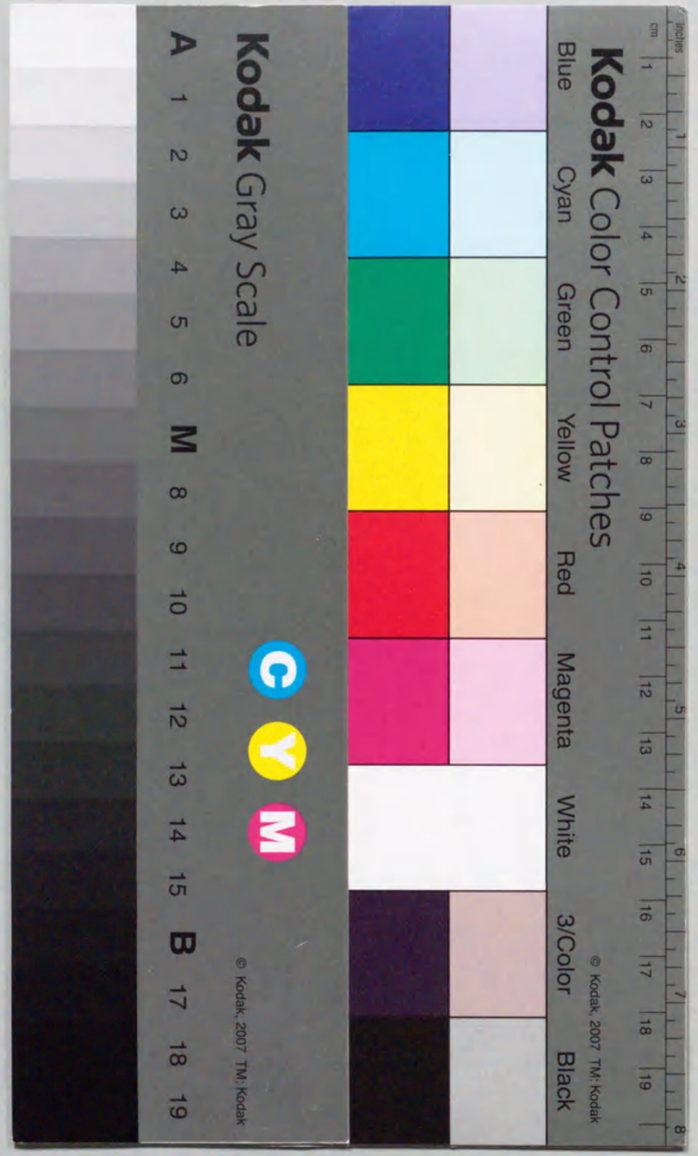

(1)

Postprandial hypotension —Hemodynamic differences between multiple system atrophy and peripheral autonomic neuropathy—

（食後低血圧 —多系統萎縮症と末梢性自律神経ニューロパチーとの血流動態の異同—）

平山正昭

論　文　目　録

報告番号	※　第　　号	氏名	ひらやま　まさあき 平山　正昭

主論文

題目　　冊

Postprandial hypotension -Hemodynamic differences between multiple system atrophy and peripheral autonomic neuropathy-
（食後低血圧 -多系統萎縮症と末梢性自律神経ニューロパチーとの血流動態の異同）
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（既に印刷公表したものについては、その方法および年月日、未公表のものについては、公表の方法および時期を記入すること。）

副論文

自律神経機能不全症における食事性低血圧発現の病態
-体内血流動態の測定-　自律神経　28巻5号、平成3年10月発行
自律神経機能不全症における食事性低血圧発現の病態（2）
-起立性低血圧との比較検討-　自律神経　29巻4号、平成4年8月発行
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-β_1刺激薬とα_1刺激薬併用による治療効果-
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進行性自律神経不全症例の食事性低血圧に対する
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参考論文

