Original Article

Postprandial Hypotension due to a Lack of Sympathetic Compensation in Patients with Diabetes Mellitus

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Postprandial hypotension is an important hemodynamic abnormality in diabetes mellitus, but few reports are available on the relationship between autonomic dysfunction and postprandial hypotension. Ten diabetic patients and 10 healthy volunteers were recruited for this study. Postural blood pressure and heart rate changes were measured before lunch, and then the hemodynamic responses to a standardized meal were investigated. Holter electrocardiogram (ECG) monitoring was conducted for assessing spectral powers and time-domain parameters of RR variations. Postural changes from the supine to the upright position decreased the systolic blood pressure of the diabetics from 133 ± 16 to 107 ± 20 mmHg ($p < 0.01$), but did not decrease the systolic blood pressure of the controls. The heart rate remained constant in the diabetics but was increased in the controls. Food ingestion decreased systolic blood pressure in the diabetics, with a maximum reduction of 25 ± 5 mmHg. This decrease was not associated with any changes in the ratio of low frequency to high frequency, and yet the heart rate remained almost constant. Indexes involving parasympathetic tone were not affected. Food ingestion did not affect blood pressure in the control group. These findings suggest that lack of compensatory sympathetic activation is a factor contributing to postprandial hypotension in diabetics, and that parasympathetic drive does not make a significant contribution to this condition.

Key words: postprandial hypotension, sympathetic tone, RR variability, diabetes mellitus

$\mathbf{P}$ostprandial hypotension, like postural hypotension, is an important hemodynamic manifestation of diseases affecting the autonomic nervous system. A decrease in systolic blood pressure of about 20 mmHg after a meal has been reported in up to 36% of elderly nursing home residents [1]. This decline is usually asymptomatic, but sometimes may lead to symptoms which include dizziness, light-headedness, blunted vision, visual loss and syncope. In addition, a recent investigation demonstrated that an elderly person with profound postprandial hypotension is at higher risk for a future fall, syncope, coronary event, stroke and total mortality [2]. Autonomic dysfunction is commonly documented in patients with diabetes mellitus, and a pressure decrease after eating appears often in such patients [3]. However, there have been

few reports on the relationship between autonomic nervous function and postprandial hypotension.

The objective of the present study was to evaluate the role of autonomic dysfunction in blood pressure and heart rate changes induced by food ingestion in diabetic patients.

Materials and Methods

Patient selection.   Postprandial changes in blood pressure and heart rate were studied in type 2 diabetic patients. Fifty two consecutive patients who entered the Iwakuni Clinical Center of the National Hospital Organization for the treatment of diabetes mellitus were recruited for this study. All patients suffered from diabetes mellitus for more than 5 years, and the blood glucose level at the time of the study was controlled fairly well in all patients. Selection criteria for the study included: 1) no clinical signs of autonomic neuropathy - including impotency, diabetic diarrhea, or gustatory sweating -other than postprandial hypotension; 2) no history of taking antihyper- or antihypotensive drugs within 2 weeks before the study; 3) no history of syncope; 4) no history of a symptomatic cerebrovascular accident; 5) no history of ischemic heart disease and clinical heart failure; 6) normal sinus rhythm. Patients who manifested pulmonary disease or renal failure were also excluded from this study. Cardioactive drugs including digitalis, diuretics and anti-anginal agents were not administered in any of the patients, while insulin and/or oral antidiabetic agents were continued during the investigation. The patients abstained from caffeine ingestion and smoking for 12 h before the study. Ten healthy volunteers, 4 men and 6 women, were recruited as controls.

All subjects signed an informed consent form before the study. The study protocol was approved by the institutional review boards at the Iwakuni Clinical Center.

