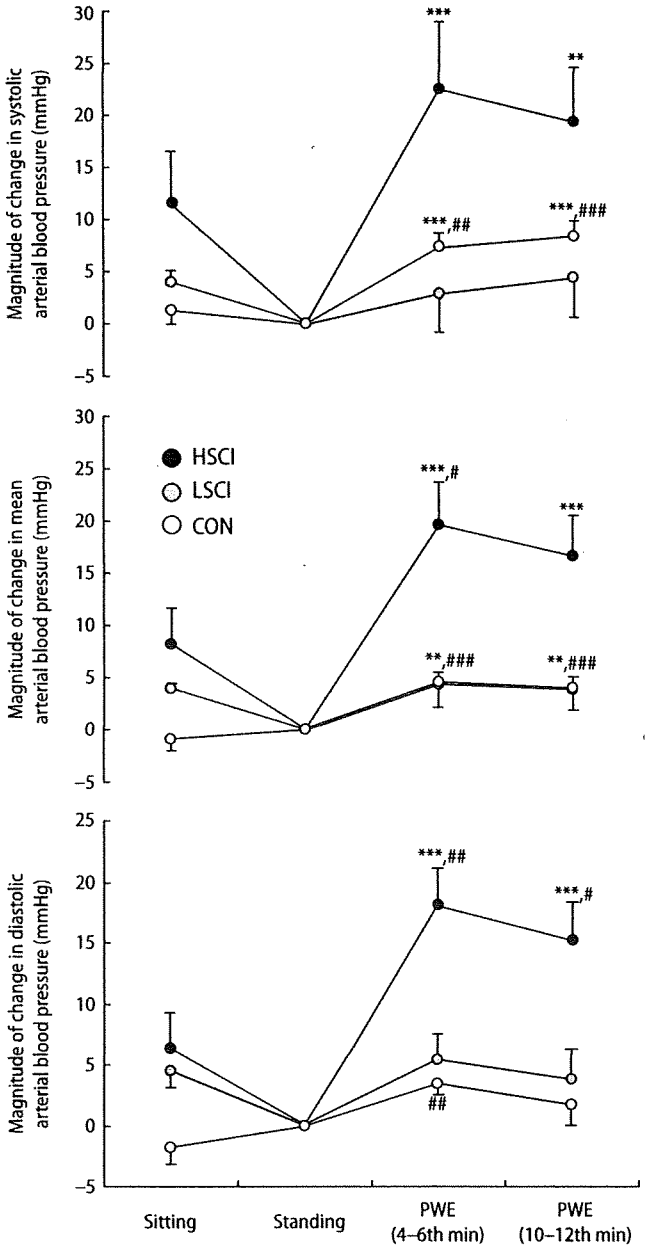

Fig. 3 Magnitudes of changes in systolic, mean and diastolic arterial blood pressures from the quiet standing level. *HSCI*: individuals with spinal cord injury at or above thoracic level 6. *LSCI*: individuals with spinal cord injury at or below thoracic level 10. *CON*: able-bodied controls. *PWE*: passive walking-like exercise. *, **, ***$P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively, compared to the quiet standing level. #, ##, ###$P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively, compared to the quiet sitting level

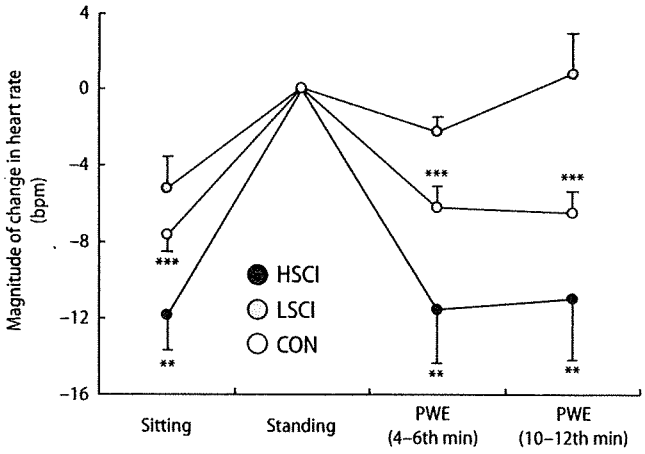

Fig. 4 Magnitudes of changes in heart rate from the quiet standing level. See legend to Figure 3 for definitions of symbols and abbreviations

At standing vs. at PWE

In both HSCI and CON, all of the blood pressure values at PWE were significantly higher than those at standing except for DAP in CON (Figure 3). In LSCI, on the other hand, there was no significant difference in either of the blood pressure values in the two conditions (Figure 3). RMS-EMG_{sum} at PWE was significantly higher than that at standing ($P < 0.001$), whereas $\dot{V}O_2$ did not differ significantly in the two conditions in any of the groups.

