Blood flow responses in celiac and superior mesenteric arteries in the initial phase of digestion

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Someya N, Endo MY, Fukuba Y, Hayashi N. Blood flow responses in celiac and superior mesenteric arteries in the initial phase of digestion. *Am J Physiol Regul Integr Comp Physiol* 294: R1790–R1796, 2008. First published April 2, 2008; doi:10.1152/ajpregu.00553.2007.—Blood flow (BF) responses in the celiac artery (CA) and superior mesenteric artery (SMA) during and immediately after a meal are poorly understood. We characterized postprandial BF responses in these arteries in the initial phase of digestion. After a baseline measurement in the overnight fasting state, healthy subjects ingested solid food (300 kcal) and water ad libitum within 5 min (4.6 ± 0.2 min, means $\pm$ SE), and then rested for 60 min in the postprandial state. Mean blood velocities (MBVs) in CA ($n = 7$) and SMA ($n = 9$) and mean arterial pressure (MAP) were measured throughout the procedure. The MAP was divided by the MBV to yield the resistance index (RI). The MBV in CA and SMA started increasing within a minute after beginning the meal. The MBV in CA rapidly reached its peak increase ($60 \pm 8\%$ change from baseline) at 5 ± 1 min after the start of the meal, whereas the MBV in SMA gradually reached its peak increase ($134 \pm 14\%$) at 41 ± 4 min after the start of the meal, reflecting a decrease in the RI for both CA and SMA. These findings suggested an earlier increase in CA and SMA MBV, implying that the increase of BF in some parts of the small intestine precedes the arrival of chyme.

visceral artery; food intake; postprandial splanchnic hyperemia

BLOOD FLOW (BF) IN THE SPLANCHNIC organs reflects motor, secretory, and absorptive activities. All of these activities increase after a meal and, consequently, induce a great increase in splanchnic BF (6). The splanchnic circulation provides nutrients and oxygen to its supplying organs, carries away the absorbed substances, and removes waste products from the organs. It is important to understand the nature and mechanism of BF regulation in the splanchnic organs.

Only a small number of previous studies reported postprandial BF in the celiac artery (CA). Qamar et al. (19) reported that the CA BF showed a peak increase (38%) immediately after the end of a 405-kcal liquid meal from baseline. On the other hand, no significant increase of the BF was observed in the CA 10 min after the end of a 350-kcal meal (11), and 40 min after the end of a 1,000-kcal meal (15). These studies obtained CA BF data every 5–15 min or obtained only one measurement, and the duration of the meal varied from 1 to 10 min. Thus, the time resolution was too low to describe the initial response to the meal.

In contrast to the CA, postprandial superior mesenteric artery (SMA) BF has been well documented. We summarized 10 studies reporting the postprandial SMA BF response in

humans for meta-analysis (Table 1). BF in the SMA increases by 58–250% in the postprandial state (17, 23). A dose-response relationship between SMA BF and the energy content of a meal has been demonstrated (13, 20). The increase in SMA BF reached its peak between 5 and 60 min after a meal (16, 20, 22). This wide-range variation among studies could result from the composition of meal nutrients. A high-carbohydrate meal rapidly increased SMA BF compared with a high-fat meal, while a high-fat meal is accompanied by a slowly induced and prolonged fall in SMA vascular resistance (17, 22).

Although the peak response of SMA BF to food is well documented, the initial phase of BF response is unknown. Food across the pylorus could be the trigger increasing SMA BF. Minderhound et al. (10) observed first gastric emptying at 3.9–16.2 min after the start of a 294-kcal solid egg meal, implying an earlier increase of SMA BF than in previous studies (13, 20–22); however, the increase of SMA BF in the initial phase of digestion has not been observed.

Food ingestion increases the heart rate (HR) and cardiac output (8, 20, 22, 28), whereas the blood pressure is reportedly stable (20). It is not clear, however, whether the increases in cardiac output and HR contribute to the increase of splanchnic BF. Previous results in the limb BF responses to food in humans are inconsistent: no change (8), reduction (20, 22), or increase (27, 29). This inconsistency could be due to the composition and amount of food. Differences in the duration of the meal and the time points of the BF measurements could also affect the inconsistent results. There are no available data showing the detailed time course of the change in postprandial limb BF in humans.

