Research article

Muscle spasticity associated with reduced whole-leg perfusion in persons with spinal cord injury

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Objective: To determine the association between peripheral blood flow and spasticity in individuals with spinal cord injury (SCI).
Design: A cross-sectional study with measurements of muscle spasticity and whole-limb blood flow in individuals with SCI.
Setting: University of Texas at Austin and Brain & Spine Recovery Center, Austin, TX, USA.
Participants: Eighteen individuals (14 males and 4 females) with SCI were classified into high ($N = 7$), low ($N = 6$), and no ($N = 5$) spasticity groups according to the spasticity levels determined by the modified Ashworth scale scores.
Interventions: Whole-limb blood flow was measured in the femoral and brachial arteries using Doppler ultrasound and was normalized to lean limb mass obtained with dual-energy X-ray absorptiometry.
Outcome measures: Limb blood flow and muscle spasticity.
Results: Age, time post-SCI, and the American Spinal Injury Association impairment scale motor and sensory scores were not different among groups with different muscle spasticity. Femoral artery blood flow normalized to lean leg mass was different ($P = 0.001$) across the three spasticity groups (high 78.9 ± 16.7, low 98.3 ± 39.8, no 142.5 ± 24.3 ml/minute/kg). Total leg muscle spasticity scores were significantly and negatively correlated with femoral artery blood flow ($r = -0.59$, $P < 0.01$). There was no significant difference in brachial artery blood flow among the groups.
Conclusions: Whole-leg blood flow was lower in individuals with greater spasticity scores. These results suggest that a reduction in lower-limb perfusion may play a role, at least in part, in the pathogenesis leading to muscle spasticity after SCI.

Keywords: Blood flow, Chemoreceptor, Paralysis, Paraplegia, Tetraplegia, Vascular

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 amplitude of peripheral stretch reflexes.[1] Muscle spasticity interferes with mobility, transfer, self-care, and activities of daily living, and has a negative impact on well-being.[2] The common prevailing theory to explain the mechanism underlying muscle spasticity is reduced descending inhibition of the muscle spindle Ia afferent following SCI, which leads to an increase in motoneuron excitability.[3,4] Studies using animal models have found that Ia afferents increase their activity levels in response to fusimotor neuron activation by small diameter Group III and IV afferents.[5] These small diameter afferents respond to muscle metabolites such as lactic acid, arachidonic acid, and bradykinin.[6] Individuals with chronic paralysis from SCI demonstrate rapid and extensive adaptations in peripheral circulation such as a decrease in vessel diameter size[7,8] and markedly reduced basal blood flow.[7,9,10] Additionally, muscles paralyzed by SCI exhibit substantially higher rates of fatigue.[11,12]

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The coexistence of reduced blood flow and high fatigability can create an environment conducive to the build-up of metabolites. It is plausible to hypothesize that the accumulation of metabolites, resulting from reduced limb perfusion, could exacerbate spasticity via activation of fusimotor neurons by Group III and IV afferents. This hypothesis, however, has not been addressed.

Accordingly, the primary aim of the present study was to determine the association between whole-limb blood flow and muscle spasticity in individuals with SCI. To address this aim, we studied femoral artery blood flow in persons with complete and incomplete SCI having high, low, and no-leg muscle spasticity. We hypothesized that reduced femoral artery blood flow levels would be associated with the greater degree of leg muscle spasticity.

Methods

Participants

Eighteen individuals (14 males and 4 females) with traumatic spinal cord injuries ranging from C3 to T12 and 8.6 ± 2.0 years post-SCI, participated in this study. Participants were excluded from the study if they had diagnoses of 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. Nine individuals were taking either analgesics or antispasmodics during the study (Table 1). However, these medications do not have known vascular actions. To reduce circadian variation in the measurements, all participants were tested between 10 am and 2 pm. All subjects refrained from physical activity prior to study. This study was approved by the local Institutional Review Board.

