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Characteristic Lower Limb Pitting Edema Post-Stroke - Identification of Risk Factors: A Comparison between the Normal and Hemiplegic Side in Stroke Patients and Healthy Elderly Controls

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Abstract

Objective: Only a few studies have investigated the factors associated with the development of post-stroke lower limb edema. This study aimed to clarify the risk factors for lower limb edema after a stroke using the depth of surface imprint as a proxy measure of the severity of pitting edema.

Methods: Sixty-five patients with chronic stroke (39 men and 26 women; average age, 70.9 ± 13.8 years) were enrolled, with 35 healthy elderly individuals (11 men and 24 women; average age, 71.9 ± 5.1 years) included in the control group. All stroke patients were medically stable. Our stroke group included patients with a history of cardiac disease and diuretics use. Depth of the surface imprint was produced by a 20-N compression force applied with a digital force gauge for 10 s to the dorsum of the foot.

Results: The depth of the imprint was greater in the stroke group, bilaterally, than in the control group. Age was positively correlated with the depth of the imprint on the non-hemiplegic side in the stroke group.

Conclusion: Our findings indicate that a main risk factor for lower limb edema in chronic stroke may be a decreased function of the skeletal muscle pump due to paralysis and/or immobility.

Keywords: Pitting edema; Surface imprint depth; Skeletal muscle pump; Stroke; Cardiac disease; Diuretics; Hemiplegia

Introduction

Although motor paralysis is the main clinical feature of stroke, the resulting paralysis and associated immobility are risk factors for other comorbidities, including venous stasis, which is a predisposing risk factor for deep vein thrombosis and pulmonary embolism [1]. Venous return from the limbs is facilitated by the presence of valves, which prevent the backflow of blood in veins, by the function of the heart and respiratory pumps, which draw blood away from the periphery, and by the skeletal muscles, which push blood out from the periphery [2]. Among patients who sustain a cerebral infarction (stroke), about 50% of deaths occur after the first week post-stroke due to complications of immobility, including pulmonary embolism and pneumonia [3]. Edema also arises due to venous and lymph stasis [2,4].

Limb edema, defined as the accumulation of fluid in the interstitial space, commonly develops after a stroke. Limb edema develops as capillary filtration that exceeds the limits of lymphatic drainage [5] and includes both pre-load (excess water from venous pathology) and after-load (due to lymphatic failure) components.

The accumulation of edema within the capillaries of the limb increases the hydrostatic pressure, which alters the permeability of the wall of vessels, allowing water to escape into the interstitial space, with a resultant decrease in the osmotic pressure of plasma, a decrease in skin compliance, or both [6].

As limb edema develops after a stroke in the absence of congestive heart failure, muscle paralysis and/or prolonged immobility might be underlying causes [4,7]. As such, post-stroke edema is considered as disuse-dependency edema. Clearly, the loss of motor function hampers the muscle pump, which increases the effect of gravity in dependent limb positions.

Although the severity of stroke is not related to the extent of post-stroke edema, to date, only a few studies have investigated the factors associated with the development of pitting edema of the hands, with many aspects of post-stroke lower limb edema remaining to be clarified [4,7-10].

The use of a novel device for the convenient and safe measurement of pitting edema was previously described, including an evaluation of the reliability and validity of using the depth of the surface imprint as a measure of the severity of the edema, as well as the clinical usefulness of this measure [6,11]. The purpose of this study was to use the validated measure of the depth of surface imprint, as a proxy measure of the severity of pitting edema, in order to clarify the risk factors for lower limb edema in patients with chronic stroke.

Methods

Participants

The study sample included 65 patients with chronic stroke (39 men and 26 women; average age, 70.9 ± 13.8 years), recruited from a convalescent unit in a rehabilitation hospital, and 35 healthy elderly individuals (11 men and 24 women; average age, 71.9 ± 5.1 years), recruited from a municipal health promotion program, who served as the control group (Table 1).