For all of the blood pressure parameters and HR, there was no significant difference between the value in the first half of PWE and that in the second half of PWE in all three groups (Figures 3 and 4). Therefore, we selected the values in the first half of PWE and compared the magnitude of changes in SAP, MAP and HR from the standing level in HSCI and CON (See Table 2). The magnitudes of increase in SAP and MAP in HSCI (22 ± 7 and 20 ± 4 mmHg, respectively) were significantly larger than those in CON (7 ± 1 and 5 ± 1 mmHg, respectively) (SAP: $P < 0.05$, MAP: $P < 0.001$). When blood pressure increases were expressed in relative terms (%) and compared, the magnitudes of increase in SAP and MAP in HSCI (30 ± 11 and 31 ± 8%, respectively) were also larger than those in CON (7 ± 1 and 5 ± 1%, respectively) (SAP: $P < 0.01$, MAP: $P < 0.001$). On the other hand, the magnitude of decrease in HR was not significantly different (12 ± 3 vs. 6 ± 1 bpm or 13 ± 3 vs. 9 ± 2% in HSCI and CON, respectively).

At sitting vs. at PWE

In HSCI, MAP and DAP during PWE were significantly higher than those during sitting, whereas there was no significant difference in the values of SAP. In CON, on the other hand, all of the blood pressure parameters showed significantly higher values during PWE than during sitting.

In HSCI and CON, HR decreased significantly during PWE compared with that during standing (Figure 4), resulting in no significant difference in HR during PWE and sitting.

Discussion

The new findings in this study were that PWE raises blood pressure above that present during quiet standing in able-bodied individuals and in SCI individuals with a lesion level at or above T6. This increase was significantly larger in the latter group. In individuals with a lesion level at or below T10, on the other hand, there was no significant change in blood pressure. We discuss below the possible physiological mechanisms underlying increases in blood pressure during PWE and the clinical implications of our results.

Circulatory responses at quiet sitting

In the present study, all of the blood pressure values in HSCI were significantly lower than those in CON, and MAP in HSCI was significantly lower than that in LSCI. On the other hand, none of the blood pressure parameters in LSCI were significantly different from those in CON. Several studies have shown that blood pressure level in a supine [6, 19, 21, 23] or seated [6, 10] resting state is lower in individuals with quadriplegia than in normal controls. However, the resting supine blood pressure level in individuals with lower thoracic and lumbar SCI is almost normal [21]. These findings are in accordance with the findings in the present study. Previous studies have shown that the lower blood pressure in individuals with quadriplegia is accompanied by a lower plasma catecholamine level [6, 10, 19, 21, 23], and the lower blood pressure has been attributed to reduction in basal sympathetic activity and subsequent low plasma catecholamine levels [6, 23].

Circulatory responses to postural change from sitting to standing

Orthostatic hypotension is characterized by a decrease in SAP by more than 20 mmHg and a decrease in DAP by more than 10 mmHg within three minutes of standing according to The Consensus Committee of the American Autonomic Society and the American Academy of Neurology [31]. In the present study, although there was no significant decrease in blood pressure by postural change from sitting to standing in any of the three groups, two individuals with cervical SCI (subject No. 1 and 2) in HSCI showed decreases in SAP and DAP to levels in the definition of orthostatic hypotension. Several studies have shown that individuals with cervical SCI are prone to orthostatic hypotension by postural change from supine to upright position, but this is not the case in individuals with thoracic SCI or able-bodied individuals [6, 18]. The development of orthostatic hypotension in chronic SCI individuals is thought be mediated by multiple factors such as sympathetic nervous system dysfunction, impaired baroreflex function, lack of skeletal muscle pumping activity and impaired water and sodium retention [7].

Possible mechanisms affecting circulatory responses during PWE

SAP and MAP increased significantly during PWE compared with those in the standing state in HSCI and CON, although DAP increased only in HSCI. In contrast to the response in blood pressure, HR decreased significantly during PWE compared to the level during standing, indicating that HR did not affect the increase in blood pressure. With regard to the HR response, HR at standing was below 100 bpm in the present study (Table 2). HR below 100 bpm is controlled mainly by cardiac vagal activity [29]. Therefore, the decrease in HR during PWE must have been due to baroreceptor-mediated parasympathetic vagal activation induced by increase in blood pressure.

