromise the prosthesis fitting and stability, increasing the risks of falling. Generally, altered stress distributions at the interface and relative movements between the limb and the socket can occur, thus causing dermatological problems and pain. To achieve the challenging objective of an optimal prosthetic interface, the socket system should be able to compensate for these changes in volume.

Overall, the results reported in this study advance the state-of-the-art concerning the volumetric changes of transfemoral residual limbs. Furthermore, they provide the required constraints - previously missing in the state-of-the-art - for the design of smart prosthetic socket solutions for transfemoral amputees.

5. Conclusion

This study aimed at investigating volume changes in the transfemoral amputee population due to the prosthesis doffing and physical activity, at different testing times (*i.e.,* morning and afternoon). The results of these tests, demonstrated a significant increasing effect of both prosthesis removal and 15-min of walking. In addition, the interaction of the three factors - *prosthesis removal*, *physical activity* and *testing time* - was found statistically significant. A two terms decay exponential function showed excellent fitting with the mean data of the post-doffing volume changes over a 60 minutes period, demonstrating the highest change rate in the initial 10 minutes after the socket removal and an average stabilization time of 30 minutes. Considering volume changes of each subject, the total range measured during this study was -4.2% ÷ +5.9%, with maximum volume reductions measured in subject 12, which is the only amputee with a prosthetic suspension system not based on vacuum. In addition, this great volume change range might have been impacted by several other factors depending on the specific subject and test day, *e.g.*, diet, weather condition, comorbidities *etc.*, making difficult to derive statistical conclusions.

The reported results could be exploited, in the future, for the design of smart prosthetic sockets able to compensate the limb volume fluctuations overtime, thus to maximize stability and comfort.

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Declarations

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Author contributions statement

LP drafted the manuscript and analysed the data. LP, MI, ER, and GM collected and processed the data. LP, MI, LR, and AM conceived of the study. LP, MI, VM, EG, LR, and AM contributed to the study design and coordination, as well as to the analysis and interpretation of the findings. All authors helped to draft the manuscript, read and approved the final manuscript.

Consent for publication

Ethics approval was obtained from the ethical committee "*Area Vasta Emilia Centro, Regione Emiglia-Romagna CE-AVEC*". Protocol ID: P-PPRAI1/2-01

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Competing interests

The authors declare that they have no competing interests.