The purpose of the present study was to comprehensively describe the time course of BF response in the CA and SMA, which would provide implications for translational studies searching for the mechanism of food-induced splanchnic hyperemia. We paid particular attention to the initial phase of the responses because there is little information on BF responses. In addition, the present study assessed the time course of central circulation and forearm BF to a meal.

METHODS

Subjects. Thirteen subjects (7 men and 6 women, age 24 ± 1 yr, height 167 ± 3 cm, weight 56 ± 3 kg, means $\pm$ SE) volunteered in the present study. We obtained blood velocity data in the CA (seven subjects) and the SMA (9 subjects). Three subjects participated in both measurements. The subjects were normotensive, not taking any medication, and had no history of autonomic dysfunction or cardio-

Table 1. *Blood flow responses to food*

First Author	Meal Type	Meal Volume, ml	Energy Contents, kcal	Energy Composition, %	Duration of Meal, min	BF at Baseline, ml/min	BF at Peak, ml/min	BF Increase, %	Peak Time, min
Cooper et al. (3)	Solid		778	P, 9; F, 37; C, 57	10	513	849	65	15
Moneta et al. (11)	Liquid	300	355	P, 15; F, 32; C, 53	1–3	538		164	30
	Liquid	300	350	High carbohydrate	1–3	538		118	20
	Liquid	300	347	High fat	1–3	538		117	30
	Liquid	300	350	High protein	1–3	538		78	30
Parker et al. (13)	Liquid	300	191		3	415		106	20
	Liquid	300	382		3	373		125	25
	Liquid	300	573		3	320		167	35
	Liquid	300	1147		3	384		240	35
Qamar and Read (16)	Liquid	400	390	P, 22; F, 36; C, 43	10	523	846	62	5
Qamar and Read (17)	Liquid	400	400	High carbohydrate	10	530		64	15
	Liquid	400	400	High fat	10	530		58	45
	Liquid	400	400	High protein	10	530		60	30
Sidery and Macdonald (20)	Solid	350	239	C, 84	<15		836		15
	Solid	520	478	C, 84	<15		825		60
	Solid	585	717	C, 84	<15		1189		15
Sidery et al. (21)	Solid	600	597	F, 7; C, 74	<15	346	611	77	20
	Solid	350	597	F, 71; C, 14	<15	351	715	104	40
Sidery et al. (22)	Solid	600	597	F, 7; C, 74	<14	217	406	87	15
	Solid	350	597	F, 71; C, 14	<14	215	478	122	60
Sieber et al. (23)	Liquid	500	750	P, 17; F, 30; C, 53		443		250	38
Sieber et al. (24)	Liquid	270	405	P, 17; F, 30; C, 53					30
	Solid		547		<30			240	45

The subjects of all studies were healthy men and women (20–52 yr). Food was ingested orally. Peak time indicates the time of the peak response of blood flow (BF) in the superior mesenteric artery obtained after the end of the meal. P, protein; F, fat; C, carbohydrate.

vascular disease. The Ethics Committee of the Institute of Health Science of Kyushu University approved the experimental protocols, and all subjects provided written informed consent. All protocols conformed to the Declaration of Helsinki, and each subject underwent a pilot examination prior to the main protocol.

Protocols. The subjects arrived at the laboratory after overnight fasting, having abstained from caffeine, intensive exercise, and smoking. The experiments were conducted in a quiet room with the subjects in a semirecumbent position and the legs extended ~130° to the trunk. After 5 min of baseline measurements, the subjects ingested solid food containing 6.5 g of protein, 16.8 g of fat, and 30.0 g of carbohydrate with a total caloric volume of 300 kcal (Calorie Mate, Otsuka Pharmaceutical, Tokyo, Japan), and drank water ad libitum (143 ± 15 ml) within 5 min (4.6 ± 0.2 min). The measurements then continued for 60 min. As a control trial, the subjects rested for 70 min (no meal and water). Each subject completed these protocols. Three subjects who participated in measurements both for CA and SMA repeated these protocols twice because blood velocity in CA and SMA was not measured simultaneously. Each protocol was performed on a separate day.