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（　同　上　）

Postprandial hypotension
-Hemodynamic differences between multiple system atrophy and peripheral autonomic neuropathy -

食後低血圧　ー多系統萎縮症と末梢神経ニューロパチーとの血流動態の異同

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Summary

To clarify the mechanism of postprandial hypotension (PPH), we performed hemodynamic investigation after oral glucose ingestion in 10 patients with multiple system atrophy (MSA), 3 patients with peripheral autonomic neuropathy (PN) and 16 normal controls. Blood pressure (BP) and heart rate (HR) were measured with an automatic sphygmomanometer: Cardiac out (CO) and lower leg blood flow (LBF) with impedance plethysmography: Portal blood flow (PBF) with B-mode pulse doppler. In normal subjects, BP, LBF and vascular resistance of the lower leg (LVR) were not changed, but HR slightly increased, and PBF and CO significantly increased after oral ingestion of 75 g glucose. While in the patients with MSA, BP fell significantly 15 min after glucose ingestion, HR and CO did not increase. PBF and LBF increased and LVR fell significantly. In PN patients, BP decreased at 15 min after glucose ingestion, but soon recovered. Increase of PBF and decrease of LVR in them were almost similar to those in MSA group, and increase of CO was greater than that in the controls. These results suggest that both systemic vasodilatation presumably due to gastrointestinal vasodilatatory peptides and lack of compensatory increase of CO and LVR play important roles in PPH.

Introduction

Patients with autonomic dysfunction often become hypotensive after standing (orthostatic hypotension; OH). OH results from dysfunction of sympathetic reflex, consequently blood pooling in the legs and decrease of cardiac filling [20]. Some patients with autonomic failure are aware of the dizziness and become hypotensive after taking food (postprandial hypotension; PPH) [4) 7) 8) 12) 16) 17) 19)]. This was first reported in Parkinson's disease with autonomic dysfunction [18)], and is seen in a variety of neurological disorders: multiple system atrophy [MSA] [4)7)12)17)], pure autonomic failure [PAF] [5)12)], aging [11)], diabetes mellitus [9)], Pakinsin's disease [5)13)]. However, little is known of hemodynamic change after eating in patients with AF, because attention has not been paid to PPH. Hoeldtke showed no increase of cardiac output [CO] in spite of considerable fall of blood pressure [BP] after eating in a patient with alcoholic neuropathy[8)]. Hakusui reported increase of muscle sympathetic nerve activity [MSNA] in normal subjects but not in patients with MSA after eating [4)], thus inadequate sympathetic compensation after eating might result in PPH. There has been no study of systemic hemodynamics to clarify the mechanism. We performed hemodynamic study directed toward this problem using simultaneous and multi recordings : impedance plethysmography (CO and blood flow of the lower legs[LBF]) and B-mode pulse doppler method (portal blood flow [PBF]).

When standing or eating, inadequate sympathetic compensatory mechanism was occasionally found as the common pathomechanism of OH and PPH. However, the discrepancy between OH and PPH has not been clarified. We experienced a case of familial amyloid polyneuropathy who presented with severe OH but PPH [6)] . We performed a comparative study on the hemodynamics of patients with peripheral autonomic neuropathy and those with MSA using 75 g glucose (225 ml of water) for the standard load, because glucose is known the best depressor factor of BP in patients with

AF[1]). For the test of glucose tolerance, 225 ml of 75 g glucose is generally used and is established as a useful and safe one in Japan.

Method

Controls and patients

Ten patients were diagnosed as MSA (9 men, 1 woman; mean 57±7 years of age). Three patients with PN comprised one case of acute autonomic sensory and motor neuropathy (45-year-old woman), two cases of familial amyloid neuropathy (type 1) (57-year-old and 35-year-old men). All patients with MSA had both PPH (decrease in mean blood pressure of more than 15 mmHg 15 min after 75 g glucose ingestion) and OH (decrease in systolic blood pressure of more than 30 mm Hg when standing). The patients with PN showed OH. BP, heart rate [HR], CO and LBF were assessed in all patients. The PBF was measured in 9 patients using B-mode pulse doppler method. The controls were 16 healthy subjects (male 14, female 2; 38±11). All the subjects (patients and control) had given theirs informed consent before the procedure.

