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Evaluation of the Changes in the Muscle Sympathetic Nerve Activity and Anterior Tibial Muscle Blood Flow Caused by the Valsalva Maneuver in Patients with Lumbago and Healthy Subjects

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Abstract

Clinical symptoms affecting the lower extremities are common among lumbar spinal disorder patients. Pain, numbness and sensory disturbance are major signs of these symptoms, and have been suggested to be related to sympathetic nerve disturbance. This study was designed to examine whether these patients experience a difference in sympathetic nerve flow in terms of muscle sympathetic nerve activity (MSA) compared to healthy subjects. Five patients with lumbar intervertebral disc herniation of the spine (LIDH) and four patients with lumbar spinal canal stenosis (LSCS) were examined along with six healthy volunteers. Basic MSAs for IDH and SCS patients that were introduced from a common peroneal nerve were found to be statistically higher than those of the control subjects. MSA behavior and muscle blood flow introduced from the tibialis anterior muscle over 30 seconds while performing the Valsalva maneuver, a well-known technique used to artificially facilitate MSA, were examined for all subjects, and showed relatively slower changes for LIDH and LSCS patients compared to the normal subjects. Muscle blood flow was inversely proportional to MSA for the normal subjects, and this relationship was observed for IDH patients as well as SCS patients. However, MSA and the muscle blood flow of patients gradually changed while performing the Valsalva maneuver relative to the control subjects. This suggests that the systemic physiological response to the maneuver is maintained, but that, some local modification mechanisms exist.

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Key words: muscle sympathetic nerve activity, muscle blood flow, Valsalva maneuver

Introduction

Clinical symptoms of the lower extremities including pain, numbness and sensory disturbance are common among lumbar spinal disorder patients,

and those are often aggravated by exercise, which is considered to be the result of blood flow disorder in the lower extremities and related to the disturbance of muscle sympathetic nerve activity (MSA)^{1,2}. Therefore, to examine the mechanism responsible for the aggravation of these symptoms, the

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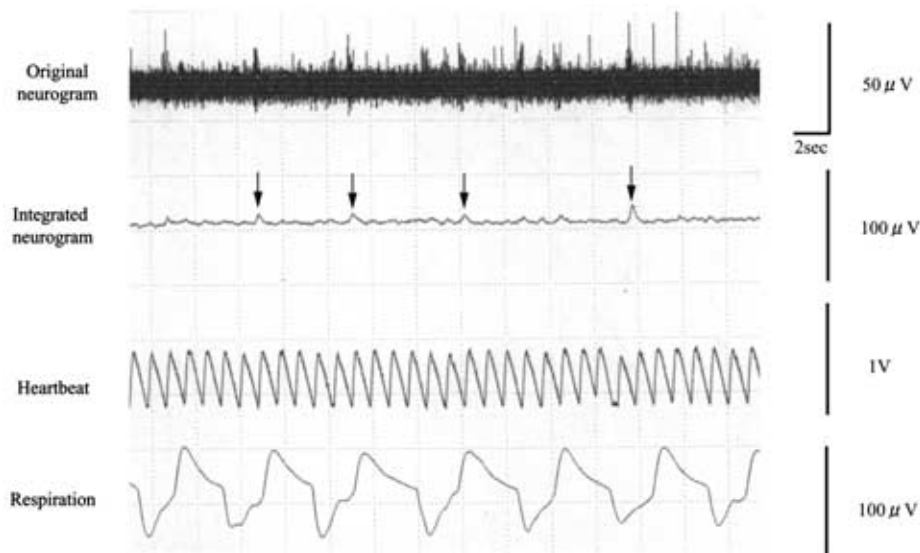


Fig. 1 Muscle sympathetic nerve activity and other biograms for a normal subject. The first upper trace shows an original neurogram of MSA, and the second is an integrated neurogram. Recorded MSAs are shown as waves indicated by arrows. The third and fourth traces are heartbeat and respiration cycles, respectively.

measurement of MSA and blood flow in the lower extremities before and after exercise is necessary. However, it is difficult to simultaneously measure these parameters during exercise even though various methods used for the examination of MSA have been developed.

