The thesis committee for Yesha Jayantilal Parmar

Certifies that this is the approved version of the following thesis:

Association between Reduced Limb Perfusion and Muscle Spasticity in Persons with Spinal Cord Injury

APPROVED BY

SUPERVISING COMMITTEE

Supervisor: _____

Lisa Griffin

_____

Hirofumi Tanaka

Association between Reduced Limb Perfusion and Muscle Spasticity in Persons with Spinal Cord Injury

by

Yesha Jayantilal Parmar, B.Physio.

Thesis

Presented to the Faculty of the Graduate School

of the University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Science in Kinesiology

The University of Texas at Austin

December, 2010

Dedication

To my love Neeraj and my parents, for all their support and encouragement

Acknowledgement

I owe my deepest gratitude to my advisor Dr. Lisa Griffin for giving me an opportunity to pursue my thesis in the field of Spinal Cord Injury research. This project would not have been possible without support from Dr. Hirofumi Tanaka and Mandeep Dhindsa from the Cardiovascular Aging Research Laboratory, Curtis Merring from Brain & Spine Recovery Center at University Medical Center Brackenridge, and staff of the Fitness Institute of Texas. Most Importantly, I would like to commend the spirit of all research participants and thank them for devoting their valuable time for the good of all people affected by SCI.

Association between Reduced Limb Perfusion and Muscle Spasticity in Persons with Spinal Cord Injury

by

Yesha Jayantilal Parmar, M.S. Kin.

The University of Texas at Austin, 2010

SUPERVISOR: Lisa Griffin

Individuals with spinal cord injury (SCI) demonstrate reduced limb blood flow and muscle spasticity. It is plausible that the accumulation of metabolites, resulting from reduced perfusion, could exacerbate spasticity via activation of fusimotor neurons by Group III and IV afferents. **PURPOSE:** To determine the association between peripheral blood flow and muscle spasticity in persons with SCI. **METHODS**: A total of 16 individuals with SCI were classified into high (N=6), low (N=5), and no (N=5) spasticity groups according to their spasticity levels indicated by the modified Ashworth scale scores. Blood flow was measured in femoral and brachial arteries using duplex Doppler ultrasound and was normalized to limb lean mass obtained with dual energy X-ray absorptiometry. **RESULTS**: There were no significant group differences in age (30.5±4.15, 38.48±4.61, 32.6±4.89 years), time post SCI (8.5±4.2, 12.6±4.74, 6.8±1.66 years), American SCI Association motor scores (39.2±7.78, 59±12.34, 53.4±1.08), or sensory scores (96±22.1, 144.4±13.97, 130±13.8). Femoral artery blood flow, adjusted for limb lean mass, was significantly different (p=0.002) across the three leg spasticity groups (high 76.03±6.44, low 95.12±15.49, no 142.53±10.86 ml/min/kg).Total leg muscle spasticity scores were significantly and negatively correlated with femoral artery blood flow (r=-0.60, p=0.014). There

was no significant difference in brachial artery blood flow between the three groups, indicating that the reduction in blood flow was confined to injured limbs and not due to systemic cardiovascular disorder. **CONCLUSION**: Among SCI patients, whole-leg blood flow is progressively lower in individuals with greater spasticity scores. These results suggest that a reduction in lower limb perfusion, among other factors, plays a significant role in the pathogenesis leading to muscle spasticity after SCI. **KEYWORDS**: Blood flow, Limb Perfusion, Paralysis, Spasticity, Spinal Cord Injury

Table of Contents

INTRODUCTION

Spasticity is one of the most debilitating complications following Spinal Cord Injury (SCI). The spastic syndrome is characterized by increased muscle tone and increased tendon reflexes.[1] It interferes with mobility, transfer, self-care, and activities of daily living, and has a negative impact on the well-being of persons with SCI.[2, 3] With increasing life expectancy of persons with SCI and increased healthcare costs, it is critical to understand the physiological mechanisms underlying spasticity. Despite existing neural theories about development of spasticity[4,5], the exact mechanism leading to spasticity following SCI has not yet been clearly identified.

The common prevailing theory to explain the mechanism underlying muscle spasticity is the reduced descending inhibition of the muscle spindle afferent (Ia afferent) due to SCI, which leads to an increase in motoneuron excitability.[4,5] The alpha motoneuron reacts with abnormal firing frequency and duration to an excitatory stimulus, which manifests as increased resistance to passive stretch and clonus.[6-9] Studies using animal models have found that Ia afferents are activated by the fusimotor system by the smaller diameter (Group III and IV) afferents.[10] These small diameter afferents respond to muscle metabolites such as lactic acid, arachidonic acid and bradykinin.[11,12] Individuals with chronic paralysis from SCI demonstrate rapid and extensive adaptations in

the peripheral circulation such as a decrease in vessel diameter size,[13-15] reduced capillarization,[16-18] and markedly reduced resting blood flow, [14, 19 -21] and muscles paralyzed by SCI exhibit substantially higher rates of fatigue.[22, 23] The coexistence of reduced blood flow and high fatigability creates an environment favoring the build-up of metabolic byproducts and can affect muscle contractile function and activate sensory afferent pathways.[24] Hence, it is plausible that the accumulation of metabolites, resulting from reduced perfusion, could exacerbate spasticity via activation of fusimotor neurons by Group III and IV afferents.