Hemodynamic measurements

Impedance plethysmography (bioimpedance plethysmography 4134, Nihondenki-sanei) was used to measure CO and LBF. An automatic sphygmomanometer (BP8800, Nihonkourin) was used for measurement of BP and HR every 5 minutes. PBF was measured with B-mode pulse doppler 3.5 MHz (EUB-165, Hitachi) every 15 minutes. The bioimpedance data of LBF and CO were stored in a multichannel FM-magnetic tape recorder (XR700l, TEAC) with ECG monitoring. The data of impedance plethysmography for each 10-second epoch were analyzed with a signal processor (7T18, Nihondenki-sanei), then calculated using Kubicek's equation. Since the absolute bioimpedance value was considerably varied even in the healthy subjects [15], we estimated percentage variations to the baseline value before glucose ingestion. Vascular resistance of the lower leg [LVR] was calculated from the data of BP and LBF.

The testing was begun at 10:00 a.m. in our laboratory with an ambient temperature of 25°C. All medications were withheld for one day before the study, and no oral intake of fluid was allowed after midnight. The subjects lay supine on a bed. BP, ECG, CO and LBF were monitored at rest for 30 min (control period), and then for 60 min after the oral ingestion of 75 g glucose (225 ml of water). Statistical analyses were performed using Wilcoxon signed-rank test and Mann-Whitney test. The results were expressed as mean ± SD, and P values less than 0.05 were considered to be significant.

Result

1) Blood pressure (Fig. 1, Table 1)

In the patients with MSA (n=10), the basal systolic BP (105±10 mmHg) was higher than in the normal subjects (83±8 mmHg) (n=16, $p<0.01$). And ingestion of glucose resulted in rapid and significant fall of systolic and diastolic BP, which appeared in 15 min (86±15 mm Hg, $p<0.05$) and continued for 60 min. BP in controls remained unchanged. These time-sequential changes of BP showed a significant difference between controls and patients . In the patients with PN, BP decreased in 15 min of oral glucose ingestion, but it soon recovered.

2) Heart rate (Fig. 2, Table 1)

In MSA patients (n=10), the basal HR was higher than in the normal subjects (n=16) (79±11 beats/min vs. 66±11) ($p<0.05$), and the HR was unchanged after glucose ingestion. Increase of HR was small in the normal subjects, while in patients with PN, it was larger.

3) Portal blood flow (Fig. 3)

Both the normal subjects and patients showed increase of PBF in almost the same degree after 15 min of oral glucose ingestion.

4) Cardiac output (Fig. 4)

In normal subjects (n=6), significant increase of CO was seen after 15 min ($p<0.05$), and maximum level was at 45 min later. Increase of CO was higher in the patients with PN (n=3) than in the control subjects, while in the patients

with MSA (n=10) it was not observed in spite of the substantial BP fall after glucose ingestion.

5) Vascular resistance of the lower leg (Fig. 5)

In the normal subjects (n=11), LVR was unchanged after glucose ingestion. On the other hand, LVR in the patients with MSA (n=10) decreased significantly in 15 min , then reached the minimum after 30 min. The decrease of LVR in MSA patients was almost the same as in the patients with PN (n=3).

In summary (Table 2), 1) both PBF and CO increased after glucose ingestion, then BP and LVR remained stationary in the controls. 2) in the patients with MSA, PBF increased almost the same as seen in normal subjects, however, LVR was decreased and CO was unchanged, then there was a substantial fall of BP. 3) in the patients with PN, increase of PBF was almost similar to other groups, LVR decreased almost the same in the patients with MSA, but CO was higher than in the controls. BP fell at 15 min later of glucose ingestion, but soon recovered.