To induce artificial changes in MSA, the Valsalva maneuver can be used, which entails holding one's breath for a short time, a simple task that is unlikely to cause variability among individuals. Therefore, this maneuver is used for the identification of MSA³⁴. We hypothesized that this maneuver is appropriate for the observation of changes in MSA because it does not induce excessive stress. In this study, to examine whether patients exhibit a difference in sympathetic nerve flow in terms of MSA compared to healthy subjects, we measured MSA and muscle blood flow while this maneuver was being carried out.

Material and Methods

The subjects consisted of 33 patients with disorders of the lumbar vertebrae and 11 healthy controls. Among the patients were 16 patients with lumbar intervertebral disc herniation of the lumbar

spine (LIDH) and 17 with lumbar spinal canal stenosis (LSCS). The healthy volunteers had neither low back or lower extremity pain, and no physical abnormalities in the lumbar region and lower extremities were detected. The patients were diagnosed as having LIDH or LSCS based on physical examination and the findings of plain radiography of the lumbar vertebrae and MRI of the lumbar region, and were admitted for treatment to Nippon Medical School Hospital in Tokyo.

Four trials involving the Valsalva maneuver were performed on each subject, but for several the examination abruptly discontinued because of pain caused by insertion of a needle electrode used for recording the MSA potential, discomfort induced by the Valsalva maneuver or failure of obtain effective potentials. Overall in 11 LIDH patients and 13 LSCS patients withdrew. Among the controls, 5 could not complete the examination. The data on these patients and controls was therefore excluded from the analysis. Four trials involving the Valsalva maneuver were completed by 5 LIDH patients aged 24~42 years with a mean age of 32.2 years, 4 LSCS patients aged 46~73 years with a mean age of 68.3 years, and 6 controls aged 28~32 years with a mean age of 30.2 years, and data on these subjects was

subsequently analyzed. Among them, one patient with LIDH and 3 with LSCS were medicated for the treatment of hypertension, but no drug that could influence sympathetic activity was used. And no subject was a diabetic. All subjects were informed about the purpose of the study and the risks involved, and gave their consent before entering it. This study was approved by the ethics committee of Nippon Medical School.

MSA and muscle blood flow used to monitor blood flow in the lower extremities were measured in the prone position at rest and during the Valsalva maneuver. In an electrically shielded room used for clinical electromyography at a temperature of 25°C, each subject lied on a bed for 15 min in the prone position. An electrode used to record MSA and a probes used for the measurement of blood flow were fixed on the side showing clinical symptoms or more severe symptoms (right or left). For the controls, measurements were taken for the lower limb on the same side as the dominant hand.

1) Recording of the Induced MSA

While each subject was in the prone position at rest, a round shaped surface silver disc electrode 1 cm in diameter was fixed as the active electrode on the region of the tibialis anterior muscle belly with the maximal diameter of the lower leg, and another as the indifferent electrode was fixed on the site where the pedal tendon is attached to this muscle to record tibialis anterior muscle action potentials. The site of the common peroneal nerve at the maximal potential induced by the tibialis anterior muscles was identified by applying electric stimulation to the skin of the popliteal fossa beneath which the nerve runs through. This site was then marked as the insertion point of an electrode subsequently used for recording. A surface silver disc electrode with a diameter of 1 cm was fixed as the reference electrode other than the ground on the skin immediately above the peroneal nerve 2 cm proximal from the insertion point. A tungsten microelectrode with a tip diameter of 43~53 μm and impedance of 2~5 $\text{M}\Omega$ was then percutaneously inserted into the common peroneal nerve from the insertion point without anesthesia. The blood

pressure and the pulse rate resulting from peripheral pulse waves were monitored using a laser Doppler rheometer fixed on the great toe on the test side, and a respiration curve was obtained for the pernasal cannula. According to the criteria of Delius³ and Mano⁴, spontaneous, pulse-synchronous, and burst impulses were identified (**Fig. 1**) using an electromyograph (MEM-4200 (Neuropack 8), Nihon Kodens Inc.). All original wave patterns were rectified using a time constant of 0.1 by the packaged program for the analysis of MSA and recorded as integrated waves.