	Stroke group (n=65)	Control group (n=35)	P value
Age, years	70.9 ± 13.8	71.9 ± 5.1	0.922
Sex, (male/female)	39/26	24-Nov	
Height, cm	159.4 ± 8.9	156.1 ± 6.6	0.048
Weight, kg	56.7 ± 12.0	55.5 ± 9.2	0.811
BMI, kg/m^2	22.2 ± 3.7	22.8 ± 3.5	0.384
Hemorrhage/Infarction, n	34/31		
Paralyzed side (right/left), n	29/36		
LEMS (FMA) (/34 points)	18.2 ± 10.0		
Period of onset (month)	37.6 ± 59.1		
Heart disease, n	20		
Kidney disease, n	4		
Endocrine disease, n	0		
Liver disease, n	0		
Orthopedic disease, n	3		

Note: Data for age, height, weight, BMI, LEMS, and period of onset are presented as the mean ± standard deviation. The P-value was calculated using the Kruskal-Wallis test.

Abbreviations: BMI: Body Mass Index; LEMS: Lower Extremity Motor Score of the Fugl-Meyer Assessment

Table 1: Participants' characteristics.

All stroke patients were medically stable, with lower limb edema observed on physical examination. As our clinical population of interest was patients with chronic stroke, our study group included patients with a history of cardiac disease and diuretic therapy. Since the effect of diuretic therapy for heart disease is bilateral, we considered that it would have minimal effects on the comparison of edema due to stroke from measurements obtained on the left and right feet. Furthermore, although diuretic therapy might have an influence on the comparison of these patients with healthy elderly individuals, we decided to include patients with this treatment in the study group. Patients with non-pitting edema, hypothyroidism, malignant tumors, dementia, bilateral paralysis, and trauma to the feet, as well as those who did not provide consent, were excluded.

The study was performed in accordance with the Declaration of Helsinki. Details of the study were sufficiently explained to the participants, who provided signed informed consent forms. The study was approved by the Ethics Committee of our institution and the rehabilitation hospital.

Measurement of the depth of the surface imprint

The depth of the imprint was measured as previously described [11]. Briefly, participants sat on the edge of a chair and were asked to lightly press the soles of their feet on the floor. Measurements were obtained from the dorsum of the foot to avoid influences of muscle spasticity.

The surface imprint was made with a digital force gauge (FG-5005, Mother Tool Co., Ltd., Nagano, Japan), consisting of a 25 mm diameter spherical end made of rubber which was pressed into the skin, applying a compressive force of about 20 N, and held for 10 s. All measurements were performed on the dorsum of the foot, at the midpoint along a line connecting the head of the first and fifth metatarsals. The depth of the imprint was measured at the end of the 10-s period of force application using a custom-designed edema gauge (KK-212-003, Unique Medical Company, Tokyo, Japan). All measurements were obtained in the morning, with the average depth for two trials for each foot used in the analysis.

Statistical analysis

The normality of the distribution of the data was evaluated using the Shapiro-Wilk test, and differences between the stroke and control group were evaluated using the Kruskal-Wallis test. The Wilcoxon signed-rank test was used for within-subject comparisons between the right and left foot in the control group and between the hemiplegic and non-hemiplegic foot in the stroke group. The Mann-Whitney U-test was used to specifically evaluate differences in imprint depth between

the 65 non-hemiplegic feet and the 70 control feet and between the 65 hemiplegic feet and the 70 control feet. The association between the imprint depth and clinical characteristics of the stroke group was evaluated using Spearman's rank correlation coefficient.

All statistical analyses were performed with SPSS for Windows (version 24, IBM Corp., Armonk, NY, USA), with the level of significance set at 5%.

Results

Relevant characteristics of the stroke and control groups are summarized in Table 1. A non-normal distribution was identified for the variables. The groups were equivalent with regard to demographic variables, with the exception of height (p=0.048), with participants in the stroke group being taller than participants in the control group (Table 1).

The surface imprint depth of the control group was 1.15 ± 0.57 mm for the right foot and 1.13 ± 0.56 mm for left foot (p=0.496; Table 2).