Hemodynamic study.   The subjects were asked to rest quietly in bed for at least 30 min before the test. At around noon basal blood pressure and heart rate were measured twice in the supine position with an interval of 10 min between measurements (the first basal data). After taking the first basal data, the subjects were asked to stand quietly beside their bed. The measurements were repeated just after standing and

5 min later, while the subjects remained standing. The subjects were then allowed to have a 10-min bed rest, and supine blood pressure and heart rate were again measured at 5 and 10 min after the conclusion of the bed rest period (the second basal data). After the second basal data were obtained, the patients were served a standardized 400-kcal meal {20 g of protein (21%), 10 g of fat (23%), and 55 g of carbohydrate (56%)}, and were requested to eat for over 15 min in a sitting position. Then, the subjects were asked to remain quietly in their beds for 180 min. The measurements were repeated in the supine position at 30, 60, 120 and 180 min after the end of the meal.

RR variability study.   Holter electrocardiogram (ECG) monitoring was performed within a week of the hemodynamic study. A Fukuda-Denshi series FM150 recording unit was used. All tracings were recorded with 2 bipolar leads of CM5 and NASA. The subjects rested in bed for at least 30 min and then were served the standardized lunch described above for the hemodynamic study. After the lunch, the subjects remained in bed for 180 min. Recordings began at about 60 min before the meal and lasted for 4 h.

Parameters for heart rate variability were analyzed using a commercially available software program (HPS-RRA; Fukuda-Denshi, Tokyo, Japan). Spectral indexes of heart rate variability were computed by fast-Fourier transformation in 30-min segments. The following frequency-domain measures were assessed: 1) low frequency (LF) (0.039 to 0.148 Hz); 2) high frequency (HF) (0.148 to 0.398 Hz); and 3) ratio of low frequency to high frequency (LF/HF ratio). The LF and HF measures were reported as their natural logs (ln). Three additional time-domain parameters were also derived: 1) SDRR (standard deviation of the RR interval); 2) CVRR (coefficient of variance of the RR interval); and 3) RR50 (number of the RR interval differing from the preceding RR interval by more than 50 msec).

Statistical analysis.   The data is expressed as the mean ± standard deviation (SD). Student's *t-test* was used to compare the data between the groups. Analysis of variance with repeated measures was applied for comparison of the measurements within the group. If a significant difference was determined overall, a comparison was made at a prespecified time interval using an unpaired *t-test* with Bonferroni's cor-

rection. A p value of $\leqq 0.05$ was considered significant.

Results

Of the 52 consecutive patients who entered our hospital during the study interval for the treatment of diabetes, 12 subjects met the inclusion criteria. Two of the 12 patients were excluded from analysis due to the inadequate technical quality of their Holter records. One patient of the remaining 10 subjects had mild retinopathy and another 2 had mild proteinuria with normal glomerular filtration rate.

The baseline characteristics of the subjects are summarized in Table 1. There were no significant differences in age, gender distribution, basal systolic and diastolic blood pressure, heart rate, or renal function between the diabetic and the control groups. There was 1 habitual alcoholic in the diabetic group but none in the control group. The incidence of alcoholics was not different between the 2 groups. Two patients received insulin and the other 8 were controlled with oral antidiabetic agents. The fasting blood glucose levels and serum HbA1c concentrations in the diabetic patients were slightly above the normal ranges. Although an abnormally high serum level of total cholesterol was observed in 3 diabetic patients and the serum HDL cholesterol concentration was below normal in 3 diabetic patients, the mean values of total cholesterol and HDL cholesterol were not statistically different between the 2 groups.

Hemodynamic study. Fig. 1 depicts the changes of blood pressure and heart rate of the 2 groups during the study. Along with the postural change from the supine to the upright position before the meal, 7 out of 10 diabetic patients exhibited a fall in systolic blood pressure of $\geqq 20$ mmHg. On average, in the 10 diabetics, systolic blood pressures declined from 126 ± 14 to 101 ± 18 mmHg ($p < 0.01$) in the absence of manifest symptoms. No subjects in the control group, however, had a pressure fall of more than 10 mmHg after the postural change. The heart rate increased significantly in the control group, but not in the diabetic group. Since the second basal blood pressures and heart rates were not significantly different from the first basal data, the average of the 4 measurements of each parameter that were taken in the supine position before the meal was used for the basal data. The effects of food ingestion on blood pressure appeared within 30 min after eating and persisted for about 2 h. The maximum magnitude of systolic pressure decline after food ingestion was similar to that induced by the postural change: 24 ± 8 mmHg *vs.* 25 ± 8 mmHg (Fig. 2). In contrast to the diabetic patients, food ingestion in the control group did not alter blood pressure, but increased heart rate significantly.