Discussion

The principal findings in this study were as follow as; after ingestion of glucose 1) Portal blood flow increased both in the patients with MSA as well as PN and in the normal subjects; 2) LVR decreased only in the patients with MSA and PN but not in the controls; and 3) CO remained unchanged in the patients with MSA. Its increase was significant in the controls and remarkable in the patients with PN. It is known that food ingestion induces an increase in mesenteric blood flow and reduces total vascular resistance [14] , and that BP is maintained, presumably by compensatory rise in heart rate, stroke volume [3] and peripheral vascular resistance of the extremities [2] in the normal subjects. Our findings in the controls well corroborated these results. HR, CO and LVR did not increase in spite of BP fall in the patients with MSA. This suggests dysfunction of the baroreflex. In the patients with MSA and in the controls, PBF increase was almost the same. Failure of the compensatory response when BP falls might be the principal pathophysiology of PPH. In the patients

with PN, LVR decrease occurred as same as in the patients with MSA, but HR and CO increased over the control level. These suggest that the PN patients had normal function of baroreflex and dysfunction of the peripheral sympathetic efferents. These different pathomechanisms of CO result in the different patterns of BP. If baroreflex arc to the heart is intact and there is increase in CO and maintaining of LVR, PPH may not occur.

As a rule, food ingestion increases mesenteric blood flow in the normal humans. This alteration of blood volume distribution after meals has been posited to compromise cardiac filling, to decrease CO, and to lead to systemic hypotension [11]. Our study revealed that CO did not decrease after glucose ingestion. This result corresponds with the results of Hoedtke [8] and Kooner [10]. Therefore PPH may be not resulted from mesenteric blood pooling but from systemic vasodilatation. Mesenteric vasodilatation occurs after glucose ingestion. Release of the vasodilatory gastrointestinal hormones is one of the possible vasodilatory causes, since the somatostatin analogue octreotide (SMS 201-995) [9] which prevented their release, inhibits the mesenteric blood flow. Release of vasodilatory gastrointestinal hormones may act as vasodilator of the peripheral vessels and lead to decrease LVR after glucose ingestion. We revealed that LVR decreased in the patients with autonomic failure after glucose ingestion. In normal subjects, muscle sympathetic nerve activity (MSNA) increases after glucose ingestion [2]. MSNA is presumed to be purely vasoconstrictive and to represent an increase in vascular resistance of the extremities. In normal subjects, increase of MSNA plays an important role in maintaining VR of the extremities to activate vasodilatation of the peripheral vessels after glucose ingestion. In patients with autonomic failure, MSNA fails to increase, and LVR decreases. These results in our study indicate that lack of compensatory increase of CO and MSNA plays important roles on PPH, and suggest that gastrointestinal vasodilatory peptides may be the principal vasodilator of the systemic blood circulation.

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Fig. 1

Change in blood pressure after oral ingestion of 75 g glucose

Pressure levels were expressed as a percentage from baseline value before glucose ingestion.

The error bar indicates the mean ± S.E. There were signifinant differences between controls and MSA, but no differences between controls and PN by Mann-Whitney test. *: $p< 0.05$ **: $P< 0.001$

Fig. 2

Change in heart rate after oral ingestion of 75 g glucose.

The error bar indicates the mean ± S.E.

Fig. 3

Change in portal blood flow after oral ingestion of 75 g glucose.

The error bar indicates the mean ± S.E.

In both normal subjects and patients, PBF increased similarly.

Fig. 4

Change in cardiac output after oral ingestion of 75 g glucose.

The error bar indicates the mean ± S.E. There were significant differences between controls and MSA, but no differences between controls and PN by Mann-Whitney test. *: $p < 0.05$ **: $p < 0.001$

Fig. 5

Change in vascular resistance of lower leg after oral ingestion of 75 g glucose.