Table 1 Medications

Subject #	Medications
High spasticity	
2	Hydrocodone, finasteride, oxybutynin, amitriptyline
3	None
6	Gabapentin
8	Ditropan
25	None
28	Baclofen
32	Hydrocodone, baclofen, gabapentin
Low spasticity	
15	None
17	None
21	None
24	Baclofen, diazepam, ditropan
30	Baclofen
31	None
No spasticity	
4	Remeron
7	Methadone, gabapentin, ativan
10	Nitric oxide supplements
13	None
18	Birth control pills

Clinical assessments

Clinical examinations were performed according to the impairment scale (AIS) of the American Spinal Injury Association by the same licensed occupational therapist. Muscle tone was graded using the modified Ashworth's scale (MAS) of grading muscle spasticity (0: flaccid muscle tone to 4: limb held rigid in flexion or extension).

Blood flow

Mean blood velocity and vessel diameter of the right brachial artery and the right common femoral artery for all participants were measured using a Duplex ultrasound (Philips HDI-5000, Bothel, WA, USA) equipped with a high-resolution linear-array transducer as previously described.[13,14] 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. 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. The day-to-day variability for blood flow measurements in the laboratory is ~8%. Before blood flow measurements, participants were instructed to lie down in a quiet, temperature-controlled laboratory room at least for 20 minutes. They remained in this position during the blood flow recording. The temperature of the room was maintained from 22 to 25°C. There were no differences in spasticity levels between the right and left sides. Thus, all vascular measurements were performed on the right side of the body. All the data were digitally recorded on the hard drive and analyzed by the software provided by the ultrasound manufacturer. Blood flow was calculated using the formula:

$$\text{Baseline blood flow}(l/\text{minute}) = [\text{Mean blood velocity} \times \text{Circular area} \times 6 \times 10^4]$$

Whole-body composition and leg fat-free mass

Whole-body composition was determined from dual-energy X-ray absorptiometry using a Lunar Prodigy (GE Medical Systems, Madison, WI, USA). Data were analyzed with enCORE software (version 11.0).

Table 2 Modified Ashworth test spasticity scores for the right leg

	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
	32	0	0	1	0	0	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
	31	0	0	0	0	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 3 Participant characteristics

Variable	High spasticity	Low spasticity	No spasticity
Sex (n)	7 men	3 men & 3 women	4 men & 1 woman
Age (years)	31.3 ± 9.5	38.0 ± 9.3	32.6 ± 10.9
Years since SCI	8.0 ± 9.5	10.7 ± 10.6	6.8 ± 3.1
AIS motor	40.7 ± 17.8	53.3 ± 28.3	53.3 ± 28.3
AIS sensory	95.0 ± 49.4	95.0 ± 49.4	130.4 ± 30.8
Height (cm)	179.6 ± 7.0	171.8 ± 11.4	178.8 ± 6.9
Body mass (kg)	80.7 ± 16.4	67.9 ± 19.2	67.4 ± 23.6
Bone mineral density (g/cm^2)	1.15 ± 0.17	1.18 ± 0.11	1.13 ± 0.22
Adipose tissue mass (kg)	25.6 ± 9.8	20.8 ± 8.9	22.9 ± 14.3
Lean mass (Kg)	51.8 ± 8.1	44.7 ± 14.9	41.4 ± 9.6
Femoral artery diameter (mm)	6.92 ± 0.33	6.86 ± 0.65	6.67 ± 0.42
Brachial artery diameter (mm)	4.41 ± 0.38	4.04 ± 0.16	4.29 ± 0.52

AIS = American Spinal Injury Association Scale.
SCI = spinal cord injury.
Values are mean ± SD.

Regional analysis of tissue mass of the right leg and arm was performed from the whole-body scans. Femoral and brachial artery blood flow values were then adjusted to the right leg and arm lean mass (i.e., metabolically active tissue mass) as previously described.[13,14]

Statistics

Group differences were assessed using one-way ANOVA with Tukey's *post-hoc* analyses. Univariate correlation and regression analyses were performed to determine associations between femoral artery blood flow and leg muscle spasticity. All data are reported as mean ± standard deviation. Statistical significance was set *a priori* at $P < 0.05$.

Results

Participants were classified into three groups based on the level of spasticity as assessed from the MAS; high ($N = 7$), low ($N = 6$), and no ($N = 5$) muscle spasticity. Participants in the high spasticity group had MAS scores of 2 and above, 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 2). There were no significant differences in age, height, body mass, body composition, time from SCI, AIS motor and sensory scores, and arterial diameter among the three groups (Table 3).

