Intestinal phase of superior mesenteric artery blood flow in man

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Abstract
Duplex ultrasound was used to investigate superior mesenteric artery haemodynamics in humans in order to study the contribution of the small intestine to the postprandial splanchnic hyperaemia, and to determine the relative potencies of the major food components in the postprandial mesenteric flow response. Duplex parameters of vessel diameter, mean velocity, and volume flow were determined serially in the basal state and after stimulation. Flow parameters were significantly (p<0.05) increased after liquid and solid oral meals. Modified sham feeding did not alter mesenteric blood flow. Intestinal perfusion of an isocaloric liquid test meal induced flow shows comparable changes with oral intake. Superior mesenteric artery blood flow also significantly (p<0.05) increased after isocaloric and iso-osmolar loads of intraduodenal carbohydrate, fat, and protein meals. Responses were similar after the test meal, fat, and protein, but were significantly (p<0.05) less for carbohydrates. Different osmolar loads of saline did not affect flow responses. We conclude that the intestinal phase is the major regulator of the postprandial mesenteric blood flow response in healthy humans and that the chemical nature of food determines the mesenteric response pattern.

Interest in the intestinal circulation has grown very rapidly in recent years, but data in man have been rare because of technical problems in measuring splanchnic blood flow in humans. The introduction of the ultrasonic pulsed Doppler technique (duplex scanning) for mesenteric blood flow measurements has made it possible to study the relation between intestinal function and intestinal blood flow in health and disease. The method is non-invasive, and gives consistent and reproducible results after physiological stimuli such as food intake.

The intake of food results in an increase in superior mesenteric artery blood flow (SMABF) in man after liquid meals. The relative contribution of different food components to the postprandial mesenteric blood flow has, however, not been thoroughly investigated up to now in humans. There are extensive data from animal experiments. From these, it is clear that the hydrolytic products of food digestion are primarily responsible for the food induced hyperaemia. Considerable variations in the magnitude of the intestinal vascular responses have been reported in these various experiments. The response seems to be greater in conscious than in anaesthetised animals. Likewise, various increases have been reported in conscious dogs after a variety of test meals. The different responses observed may be related to meal composition, the method used to measure blood flow, or they could be the result of species differences.

The primary objective of this study was to investigate the contribution of the small intestine to postprandial splanchnic hyperaemia and to determine the relative potencies of the major nutrient stimuli in healthy human subjects.

METHODS
Subjects
Six healthy male volunteers, aged 21–27 years (mean 23 years), and with body weights averaging 64 kg (range 58–76 kg) were studied on different days and in random order in the morning after overnight fasting in resting conditions, lying in the supine position. Each subject was within 10% of his ideal body weight, and none was taking any medication or had a history of gastrointestinal or endocrine disorder. The studies were approved by the local Ethical Human Research Committee on 16 October 1987, and informed consent was obtained in each case.

EXPERIMENTAL DESIGN
The examinations were started after overnight fasting with the subjects at rest for 30 minutes. SMABF was measured by the duplex technique consisting of a real time sector scanner (3.5 MHz) and a pulsed Doppler flowmeter (3.0 MHz) (Diasions DRF-400, CRV). The vessel of interest can be identified with the real time B-mode image. The B-mode picture allows detection of anatomical variations and measurement of the diameter of the artery. It is also used to adjust the size of the sample volume of the Doppler beam into the artery and to ascertain the angle between the incident Doppler beam and the long axis of the vessel. The orientation of the Doppler beam, the Doppler angle, and the sample volume are electronically displayed on the screen. The Doppler signals are analysed by real time spectrum analyser that employs a digital fast Fourier transform technique. With the Doppler equation, the system then computes the blood flow velocity. The instantaneous velocity as well as the mean velocity can be determined by the software. The product of the mean velocity and the cross-sectional area of the vessel lumen then yields the volume flow. To achieve accurate measurements, the vessel must follow a straight course of about 2 cm and no bifurcation should be present.