The primary aim of the present study was to determine whether there is an association between peripheral blood flow and muscle spasticity in persons with SCI. To address this aim, we studied limb blood flow in persons with complete and incomplete SCI having high, low and no muscle spasticity. We hypothesized that reduced femoral blood flow would be correlated to the degree of muscle spasticity.

METHODS

Participants

Sixteen SCI individuals (12 Males and 4 Females) with injuries ranging from C3 to T12 and 9.25±2.16 years post SCI, participated in this study. Potential participants were excluded from the study if they were diagnosed with cardiovascular disease, hypertension, diabetes mellitus, peripheral vascular disease, recent fractures and open wounds, or pregnancy. All procedures and risks involved were explained, and all participants gave their written informed consent. This study was approved by the Institutional Review Boards of University of Texas at Austin, and Seton family of hospitals, Austin, TX. Participants were asked to not alter either their usual medications or smoking habits.

Clinical Assessments

Clinical examinations were performed on one visit according to the impairment scale of the American Spinal Injury Association (ASIA) by a licensed occupational therapist (CAM). Muscle tone was graded using the modified Ashworth's scale of grading muscle spasticity (0 flaccid muscle tone, to 4, limb held rigid in flexion or extension).

Blood flow

Blood velocity and vessel diameter of the right brachial artery (BA) and the right common femoral artery (CFA) were measured on a separate visit using a Duplex ultrasound machine (Philips HDI-5000, Bothel, WA) equipped with a high-resolution linear array transducer. Arterial diameter was determined by a perpendicular measurement from the media interface of the near wall to the intima interface of the far wall of the vessel. Arterial diameter and mean blood flow velocity were captured simultaneously. Mean blood velocity measurements were performed with the insonation angle <60°. The sample volume gate was adjusted to cover the width of the vessel. To minimize turbulence from the bifurcation, the measurements on the common femoral artery were performed approximately 2–3 cm proximal to its bifurcation. Measurements on the brachial artery were performed 3 cm proximal to the olecranon process. All the data were digitally recorded directly on the hard drive and analyzed by the software provided by the ultrasound machine manufacturer. Blood flow was calculated using the formula:

Baseline Blood Flow (l/min) = [Mean blood velocity • Circular area • $6 \bullet 10^{4}$]

Whole body composition and leg fat-free mass

Whole body composition was determined from Dual Energy X-ray Absorptiometry (DEXA) technology using a Lunar Prodigy (G. E. Medical Systems, Madison, WI). All selected data were analyzed with enCORE software (version 11.0). Regional analysis of tissue mass of the right leg and arm was

performed from the whole body scans. Femoral and brachial blood flow values were then adjusted to the right leg and arm lean mass (i.e., metabolically active tissue mass).

Statistics

Group differences in age, time post SCI, ASIA motor and sensory scores, height, weight, lean mass, adipose mass, brachial and femoral adjusted blood flow were assessed using one-way ANOVA with Tukey's post-hoc analyses. Univariate correlation using Pearson's product moment correlation was performed to determine associations of interest. All data are reported as mean±SEM. Statistical significance was set *apriori* at $P<0.05$.

RESULTS

Participants were classified into three groups (high, low and no muscle spasticity) based on the level of spasticity as assessed from the modified Ashworth's scale (MAS) of grading muscle spasticity. Participants in the high spasticity group had scores of 2 and above on MAS, the low group had MAS scores of 1 and 1+, and the no spasticity group had MAS scores of 0 in the right leg muscles (Table 1). There were no significant differences in age, time from SCI, ASIA motor and sensory scores among the three groups (Table 2 and 3).