2) Measurement of Muscle Blood Flow

The measurement and recording of muscle blood flow were performed by direct intramuscular insertion of a needle probe with a diameter of 0.6 mm and length of 40 mm fixed to a laser Doppler rheometer (ALF-21, Advance Inc.). The skin in the central area of the tibialis anterior muscle with a maximal belly width of 6~8 cm distal from the tibial tuberosity on the test side was marked as the insertion point, and the probe was percutaneously inserted into the muscle through a hole made using a 23G needle without anesthesia. Blood flow was measured via the Doppler effect within a spherical volume with a diameter of 2 mm formed by irradiation via a laser beam fitted to the probe. Abnormally high or unstable blood flow was sometimes obtained depending on the insertion site because of the measurement characteristics of the probe. Therefore, the probe tip was slowly inserted into the deep region and fixed when a relatively stable blood flow level was observed without fluctuations. After fixation, blood flow was confirmed to be stable without large fluctuations for 3 min while each subject was in the prone position at rest, after which the Valsalva maneuver performed and measurements were taken.

3) The Valsalva Maneuver and Measurements

Each trial involving the Valsalva maneuver was conducted with the subject lying on a bed in the prone position at rest for 30 sec before the start, after which the maneuver was carried out for 30 sec after deep respiration. Subsequent to this, rest was

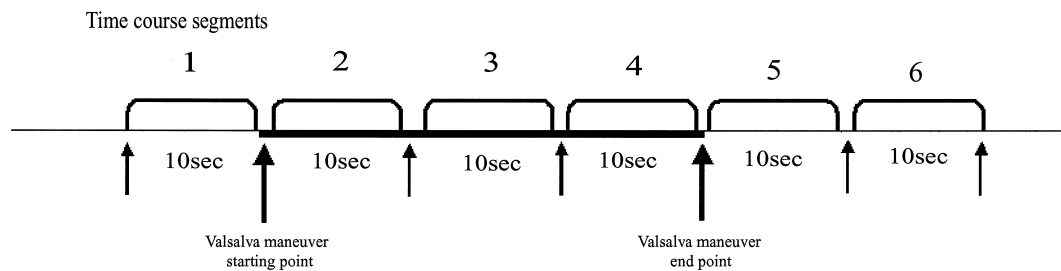


Fig. 2 Time course segments for before and after the Valsalva maneuver.
 Segment 1: The 10 seconds interval before starting the maneuver.
 Segment 2: The first 10 seconds after starting the maneuver.
 Segment 3: The middle 10 seconds during the maneuver.
 Segment 4: The last 10 seconds after the maneuver was started.
 Segment 5: The 10 second interval just after the maneuver was terminated.
 Segment 6: The next 10 seconds after the maneuver was terminated.

maintained for 30 sec via discontinuation of the maneuver and the return to routine respiration. Each trial was repeated 4 times, for which measurement of the burst rate (BR) converted into the number of bursts per unit time/the number of ignition bursts per min of MSA over 10 sec was performed. For the 10 seconds interval prior to starting the maneuver, that after starting the maneuver, during the middle, the last 10 seconds after, that just after termination, and the next 10 seconds following termination were taken as the time course. Muscle blood flow was recorded for all segmental starting points. These time courses are indicated by the time course segments 1, 2, 3, 4, 5, and 6 respectively, for the analysis and discussion (Fig. 2).

To examine the changes in muscle blood flow within a short time caused by the Valsalva maneuver, it was measured every 2 sec.

