Prevention of postprandial hypotension-related syncope by caffeine in a patient with long-standing diabetes mellitus

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Abstract. A 74-year-old man who had type 2 diabetes mellitus of a duration of 20 years was admitted for syncope after eating a high carbohydrate meal. Although he had had episodes of pallor or syncope after carbohydrate-rich meals, such as with large amounts of white rice, several times within a year and he had been taken to hospitals emergently, the etiology of these episodes had remained unclear despite his undergoing several studies. Studies did show severe orthostatic hypotension during the head-up tilt test and a decrease in the coefficient of variation of the R-R interval (CVR-R) on resting electrocardiogram, suggesting severe autonomic nervous dysfunction. Because of the episodes of syncope after eating a carbohydrate-rich meal, we investigated whether he had postprandial hypotension (PPH). The 75 g oral glucose tolerance test revealed a significant decrease in his postprandial blood pressure by about 40 mmHg, leading to the diagnosis of PPH. The carbohydrate-rich meal test induced syncope with systolic blood pressure under 40 mmHg. Then 150 mg caffeine was administered before a second carbohydrate-rich meal. The marked decline in postprandial blood pressure was suppressed and plasma noradrenaline levels were gradually increased over a period of 60 minutes. Caffeine could be useful for prevention of postprandial hypotension-related syncope.

Key words: Postprandial hypotension, Diabetes mellitus, Autonomic neuropathy

POSTPRANDIAL HYPOTENSION (PPH), defined by a decrease in systolic blood pressure (SBP) of >20 mmHg occurring within 2 hours of a meal [1], is clinically significant, as it can lead to syncope, falls, and stroke in the elderly and patients with autonomic dysfunction such as diabetes mellitus and Parkinson’s disease [2, 3]. Although the mechanisms underlying PPH are poorly understood, several factors, including aging, high carbohydrate intake, antihypertensive drugs, and autonomic neuropathy, can contribute to the onset of PPH [4]. Although curative treatments for PPH have not been established, some strategies such as caffeine, α-glucosidase inhibitor, somatostatin, gastric emptying, and avoiding acute high carbohydrate intake, can be effective for prevention of a blood pressure drop after meals in patients with PPH [1]. Here, we report the case of a long-standing diabetic patient with PPH who had syncope after carbohydrate-rich meals that was suppressed by administration of caffeine before meals.

Case report

A 74-year-old man was admitted to our hospital with pallor and syncope after a meal containing a large amount of carbohydrates including dishes featuring white rice such as the Japanese seafood rice bowl (“Kaisen-don”) and a deep-fried pork cutlet rice bowl (“Katsu-don”). When at home, he usually ate quickly in a sitting position consuming the rice first. He had a history of hypertension and type 2 diabetes mellitus, with...
the presence of diabetes for approximately 20 years. A year previously, he had undergone a percutaneous car‐diac intervention for angina pectoris. He had no custom of taking caffeinated drinks such as green tea during meals. On arrival at the hospital, his pulse rate was relatively low at 68 beats/min (regular) and his blood pressure was unmeasurable with an automatic blood pressure measuring instrument. Consciousness was impaired (Glasgow Coma Scale, E3V4M5). After rapid infusion of normal saline, blood pressure was raised to 110/74 mmHg and he gradually regained consciousness. He was 160-cm tall, weighed 70 kg, and had a body mass index of 27.3 kg/m^2. Electrocardiogram showed a sinus rhythm of 78 beats/min and first degree arterial ventricular block. On admission, his medications included antiplatelet drugs (clopidogrel 75 mg, aspirin 100 mg), diuretic (furosemide 20 mg), angiotensin-receptor blocker (enalapril 2.5 mg), statin (rosuvastatin 5 mg), beta blocker (carvediol 2.5 mg), and oral hypoglycemic agents (metformin 500 mg, glimepiride 1 mg, sitagliptin 50 mg). Physical examination revealed loss of Achilles tendon reflex and a decrease in peripheral vibration sensation. Periperal nerve conduction velocity tests showed a decrease in sensory and motor nerve velocity. He had proliferative retinopathy and chronic kidney disease without albumi-nuria.