In all studies, SMABF was measured at 15 minute intervals, with measurements being performed while the subject was holding his breath.
The superior mesenteric artery was identified and the diameter measured 1 to 2 cm distally to its origin but proximally to the first side branches. The ECG-triggered diameter was recorded before the pulsed Doppler beam that encompassed the vessel lumen was placed. At each time point, three separate measurements of the diameter and time averaged velocity (TAV) were performed and the results were averaged. The TAV was computed from the envelope of the Doppler spectra over three heart beats with the software of the duplex unit. Blood pressure and heart rate were monitored throughout in all studies.

**EXPERIMENTAL PROCEDURE**

**Ingestion of a liquid test meal**
All subjects ingested 270 ml of a liquid test meal (Ensure plus) after a basal period. The meal contained 16.7% protein, 30% fat, and 53.3% carbohydrate giving a total caloric value of 405 kcal (equivalent to 1648 kJ). The osmolarity of the meal was 442 mOsm/l and pH 7.0. SMABF was recorded during a 30 minute basal period and after the test meal at 15 minute intervals.

**Infusion of the liquid meal into the duodenum**
In this part of the study, volunteers swallowed a double lumen duodenal tube which was positioned under fluoroscopic observation. The duodenum was perfused at the site between the second and third portion. The gastric openings were placed in the antrum and used for continuous aspiration of gastric contents. After a basal period, the test meal (Ensure plus), containing polyethylene glycol 4000 (PEG4000) as a non-absorbable marker, was infused over 90 minutes into the duodenum at a rate of 3 ml/minute. This perfusion rate was used to simulate the rate of gastric emptying of a liquid meal. Gastric contents were continuously aspirated and the PEG4000 concentration in the pooled contents was measured. The percentage of reflux of the duodenal contents into the stomach was measured by recovery of PEG4000 in the gastric aspirate.

**Ingestion of a solid meal**
The meal consisted of two sandwiches - 120 g bread with 20 g butter and 100 g ham, giving a total caloric value of 547 kcal (equivalent to 2289 kJ). Care was taken to prevent the subjects from seeing or smelling the food before the meal. The sandwiches were eaten within 30 minutes and SMABF was recorded at 15 minute intervals.

**Modified sham feeding**
The same meal was used for modified sham feeding, which was performed with a technique previously described. 16 Saliva was expectorated.

**Small intestine studies**
Subjects swallowed a double lumen duodenal tube described above. All test solutions contained PEG4000 to quantitate reflux of the perfusates into the stomach. The duodenum was perfused between the second and third portion as described earlier. On different days, and in random order, the following experiments were performed after a 30 minute basal period: isocaloric solutions (178 kcal/l) of Ensure plus, carbohydrate, fat, and protein were used. All solutions were adjusted to pH 7.4 and had an osmolarity of 280 mOsm/l (Table I). In all the experiments, the perfusion rate was 5 ml/minute giving a caloric load of 53.4 kcal per hour. Normal saline and a hyperosmolar solution of saline (560 mOsm/l) were also tested in further experiments. Gastric contents were aspirated as described above to quantitate duodenal reflux into the stomach. SMABF was recorded at 15 minute intervals.

**Materials**
Ensure plus was purchased from Abbott Co Ltd, Zug, Switzerland, Intralipid from Globopharm, Künzacht, Switzerland, and bovine serum albumin (>96% pure) from Fluka, Buchs, Switzerland.

**Data analysis**
The blood flow responses (SMABF) were expressed as percentages of basal responses to normalise for variations in basal SMABF measurements. For each subject and each test, the area under the blood flow curve (AUC) for the various stimulants over basal values was then calculated. Group means (SEM) were determined from these individual subject values and used for statistical analysis. Diameter and TAV are expressed as mean (SEM). The significance of differences between the AUC or between mean values was tested using Student's paired t test. Differences were considered significant if p was <0.05. Furthermore, analysis of variance for repeated measures were used to analyse the data.