RR variability study. The records of the 10 diabetic patients and the 10 healthy controls were used for analysis.

To evaluate the effects of food ingestion on the RR variability, the measures of the RR variability were analyzed for a 30-min period (30 to 60 min after the meal) and the results are shown in Table 2. The data points after the meal coincide with the time of maximal blood pressure reduction in the diabetic group. Prior to food ingestion, LF and HF were significantly lower in the diabetics than in the control group. LF/HF in the diabetic group tended to be lower than that in the control group, but the difference did not reach the level of statistical significance. With respect to the time domain parameters, significantly small SDRR and CVRR were observed in the diabetics compared to the controls. After eating, LF and HF remained almost constant in the diabetics, resulting in no changes in LF/HF, while LF/HF of the healthy controls slightly but significantly ($p = 0.041$) increased after the

Table 1 Baseline characteristics of the subjects

	Diabetics (n = 10)	Control (n = 10)
Age (years)	61 ± 11	59 ± 12
Sex (M : F)	7 : 5	5 : 5
BPs (mmHg)	126 ± 14	130 ± 12
BPd (mmHg)	72 ± 6	75 ± 5
HR (beat/min)	72 ± 8	68 ± 9
FBS (mg/dl)	133 ± 14*	90 ± 6
HbA1c (%)	7.8 ± 1.9*	5.4 ± 1.2
AST (IU/l)	25 ± 7	27 ± 6
ALT (IU/l)	21 ± 5	19 ± 8
BUN (mg/dl)	16 ± 7	15 ± 6
CRTN (mg/dl)	0.92 ± 0.16	0.90 ± 0.09