Table 1: Modified Ashworth's scores of spasticity for the right leg muscles

	Subject #	Hip Extensor	Hip Flexor	Hip Adductor	Knee Extensor	Knee Flexor	Ankle Plantarflexor
High Spasticity	2	3	1+	3	3	1+	1
	3	4	0	4	0	3	3
	6	4	3	4	4	1+	2
	8	3	2	4	0	2	3
	25	1	0	3	0	0	2
	28	0	1	3	2	2	2
Low Spasticity	15	1	0	1+	0	0	1+
	17	1+	0	1+	0	0	0
	21	0	0	1	0	1+	1+
	24	0	0	1+	0	1+	1+
	30	1	0	0	1	0	1
No Spasticity	4	0	0	0	0	0	0
	7	0	0	0	0	0	0
	10	0	0	0	0	0	0
	13	0	0	0	0	0	0
	18	0	0	0	0	0	0

Table 2: Subject characteristics

	Subject #	Sex	Age (Years)	Time from SCI (Years)
High Spasticity	2	M	32	8
	3	M	38	4
	6	M	46	29
	8	M	19	4
	25	M	24	5
	28	M	24	1
Mean ± SE			30.50 ± 4.15	8.50 ± 4.20
Low Spasticity	15	F	45	23
	17	F	47	24
	21	M	34.9	4
	24	M	22	1
	30	F	43.5	11
Mean ± SE			38.48 ± 4.61	12.6 ± 4.74
No Spasticity	4	M	19	2
	7	M	38	5
	10	M	36	11
	13	M	46	6
	18	F	24	10
Mean ± SE			32.60 ± 4.89	6.80 ± 1.66
P value			**0.45**	**0.58**

Table 3: ASIA level and classification with motor and sensory scores

	Subject #	ASIA Level	ISCSCI Type	C/I	P/T	ASIA Motor	ASIA Sensory
	2	T10	B	I	Para	50	166
High	3	T1	C	I	Tetra	53	146
Spasticity	6	C4	A	C	Tetra	49	49
	8	T4	C	I	Para	50	115
	25	C4	B	I	Tetra	5	35
	28	C6	C	I	Tetra	28	65
Mean ± SE						39.2 ± 7.78	96 ± 22.10
	15	C5	C	I	Tetra	23	176
Low	17	T4	A	C	Para	50	94
Spasticity	21	T12	C	I	Para	54	152
	24	C7	D	I	Tetra	98	139
	30	C3	D	I	Tetra	70	161
Mean ± SE						59 ± 12.34	144.4 ± 13.97
	4	T10	A	C	Para	54	140
No	7	T10	C	I	Para	56	147
Spasticity	10	T6	A	C	Para	50	111
	13	T4	A	C	Para	52	88
	18	T12	C	I	Para	55	166
Mean ± SE						53.4 ± 1.08	130.4 ± 13.8
P value						**0.24**	**0.17**

ISCSCI, International Standards for Neurological Classification of Spinal Cord Injury; C/I, Complete/Incomplete; P/T, Paraplegic/Tetraplegic

Physical characteristics and body composition as measured by DEXA scans did not differ significantly among the three spasticity groups (Table 4). In addition, there were no significant differences among the three groups in the regional lean masses of the right arm (3.62±0.4, 3.1±0.63, 3.55±0.48 kg, P=0.74), and right leg (7.9±0.65, 6.97±1.39, 5±0.64 kg, P=0.11).

Table 4: Physical characteristics

	Subject #	Height (cm)	Weight (Kg)	BMD (g/cm^2)	Adipose (Kg)	Lean Mass (Kg)
	2	180.34	89.6	1.31	31.54	54.80
High	3	185.42	76.4	1.13	15.13	58.31
Spasticity	6	180.34	99.8	1.31	39.00	57.37
	8	172.72	77	1.09	25.82	48.67
	25	177.80	60.3	0.85	21.03	37.49
	28	190.50	100	1.32	34.01	60.0
Mean ± SE		181.2 ± 2.51	83.85 ± 6.34	1.14 ± 0.08	27.76 ± 3.6	52.77 ± 3.46
	15	177.80	57.3	1.05	19.44	35.42
Low	17	157.48	37.7	1.14	8.36	27.34
Spasticity	21	180.34	85.3	1.25	24.67	57.23
	24	182.88	85.3	1.36	14.12	67.39
	30	157.48	60.9	1.15	24.04	36.83
Mean ± SE		171.2 ± 5.66	65.3 ± 9.07	1.19 ± 0.05	18.13 ± 3.09	44.84 ± 7.49
	4	177.80	48.6	0.86	7.45	39.45
No	7	180.34	67.5	1.17	25.12	39.36
Spasticity	10	182.88	91.4	1.24	40.73	46.85
	13	185.42	89.5	1.42	31.69	53.59
	18	167.64	38.7	0.97	9.24	27.76
Mean ± SE		178.8 ± 3.07	67.14 ± 10.59	1.13 ± 0.10	22.85 ± 6.42	41.40 ± 4.31
P value		**0.19**	**0.26**	**0.87**	**0.33**	**0.29**

No significant differences were found in the brachial artery and common femoral artery diameters or mean blood velocities across the three groups (Table 5). Brachial artery normalized blood flow did not differ significantly across the groups (108.21±27.49, 92.6.6±25.84, 115.38±36.03 ml/min/kg, P=0.86). Femoral artery blood flow normalized to leg lean mass varied significantly ($P < 0.01$) across the groups with a statistically significant difference between the high and no muscle spasticity groups (Figure 1). As illustrated in Figure 2, the sum of modified Ashworth's scores of muscle spasticity was significantly and inversely

associated with the whole leg normalized femoral blood flow values (r= -0.60, $p<0.05$).