Nobrega et al. [27] demonstrated that MAP increased during passive leg cycling via an increase in stroke volume in able-bodied individuals. They attributed the increase in stroke volume to an increase in venous return from the passively moved lower limbs (muscle pump effect) or to a muscle mechanoreceptor-evoked increase in myocardial contractility, the latter being thought to be mediated by a reflex neural mechanism that involves the brainstem cardiovascular center by afferent signals from the legs. Therefore, the pressor responses during PWE in CON might have been caused by a brainstem-mediated neural reflex mechanism and/or muscle pump effect. In SCI individuals, on the other hand, the possibility of contribution of a brainstem-mediated neural reflex mechanism to pressor response can be excluded because it is assumed that there is little or no afferent input to the brainstem cardiovascular center due to the spinal cord lesion.

The magnitudes of increase in SAP and MAP from the quiet standing level to the PWE level were larger in HSCI than in CON despite the fact that the magnitudes of decrease in HR in the two groups were not significantly different. It is possible that the larger

increase in blood pressure in HSCI is due to the greater muscle pump effect that enables venous return to increase by squeezing the blood out of the veins and venules of the dependent leg. The presence of this effect is suggested by the presence of electromyographic activity during PWE. However, the muscle activity level in HSCI is assumed to be very small and to be almost the same as that in CON because of no significant increase in $\dot{V}O_2$ in either HSCI or CON. Not only muscle activity level but also blood volume in the legs determines the muscle pump effect. However, Hopman et al. [16] found a decrease in venous capacity, venous distensibility and enhanced venous outflow resistance in the upright seated position in paraplegic individuals compared to those in able-bodied individuals and they attributed these changes to inactivity and muscle atrophy of the legs. From these findings, Hopman et al. [16] suggested that venous blood pooling in paralyzed legs is very unlikely. The lower blood volume capacity and the unlikelihood of blood volume pooling in the upright position suggest that the blood volume in paralyzed legs during quiet standing is also smaller in HSCI than in CON, resulting in a smaller muscle pump effect on venous return during PWE in the former group. Therefore, it is unlikely that the larger increase in blood pressure during PWE in HSCI is solely dependent on the magnitude of the muscle pump effect.

As far as we know, spinal reflexes are the only factor other than the muscle pump effect that can cause pressor responses in SCI individuals during PWE. This effect might have enhanced the magnitude of increase in blood pressure in HSCI. Mizushima et al. [23] found that MAP increased during ice-water immersion of the foot in individuals with cervical spinal cord injury with concomitant increase in plasma norepinephrine and they concluded that the rise in blood pressure by ice-water immersion was caused by a reflex sympathetic discharge through the isolated spinal cord. Mizushima et al. [23] also found that the rise in MAP during ice-water immersion, expressed as percent rise from pre-immersion baseline, was significantly higher in patients than in normal subjects. This finding is in accordance with the finding in the present study. Mizushima et al. [23] attributed the enhanced pressor response in SCI individuals to increased noradrenergic receptor sensitivity, postjunctional changes in the effector organs resulting from prolonged inactivity, and a lack of baroreceptor reflexes restraining a rise in blood pressure.

In LSCI, blood pressure was not changed significantly during PWE. In LSCI, there is little or no afferent input to the brainstem cardiovascular center from the legs as is the case in HSCI. However, the pool of blood vessels affected by spinal reflexes is smaller than that in HSCI because the affected area is limited mostly to the splanchnic vasculature innervated by the lesser (LSN) and/or least splanchnic nerves (lSN) [33] as well as to the leg vasculature. Garrison et al. [14] recently demonstrated that systemic pressure response due to spinal reflexes elicited by electrocutaneous stimulation to the arch of the foot is confined to upper level injured individuals (above T6) who have a larger pool of blood vessels affected, including the leg vasculartur and splanchnic vasculartur innervated not only by the LSN and lSN but also by the GSN. Therefore, the absence of pressor response in LSCI is logically explained by the loss of afferent input to the brainstem and the smaller effect of spinal reflexes. In other words, the results suggest that the enhanced pressor response in HSCI is due to exaggerated spinal reflexes resulting from a larger pool of blood vessels affected by stimuli imposed on the paralyzed area. Another possible explanation for enhanced pressure response in HSCI is as follows. Central and peripheral changes that may lead to exaggerated spinal reflexes, such as aberrant sprouting of sensory fibers in the dorsal horn [1, 32], inappropriate innervations of preganglionic axons to postganglionic neurons [22], and enhanced and prolonged contractile responses to nerve activity in arterial vessels [22], occur after SCI. These changes might have contributed to enhanced blood pressure response in HSCI.