Data are expressed mean ± standard deviation. *Significantly different from the control at a level of $p < 0.02$. BUN, blood urea nitrogen; BPd, diastolic blood pressure; BPs, systolic blood pressure; CRTN, serum creatinine; FBS, fasting blood glucose; HR, heart rate.
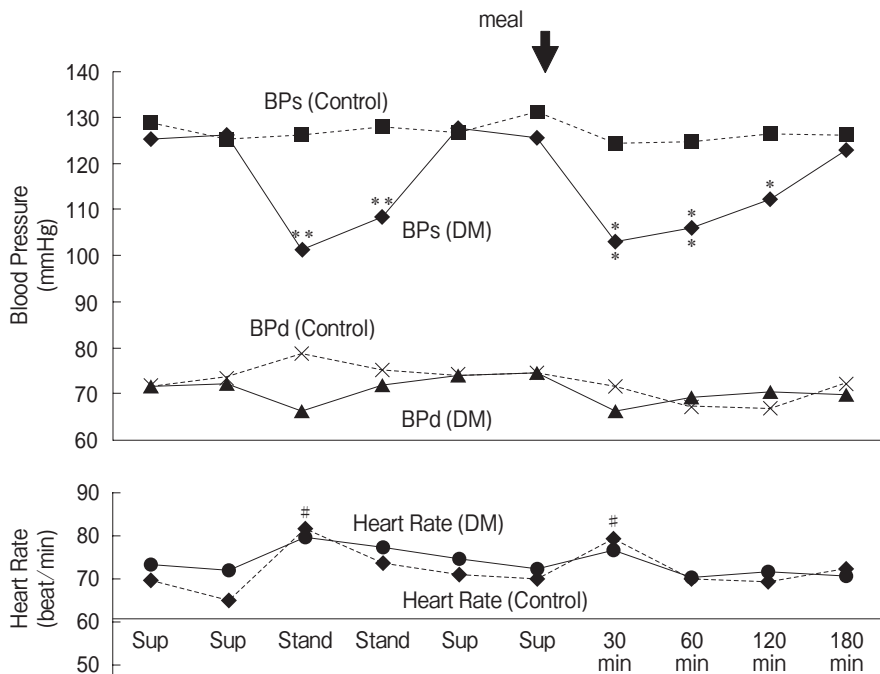
Fig. 1   Mean blood pressure and heart rate of patients with diabetes mellitus and healthy controls.
Systolic and diastolic blood pressures decreased in diabetic patients during the upright posture and after eating without significant changes in heart rate. In the control group blood pressures as well as heart rates were not affected by food ingestion.
BPd, diastolic blood pressure; BPs, systolic blood pressure; DM, diabetes mellitus; Sup, supine position; Stand, standing position.
Significantly different from the baseline data of diabetic patients at the levels of **$p < 0.01$ and *$p < 0.05$, and from the baseline data of healthy controls at the level of #$p < 0.05$. Diamond with a solid line (—◆—), systolic blood pressure in diabetics; rectangle with a dashed line (--■--), systolic blood pressure in healthy controls; triangle with a solid line (—▲—), diastolic blood pressure in diabetics; X with a dashed line (--✕--), diastolic blood pressure in healthy control; circle with a solid line (—●—), heart rate in diabetics; diamond with a dashed line (--◆--), heart rate in healthy controls.
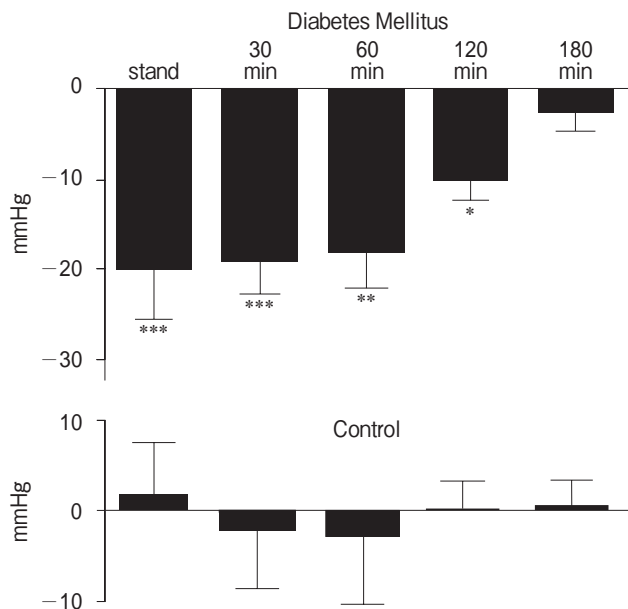

Fig. 2   The maximum decrease in systolic blood pressure induced by upright postural change and by food ingestion in diabetics (upper panel) and healthy controls (lower panel). The magnitude of pressure decline 30 min after eating was almost identical to that after standing postural change. Significantly different from zero change at the levels of ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$.

meal. The time domain parameters, *i.e.*, SDRR, CVRR and RR50, were not significantly influenced by food ingestion in either subject group (Table 2).

Discussion

This study demonstrated that all diabetic patients exhibited postprandial hypotension without any significant changes in the measures of the RR variability.

Heart rate power spectral density contains major components, reflecting respiratory arrhythmia (high frequency, HF) and fluctuation in the cardiovascular sympathetic system (low frequency, LF). It has been established that cardiac vagal activity causes short-term, respiration-related variations of the cardiac cycle, while sympathetic modulation of the cardiac cycle creates variations over longer periods. The baseline width of the distribution curve of the RR interval (SDRR and CVRR) has been used as an index of heart rate variability in patients with myocardial infarction [3], and was found to be useful in assessing parasympathetic nerve tone. All these studies indicate that SDRR, CVRR and RR50, which are used as time-domain indicators of heart rate variability, represent the activity of the vagal nerve. In contrast to the magnitude of HF, which provides quantitative and specific indexes of cardiac vagal nerve tone, the LF represents sympathetic activity with vagal modulation. Pagani *et al.* [4] demonstrated that the LF/HF ratio is a more sensitive and specific measure of increased sympathetic drive, because the vagal modulation affects LF significantly. Therefore, the SDRR, CVRR, RR50 and the HF were used in this study as indexes of vagal nerve activity, and the LF/HF was used as an indicator of sympathetic nerve drive.