There were no significant differences in the regional lean masses of the right brachial (3.6 ± 1.1, 3.1 ± 1.5, 3.6 ± 0.9 kg, $P = 0.60$), and femoral (7.7 ± 1.5, 6.9 ± 3.5, 5.0 ± 1.4 kg, $P = 0.10$) artery diameters or mean blood velocities among the three groups. There was a significant main effect ($P < 0.01$) for femoral artery blood flow normalized to lean leg mass across the groups (high 78.9 ± 16.7, low 98.3 ± 39.8, no 142.5 ± 24.3 ml/minute/kg). *Post-hoc* analysis revealed a

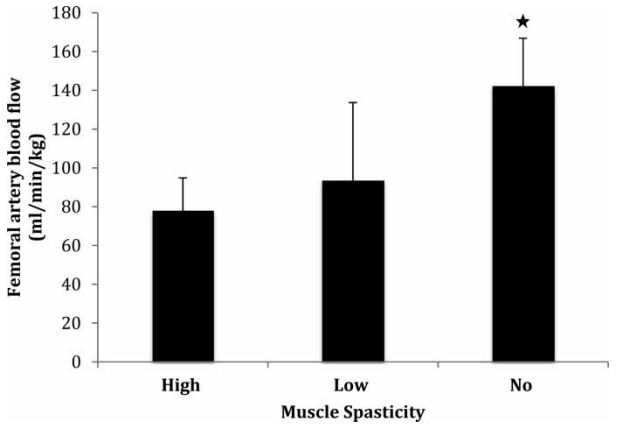

Figure 1 Normalized femoral artery blood flow (ml/minute/kg) in the high, low, and no muscle spasticity groups. There was a significant main effect for blood flow across the three spasticity groups. The asterisk indicates a significant difference between the high and low spasticity groups revealed in *post-hoc* analysis.

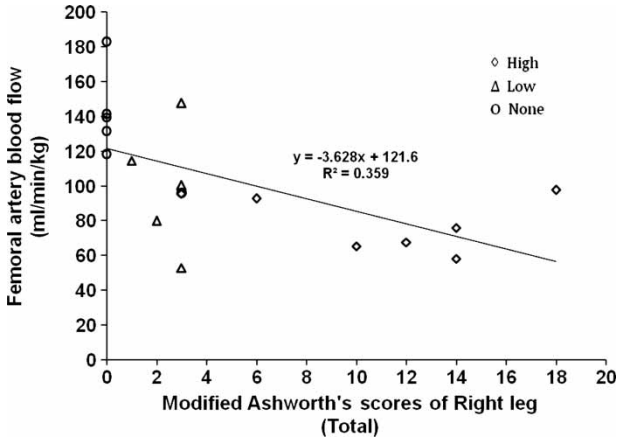

Figure 2 Association between modified Ashworth's scores of right leg and normalized femoral artery blood flow.

statistically significant difference between the high and no muscle spasticity groups (Fig. 1). As illustrated in Fig. 2, modified Ashworth's scores of muscle spasticity were significantly and inversely correlated to the whole-leg blood flow values ($r = -0.59$, $P < 0.01$). For every 1 unit change in MAS, there was a 3.65 ml/minute/kg decrease in blood flow. Absolute and normalized brachial artery blood flows were not different among the groups (101 ± 74, 94 ± 73, 115 ± 72 ml/minute/kg, $P = 0.86$) and were not related to modified Ashworth's scores of muscle spasticity.

Discussion

The salient findings of the present study are that femoral artery blood flow was significantly lower in individuals with higher spasticity scores and that increased muscle spasticity scores were significantly correlated with reduced femoral artery blood flow. After determining patient groups based on degree of spasticity, there were no differences in age, physical characteristics, time from SCI, and AIS motor and sensory scores between the three groups. These results suggest that reduced limb perfusion may play a role, at least in part, in the pathophysiology leading to exaggerated muscle spasticity. To the best of our knowledge, this was the first study to demonstrate the significant association between muscle spasticity and peripheral blood flow in individuals with SCI.