The error bar indicates the mean ± S.E. There were significant differences between controls and MSA, but no differences between controls and PN by Mann-Whitney test. *: $p < 0.001$

Table 1

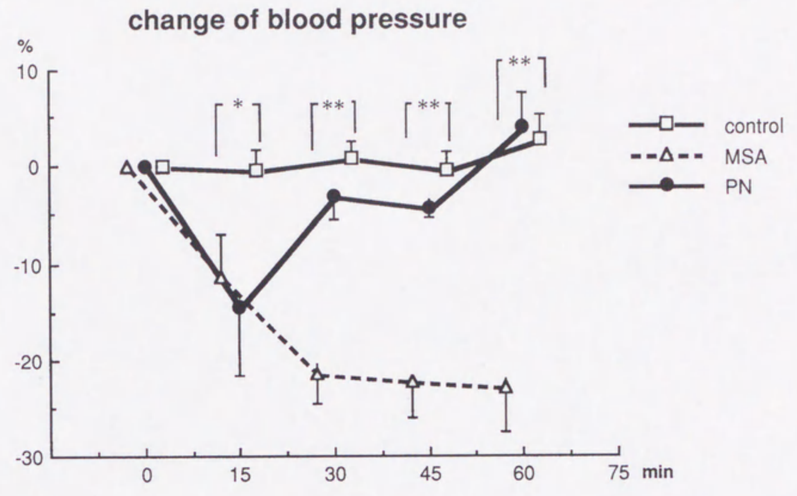
control (N=16)	baseline	15 min	30 min	45 min	60 min
mean BP	83±8	85±10	84±8	86±11	87±11
HR	66±11	68±12*	68±11	69±12	69±10*
MSA (N=10)					
mean BP	105±10	93±16*	83±13*	82±14*	84±14*
HR	79±11	80±12	83±12	82±8	81±10
PN (N=3)					
mean BP	95±11	80±5	92±8	91±9	99±13
HR	80±18	85±21	88±20	87±18	86±16

(* $p < 0.05$, ** $p < 0.01$)