Results

1) Results at Rest

The mean BR \pm standard deviation obtained in the prone position at rest before starting the Valsalva maneuver was 34.3 ± 1.2 for the control group, 42.2 ± 4.3 for the LIDH group, and 46.5 ± 5.7 for the LSCS group. Statistical analysis of the BR carried out using the Mann-Whitney's U-test showed that there were significant differences between the control and LIDH groups ($p=0.0042$) and between

the control and LSCS groups ($p=0.0086$), but no difference was observed between the LIDH and LSCS groups (Table 1).

2) Changes in MSA Induced by the Valsalva Maneuver

The mean BR of MSA over the time course was 24.5, 22.5, 28.7, 32.5, 26.7, and 24.8 for the control group, 37.2, 35.6, 41.6, 42.3, 42.0, and 40.1 for the LIDH group, and 44.7, 42.5, 53.9, 54.9, 49.2, and 50.1 for the LSCS group. Since there were differences in the mean BR at rest between the control and patient groups, simple comparisons of the BR were considered inadequate. Therefore, the relative BR was determined using the BR for segment 1 as the standard, and the differences were then re-analyzed. For the control group, the relative BR determined using the BR (24.5) was 1, 0.93, 1.19, 1.33, 1.10, and 1.02. Similarly, the relative BR was 1, 0.96, 1.18, 1.13, 1.12, and 1.08 for the LIDH group, and 1, 0.95, 1.20, 1.22, 1.10, and 1.11 for the LSCS group (Fig. 3). There were no differences in the reaction induced by the Valsalva maneuver among the groups, but the increase in the relative BR after the decrease for segment 2 was slower for the patient groups than for the control group, and was marked for the LSCS group. Statistical analysis of the relative BR for each segment as seen by the Mann-Whitney's U-test showed that the difference in the relative BR was significant only for segment 4 between the control and LIDH groups ($p=0.0089$).

Table 1 The averaged burst rate and its standard deviation for each patient at rest.

No.	LIDH patients	No.	LSCS patients	No.	Controls
1	52.0 \pm 7.20	1	38.4 \pm 1.33	1	33.0 \pm 3.60
2	43.6 \pm 3.68	2	52.0 \pm 4.00	2	38.4 \pm 6.70
3	40.0 \pm 2.40	3	48.8 \pm 1.77	3	37.2 \pm 3.84
4	38.4 \pm 1.44	4	46.8 \pm 2.24	4	34.0 \pm 3.20
5	37.2 \pm 0.96			5	28.4 \pm 1.28
				6	34.8 \pm 2.56
Mean \pm S.D	42.2 \pm 4.30		46.5 \pm 5.7		34.3 \pm 1.2
	* 1				
	* 2				

LIDH, lumbar intravertebral disc herniation; LSCS, lumbar spinal canal stenosis. The burst rate was defined as the number of MSA bursts over one minute. The measured BRs consisted of a number of bursts over ten seconds, and thus the measured values were converted into the values that is magnified to 6 times. There was a statistically significant difference between the LIDH patients and the controls (* 1 $p < 0.0042$) and between the LSCS patients and the controls (* 2 $p < 0.0086$).