The analysis of heart rate variability before the meal demonstrated that parasympathetic nerve function was impaired in the diabetics, because the measures of providing parasympathetic nerve tone, HF, SDRR and CVRR, were significantly lower in the diabetic group than the control. In contrast, the insignificant difference of LF/HF ratio between the 2 subject groups suggested that little sympathetic dysfunction would appear before food ingestion in this patient group. These findings were consistent with the observations of Ewing *et al.* [5], who reported that the parasympathetic involvement occurred in the earlier phase of the disease, and then sympathetic impairment followed.

Postprandial hypotension is frequently observed in elderly persons [6, 7], and in patients with autonomic dysfunction [8–10]. Lipsitz *et al.* [6] demonstrated maximum declines of 25 ± 5 mmHg (mean $\pm$ SEM) and 24 ± 9 mmHg in systolic blood pressure in elderly patients with and without histories of syncope, respectively, while demonstrating that there were no changes in blood pressure in young subjects. In this study, 7 out of 10 diabetic patients (70%) showed a systolic blood pressure fall of more than 20 mmHg after the meal. The previous reported prevalence rates of postprandial hypotension in diabetes have varied over a wide range of 20% to 60%. Jones *et al.* [11] reported that postprandial hypotension was evident in 7 out of 16 (44%) cases of recently diagnosed NIDDM. Since our patients had a longer history of diabetes (more than 5 years), they may have been more likely to show autonomic dysfunction. Further, most of the previous studies used 75 g of glucose as a test-meal, whereas we supplied a standard meal (20 g

Table 2   Parameters of RR variability before and after the meal

		mean RR (msec)	SDRR (msec)	CVRR	RR50 (/225 min)	LF (msec^2)	HF (msec^2)	LF/HF
Diabetics	Before meal	851 ± 121	37 ± 16**	4.40 ± 0.79**	0.7 ± 1.1	180 ± 66**	96 ± 29**	2.52 ± 1.22
(n = 10)	After meal	869 ± 122	$42 \pm 15$$^{\$\$}$	$4.51 \pm 0.89$$^{\$\$}$	1.1 ± 1.6	$196 \pm 74$$^{\$\$}$	$100 \pm 41$$^{\$\$}$	$2.40 \pm 0.71$$^{\$\$}$
Control	Before meal	894 ± 116	89 ± 24	10.9 ± 2.01	1.9 ± 1.5	1543 ± 879	493 ± 188	3.29 ± 1.48
(n = 10)	After meal	819 ± 90	101 ± 34	11.7 ± 3.42	1.6 ± 1.4	3192 ± 1098	486 ± 285	7.58 ± 4.05#

Significantly different from the control before meal at the level of **$p < 0.01$, from the control after meal at a level of $^{\$\$}p < 0.01$, and from the values of each group before the meal at a level of #$p < 0.05$, mean RR, mean RR interval; SDRR, standard deviation of RR interval; CVRR, coefficient of variance of RR interval; RR50, number of RR interval different from the preceding RR interval more than 50 msec; LF, low frequency; HF, high frequency.

protein, 10 g of fat and 55 g of carbohydrate). This difference in the test meals may have been responsible for the higher prevalence of hypotension in our study.