Control group	**Right side**	**Left side**	**P value**
	(legs, n=35)	(legs, n=35)	
	1.15 ± 0.57	1.13 ± 0.56	0.496
Stroke group	Hemiplegic side (legs, n=65)	Non-hemiplegic side (legs, n=65)	P value
	3.37 ± 1.08	2.63 ± 1.15	<0.001
Note: Data are presented as the mean ± standard deviation, Mann-Whitney U test			

Table 2: Comparison of the surface imprint depth for side.

In the stroke group, the surface imprint depth was 3.37 ± 1.08 mm for the hemiplegic foot and 2.63 ± 1.15 mm for the non-hemiplegic foot (p<0.001; Table 2). Moreover, the imprint depth was significantly greater for the hemiplegic and non-hemiplegic foot in the stroke group than in the control group (p<0.001; Table 3).

Stroke (legs, n=65)		**Control (legs, n=70)**	**P value**
Hemiplegic side	3.37 ± 1.08	1.14 ± 0.56	< 0.001
Non-hemiplegic side	2.63 ± 1.15		< 0.001
Note: Data are presented as the mean ± standard deviation, Mann-Whitney U test.			

Table 3: Comparison of the surface imprint depth for the stroke and control group.

We identified a significant correlation between increasing age and imprint depth for both the hemiplegic (r=0.305; p=0.013) and non-hemiplegic (r=0.427; p<0.001) foot in the stroke group.

A negative correlation was identified between height and imprint depth of the hemiplegic (r=-0.337; p=0.006) and non-hemiplegic (r=-0.282; p=0.023) foot, as well as between body weight and imprint depth in the non-hemiplegic foot (r=-0.296; p=0.017). The imprint depths of the hemiplegic and non-hemiplegic foot were also correlated (r=0.439; p<0.001; Table 4).

Parameters	**Age**	**Height**	**Weight**	**BMI**	**Imprint depth, hemiplegic side**	**Imprint depth, non-hemiplegic side**
Age						
Height	- 0.517**					
Weight	- 0.566**	0.569**				
BMI	- 0.370**	0.092	0.832**			
Imprint depth, hemiplegic side	0.305*	- 0.337**	-0.152	0.014		
Imprint depth, non-hemiplegic side	0.427**	- 0.282*	- 0.296*	-0.164	0.439**	
BMI: Body Mass Index						
Spearman's correlation coefficients, *p<0.05, **p<0.01						

Table 4: Correlation coefficients between the surface imprint depth and characteristics of the stroke group (n=65)

Discussion

The significantly greater imprint depth for both the hemiplegic and non-hemiplegic foot for the stroke group, compared to that of the control group, is indicative of the higher incidence of pitting edema among chronic stroke patients than among the healthy elderly population. Moreover, pitting edema was more prominent in the hemiplegic lower limb than in the non-hemiplegic lower limb. The cause of pitting edema of the limbs after a stroke has largely been attributed to immobilization due to motor impairment, which impairs the regulatory function of venous return [12,13] and exacerbates the effect of gravity on circulation when the limbs are in a dependent position [8]. There is no evidence that pitting edema is related to the severity of the stroke [8]. However, Meng et al. reported an increased thickening of the tendons of the finger extensors of the hemiplegic hand of patients with chronic stroke, as assessed by ultrasound imaging, which possibly reflects a change in the amount and quality of protein synthesis in these tendons due to increased intra-tendinous stress [14]. It is possible that similar changes in protein synthesis would affect the vessel walls. We propose that the greater pitting edema of the