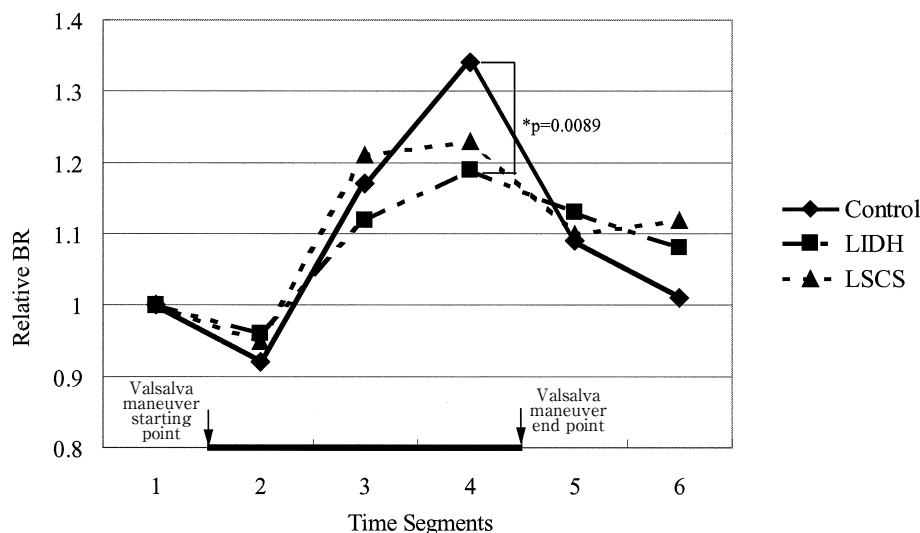


Fig. 3 The results for modified BRs for patients for each time segment. The relative BR results to the relative value of the converted BR value for each segment divided by the BR for the first time segment. For the fourth time segment, there was a significant difference between the LIDH patients and the controls (* $p = 0.0089$).

Muscle blood flow over the time course was 1.75, 1.97, 1.52, 1.47, 1.83, and 2.47 for the control group, 1.83, 2.17, 1.82, 1.72, 2.0, and 2.09 for the LIDH group, and 2.22, 2.5, 2.21, 2.29, 2.46, and 2.53 for the LSCS group. Relative muscle blood flow determined using the level before starting the Valsalva maneuver, as for the BR, was 1, 1.12, 0.86, 0.84, 1.05, and 1.52 for the control group, 1, 1.19, 0.99, 0.94, 1.09, and 1.12 for the LIDH group, and 1, 1.08, 0.99, 1.02, 1.10, and 1.11 for the LSCS group (Fig. 4). The change in the

pattern of muscle blood flow for the patient groups was similar to the change pattern for the control group, as for the BR, but the changes for the former groups were slow. Statistical analysis using the Mann-Whitney's U-test revealed significant differences in relative muscle blood flow for segment 3 between the control group and LIDH or LSCS group ($p = 0.004$, $p = 0.0089$) and a significant difference in relative muscle blood flow for segment 4 between the control and LSCS groups ($p = 0.019$).

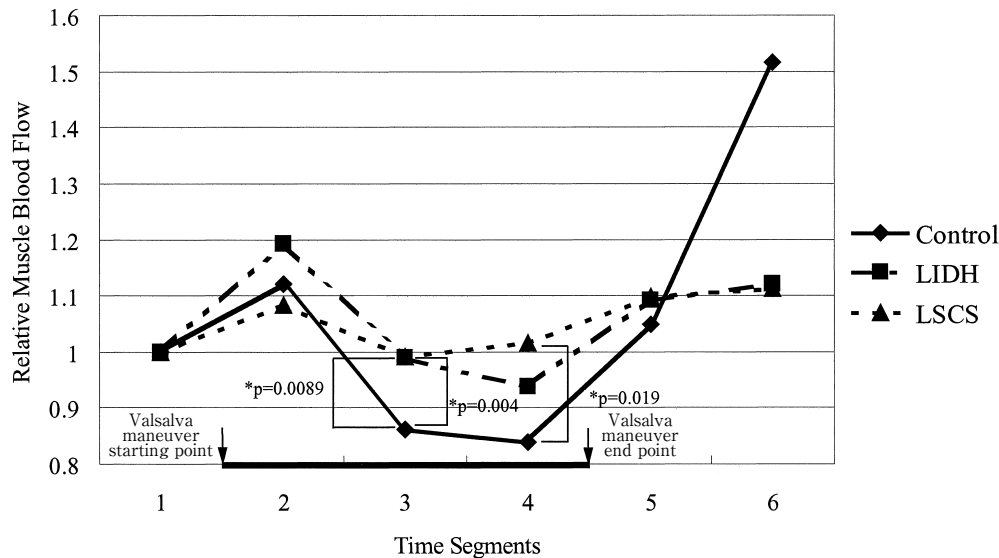


Fig. 4 The results for modified muscle blood flow for patients for each time segment. Relative muscle blood flow denotes the relative value for the converted muscle blood flow for each segment divided by the muscle blood flow for the first time segment. For the third time series 3, there was a significant difference between the LIDH patients and the controls (* $p=0.004$), and between the LSCS patients and the controls (* $p=0.0089$). For the fourth time segment, there was a significant difference between the LSCS patients and the controls (* $p=0.019$).