In contrast to the increased LF/HF in the control group, the LF/HF in the diabetics did not increase after the meal in this study. This suggests an impaired response of sympathetic activity to the meal, even in cases where no apparent signs exhibiting sympathetic involvement were observed before eating. These findings were consistent with the study of Ryan *et al.* [12], in which there was no significant increase in LF after a meal in older subjects, even though the investigations did not calculate the LF/HF. In the present study, however, a standardized meal did not affect the blood pressure of a healthy controls. An associated rise in heart rate appeared to provide adequate compensation against the blood pressure fall by increasing sympathetic tone. The postprandial increase in LF/HF of the control group also suggested that cardiac sympathetic tone was activated. The cardiac vagal nerve did not play a significant role in the blood pressure decline after food ingestion. This was based on the finding that the parasympathetic indexes of heart rate variability measured did not change after the food ingestion in the controls as they did in the diabetics. Hirayama and his associates [13] demonstrated that in patients with peripheral autonomic neuropathy, blood pressure decreased at 15 min after glucose ingestion but soon recovered with a significant increase in heart rate and cardiac output. In contrast, blood pressure reduction in patients with multiple system atrophy continued more than 60 min after glucose ingestion in the absence of increases in heart rate and cardiac output. This suggests that the patients with peripheral neuropathy had normal baroreflex arc to the heart and dysfunction of the peripheral sympathetic efferents. If the baroreflex arc to the heart is impaired, a compensatory increase in cardiac output and heart rate in response to the blood pressure fall may not occur, and the postprandial hypotension will be prolonged. In the present study, the heart rate variability of the diabetic patients revealed the impaired sympathetic nerves to the heart, and long-lasting postprandial hypotension was observed. This result was consistent with the findings of Jones *et al.* [11] and Hoeldtke and his associates [14], who reported that food ingestion by patients with diabetic neuropathy produced a prolonged blood pressure fall

without a change in cardiac output and heart rate.

The magnitude of postprandial hypotension appears to be dependent on the composition of the meal. Ingestion of carbohydrates has been shown to have the largest effect on blood pressure, while ingestion of fat, protein, or water results in little or no pressure fall [7, 15]. The test meal used in this study was composed of 56% carbohydrate, 21% protein and 23% fat. The composition of the test meal approximates a standard meal for most Japanese people [16]. Under this condition, the magnitude of the maximum fall in blood pressure after food ingestion was almost identical on average to that induced by the upright postural change. This finding suggests that ingestion of a standard Japanese meal constituted an at least equal risk of cerebral ischemia as did postural hypotension for elderly diabetic subjects.

The pathophysiologic mechanism of postprandial hypotension is not fully understood. Although clarifying this mechanism was not one of the goal of this study, splanchnic blood pooling or other local intestinal factors may be responsible for the hypotensive effect of food ingestion in the presence of inadequate baroreflex compensation. In the absence of effective autonomic function, blood pressure becomes highly volume-dependent [17]. When a person assumes an upright position, 500 to 700 ml of blood is pooled in the lower extremities and splanchnic circulation [1], resulting in a reduction of cardiac output and blood pressure secondary to reduced venous return to the heart. It may be supposed that this amount of blood is pooled in the splanchnic vascular bed after eating a standard Japanese meal, because the maximum pressure reduction after the meal was quite similar in magnitude to that of orthostatic hypotension. A significant correlation between postprandial and orthostatic pressure drop could support this speculation.

Study limitation.   The subjects of this study were limited to mild, type 2 diabetic patients, aged 50–75 years, who did not manifest signs of autonomic dysfunction except postural hypotension. Since the hemodynamic responses to food ingestion depend on the composition of food, age, level of basal blood pressure [18], and degree of autonomic dysfunction, it is hard to apply the present results quantitatively to the different age groups and different levels of autonomic dysfunction. In addition, only limited information on postprandial hypotension can be interred from this

study due to the very small number of subjects examined.

This study did not provide information on hemodynamic changes induced by standing during the peak period of postprandial hypotension. There have been only a few reports [19–21] concerning the potentiating effect of food ingestion on postural hypotension. The results of the previous reports were controversial: 2 reports [19, 20] observed an additive effect of food ingestion on orthostatic hypotension, while a third report [21] did not. Further investigations are needed to evaluate the additional effects of food ingestion.

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