Blood flow and vascular functions have been studied in the SCI population, but few studies have evaluated its relation to the secondary complications that could impact functions and activities of daily living. Plethysmography and Doppler studies of lower limbs have shown that blood flow and arterial diameter are significantly lower in persons with paraplegia compared with able-bodied controls,[7–10] although other studies have reported that femoral artery diameter and blood flow did not differ between SCI and able-bodied individuals when they were adjusted per unit muscle volume.[15] These arterial adaptations were attributed mainly to the loss of supraspinal control of somatic efferents, which causes extreme deconditioning of the leg muscles. Deconditioning and long-term inactivity are 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.[16] Absolute values of femoral artery diameter in this study (≈7 mm) were consistent with previous studies of patients with SCI (5–7 mm) and smaller than able-bodied controls (7–10 mm).[7,8]

Long-term inactivity in patients with lower motor neuron paralysis leads to structural and functional changes in the muscle fibers below the level of lesion, including changes in the fiber population toward more fatigable types.[17] Paralyzed muscles fatigue rapidly due to chronic changes in metabolism, vascularization, muscle perfusion pressure, and/or fiber-type composition. The combination of reduced peripheral blood flow and high fatigability[12] creates an environment that favors the accumulation of metabolic by-products, which can affect muscle contractile function and activate Group III and IV afferent pathways.

Spasticity is most commonly believed to stem from increased Ia afferent transmission to α-motor neurons.[18–20] However, other pathways that could facilitate motor neuron excitation have also been proposed. These pathways include decreased reciprocal

inhibition,[21] reciprocal facilitation,[22] decreased presynaptic inhibition of Ia afferents,[23] changes in flexor reflex afferent pathways,[24,25] reduced recurrent inhibition,[26] and enhanced α-motor neuron self-sustained firing.[27]

Animal studies have clearly shown that blood flow restriction can increase Ia afferent firing by fusimotor activation from Group III and IV afferents that respond to a build-up of metabolites in the muscle.[5,28] Increased EMG response to tendon tap and vibration after muscle fatigue have also been observed in humans, suggesting an up-regulation of Ia afferent activity during fatigue.[29–31] Hence, Ia afferent activity may be exacerbated by the physiological changes and increase in fatigability of the paralyzed muscle as well as the absence of adequate perfusion to remove the accumulated metabolites. Muscle metabolites were not measured in the present study as peripheral venous blood samples may not correctly represent the muscle metabolite concentration and muscle biopsies have a high risk of infection in this patient population.

De Groot *et al.*[32] observed 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 show relatively rapid changes in lower limb vasculature and 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 individuals with SCI.

There are a number of limitations that should be emphasized in the present study. First, the number of the subjects studied is relatively small. This was due in part to the criteria of excluding patients with cardiovascular disease, hypertension, diabetes mellitus, peripheral vascular disease, recent fractures and open wounds, or pregnancy. This small sample size may have masked some statistical differences in the physiological parameters. There may also be factors related to gender/sex that are unknown at this time. Second, because this is a cross-sectional study, we cannot determine the cause and effect relation. In contrast to our accepted hypothesis, it is possible that high levels of muscle spasticity may be driving reduced levels of leg blood flow. Finally, 4 of the 18 participants had very low levels of spasticity in the upper extremities. The brachial artery blood flow in these individuals was not different when compared with the rest of the study participants. The finding that brachial artery blood flow was normal across all groups indicates that the reduced blood flow in the lower extremities was due to disuse atrophy rather than to systemic cardiovascular disease.

Conclusion

In summary, the present study demonstrates that increased levels of muscle spasticity is significantly associated with reduced peripheral blood flow and that lower limb perfusion in persons with SCI experiencing high leg spasticity was significantly lower than those without spasticity. These results are consistent with the hypothesis that lower levels of leg perfusion may contribute to muscle spasticity in individuals with SCI. Future studies are needed to investigate the effects of changes in spasticity following interventions designed to improve peripheral blood flow in clinical populations with spasticity.