3) Changes in Blood Flow within a Short Time during the Valsalva Maneuver

Muscle blood flow was measured at intervals of 2 sec from 6 sec before starting the Valsalva maneuver to 12 sec onward for which measuring points were shown as -6, -4, -2, 0, 2, 4, 6, 8, 10 and 12. Relative muscle blood flow determined using time point -6 as the standard was 1, 0.94, 0.95, 0.99, 1.38, 1.25, 0.98, 0.94, 0.89, and 0.89 for the control group, 1, 1.00, 1.03, 1.19, 1.33, 1.38, 1.30, 1.25, 1.22, and 1.12 for the LIDH group, and 1, 0.90, 0.98, 1.09, 1.12, 1.11, 1.11, 1.03, 1.01, and 1.03 for the LSCS group (Fig. 5A). After the increase in muscle blood flow, it rapidly recovered to the level before the start of the maneuver for the control group, while for the patient groups the increase and its recovery were slow. For the LSCS group, the increase in blood flow was lower than for the control and LIDH groups. Statistical analysis using the Mann-Whitney's U-test showed significant differences in the relative muscle blood flow at times -4, -2, 0, 4, 6, 8, 10, and 12 between the control group and LIDH group ($p=0.016, 0.012, 0.004, 0.081, 0.004, 0.004, 0.004$), significant differences at times 0 and 2 between the

control group and LSCS group ($p=0.019, 0.02$), and significant differences at times 0, 6, 8 and 10 between the LIDH group and LSCS group ($p=0.032, 0.019, 0.013, 0.014$) (Fig. 5B).

Discussion

MSA mainly occurs vasopressor efferent impulses, where high MSA enhances the resistance of peripheral blood vessels in response to sympathetic nerve and reduces muscle blood flow. It has been suggested that the causes of symptoms of the lower extremities of patients with disorders of the lumbar vertebrae include inflammation and circulatory disorder of the cauda equina nerve, nerve roots, or lumbar nerve plexus⁵, and that those of the lower extremities are closely related to circulatory disorders of this region as observed by thermography⁶. These studies indicate that these symptoms are closely related to abnormalities in MSA⁷. MSA is enhanced in patients with disorders of the lumbar vertebrae⁸, and latent changes in blood flow in the peripheral circulation in such patients may occur not only under a systemic