Table 5: Blood flow indices

Groups	Brachial Artery		Common Femoral Artery	
	Baseline Diameter (mm)	**Mean Blood Velocity (m/s)**	**Baseline Diameter (mm)**	**Mean Blood Velocity (m/s)**
High Spasticity	4.52 ± 0.44	0.36 ± 0.06	7.05 ± 0.37	0.26 ± 0.02
Low Spasticity	4.0 ± 0.19	0.32 ± 0.06	6.72 ± 0.78	0.29 ± 0.03
No Spasticity	4.29 ± 0.52	0.41 ± 0.08	6.67 ± 0.42	0.34 ± 0.04
P Value	**0.64**	**0.68**	**0.85**	**0.19**

Values are means ± S.E

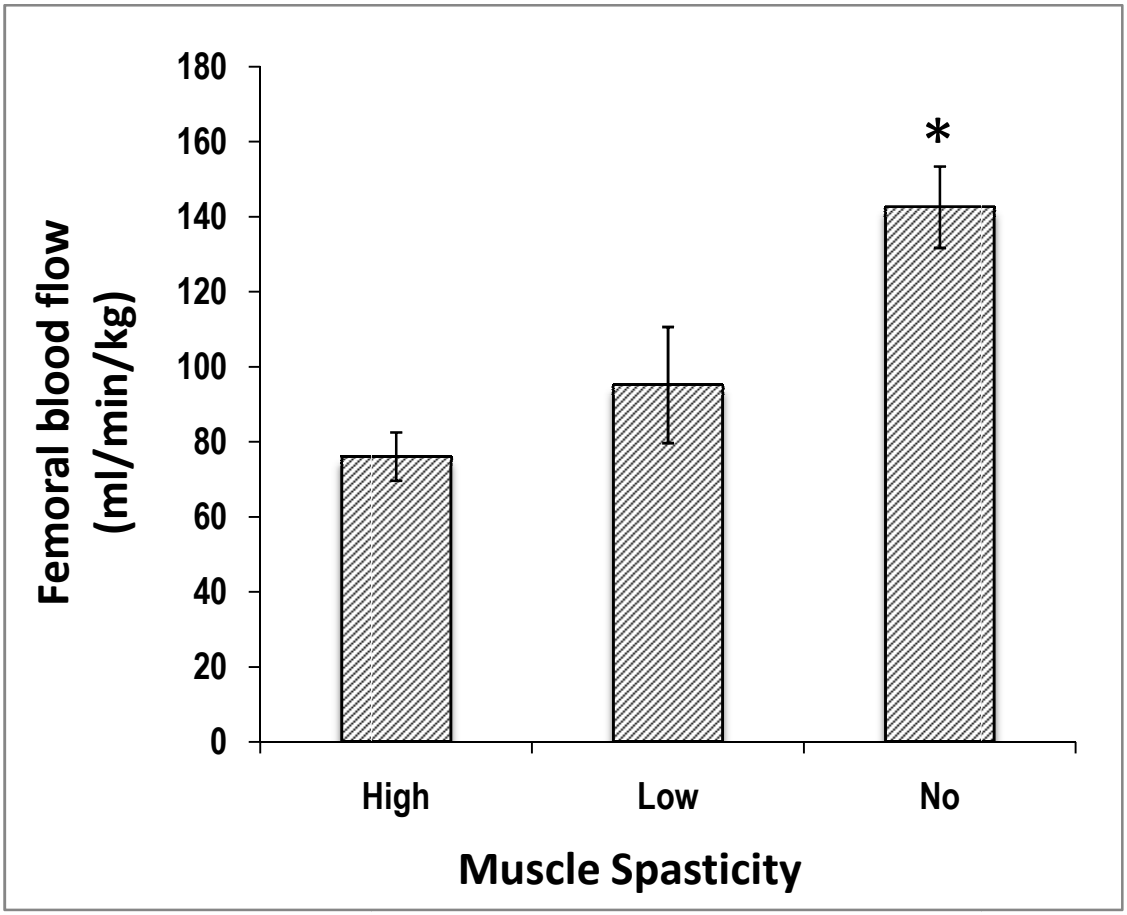

Figure 1. Normalized femoral blood flow (ml/min/kg) in the high, low and no muscle spasticity groups