Measurements. Throughout the protocol, HR, mean arterial pressure (MAP), mean blood velocities (MBVs) and vessel diameters in CA and SMA, and BF in the forearm, were measured. Continuous HR was determined using a standard ECG (MEG2100, Nihon-Kohden, Tokyo, Japan). Beat-by-beat MAP was monitored with an automatic sphygmomanometer (Jentow, Colin Medical, Aichi, Japan).

Simultaneous pulsed and echo Doppler ultrasound flowmetry was used to measure MBV in the CA and SMA. A curved-array Doppler-scan probe with a 3.3-MHz-pulsed Doppler frequency was used (LOGIQ3; GE Medical Systems, Piscataway, NJ). This machine allows a real-time cross-sectional image (i.e., B-mode echo) to be displayed simultaneously with real-time Doppler spectral display and sound. The focal zone was at the depth of the CA or SMA, as well as at the proximal segment of each artery. The Doppler beam insonation angle was maintained 60° or less to the blood vessel. High-quality Doppler tracings were obtained by determining the optimal positions of the Doppler probe for each subject (via an anterior abdominal approach) before the trial (14, 19). The experimenter adjusted the probe angle and position throughout the protocol. After adjusting the sample volume width to cover the target artery, the Doppler transducer was maintained in a constant position on the subject's anterior abdominal wall. When the target artery moved out of observation range for five consecutive beats, the probe was readjusted. No sudden changes in the MBV were observed during such readjustments of the probe. Duplex scan examinations were videotaped to measure vessel diameters in CA and SMA by cross-sectional resolution for 1 min every 5 min.

The signals for antegrade and retrograde blood-cell velocities, as well as the ECG signal, were digitally sampled at 20 kHz using an A/D converter (PowerLab 8s/30; ADInstruments, Colorado Springs, CO). The spectra of the signals were manipulated offline by our Doppler signal processing software, and beat-by-beat MBV values were calculated (7).

BF in the forearm was measured by venous occlusion plethysmography using a mercury-in-Silastic strain gauge (EC-6; Hokanson, WA). The strain gauge was placed around the largest area of the left forearm. The left forearm was positioned slightly above the heart level, and venous occlusion pressure of 40 mmHg was used. The value was calculated from the increase rate in forearm volume during venous occlusion and expressed as milliliter per minute per 100 ml of the forearm volume. Two measurements were performed every minute, and their average was taken as the value per minute.

To obtain minute-by-minute MBV data, the 10 largest values of beat-by-beat MBV were averaged every minute because a lower value indicates measurement failure, mainly because of respiration. We obtained reliable velocity data using this method and data reduction (25). On a minute-by-minute basis, vascular resistance indexes in CA and SMA were calculated from MAP/MBV and represented as RI_{MBV}.

Because the same protocols were repeated twice to obtain the MBV data from CA and SMA in three subjects, the data of minute-by-minute MAP, HR, and BF in the forearm in each subject were averaged in repeated measurements. Minute-by-minute data of each variable were averaged every 5 min. BF (ml/min) in the CA and SMA was calculated from $\pi \cdot r^2 \cdot MBV \times 60$; where r is the radius of the artery. Then, MAP was divided by BF in the CA and SMA to yield the

vascular resistance indexes (RI$_{BF}$). Individual peak value was detected from minute-by-minute velocity data, whereas this was not detected in BF data because of limited time resolution.

Statistics. Data are expressed as means $\pm$ SE. Paired *t*-test was used to compare baseline values between control and experimental trials. The main effect of time and trial on absolute variables was examined by repeated-measures ANOVA. When a significant *F* value was detected, this was further examined by Dunnett's post hoc test for assessing the effect of time and paired *t*-test for comparing the values at each time point between trials. Statistical significance was accepted at $P < 0.05$. These statistical analyses were performed with SAS (ver. 8.2, SAS Institute, Cary, NC) at the Computing and Communications Center at Kyushu University.