He displayed severe hypotension (reduction in systolic blood pressure from 110 mmHg to 58 mmHg) after raising the tilt table rapidly in the head-up tilt test. The coefficient of variation of the R-R (CVR-R) interval on electrocardiogram at rest was 1.26%; this finding along with the decrease in systolic blood pressure suggested that he had severe autonomic neuropathy due to long-standing diabetes mellitus. Table 1 shows laboratory data on admission. Brain magnetic resonance imaging (MRI) revealed no aberrant findings. No new obstructions or stenosis of cardiac arteries were detected by cardiac catheterization. This patient had had several episodes of syncpe after eating a carbohydrate-rich meal that included large amounts of white rice. Based on his history, we suspected that he had PPH and conducted some loading tests.

### Methods

#### Experimental design

After admission, he was served an energy-controlled diet of 1,440 kcal/day (198 g carbohydrate, 72 g protein, 40 g fat and 6 g sodium). After the patient had fastened overnight, the 75g oral glucose tolerance test (OGTT) and high-carbohydrate meal test were administered at 8:30 and 12:00, respectively, on the same day, because he had episodes of fainting after lunch. The next day at 12:00 noon, he was given a high-carbohydrate meal test after ingestion of 150 mg caffeine, which was in 250 mL of black coffee. After insertion of an intravenous cannula, he underwent these tests in a silent room maintained at an ambient of temperature 23–25°C. After a 10-min rest, the patient drank 75 g of glucose water (300 kcal) or ate a high-carbohydrate meal (674 kcal; carbo-

| Blood count          | TP  | 7.8 g/dL | Cortisol | 11.1 μg/dL |
|----------------------|-----|----------|----------|------------|
| WBC 5.650/μL         | 4.4 g/dL | ACTH | 25.8 pg/mL |
| RBC 391×10^4/μL      | 9.8 mg/dL | FT3 | 2.4 pg/mL  |
| Hb 11.3 g/dL         | 5.4 mg/dL | FT4 | 0.9 ng/dL  |
| Ht 34.3%             | 97 mg/dL | TSH | 3.59 μU/mL |
| Plt 15.4×10^4/μL     | 7.5% | Adrenaline | 0.03 ng/mL |
| Blood chemistry      | LDL-Chol | 58 mg/dL | Noradrenaline | 0.28 ng/mL |
| BUN 26 mg/dL         | HDL-Chol | 33 mg/dL |
| Cre 1.42 mg/dL       | Triglycerides | 108 mg/dL |
| eGFR 38.44 mL/min/1.73 m^2 | Endocrinological data |
| Na 138 mEq/L         | BNP | 26.6 pg/mL |
| K 4.2 mEq/L          | f-CPR | 3.3 ng/mL |
| Cl 104 mEq/L         | f-IRI | 13 μU/mL |

WBC, white blood cells; RBC, red blood cells; Ht, hematocrit; Plt, platelets, BUN, blood urea nitrogen; Cre, creatinine; TP, total protein; Alb, albumin; Ca, calcium; IP, inorganic phosphorus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LDL-Chol, low density lipoprotein cholesterol; HDL-Chol, high density lipoprotein cholesterol; BNP, brain natriuretic peptide; f-CPR, fasting C-peptide immunoreactivity; f-IRI, fasting immunoreactive insulin; ACTH, adrenocorticotropic hormone; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.
hydrate 60%, protein 12.7% and fat 22.4%) in a sitting position. Blood pressure and heart rate were evaluated by cannulation of the radial artery every 5 min up to 120 min after the patient drank the 75 g of glucose water or ate the meal. Glucose water and coffee were consumed within 5 min and high-carbohydrate meals were ingested within 15–20 min. When undergoing the high-carbohydrate meal tests, the patient had to eat the carbohydrate (white rice) first, as was his usual habit. Arterial blood samples were taken before the test (0 min) and 15, 30, 60, 90 and 120 min during or after the test for measurements of plasma glucose, plasma insulin, and norepinephrine. During these trials, the patient was routinely provided with antidiabetic medications, antihypertensive medications, diuretics, and antiplatelet medications to confirm postprandial blood pressure drop and syncope after meals actually.

Analysis of heart rate variability

Because patients with PPH have dysregulation of the autonomic nervous system [1], we analyzed heart rate variability (HRV) by assessing spectral power and time-domain parameters of RR variations during the carbohydrate-rich meal test. For spectral analysis of HRV, the low frequency component (LF power; 0.04–0.15 Hz), high frequency component (HF power; 0.15–0.40 Hz), and the ratio of LF power to HF power (LF/HF) were calculated by a fast Fourier transform (FFT) algorithm at intervals of 15 min.