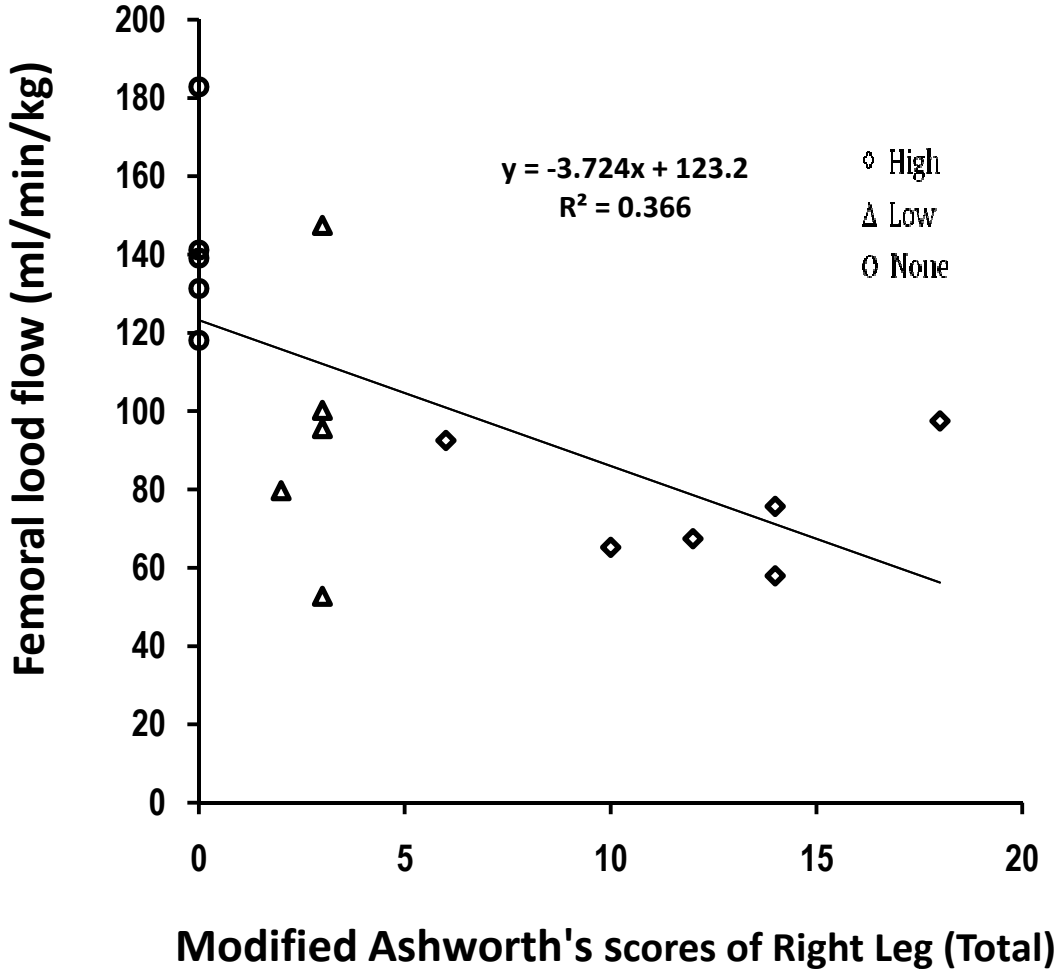

Figure 2. Sum of modified Ashworth's scores of right leg versus femoral blood flow (ml/min/kg) of high, low and no muscle spasticity groups

DISCUSSION

In the present study, we found that among the three spasticity SCI groups that are matched for age, time from SCI, ASIA motor and sensory scores and physical characteristics across the groups, whole-leg blood flow was lower in individuals with higher spasticity scores. Additionally, total muscle spasticity MAS scores were significantly and inversely associated with femoral artery blood flow normalized for leg lean muscle mass. These results demonstrate that reduced limb perfusion likely plays a role in the mechanisms leading to exaggerated muscle spasticity. This was the first study to demonstrate a significant association between muscle spasticity and blood flow in individuals with SCI.

Blood flow and vascular functions have been studied in the SCI population, but very few studies have evaluated its relation to the secondary complications that could impact function and activities of daily living. Plethysmography and Doppler studies of lower limbs have indicated that blood flow values and arterial diameter are significantly lower in persons with paraplegia compared with able-bodied controls [13, 14, 19 - 21] though other studies have reported that femoral artery diameter and blood flow per unit muscle volume did not differ between SCI and able-bodied individuals.[25, 26] These arterial adaptations are attributed mainly to the loss of supraspinal control of somatic efferents, which causes extreme deconditioning of the leg muscles.