RESULTS

Baseline values did not differ between experimental and control trials except for BF in the forearm (Table 2). In the control trial, the MBV, vessel diameter, and BF in CA and SMA, and MAP showed no change throughout the measurement. The HR decreased 15–30 and 60–65 min after the start of measurement, and the BF in the forearm decreased 55–60 and 65–70 min after the start of measurement in the control trial.

Central circulation. The HR during the meal, and 0–5 min and 30–55 after the end of the meal in the experimental trial was greater than that in the control trial (Fig. 1). Compared with the baseline, the HR increased during the meal (from 57 ± 2 to 69 ± 2 bpm), and this increase persisted 0–5 min after the end of the meal. The MAP increased during the meal (from 77 ± 3 to 84 ± 3 mmHg) and returned to the baseline within 5 min after the end of the meal. The MAP 30–60 min after the end of the meal was lower in the experimental trial than in the control trial.

Postprandial splanchnic blood velocities. The MBV in the CA during the meal and 0–10 min after the end of the meal was higher in the experimental trial than the control trial (Fig. 2). The MBV in the CA increased during the meal and 0–10 min after the end of the meal compared with the baseline. The MBV in the CA rapidly reached its peak increase (from 0.36 ± 0.03 to 0.57 ± 0.03 m/s) at 0 ± 1 min after the end of the meal. This rapid increase of MBV in the CA returned to the baseline value 10 min after the end of the meal. The MBV in the SMA was higher in the experimental trial than control trial during the

Table 2. *Baseline values*

	Experimental Trial	Control Trial
HR, beats/min	57 ± 2	57 ± 2
MAP, mmHg	77 ± 3	78 ± 2
CA		
MBV, m/s	0.36 ± 0.03	0.37 ± 0.03
diameter, mm	5.2 ± 0.3	5.0 ± 0.2
BF, ml/min	463 ± 59	456 ± 60
SMA		
MBV, m/s	0.28 ± 0.02	0.28 ± 0.02
diameter, mm	5.4 ± 0.4	5.4 ± 0.3
BF, ml/min	374 ± 40	381 ± 31
Forearm		
BF (ml/min/100 ml tissue)	10 ± 2	6 ± 2#

Values are the means $\pm$ SE. HR, heart rate; MAP, mean arterial pressure; CA, celiac artery; SMA, superior mesenteric artery; MBV, mean blood velocity; BF, blood flow. Baseline values did not differ between trials except for forearm BF. #Difference between trials ($P < 0.05$).
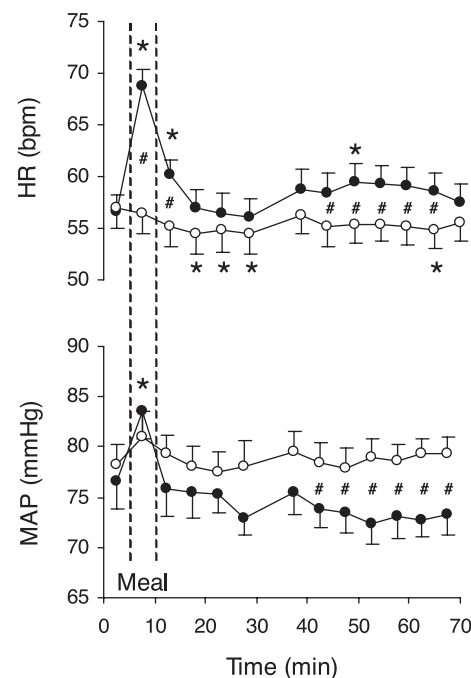

Fig. 1. Central circulation during experimental (●) and control (○) trials. The subjects ingested the meal within 5 min after 5 min of baseline measurement. Increase in heart rate (HR) was observed during and 5 min after the meal. Mean arterial pressure (MAP) increased during the meal. Values are the means $\pm$ SE. *Difference from baseline values. #Difference between trials ($P < 0.05$).

meal, and this difference between trials persisted until the end of measurement. The MBV in the SMA increased from the baseline 10 min after the end of the meal and reached its peak increase (from 0.28 ± 0.02 to 0.64 ± 0.03 m/s) at 36 ± 4 min after the end of the meal.