hemiplegic foot than of the non-hemiplegic foot in our study group resulted from impairment in the water recovery system due to paralysis of the skeletal muscle pump, as well as from impaired venous reabsorption of fluid filtered in the capillary bed [15]. Consequently, venous stasis would develop and promote the accumulation of pitting edema. The relationship between an impaired skeletal muscle pump and venous insufficiency is supported by the findings of Nådland et al. who showed that there was no transient or steady-state change in femoral artery blood flow, measured by Doppler ultrasound, with a change in position, from sitting to standing, among patients with venous insufficiency [16]. Therefore, the muscle pump effect is either reduced or lacking in patients with venous insufficiency. This aligns with findings on the functional Timed Up-and-Go task, with chronic stroke patients exhibiting a decrease in active ankle dorsiflexion during the task, compared to healthy controls, with an overall slowing of the task performance due to muscle paralysis and spasticity [17]. Based on this evidence, Bamford et al. proposed that the development of post-stroke edema results, principally, from venous stasis and disturbances in lymphatic drainage due to impaired skeletal muscle pump function owing to increased muscle tone and motor paralysis [3]. Similarly, in our study, we consider that the impairment of the skeletal muscle pump was the principal contributing factor to the greater surface imprint depth on the dorsum of the foot in the stroke group, when compared to that of the control group, resulting in insufficient function of the water recovery system and pooling of the capillary bed filtrate [15].

In our study cohort, increasing age was associated with a greater imprint depth of the non-hemiplegic foot in the stroke group. Aging is an important cardiovascular risk factor, being associated with an increased risk of thrombotic cardiovascular complications, both in the arterial (acute myocardial infarction, stroke) and venous (deep vein thrombosis, pulmonary embolism) systems, which cannot be explained by the age-associated increase in cardiovascular risk factor alone [18]. Moreover, venous valves have been reported to increase in thickness with aging, with this thickening increasing the risk of venous thrombosis [19]. This age-related decline in venous return function would explain our finding of a positive correlation between aging and greater surface imprint depth in the non-hemiplegic foot of the stroke group.

We also identified a negative correlation between the imprint depth of the non-hemiplegic foot and increasing height and weight. A study examining the venous blood flow in the popliteal fossa, with the goal of identifying the most effective exercise regimen to prevent venous stasis, reported a significant 41% decrease in blood flow velocity and 42% in blood flow volume after 100 minutes of sitting still, with the feet flat on the ground [20]. Moreover, a change in posture from supine to standing produced a decrease in both cardiac output and venous return, which was associated with a rapid increase in blood pressure and heart rate due to reflex adjustment [21]. Specifically, when moving from the supine to the standing position, gravity produces a strong hydrostatic effect that increases the intravascular pressure [2]. In contrast, effects of a change in posture on venous return are not influenced by the hydrostatic pressure but, rather, by the pumping action of the heart [2]. Therefore, as the driving pressure increases due to an increase in blood pressure and heart rate, venous return will be promoted. Certainly, this effect is modulated by the compliance of the vein and the sympathetic vasoconstrictor drive, which reduce the extensibility of the blood vessel wall to regulate venous volume [2]. We consider that these factors would have a greater effect, such that height, ultimately, would have a negligible effect. With regard to body weight, Kuniyoshi et al. reported excessive sympathetic activity and greater forearm vascular resistance in obese individuals than in a lean control group [22]. In our study group, the higher sympathetic drive in patients with greater body weight would have improved venous return and, therefore, decreased the imprint depth on the non-hemiplegic foot. However, based on our correlation analysis, we consider that any effect of body weight would be weak. In the same way, we consider that any effect of age and height, which were correlated with imprint depth on the hemiplegic foot, would be negligible, with impairment in the skeletal muscle pump being the dominant factor leading to the development of pitting edema post-stroke.

Conclusions

We identified post-stroke pitting edema in both the hemiplegic and non-hemiplegic foot of stroke patients, with the imprint depth being greater on the hemiplegic side, and compared the measurements to those obtained from the feet of a control group of healthy elderly individuals. As we included patients with a history of cardiac disease and those who used diuretics in the chronic stroke group, there are limitations to our results since they cannot be entirely attributed to the effects of stroke. Although we did not use a specific cut-off value for pitting edema, considering the significant difference noted between the hemiplegic and non-hemiplegic foot, we believe our results to be highly reliable. It has been shown that among the risk factors for edema after stroke, the function of skeletal muscle pump may be decreased due to paralysis and/or immobility. However, considering that we did not specifically measure the actual amount of venous return in the lower limbs, future research is needed to identify factors that specifically influence venous return.

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