Deconditioning and long-term inactivity is associated with reduced oxygen demand and subsequently with profound vascular adaptations. A decrease in blood flow can result in arterial constriction, thickening of the arterial wall, and reduced clearance of blood glucose and lipids, all of which could lead to cardiovascular disease.[27] Absolute values of femoral diameter in this study (≈7 mm) were in agreement with previous studies of patients with SCI (5-7 mm) and smaller than able-bodied controls (7-10 mm)[13-15, 20, 25, 28]. However, the baseline femoral blood flow values were higher (≈641 ml/min) than those reported previously for SCI individuals (150–300 ml/min) and closer to values of able bodied individuals (400–700 ml/min).[19 – 21, 25, 28]

Long-term inactivity in patients with upper motor neuron weakness leads to structural and functional changes in the muscle fibers below the level of lesion, including changes in the fiber population towards more fatigable types.[17, 22] Indeed, paralyzed muscles fatigue rapidly with different types of electrical stimulation protocols.[23, 29] High muscle fatigability results from chronic changes that occur in muscle use, metabolism, vascularization, muscle perfusion pressure, and/or fiber type composition.[29-33] The combination of reduced blood flow and high fatigability would create an environment that favors the accumulation of metabolic by-products, which can affect muscle contractile function and activate Group III and IV afferent pathways.[23]

Muscle spasticity is most likely caused by reduced descending inhibition of the Ia afferent following SCI.[4,5, 34, 35] Animal studies have shown that reduced blood flow conditions can increase Ia afferent firing by fusimotor activation from small diameter afferents that respond to a build-up of metabolites in the muscle.[10] It is likely that the fusimotor pathway previously identified only in the decerebrate cat also exists in humans. Indeed, increased EMG response to tendon tap after muscle fatigue has been observed in humans, suggesting an up-regulation of Ia afferent activity during fatigue. [36] Hence, Ia afferent activity may be exacerbated by the physiological changes in the paralyzed muscle as well as the absence of adequate perfusion to remove the accumulated metabolites.

To the best of our knowledge, only one study is available to evaluate the time course of arterial adaptations to paralyses and inactivity [28]. There was a 30% reduction in both femoral arterial diameter and blood flow within 6 weeks of SCI. No further changes were observed in the femoral artery properties between 6 weeks and 13 months post SCI. Moreover, no significant changes were observed in the brachial and carotid arteries in that study. These results showing relatively rapid changes in lower limb vasculature suggest that the vascular adaptations seen in the legs are due to pathology related to injury in the spinal cord and not due to a delayed systemic cardiovascular disorder occurring in SCI individuals. Because the lower extremities play a more active role in standing and locomotion, it is possible that they are affected more greatly by the intense

deconditioning that occurs due to the SCI. This may be one of the reasons for no significant group differences in brachial blood flow values observed in the present study.

Treatment modalities such as whole body vibration exercise, resistance training, and endurance exercise can lead to increases in blood flow in able-bodied individuals,[37 - 39] but their effects on vascular function in SCI have not been investigated. Interventions such as few weeks of Functional Electrical Stimulation (FES) training have been used to improve peak leg blood flow and arterial diameter in SCI.[40-42] Muscle spasms of underlying neuropathological causes have been treated with the use of heat by therapists for many decades.[43] The reduction in spasm is believed to be caused by the counter-irritant effect of heat on both primary and secondary afferents from muscle spindle. However, heating is also known to improve local blood flow.[44] It is possible that improvement in blood flow through heating may be one of the alternative mechanisms for the transient reduction in muscle spasticity. Further research is needed to investigate the effects of clinical interventions on limb spasticity in relation to changes in the limb blood flow.

There are several study limitations that should be emphasized. We did not exclude participants who were smoking or using their routine medications though potential participants with diagnosed cardiovascular, peripheral artery disease,

and diabetes were excluded. Four participants reported smoking occasionally, and participants reported using a variety of prescription medications, including opiod analgesics, benzodiazepines, inhaled corticosteroids, anticonvulsants, and antispasmodic/antimuscarinic, which could affect vascular function. Most participants were actively engaged in rehabilitation while others did not attend organized rehabilitations. Hence, the activity levels of different individuals who participated in this study may not have been uniform. The effects of different types of exercise modalities on vascular properties in able-bodied humans are variable. While regular aerobic activity does not seem to affect vascular function,[45] resistance training,[38] and regular endurance exercise[39] increases basal limb blood flow and diameter. Effects of these exercise modalities in SCI persons are not fully understood and may affect baseline vascular characteristics.