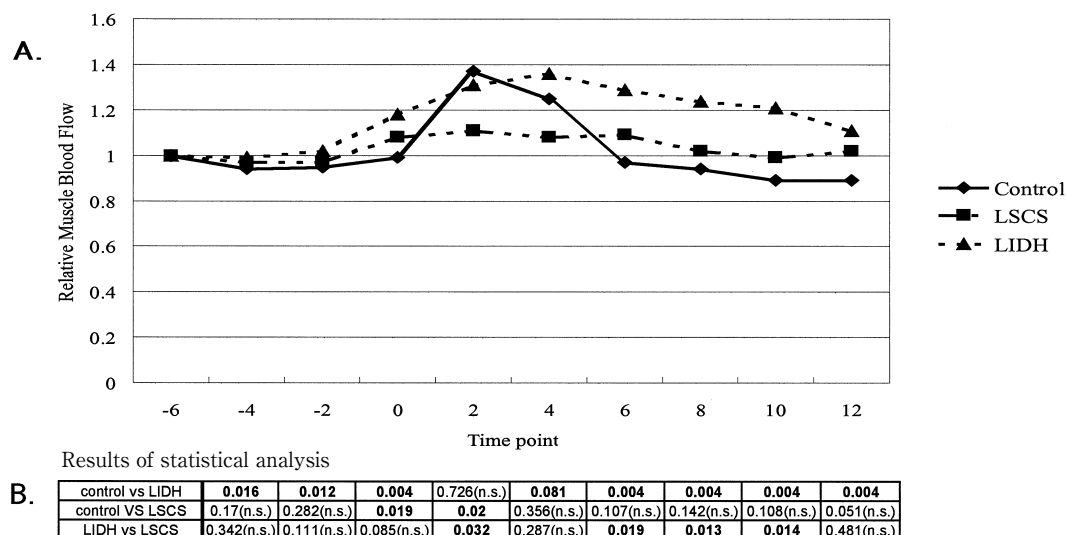


Fig. 5A The results for relative muscle blood flow for patients for short time segments around the start of the Valsalva maneuver. Time 0 indicates the starting time of the maneuver. Modified muscle blood flow was also calculated.

B The results for the statistical analysis of each time point.

Control vs LIDH: Significant differences between the control and LIDH patients

Control vs LSCS: Significant differences between the control and LSCS patients

LIDH vs LSCS: Significant differences between the LIDH patients and LSCS patients

n.s.: No significant difference

condition but also for local conditions. In this study, we examined the basic differences in MSA and the relationship between changes in it and blood flow in the lower extremities of patients with LIDH and LSCS, which are representative of many disorders of the lumbar vertebrae.

There were significant differences in MSA represented by the BR between the control and patient groups. The BR for the LIDH and LSCS groups was higher than for the control group. The LSCS patients in this study were older than the controls and MSA is higher among the elderly. The structural degeneration of blood vessels may occur in elderly subjects, and the reactive dilation of vessels may decrease with age. However, stimulation of the sympathetic nerve trunk in the lumbar region during the muscular contraction reduces the blood flow not only by passive decreases in the vascular diameter caused by the contraction of muscular fibers but also by increases in vascular resistance induced by the enhancement of MSA, indicating that muscle blood flow is mainly regulated by MSA⁹. In addition, the reaction of MSA via the cardiopulmona baroreflex is preserved or

elevated among the elderly¹⁰. According to these reports, the relationship between sympathetic nerve activity and peripheral blood flow during the Valsalva maneuver is preserved even in the elderly, and thus it is thought to be correct to evaluate changes in the pattern by comparing the relative BR and blood flow among the elderly and control subjects. Furthermore, the difference in MSA between the elderly subjects and young subjects is considered to be about 30%⁸. Even though there was almost no difference in the ages between the LIDH patients and controls, the BR was higher for the former group. For the LSCS group, the BR was higher by 40% than for the control group. These results suggest that mechanisms, which enhance MSA other than age, exist for low back pain related disorders. Although these mechanisms have not been clarified, lower back pain and symptoms in the lower extremities can be alleviated by blocking the sympathetic nerve in the lumbar region in patients with disorders of the lumbar vertebrae¹¹, suggesting that factors exist which cause dysfunction in MSA.

The BR decreased immediately after starting the Valsalva maneuver, and then rapidly increased to

recover to the initial level after its completion. This pattern was observed for the control and patients groups. The control group showed a 1.34-fold increase from the initial level, but the LIDH and LSCS groups only showed increases of 1.23-fold and 1.19-fold, respectively. Recovery to the initial level was slower for the patient groups during observation, indicating that the changes in the BR were slower for these groups. The differences in the changes between the control and patient groups were not significant, but there were slight differences in the changes in MSA induced by the Valsalva maneuver between the control and patient groups. On the other hand, the changes in the blood flow were almost opposite to those in the BR. Blood flow increased immediately after starting the Valsalva maneuver, then gradually decreased, and slightly increased again after its completion, which was common for all groups. For the LIDH group, the increase after the start was larger than for the control group and a decrease with fluctuations around the initial level was observed, while for the LSCS group the decrease was smaller without going below the initial level. Although the differences in the changes in blood flow were not significant, there were slight differences in the reaction induced by the Valsalva maneuver as for the BR.

