Early Detection of Orthostatic Hypotension by Quantitative Sudomotor Axon Reflex Test (QSART) in Type 2 Diabetic Patients

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Abstract

Objective Orthostatic hypotension is caused by autonomic nerve dysfunction, mainly by severe sympathetic nerve dysfunction in diabetic patients. Diabetes affects the peripheral nerves in a length-dependent manner. Quantitative sudomotor axon reflex test (QSART) is one of the sensitive tests for detecting sympathetic nerve function. We examined the relation between orthostatic hypotension and QSART at the foot and hand in type 2 diabetic patients.

Methods Thirty-eight type 2 diabetic patients (age, 48.9±11.9 years; duration of diabetes, 13.4±8.6 years) and 13 age-matched non-diabetic controls were evaluated. All subjects aged under 65 years old were recruited. All subjects underwent Schellong tests and quantitative sudomotor axon reflex tests (QSART) at the back of the hand and dorsum of the foot.

Results The sweating volume at the foot dorsum, but not the back of the hand, during the first 10 minutes of QSART was significantly related to the orthostatic hypotension on the Schellong test. In patients with normal, borderline and abnormal blood pressure response to standing, 6 out of 17 (35.3%), 9 out of 12 (75.0%) and 9 out of 9 (100%) had decreased sweating volume of the foot dorsum, respectively.

Conclusions Our results suggest that orthostatic hypotension may be detected early by QSART at the dorsum of the foot in type 2 diabetic patients.

Key words: Diabetic neuropathy, quantitative sudomotor axon reflex test

Introduction

Diabetic peripheral polyneuropathy is a major complication in patients with diabetes mellitus (1). Severe peripheral polyneuropathy can lead to autonomic symptoms including orthostatic hypotension (2). It has been reported that postural hypotension might be a consequence of damage to sympathetic postganglionic innervation of resistance vessels mainly in the lower extremities with loss of reflex vasoconstriction (3–7). Although the Schellong test is a well-known test estimating orthostatic hypotension (OH) defined as a fall in systolic blood pressure of 30 mmHg or more when changing from lying to standing position (8), diabetic patients suffering from OH often have severe subjective symptoms including postural weakness, faintness, visual impairment and syncope. Quantitative sudomotor axon reflex test (QSART) is a method to assess the integrity of postganglionic sympathetic sudomotor efferents which are activated via an axon reflex by controlled iontophoretic stimulation with acetylcholine (9). It has been suggested that diabetic peripheral nerve function is disturbed in nerve length-dependent manner (10). Therefore, OH may be detected by QSART earlier than the Schellong test. In this study, we examined the relationship between QSART and the Schellong test.

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Patients and Methods

Subjects

Thirty-eight outpatients with diabetes mellitus aged under 65 years old were recruited from the diabetes clinic of Asahikawa Medical College. As controls 13 age-matched non-diabetic healthy volunteers aged under 65 years old were also studied. The clinical characteristics of the subjects are summarized in Table 1. There was no difference in age or sex between the non-diabetic healthy controls and the dia-
Orthostatic Hypotension and QSART

Half of the diabetic patients had retinopathy, and about 39.5% had nephropathy. No diabetic patient had an elevated serum creatinine concentration and no patient was taking drugs such as alpha-blocker, diuretics, tricyclic antidepressants, phenothiazines, vasodilators and glyceryl trinitrate. The study was reviewed by the Ethics Committee of the Asahikawa Medical College and all participants gave their informed consent prior to participation.

**Schellong test**

Schellong test was performed according to a standard protocol described by Ewing and Clarke (11). Briefly, after resting for 5 minutes, blood pressure was measured by sphygmomanometer with the subject in the supine position. The subject then stood up voluntarily, and blood pressure

| Table 1. Clinical Characteristics of Diabetic Patients and Age-matched Healthy Controls |
|-----------------|-----------------|
| Control         | Diabetic        |
| n               | 13              | 38              |
| Age             | 47.9±7.5        | 48.9±11.9       |
| Sex (m/f)       | 6/7             | 16/22           |
| Body mass index (kg/m/m) | 23.1±1.9        | 22.8±3.5        |
| Duration of diabetes (yrs) | –              | 13.4±8.6        |
| Fasting plasma glucose (mg/dl) | 93.7±9.4        | 140.6±34.9*     |
| Glycated hemoglobin (%) | not evaluated   | 7.8±1.6         |
| Retinopathy (NDR/SDR/PPDR/PDR) | –              | 20/17/10        |
| Nephropathy (normo/micro/macro) | –              | 23/8/7          |


![Figure 1. Correlation of sweating volume at the left foot dorsum to sweating volume at the back of the left hand in type 2 diabetic patients.](image1)

![Figure 2. Correlation of sweating volume at the left foot dorsum (A) and the back of the left hand (B) to the blood pressure response to standing in type 2 diabetic patients.](image2)
was measured 1', 3', 5', 10', and 15' after standing. The patients were divided into three groups according to the fall in systolic blood pressure (normal, ≤10 mmHg; borderline, 11–29 mmHg; abnormal, ≥30 mmHg).