CONCLUSIONS

In summary, lower limb perfusion in persons with SCI having high leg muscle spasticity was significantly lower than those without spasticity. Additionally, there was a significant inverse correlation between spasticity (modified Ashworth's scores) and femoral blood flow. These results are consistent with the hypothesis that lower levels of blood flow may be involved in muscle spasticity in persons with SCI.

REFERENCES

1. Lance JW. Symposium Synopsis. In: Young RR, Koella WP, editors. Spasticity: disordered motor control. Chicago: Yearbook Medical Publishers; 1980, 485-94.

2. Parziale JR, Akelman E, Herz DA. Spacticity: pathophysiology and management. *Orthopedics* , 1993,16: 801-811.

3. Jozefczyk PB. The management of focl spacticity. *Clin Neuropharmacol*, 2002, 25: 158-173.

4. Hagbarth KE, Wallin G, Leofstedt L, Aquilonius SM. Muscle spindle activity in alternating tremor of Parkinsonism and in clonus. *J Neurol Neurosurg Psychiatry* 1975, 38: 636-641.

5. Szumski AJ, Burg D, Struppler A, Velho F. Activity of Muscle Spindles during muscle twitch and clonus in normal and spastic human subjects. *Electroencephalor Clin Neurpphysiol* 1974, 37: 589-597.

6. Kandel ER, Schwartz JH, Jessel TM. Principles of Neural Science, 4th ed. New York, NY: McGraw-Hill, 2000 : 730.

7. Shefner JM, Berman SA, Sakarati M, et al. Recurrent inhibition is increased in patients with spinal cord injury. *Neurology* 1992, 42:2168-8.

8. Young RR. Spasticity: a review. *Neurology* 1994, 44(suppl 9): 12-20.

9. Brodal P. The Central Nervous System: Structure and Function, New York, NY: Oxford University Press, 1998, 367.

10. Ljubisavljevic M, Jovanovic K, Anastasijevic R. Changes in discharge rate of fusimotor neurones provoked by fatiguing contractions of cat triceps surae muscle. *J Physiol (Lond)* 1992, 445: 499-513.

11. Rotto DM, Kaufman MP. Effect of metabolic products of muscular contraction on discharge of group III and IV afferents. *J Appl Physiol* 1998, 64: 2306-13.

12. Mense S. Nervous outflow from skeletal muscle following chemical noxious stimulation. *J Physiol* 1997, 267: 75-88.

13. Hopman MTE, Nommensen E, Van Asten WNJ, Oeseburg B, Binkhorst RA. Properties of the venous vascular system in the lower extremities of individuals with paraplegia. *Paraplegia* 1994, 32: 810 – 816.

14. Boot CR, Groothuis JT, Van Langen H, Hopman MT. Shear stress level in paralyzed legs of spinal cord-injured individuals with and without nerve degeneration. *J Appl Physiol* 2002, 92:2335-2340.

15. Nash MS, Montalvo BM, Applegate B. Lower extremity blood flow and responses to occlusion ischemia differ in exercise-trained and sedentary tetraplegic persons. *Arch Phys Med Rehabil* 1996, 77: 1260 – 65.

16. Rochester L, Barron MJ, Chandler CS, Sutton RA, Miller S, Johnson MA. Influence of electrical stimulation of the tibialis anterior muscle in paraplegic subjects. 2. Morphological and histochemical properties. Paraplegia 1995, 33: 514 – 22.

17. Martin TP, Stein RB, Hoeppner PH, Reid DC. Influence of electrical stimulation on the morphological and metabolic properties of paralyzed muscle. *J of Appl Physiol* 1992, 72: 1401-1406.

18. Chilibeck PD, Jeon J, Weiss C, Bell G, Burnham R. Histochemcial changes in muscle of individuals with spinal cord injury following functional electricl stimulated exercise training. Spinal Cord, 1999, 37: 264-8.

19. Taylor PN, Ewins DJ, Fox B, Grundy D, Swain ID. Limb flow, cardiac output and quadriceps muscle bulk following spinal cord injury and the effect of training for the Odstock functional electrical stimulation standing system. *Paraplegia* 1993, 31: 303-310, 1993.

20. Hopman MT, Asten van WN, Oeseburg B. Changes in blood flow in the common femoral artery related to inactivity and muscle atrophy in individuals with long- standing paraplegia. *Adv Exp Med Biol* 1996, 388: 378-383.

21. Schmidt-Truckass A, Schmid A, Brunner C, et al. Arterial properties of the carotid and femoral artery in endurance-trained and paraplegic subjects. *J Apply Physiol* 2000, 89: 1956-63.

22. Lenman AJ, Tulley FM, Vrbova G, Dimitrijevic MR, Towle JA. Muscle fatigue in some Neurological Disorders. *Muscle Nerve* 1989, 12: 983-942.