The standard deviation of MSA ignition intervals is large during high velocity peripheral nerve conduction among healthy people, and this relationship is almost maintained among LSCS patients¹². The biological reaction induced by the Valsalva maneuver used in the present study resulted in systemic arrangement with changes in intravascular pressure, which were caused by changes in cardiac output resulting from changes in the venous return to the heart. Venous return is probably regulated by internal pressure in the thoracic and abdominal cavities, which is easily changed by the breath-holding maneuver. The relationship between these changes and changes in MSA has not been clarified^{13,14}, but the Valsalva maneuver has been established as a simple method for the artificial induction of changes in MSA. In the present study, changes in the BR were observed during the Valsalva maneuver. The changes in the

patterns of the BR and muscle blood flow were almost the same for the control and patient groups. Therefore, these changes as biological reactions were maintained among numbers of the patient groups.

The differences in the degree of changes between the groups suggest that there were other local or peripheral factors involved. In particular, the differences in the changes in blood flow measured every 2 sec before and after stimulation by the Valsalva maneuver were large between the control and patient groups. Even though the basic change in pattern showing increases in muscle blood flow with decreases in MSA was similar between the control and patient groups, the changes were slow so as to avoid rapid changes in blood flow for the latter groups. These slow changes were marked for members of the LSCS group with chronic disorders of the cauda equina nerve compared to the LIDH group, suggesting that mechanisms exist which induced buffer action against rapid biological changes by reducing changes in peripheral blood flow. Pain may be transmitted through the afferent pathway in muscle sympathetic nerves¹⁵, and the elevation of blood pressure in elderly subjects with enhanced MSA resulting from a load that increases MSA is delayed compared to that of young subjects¹⁶, suggesting the involvement of feedback via local reaction. Furthermore, there was no significant difference in blood flow measured every 2 sec before and after the stimulation by the Valsalva maneuver between the control and LSCS groups. Accordingly we hypothesize that basic changes in the pattern of muscle blood flow were maintained among LSCS patients. In addition, only changes in the rate of muscle blood flow were different, suggesting that mechanisms by which buffer activity against rapid biological changes was induced by reducing changes in peripheral blood flow for the LSCS group. On the other hand, there was a significant difference between the control group and LIDH group over almost all time points. Although this may suggest that the involvement of feedback by local reaction due to blood flow disorders in the lower extremities is different for symptoms of the lower extremities induced by the nerve root and

those of the lower extremities induced by the cauda equina, such mechanisms have not been identified. Biochemical and pharmacological studies other than electrophysiological studies are necessary for this in the future.

In this study, the relationship between MSA and lower back pain or symptoms of the lower extremities among patient groups was not clearly elucidated, but we found that the relationship between MSA changes as a biological reaction and their relationship to changes in muscle blood flow was maintained even among members of the patient groups, suggesting that local modification mechanisms exist. Since trials involving the Valsalva maneuver should be completed within a short period of time because of the load placed on the subject, the loading performed during this study could have been insufficient for the evaluation of mechanisms related to clinically important symptoms, such as intermittent claudication during walking for a long time for LSCS. In the future, mechanisms responsible for the occurrence of symptoms associated with disorders of the lumbar vertebrae should be clarified by various methods including methods equivalent to the motion we usually do in daily life.

Conclusions

We evaluated the changes in MSA and muscle blood flow in healthy subjects and LIDH or LSCS patients. Changes in the patterns of MSA and muscle blood flow induced by the Valsalva maneuver were similar among members of the control and patient groups, but the degree of change differed. This suggests that local mechanisms exist which reduces the rate of change in muscle blood flow among LIDH and LSCS patients.

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