In previous studies [24, 25, 30], SCI individuals performed passive leg cycling (PLC) in the sitting position, but this failed to increase blood pressure. The present study clearly demonstrated that whether blood pressure increases or not is dependent on lesion level. In addition, the difference in response might be dependent on the difference in stimuli imposed on the paralyzed area between PLC and PWE. It is possible that PWE is more noxious than PLC, but PWE itself is assumed to be "innocuous." Despite this, innocuous stimuli have recently been shown to have the potential to provoke spinal reflexes [20]. Since PWE is characterized by rhythmic hip joint flexion and extension with large body load on the foot, whereas PLC may produce lesser hip joint movement and body load on the foot, differences in mechanical stimuli associated with exercise modes such as joint movements and/or body load may lead to the difference in pressor response between PWE and PLC.

Clinical implications of our results

Disuse syndrome is one of the many health issues that arise following spinal cord injury and is characterized by muscle atrophy, loss of bone mineral density, joint

contracture, and circulation disorders (which can lead to the occurrence of deep vein thrombosis and pressure sores) in the paralyzed area. Passive standing therapy is thought to be useful for preventing bone mass loss [3, 13] (which is caused by mechanical stress due to weight bearing) [15], preventing joint contracture by providing an adequate range of motion [3, 13] and allowing sustained periods of relief to the sacral and ischial high-pressure areas of the buttocks, thus reducing the incidence of pressure sores [3, 13]. In addition to these positive effects, it has been shown that the imposition of passive walking-like movement in the standing posture induces locomotor-like muscle activity and an increase in oxygen supply in the paralyzed lower limb muscles in individuals with motor-complete spinal cord injury [17]. Furthermore, 4 months of thrice-weekly body weight-supported treadmill training has been shown to improve muscle morphology in a chronic motor-complete individual with spinal cord injury [2]. These physiological and morphological responses indicate that PWE has the potential to attenuate deterioration of disuse syndrome that arises in paralyzed lower limbs.

On the other hand, with the upright position, there are risks of orthostatic hypotension and its secondary symptoms such as dizziness, nausea, lightheadedness, and even loss of consciousness. In the present study, although two individuals with cervical SCI showed decreases in SAP and DAP at standing to levels in the definition of orthostatic hypotension, they also showed increases in SAP and DAP during PWE above the level at sitting. Therefore, we believe that PWE itself has an inhibitory effect on orthostatic hypotension.

In the present study, one of the SCI individuals (subject No. 2) showed an increase in SAP during PWE by more than 20 mmHg from the sitting level (usual level). This value matches that of autonomic dysreflexia defined by the Consortium for Spinal Cord Medicine [8]. If other hypertensive stimuli such as bladder distension and bowel impaction are added during PWE, extreme hypertension may be induced. Therefore, appropriate treatment or preparation, such as urination, is needed for SCI individuals before the start of PWE.

Limitations

Since the population of SCI individuals is a very specific and complex population, it was difficult to find a large number of subjects who fulfill the inclusion criteria. However, even with the relatively small number of subjects, it was shown that the main outcome parameter of the present study, i.e., blood pressure, was increased significantly during PWE even in SCI individuals, especially in SCI individuals with lesion level at or above T6. Therefore, we do not believe that a larger number of subjects would have dramatically influenced the main outcome of the study. On the other hand, blood pressure responses in LSCI might have been different with a large number of subjects and/or depending on the choice of subjects. For example, in the present study, one subject in LSCI (subject No. 10) had been performing regular body weight-supported treadmill training. Ditor et al. [12] found that thrice-weekly 4-month treadmill training in motor-complete SCI individuals affected resting heart rate variability. Such an adaptation to training may also have occurred in response to PWE in subject No. 10 and thus have altered our results, although the statistical results for cardiovascular responses in LSCI were the same even when subject No. 10 was removed.

Conclusion

Blood pressure increases during passive walking-like exercise in SCI individuals with lesion level at or above thoracic 6. The increase in blood pressure elicited by the application of passive walking-like exercise could represent an integrated response involving both an effect of spinal reflex in the region below the spinal cord injury and a muscle pump effect. Our findings aid evaluation of the safety of passive walking-like exercise, which is becoming a common rehabilitation technique, in SCI individuals of various lesion levels, including high level SCI individuals who are susceptible to orthostatic hypotension and autonomic dysreflexia.

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