Postprandial splanchnic vessels' diameters and BF. Vessels' diameters did not show significant change in both arteries (Fig. 2). BF in CA was greater in the experimental trial than control trial during the meal and 0–5 min after the end of the meal. Compared with the baseline, BF in CA increased during the meal and returned to the baseline 5 min after the end of the meal. The RI$_{BF}$ in CA was lower in the experimental trial than in the control trial and decreased from the baseline during and 0–15 min after the end of the meal.

SMA BF in the experimental trial was greater than in the control trial from the start of the meal to the end of the measurement. SMA BF increased from baseline to 15 min after the end of the meal. During the meal, the RI$_{BF}$ in the SMA tended to decrease in the experimental trial than in the control trial ($P = 0.08$) and was lower than the control trial after the end of the meal. The RI$_{BF}$ in SMA decreased from baseline to 5 min after the end of the meal throughout the postprandial state.

Splanchnic circulation during meal. Compared with the baseline, the MBV in both CA and SMA showed a greater value immediately after the start of the meal (0.08 ± 0.02 and 0.03 ± 0.01 m/s increase from the baseline, respectively) (Fig. 3). Compared with the control trial, MBVs in the experimental trial were greater during a meal. The RI$_{MBV}$ started decreasing from baseline within 1 min in the CA and tended to decrease 4 min after the meal in the SMA. The RI$_{MBV}$ in both
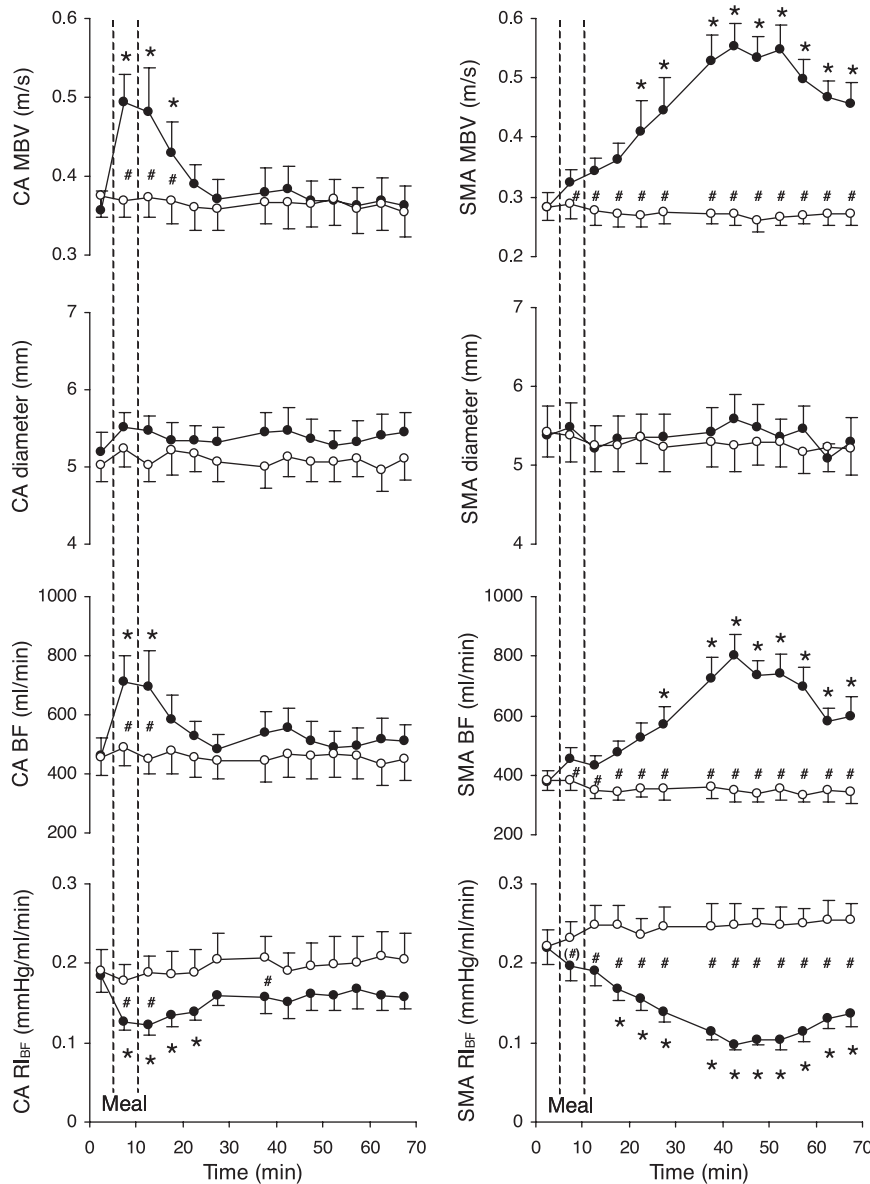
Fig. 2. Splanchnic circulation during experimental (●) and control (○) trials. The subjects ingested the meal within 5 min after baseline measurement. Mean blood velocity (MBV) and blood flow (BF) in celiac (CA) and superior mesenteric arteries (SMA) increased from the baseline during and after the meal. Resistance indexes (RI_{BF}) in both arteries decreased from the baseline during and after the meal. Values are the means $\pm$ SE. *Difference from baseline values. #Difference between trials (*,#$P < 0.05$; (#)$P = 0.08$).