Results

Forty-five min after the 75 g OGTT, the patient’s systolic blood pressure gradually decreased from 144 mmHg to 86 mmHg, representing a drop of about 60 mmHg, and heart rate slightly increased from 49 beats/min to 64 beats/min (Fig. 1a). Based on these results, he was then diagnosed with PPH. To investigate whether eating a carbohydrate-rich meal, such as he had eaten when the syncope occurred, would induce syncope through a severe drop in blood pressure, we administered a carbohydrate-rich meal test (674 kcal; carbohydrate 60.0%, protein 12.7%, and fat 22.4%) and continuously measured blood pressure by cannulation of the radial artery. Results of this carbohydrate-rich meal test showed a decline of systolic blood pressure to under 40 mmHg and he developed facial pallor (Fig. 1b). The plasma glucose level dropped in the initial 30 min after starting ingestion of the high-carbohydrate meal without caffeine at 12:00 noon. Because 75 g OGTT was performed at 9:00 AM on the same day, this can be explained by that insulin delay section which induced by the oral glucose test could affect glucose metabolism in the high carbohydrate meal test. After rapid intravenous administration, his blood pressure became elevated to over 80 mmHg and his consciousness was restored. Fig. 2 shows the time course of indices of HRV analysis. The values for LF/HF before the meal, within 15 minutes after starting the meal and from 15 min to 30 min after starting the meal were 0.56, 0.89, and 0.54, respectively. Within 15 min after starting the meal, the LF/HF ratio increase slightly only and the patient’s systolic blood pressure started to fall rapidly.

Although recent reports have indicated that caffeine acts to attenuate the decrease in blood pressure in patients with PPH [5, 6], it is unclear that administration of caffeine is effective to prevent syncope in PPH. Therefore, we studied the efficacy of caffeine to prevent PPH-related syncope when this patient consumed a carbohydrate-rich meal. Indeed, therapy with 150 mg caffeine attenuated the fall in blood pressure after consumption of the high-carbohydrate meal and, as a result, prevented onset of PPH-induced syncope (Fig. 1c). The changes in plasma levels of glucose and insulin after meals with or without administration of caffeine did not appear to be correlated with the marked reduction in post-meal blood pressure (Fig. 1b, Fig. 1c).

In addition, we assessed norepinephrine changes from before (0 min) and at 15, 30, 60, 90, and 120 minutes after the meal in the carbohydrate-rich meal tests with and without caffeine, respectively (Fig. 3a, Fig. 3b, Fig. 3c). Fig. 3a shows values for norepinephrine and Fig. 3b shows changes in the norepinephrine concentrations before and after a carbohydrate-rich meal with or without 150 mg caffeine. The postprandial norepinephrine level after ingestion of 150 mg caffeine increased more rapidly and drastically by 60 minutes compared with values without caffeine. On the other hand, with only the carbohydrate-rich meal, the norepinephrine level was elevated slightly and reached a maximum at 30 min after the meal. After discharge from our hospital, the patient has not had a syncope episode associated with postprandial hypotension under therapy with caffeine when consuming a carbohydrate-rich meal.

Discussion

We experienced a type 2 diabetic patient with severe neuropathy who manifested severe hypotension after a carbohydrate-rich meal. In this patient, administration of caffeine before eating a carbohydrate-rich meal prevented syncope by suppression of a post-meal blood pressure drop. In comparison with only a carbohydrate-rich meal, with the additional administration of caffeine, the peak of the elevation of norepinephrine was delayed by 30 min. This suggested that alterations in norepinephrine
levels before and after a meal play an important role in attenuation of a postprandial blood pressure fall in patients with PPH.