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References

1 Lance JW. Symposium synopsis. In: Young RR, Koella WP (eds.) Spasticity: disordered motor control. Chicago: Yearbook Medical Publishers; 1980. p. 485–94.
2 Parziale JR, Akelman E, Herz DA. Spasticity: pathophysiology and management. Orthopedics 1993;16(7):801–11.
3 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(7):636–41.
4 Szumski AJ, Burg D, Struppler A, Velho F. Activity of muscle spindles during muscle twitch and clonus in normal and spastic human subjects. Electroencephalogr Clin Neurophysiol 1974; 37(6):589–97.
5 Ljubisavljevic M, Jovanovic K, Anastasijevic R. Changes in discharge rate of fusimotor neurons provoked by fatiguing contractions of cat triceps surae muscle. J Physiol 1992;445(1):499–513.
6 Rotto DM, Kaufman MP. Effect of metabolic products of muscular contraction on discharge of group III and IV afferents. J Appl Physiol 1998;64(6):2306–13.
7 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(6): 2335–40.
8 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(12):1260–5.
9 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(5): 303–10.
10 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;388:378–83.
11 Lenman AJ, Tulley FM, Vrbova G, Dimitrijevic MR, Towle JA. Muscle fatigue in some neurological disorders. Muscle Nerve 1989;12(11):938–42.
12 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(4):2055–64.
13 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(5):1351–5.
14 Dinenno FA, Jones PP, Seals DR, Tanaka H. Limb blood flow and vascular conductance are reduced with age in healthy humans: relation to elevations in sympathetic nerve activity and declines in oxygen demand. Circulation 1999;100(2):164–70.
15 Olive JL, Dudley GA, McCully KK. Vascular remodeling after spinal cord injury. Med Sci Sports Exerc 2003;35(6):901–7.
16 Lee RDB, Langille BL. Arterial adaptations to altered blood flow. Can J Physiol Pharmacol 1991;67(7):978–83.
17 Taylor JL, Butler JE, Gandevia SC. Changes in muscle afferents motoneurons and motor drive during muscle fatigue. Eur J Appl Physiol 2000;83(2–3):106–15.
18 Szumski AJ, Burg D, Struppler A, Velho F. Activity of muscle spindles during muscle twitch and clonus in normal and spastic human subjects. Electroencephalogr Clin Neurophysiol 1974;37(6):589–97.
19 Hagbarth KE, Wallin G, Lofstedt L. Muscle spindle activity in man during voluntary fast alternating movement. J Neurol Neurosurg Psychiatry 1975;38(7):625–35.
20 Hidler JM, Rymer WZ. A simulation study of reflex instability in spasticity: origins of clonus (in process citation). IEEE Trans Rehabil Eng 1999;7(3):327–40.
21 Crone C, Nielsen J, Petersen N, Ballegaard M, Hultborn H. Disynaptic reciprocal inhibition of ankle extensors in spastic patients. Brain 1994;117(5):1161–8.
22 Crone C, Johnsen LL, Biering-Sorensen F, Nielsen JB. Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury. Brain 2003;126(2):495–507.
23 Faist M, Mazevet D, Dietz V, Pierrot-Seseilligny E. A quantitative assessment of presynaptic inhibition of la afferents in spastics. Difference in hemiplegics and paraplegics. Brain 1994;117(6): 1449–55.
24 Roby-Brami A, Bussel B. Long-latency spinal reflex in man after flexor reflex afferent stimulation. Brain 1987;110(3):707–25.
25 Remy-Neris O, Barbeau H, Daniel O, Boiteau F, Bussel B. Effects of intrathecal clonidine injection on spinal reflexes and human locomotion in incomplete paraplegic subjects. Exp Brain Res 1999;129(3):433–40.
26 Mazzocchio R, Rossi A. Involvement of spinal recurrent inhibition in spasticity: further insight into the regulation of Renshaw cell activity. Brain 1997;120(6):991–1003.
27 Gorassini MA, Knash ME, Harvey PJ, Bennett DJ, Yang JF. Role of motoneurons in the generation of muscle spasms after spinal cord injury. Brain 2004;127(10):2247–58.
28 Jovanovic K, Anastasijevic R, Vuco J. Reflex effects on gamma fusimotor neurons of chemically induced discharges in small-diameter muscle afferents in decerebrate cats. Brain Res 1990;521(1–2): 89–94.
29 Marsden CD, Merton PA, Morton HB. Servo action in human voluntary movement. Nature 1972;238(5360):140–3.
30 Biro A, Griffin L, Cafarelli E. Reflex gain of short- and long-loop muscle spindle pathways during fatigue. Exp Brain Res 2007; 177(2):157–66.
31 Hayes KC. Effects of fatiguing isometric exercise upon achilles tendon reflex and plantar flexion reaction time components in man. Eur J Appl Physiol 1975;34(2):69–79.
32 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(12):1977–85.