23. Thomas CK, Griffin L, Godfrey S, Ribot-Cisar E, Butler JE. Fatigue of paralyzed and control thenar muscles induced by variable or constant frequency stimulation. *J. Neurophysiol* 2003, 89: 2055- 2064.

24. Taylor JL, Butler JE, Gandevia SC. Changes in muscle afferents motoneurons and motor drive during muscle fatigue. *E Jour of Appl Physiol* 2000, 83: 106-115.

25. Olive JL, Dudley GA, McCully KK. Vascuarl remodeling after spinal cord injury. *Med Sci Sports Exerc* 2003, 35: 901-7

26. Olive JL, Slade JM, Dudley GA, McCully KK. Blood flow and muscle fatigue in SCI individuals during electrical stimulation. *J Appl Physiol* 2003, 94: 701 – 8.

27. RDB Lee, BL Langille. Arterial adaptations to altered blood flow. *Canadian Journal of Physiology and Pharmacology* 1991, 67(7): 978-983.

28. De Groot PC, Van Kuppevelt DH, Pons C, Snoek G, Van der Woude LH, Hopman MT. Time course of arterial vascular adaptations to inactivity and paralyses in humans. *Med Sci Sports Exerc* 2003, 35: 1977-85

29. Grimby G, Broberg C, Krotkiewska I and Krotkiewski M. Muscle fiber composition in patients with traumatic spinal cord lesion. Scand J Rehabil Med 1976, 8:37-42.

30. Butler JE, McKenzie DK, Gandevia SC, Discharge properties and recruitment of human diaphragmatic motor units during voluntary inspiratory tasks. *J Physiol* 1999, 518: 907 – 20.

31. Castro MJ, Apple Jr DF, Hillegass EA, Dudley GA. Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first six months of injury. *Eur J Appl Physiol* 1999, 80: 373-378.

32. Thorstensson ALF, Grimby Gunnar, and Karlsson Jan. Force velocity relations and fiber composition in human knee extensor muscles. *Journal of Appl Physiol* 1976, 40: 12-16.

33. Mohr T, Podenphant J, Biering-Sorensen F, Galbo H, Thamsborg G, Kjaer M. Increaed bone mineral density after prolonged electrically induced cycle training of paralyzed limbs in spinal cord injured man. *Calcif Tissue Int* 1997, 61:22-25.

34. Hidler JM, Rymer WZ. A stimulation study of reflex instability in spasticity: origins of clonus. *IEEE Trans Rehabil Eng* 1999, 7:327-340.

35. Hidler JM, Rymer WZ. Limit cycle behavior in spasticity: analysis and evaluation. *IEEE Trans Biomed Eng 2000*, 47: 1565- 1575.

36. Biro A, Griffin L, Cafarelli E. Reflex gain of short and long- loop muscle spindle pathways during fatigue. Exp Brain Res 2007, 177: 157 – 166.

37. Kerschan-Schindl K, Grampp S, Henk C, Resch H, Preisinger E, Fialka-Moser V and Imhof H. Whole body vibration exercise leads to alterations in muscle blood volume. *Clin Physiol* 2001, 21: 377-382.

38. Anton MM, Cortez-Cooper MY, DeVan AE, Neidre DB, Cook JN, Tanaka H. Resistance training increases basal limb blood flow and vascular conductance in aging humans. *J Appl Physiol* 2006, 101: 1351-55.

39. DeSouza CA, Seals DR. Regular endurance exercise induced expansive arterial remodeling in the trained limbs of healthy men. *J Physiol* 2001, 534:287-295.

40. Stoner L, Sabatier MJ, Mahoney ET, Dudley GA, McCully KK. Electrical stimulation-evoked resistance exercise therapy improves arterial health after chronic spinal cord injury. *Spinal Cord* 2007, 45: 49-56.

41. Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training and detraining in persons with spinal cord injury. *Arch Phys Med Rehabil 2007*, 87: 474-81.

42. Gerrits HL, De Haan A, Sargeant AJ, Van Langen H, Hopman MT. Peripheral vascular changes after electrically stimulated cycle training in people with Spinal Cord Injury. *Arch Phys Med Rehabil* 2001, 82: 832 -9.

43. Lehmann JF. Therapeutic Heat and Cold, 4th Edition, 1974. Williams and Wilkins.

44. Rabkin JM, Hunt TK. Local heat increases blood flow and oxygen tension in wounds. *Arch Surg* 1987, 122(2): 221 - 5.

45. Dinenno FA, Seals DR, DeSouza CA, Tanaka H. Age related decreases in basal limb blood flow in humans: time course, determinants and habitual exercise effects. *J of Physiol* 2001, 531.2 : 573-79.