The mechanism by which the decrease in blood pressure occurs in patients with PPH has yet to be fully understood. However, from previous studies, PPH seems to result from inadequate compensation for the normal physiologic postprandial decrease in blood pressure rather than to an exaggerated splanchnic and mesenteric arterial flow and peripheral vascular dilatation due to severe autonomic nervous dysfunction [2, 7, 8]. Patients with severe autonomic dysfunction such as in long-
standing diabetes mellitus have a delayed compensatory blood pressure elevation with the probability of hypotensive episodes such as dizziness and syncope. Caffeine, an adenosine receptor antagonist, was useful for amelioration of the postprandial blood pressure decrease in patients with PPH [5, 6]. The mechanism by which caffeine exerts its effects on blood pressure has not been fully elucidated. However, inhibition of adenosine receptors not only may bring about a reduction in vasodilation but also may lead to the release of neurotransmitters (e.g., noradrenaline, dopamine, acetylcholine) with a strong impact on the excitatory neurotransmitters, resulting in a rise in postprandial blood pressure. Additionally, caffeine directly increases the function of the sympathetic nervous system [9]. In the present case, 150 mg of caffeine, which was in 250 mL of coffee, repressed the expected decline in postprandial blood pressure and did not affect the increase in heart rate during consumption of a carbohydrate-rich meal (Fig. 1c).

During the high-carbohydrate meal test, which took place at noon, the plasma glucose concentration reached its minimum 30 min after starting the meal, and then gradually increased. This can be accounted for by the delay in insulin secretion induced by the OGTT, which was given the morning of the same day. For this reason, it can be difficult to compare changes in glucose metabolism when a high-carbohydrate meal was given with or without caffeine. However, regarding this point, it may be necessary to consider the direct effects of caffeine on glucose metabolism. As an acute effect, caffeine reduces insulin sensitivity and raises the blood glucose level through noradrenaline elevation [10]. Johnston et al. reported that while plasma glucose concentrations were significantly higher after consumption of caffeinated coffee than a control beverage, in a comparison of the means and of the total area under the curve (TAUC) for glucose, glucose-dependent insulinotropic polypeptide (GIP) but not glucagon-like peptide-1 (GLP-1) was lower after ingestion of the caffeinated coffee compared to the control beverage [11]. Gastric emptying time can also affect a postprandial blood pressure drop in patients with type 2 diabetes mellitus [12]. However, it is controversial whether caffeine can affect gastric emptying in patients with postprandial hypotension; while some studies reported that caffeine accelerated gastric emptying [13, 14], others showed no differences between caffeine groups and a control group with regard to gastric emptying [15]. In this case, although we did not evaluate changes in gastric emptying time with or without caffeine, the difference of glucose concentration in the initial 30 min of the carbohydrate-rich meal with or without caffeine may reflect that of GIP secretion and accelerated gastric emptying time.

We also observed a hormonal change in plasma glucose and several hormones such as insulin and catecholamines (noradrenaline) during the carbohydrate loading tests with or without 150 mg caffeine. No hormones other than noradrenaline were associated with a decrease

| Time (min) | 0  | 15 | 30  | 60  | 120 |
|-----------|----|----|-----|-----|-----|
| HC        | 0.51 | 0.65 | 0.76 | 0.69 | 0.54 |
| HC with caffeine | 0.35 | 0.5  | 0.57 | 0.61 | 0.56 |

Fig. 3  a, Blood noradrenaline levels (ng/mL) before (0 minutes) and after high-carbohydrate meal (HC) with or without 150 mg caffeine. b, Changes in noradrenaline concentrations during HC tests with or without 150 mg caffeine. HC; black squares, HC with caffeine; black triangles.
in blood pressure in the two carbohydrate-rich meal tests. Although the plasma noradrenaline level and the change in response to the carbohydrate-rich meal without caffeine peaked at 30 min and then decreased relatively rapidly, these values after the addition of caffeine quickly and markedly became elevated until 60 min from the start of the carbohydrate-rich meal (Fig. 3a, Fig. 3b). Of note, the postprandial noradrenaline concentration after ingestion of caffeine was maintained at a relatively high level over time as compared with the baseline concentration, while the noradrenaline concentration without caffeine peaked at 30 minutes after the patient started to eat the carbohydrate-rich meal, and then declined to the baseline level quickly within 120 minutes. This inconsistency in noradrenaline changes and peaks between these two loading tests may suggest that caffeine has a hormonal effect in slowly stimulating sympathetic nerve activity, leading to attenuating excessive blood pressure reductions. In patients with autonomic failure, plasma noradrenaline levels after a meal were increased slightly at 30 min and then fell to baseline values within 90 min [16]. On the other hand, it was reported that caffeine enhanced the postprandial noradrenaline level at 60 min after a meal [17]. In the present case, the plasma noradrenaline concentration reached its peak 60 min after the high carbohydrate meal with caffeine, a time that is consistent with a previous report [17]. However, the effect of the time course of the noradrenaline level on postprandial hypotension after caffeine ingestion has not been clarified. In this regard, a large difference in the change in the noradrenaline ratio was observed between the carbohydrate-rich meal test with and without caffeine 60 min after the start of the meal. On the other hand, without caffeine, a remarkable reduction in postprandial blood pressure and syncope within 30 min after the meal occurred. Since the maximum decrease in blood pressure typically occurs within the first 35 min to 1 h after a meal [18], maintaining high noradrenaline levels 60 min after the meal with caffeine may act to keep blood pressure from dropping. In this present case, it should be noted that these discussion can be limited by differences in baseline values of noradrenaline between the two meal load tests.