arteries was lower in the experimental trial than in the control trial.

Forearm vascular responses. The BF in the forearm decreased 15 min after the end of the meal, and this decrease persisted to the end of measurement (Fig. 4).

DISCUSSION

This study showed minute-by-minute blood velocity data in human splanchnic arteries during and after a meal. The main finding is that the MBV in CA and SMA started increasing in the first minute of the meal and reached a peak at 0 ± 1 min after the end of the meal in CA and at 36 ± 4 min in SMA. These increases are not only due to increased central circulation, but also decreased vascular resistance, i.e., the increase in splanchnic BF is based on local vasodilatory responses.

The MBV in CA started increasing within 1 min after the start of the meal. This result is similar to the study of Qamar et al. (19), who reported a 38% increase in CA BF immediately

after a meal. Matheson et al. (9) proposed that BF in the splanchnic organs should start increasing when digestive chyme reached these organs. Thus, the earlier increase of MBV in the CA observed in the present study can support these previous considerations; however, it is unclear to what extent the increased CA BF was distributed to the stomach since the CA also supplies the liver and spleen.

Surprisingly, the MBV in SMA also increased within a minute of the meal. The SMA supplies BF only to the small intestine, except that it supplies a small portion of BF to pancreas via its inferior pancreaticoduodenal branch (12). The MBV in SMA observed in the present study, therefore, could start increasing before chyme reached the small intestine. The first gastric emptying episode was 6.9 (range: 3.9–16.2) min after the start of a 294-kcal solid meal (10). The energy content was almost the same and, therefore, the emptying time may have been roughly 7 min in the present study.

Fig. 3. MBV and resistance index (RI_{MBV}) response in CA and SMA in the initial phase of meal (●) and control trials (○). MBV in CA and SMA increased within a minute from the start of the meal. Values are the means ± SE. *Difference from baseline values. #Difference between trials ($P < 0.05$).
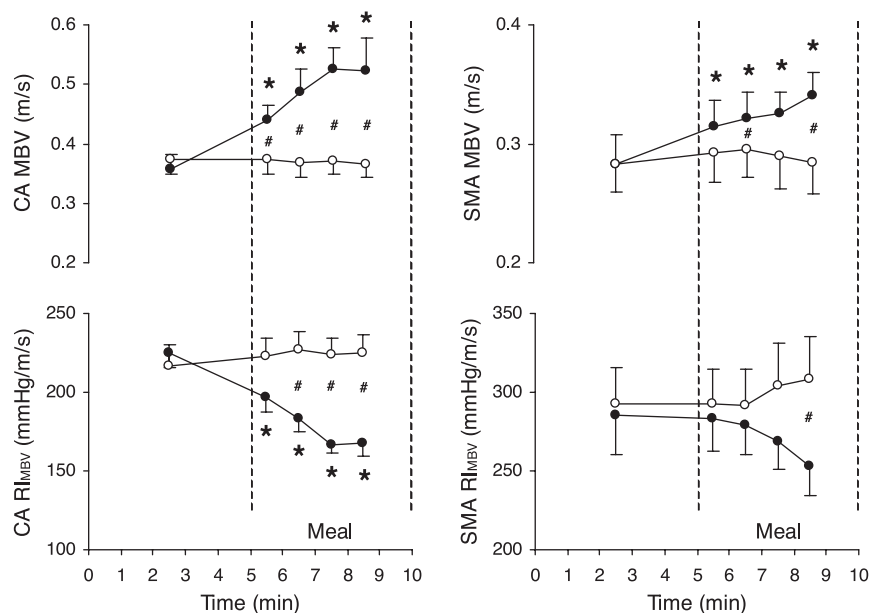
We can speculate several effective stimuli increasing the MBV in SMA in the initial phase of digestion. Stimulation of a higher brain center and/or oral cavity could increase the blood velocity. Feldman and Richardson (4) reported that thinking about food, the sight and smell of food, and chewing and expectorating in sham feeding are potent stimulants of gastric secretion. Gastrin, one of the gastric secretions, has a vasoactive property (6). Chen et al. (2) reported that gastric electrical activity can be altered by sham feeding, which could induce the gastrointestinal motility. Deficit of oxygen concentration in the smooth muscle induced by motility enhanced in the gastrointestinal tract can increase intestinal BF (6). These studies led to the idea that stimulation of the higher brain center and/or oral cavity increase splanchnic BF.