**Quantitative sudomotor axon reflex test (QSART)**

Subjects rested in supine position for at least 10 minutes in a quiet room maintained at a controlled temperature (22–25°) and relative humidity (50%). QSART, which quantitatively evaluates postganglionic sympathetic sudomotor axons, was done by recording responses from the left foot dorsum and the back of the left hand with a sudorometer, (AMU-100II, Unique Medical Co., Ltd., Tokyo, Japan). A stimulus of 2 mA was delivered by iontophoresis with 10%...
acetylcholine solution for 10 minutes. The responses were recorded in a multicompartmental sweat cell compartment, separate from the stimulus compartment. The area under the curve was integrated by computer, and the response was displayed as sweat output in microliters/square centimeter/10 minutes. The sudorometer used had a sensitivity of <0.01 μl/min.

Statistical analysis
Data were analyzed by analysis of variance (ANOVA) and are expressed as means±SD. Also, the chi-square test was used as indicated. The significance level was set at p<0.05.

Results
There was a significant correlation (r=0.34, p=0.038) between sweat output at the left foot dorsum and the back of the hand (Fig. 1). There was a significant correlation between the fall in systolic blood pressure in Schellong test and sweating volume at the left foot dorsum. Whilst, there was no significant correlation between the fall in systolic blood pressure in Schellong test and sweating volume at the back of left hand (Fig. 2). Also, the sweating volume at the left foot dorsum was decreased with the blood pressure response to standing (Fig. 3A) but the volume at the back of left hand did not change (Fig. 3B). Sweating volume was defined to be decreased if the sweating volume was below the value of the mean minus SD in healthy controls. Figure 4A demonstrates that the incidence of patients who had a decreased sweating volume of the left foot dorsum was significantly (p=0.003 by chi-square test) increased with the impairment of the blood pressure response to standing. In patients with a normal, borderline and abnormal blood pressure response to standing, 6 out of 17 (35.3%), 9 out of 12 (75.0%) and 9 out of 9 (100%) had decreased sweating volume of the foot dorsum, respectively. However, the incidence of the patients who had a decreased sweating volume of the back of the left hand did not change (Fig. 4B).

Discussion
QSART is a sensitive test used to estimate the function of postganglionic peripheral sympathetic nerves, consisting of C-fibers innervating sweat glands (9). The results of QSART reflect terminal sympathetic nerve function, which may be impaired early in diabetic peripheral neuropathy (12). The postganglionic sympathetic nerve innervating the foot skin originates from the sympathetic ganglion of the related lumbar spinal level and runs through the lower extremity, while the nerve innervating the hand skin originates from the sympathetic ganglion of cervical spinal level and runs through the upper extremity. Based on these anatomical findings, the postganglionic sympathetic nerves innervating the foot skin were considered to be longer than the nerves innervating the hand skin. Because peripheral nerve function has been considered to be disturbed in a nerve length-dependent manner in diabetic patients (10), it may be considered that the terminals of the sympathetic nerves innervating foot may be impaired earlier than the nerves innervating the hand in diabetic patients. Therefore, in this study, the back of the hand and the foot dorsum were selected for the sites of QSART procedures. Shimada et al (13) demonstrated the nerve length-dependent pattern described by Low (14) in QSART using the skin of foot dorsum and distal leg in early diabetic neuropathy. Although the correlation of the sweating volume at the left foot dorsum to the volume at the back of the left hand was significant (p=0.038, Fig. 1) in this study, there was no significant difference in the sweating volume at the back of hand among the groups of patients with abnormal, borderline, normal blood pressure response to standing and non-diabetic controls (Fig. 3B and 4B). On the contrary, the sweating volume was significantly decreased with the grade of the blood pressure response to standing (Fig. 3A). Moreover, the incidence of the patients who had decreased sweating volume at the back of the foot was 35.3% (six out of 17) in the normal blood pressure response to standing and the incidence was increased with the grade of the blood pressure response (Fig. 4A). This data suggests that decrement of sweating volume at the foot dorsum in QSART may precede the decrement of the blood pressure response to standing. Because the postganglionic sympathetic nerves are separated to innervate both the resistance vessels related to postural hypotension and sweating glands related to impaired sweating output in QSART at the terminals, it could be accepted that sweating function and blood pressure regulation are altered in parallel. Blood pressure response to standing reflects a polysynaptic reflex (15), while QSART reflects a simple axon reflex at the nerve terminals (16–18). Therefore, impairment of QSART applied to the foot may appear earlier than the decline in blood pressure response to standing in our study.

Low et al (19) reported that sex and age should be considered when evaluating autonomic function. They found that sweating volume on QSART is greater in men and progressively declines with age at lower extremity sites. Also, there is a report that the density of sweating glands was decreased with aging (20). In this study, all subjects aged under 65 years old were recruited and there was no significant difference in age or sex between non-diabetic controls and diabetic patients (Table 1).

In conclusion, our data suggests that QSART at the foot dorsum may be a good method for detecting orthostatic hypotension earlier in type 2 diabetic patients.

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