Table 2

	BP	HR	PBF	CO	LVR
control	→	slightly ↑	↑	↑	→
MSA	↓	→	↑	→	↓
PN	temporary ↓	↑	↑	↑	↓

BP, blood pressure; HR, heart rate; PBF, portal blood flow; CO, cardiac output; LVR, vascular resistance of lower leg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min
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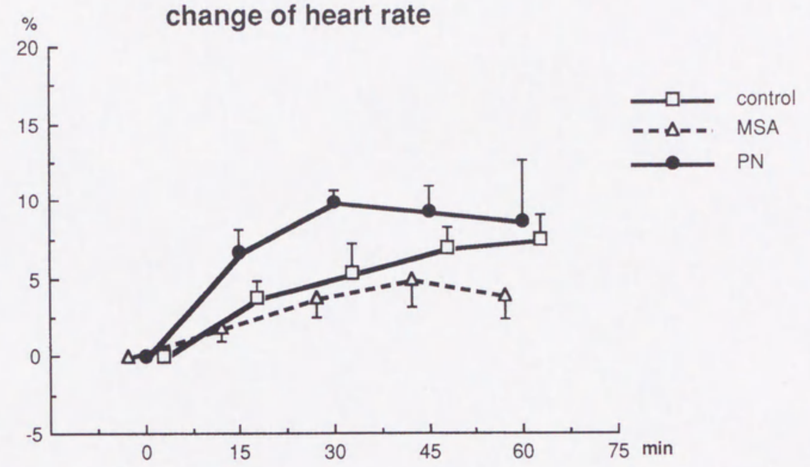
**
control
MSA
PN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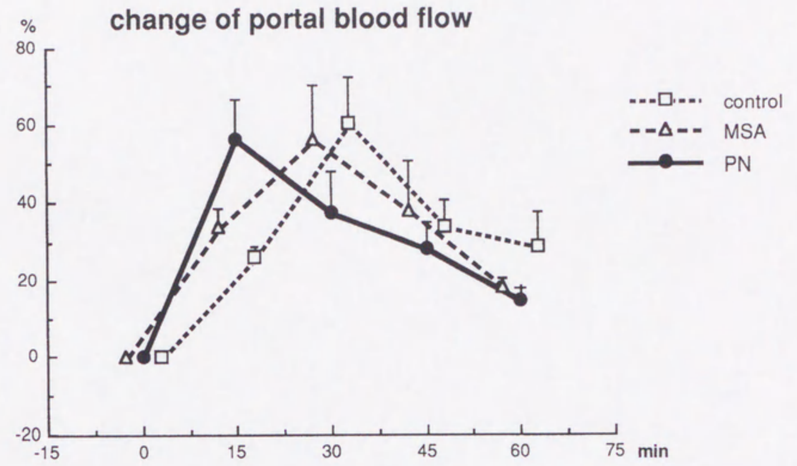
min
control
MSA
PN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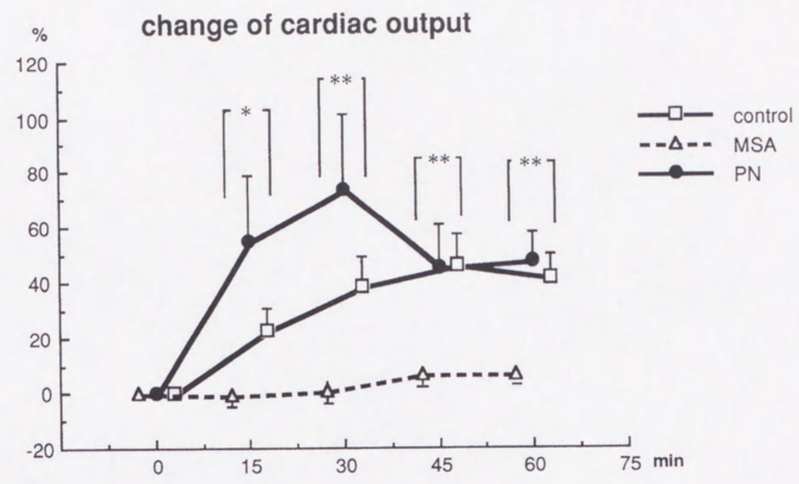
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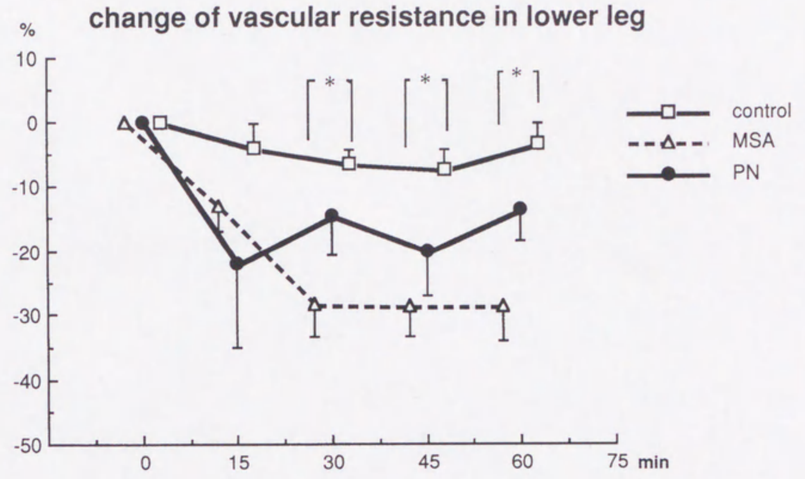
control
MSA
PN


change of vascular resistance in lower leg
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75 min
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*
control
MSA
PN