After the increase in MBV in the initial phase of the meal, the MBV in CA and SMA showed different time courses. The MBV in CA reached its peak response at 5 min after the start of the meal and began to fall toward the baseline value, even though it was reported that most of the ingested food may have stayed in the stomach (21). On the other hand, the magnitude of the initial increase of MBV in SMA was maintained for ~10

min, and then MBV in SMA markedly increased about 30 min after the meal.

These responses could be triggered by the digestive chyme reaching the duodenum. Geelkerken et al. (5) reported that
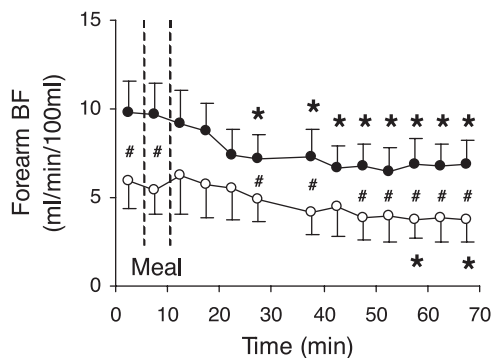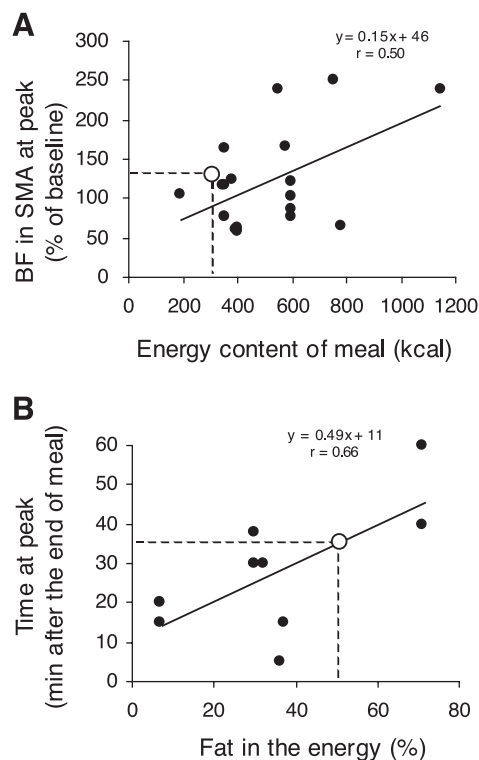

Fig. 5. Meta-analysis of relationships between the energy content of the meal and BF peak response in the SMA (*A*) and the ratio of fat in the meal and the time of the peak response of BF in SMA (*B*). Positive correlation between the energy content (kcal) and peak increase of BF in SMA (% of baseline) was shown ($P < 0.05$, $n = 19$). Positive correlation of the ratio of fat in the energy content (%) and time of peak response of BF in SMA (minutes after the end of the meal) was shown ($P < 0.05$, $n = 9$). Open circles show the data from the present study, and closed circles show previous data.