Smith et al. reported that although increases in sympathetic nervous system activity, serum adrenaline, and renin have been causally linked to elevations of blood pressure, the acute pressor effect of caffeine is also seen in adrenalectomized patients [19]. In addition, caffeine and its metabolites are non-specific adenosine receptor antagonists and adenosine receptors can be involved in blood pressure regulation. It has been suggested that inhibition of adenosine A1 expressed in the microcirculation of the anterior glomeruli is related to blood pressure regulation by renal vasoconstriction [20] and tubuloglomerular feedback [21]. Caffeine was also shown to have an acute direct pressor effect regarding the enhancement of arterial stiffness and pulse wave velocity [22]. These findings suggest that in this patient, the administration of caffeine suppressed the excessive fall in postprandial blood pressure 30 min after the carbohydrate-rich meal and prevented the onset of PPH-induced syncope with the delay in the peak time of plasma noradrenaline concentration by the direct pressor effect other than by noradrenaline release during eating. This is the first report of differences in the delayed effect on the noradrenaline elevation in postprandial hypotension between a carbohydrate-rich meal with and without caffeine.

HRV analysis showed only a slight increase in the LF/HF ratio when this patient’s blood pressure dropped after a carbohydrate-rich meal. It was noted that the LF components express sympathetic nervous function and the HF components express parasympathetic nervous function related to respiration [23]. Especially, the LF/HF ratio is a more sensitive and specific measure of increased sympathetic drive because the vagal modulation is significantly affected by the HF [24]. In this case, the results of HRV analysis suggested that relative parasympathetic dominance was one of the causes of the postprandial hypotension. In the middle of eating, sympathetic activity is generally potentiated and is greater than during daily activity. Reports showed that although the LF/HF ratio in elderly persons without PPH was increased significantly within 30 min of starting a meal compared to that before meals, the ratio in elderly persons with PPH or diabetes mellitus is decreased or hardly increased [2, 25]. The normal range of the LF/HF value varies according to reports, but the postprandial elevation appears to be mild or reduced in patients with PPH. Tanakaya et al. reported that the average value of LF/HF in diabetic patients with PPH decreased only slightly from 2.52 to 2.4 before and after the meal, while that in healthy controls without PPH increased significantly from 3.29 to 7.58 [2]. In this case, the value of LF/HF increased only slightly from 0.56 to 0.89 before and 15 min after starting the carbohydrate-rich meal. This modest increase in LF/HF was comparable to that of other previous reports on postprandial HRV analysis in PPH patients [25, 26]. These findings may indicate that the lack of compensatory sympathetic activation during eating contributes to postprandial hypotension and syncope in those with long-standing diabetes mellitus.

A postprandial drop in blood pressure has been observed in patients with type 2 diabetes mellitus, a phenomenon that has been reported in some small studies [2, 27]. In patients with type 2 diabetes mellitus of a dura-
tion of over 5 years without clinical signs of autonomic neuropathy, PPH occurred in up to 70% of the patients after a mixed meal [2]. Thus, the onset of PPH could probably be associated with diabetes duration and the progression of complications. In this patient, anti-hypertensive drugs such as diuretics and beta blockers, in addition to the long duration of diabetes, could have contributed to the severe postprandial blood pressure drop.

In summary, we report a case of postprandial hypotension-related syncope due to severe autonomic dysfunction in a patient with long-standing diabetes. The administration of caffeine improved the patient’s postprandial hypotensive episodes by slowing the activity of the sympathetic nervous system through the gradual elevation of plasma noradrenaline.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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