Fig. 4. Forearm BF during experimental (●) and control (○) trial. BF in the forearm decreased from the baseline in both trials. Values are the means ± SE. *Difference from baseline value. #Difference between trials ($P < 0.05$).

food injection into the duodenum elicits vasoconstriction in the CA and alternatively elicits vasodilatation in the SMA. Chyme reaching the duodenum could switch the BF distribution. It is likely that vasoconstriction of the CA is mediated by reverse enterogastric reflex, transmitted through the mesenteric and vagus nerves, which inhibit gastric secretion and motility. This inhibition of gastric secretion and motility induced the reduction of CA BF as a result of reduced stomach blood flow (6).

The gradual and marked increase in MBV in the SMA may be induced by neural and humoral mechanisms and metabolic products: cholinergic nerve, adrenomedullary hormone, gastrointestinal hormone, as well as adenosine and NO induced by metabolic products (1, 9, 23, 26). This suggests that absorption of a nutrient induces vasodilatation in the splanchnic organs. In fact, some studies report that ingestion of water, saline, or lactulose solution, which is a nonabsorbable disaccharide, did not increase SMA BF (11, 17, 18, 23). The marked increase in SMA BF may be induced by a combination of the above mechanisms.

On the other hand, splanchnic vasodilatation in the initial phase of digestion, which was observed in the present study, could not be fully explained by these mechanisms; higher brain center and/or oral cavity play a role in initial splanchnic vasodilatation as mentioned above.

We summarized 11 studies reporting the postprandial SMA BF response in humans (Table 1). Significant correlation between the energy content (kilocalories) and relative peak response in SMA BF (% of baseline) were shown in Fig. 5A ($r = 0.50$), indicating the association of energy content and SMA BF increase. The relative peak response of MBV in the SMA of the present result was close to this regression line calculated from previous studies. In addition, summarizing the nine previous sets of data, significant correlation of the fat ratio in the energy content and time-of-peak BF response in the SMA are shown in Fig. 5B ($r = 0.66$). This meta-analysis implies the effects of energy content and meal nutrients on SMA BF. The peak time of MBV in the SMA in the present result was close to this regression line. The vessel diameter of CA and SMA did not change during and after the meal (Fig. 2), implying that the increase in splanchnic BF during and after the meal was mainly due to an increase in MBV. This was supported by significant correlations between relative increases in MBV and BF in both CA and SMA ($r = 0.87$ and $r = 0.83$, respectively) in the present study.

Increased central circulation and/or decreased peripheral circulation other than splanchnic organs can increase splanchnic BF. To test the contribution of the HR and BF in the forearm to splanchnic hyperemia, the relation between changes in HR and BF in the forearm and the change in BF in CA and SMA was investigated in a postprandial data set of 12 measurements in all subjects using multiple regression analysis. There was significant correlation between BF in CA and HR ($r = 0.37$), suggesting that central circulation plays a role for an increase in CA BF. There was also significant correlation between BF in SMA and BF in the forearm ($r = -0.27$). This result seems to imply an association between the decrease in forearm BF and an increase in SMA BF; however, during a control trial, that is, 70 min of rest without a meal, forearm BF also decreased. A possible factor in decreasing BF in the forearm could be repetitive cuff occlusion and release. So, this study could not draw a clear conclusion about these points.

There was no significant correlation between HR and SMA BF. This implies that the increase in central circulation did not contribute to the increase in SMA BF.

In conclusion, we examined the effect of a meal on the splanchnic circulation, and confirmed earlier increase of MBV in the CA and SMA than in previous studies. These increases were induced by the local vasodilatation response. We suppose that the BF response in the splanchnic organs starts increasing before the digestive chyme reaches the corresponding organs.

Perspectives and Significance

The determination of postprandial responses in splanchnic BF should provide useful information for future studies around the field of neural control of cardiovascular system during and after food intake in physiological and clinical standpoints. The present study could provide fundamental information to investigate the digestive mechanisms in health and disease.

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