**Results**

**MEAL STUDIES**
Basal SMABF measurements were similar for each of the studies. The mean increase in SMABF in response to the oral intake of both a liquid or a solid meal is shown in Figure 1. An immediate and marked increase in mesenteric blood flow was observed, and the maximum was reached within 45 minutes of taking either meal. Sixty minutes after food intake, SMABF decreased gradually, but was still significantly (p<0.05) above basal values at the end of the experiments. The increase in blood flow was mainly the result of an increase in velocity, as sharp increases (p<0.05) in TAV were seen after both liquid and solid food intake (Table II). Liquid and solid oral test meals induced small but significant (p<0.05) increases in vessel diameter amounting to 16 (1%) and 13 (2%) (mean (SEM)) respectively (data not shown).

Intraduodenal perfusion of the liquid test meal induced a significant increase of SMABF, reaching a steady state within 30 minutes of starting the meal perfusion. The increase in mesenteric blood flow was sustained for the duration of the experiment. Perfusion of the liquid test meal caused a mean (SEM) increase in vessel diameter of 11 (2%) (data not shown) and a sharp increase in the mean TAV (Table II).
TABLE I  Intestinal perfusates

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Omolality (mOsmal)</th>
<th>pH</th>
<th>kcal</th>
<th>Concentration (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed test meal</td>
<td>Carbohydrate</td>
<td>280</td>
<td>7-4</td>
<td>178</td>
</tr>
<tr>
<td>Fat</td>
<td>Protein</td>
<td>6-3</td>
<td>7-8</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Glucose</td>
<td>280</td>
<td>7-4</td>
<td>178</td>
</tr>
<tr>
<td>Fat</td>
<td>Intrapalipid*</td>
<td>280</td>
<td>7-4</td>
<td>175</td>
</tr>
<tr>
<td>Protein</td>
<td>Rovine albumin</td>
<td>280</td>
<td>7-4</td>
<td>178</td>
</tr>
<tr>
<td>Normal saline</td>
<td>None</td>
<td>380</td>
<td>7-4</td>
<td>0</td>
</tr>
<tr>
<td>Hypertosmolar saline</td>
<td>None</td>
<td>360</td>
<td>7-4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Composition as indicated by the manufacturer: 22:3 g glycerol; 12 g lecithin; soya oil 200 g; dissolved in 1000 ml water.

TABLE II  Blood flow velocities in the superior mesenteric artery in response to different types of meal stimulation in healthy subjects (mean (SEM))

<table>
<thead>
<tr>
<th>Time averaged velocity (cm/s)</th>
<th>Fasting</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral liquid meal</td>
<td>29-7 (1-0)</td>
<td>79-4 (6-9)</td>
<td>62-4 (5-3)</td>
<td>49-6 (4-7)</td>
</tr>
<tr>
<td>Oral solid meal</td>
<td>23-2 (0-6)</td>
<td>52-9 (2-9)</td>
<td>36-9 (3-4)</td>
<td>47-7 (0-3)</td>
</tr>
<tr>
<td>Intraluminal liquid meal</td>
<td>33-0 (2-3)</td>
<td>65-2 (5-0)</td>
<td>63-4 (7-2)</td>
<td>63-0 (7-8)</td>
</tr>
<tr>
<td>Sham feeding</td>
<td>24-2 (0-9)</td>
<td>26-2 (2-2)</td>
<td>25-7 (1-2)</td>
<td>27-4 (2-0)</td>
</tr>
</tbody>
</table>

N=6 for oral and intraduodenal liquid meal, and n=4 for solid meal and sham feeding experiments.

TABLE III  Blood flow velocities in the superior mesenteric artery in response to intestinal perfusion (0-90 minutes) of isocaloric and isovolemic nutrient solutions in six healthy subjects (mean (SEM)). The caloric load was 53-4 kcal per hour

<table>
<thead>
<tr>
<th>Time averaged velocity (cm/s)</th>
<th>Fasting</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed test meal</td>
<td>28-0 (1-0)</td>
<td>39-2 (4-1)</td>
<td>36-5 (4-3)</td>
<td>34-9 (3-1)</td>
<td>28-7 (2-3)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>27-0 (0-2)</td>
<td>39-9 (2-7)</td>
<td>29-5 (2-5)</td>
<td>30-9 (2-4)</td>
<td>25-2 (0-5)</td>
</tr>
<tr>
<td>Fat</td>
<td>26-7 (0-8)</td>
<td>42-7 (6-3)</td>
<td>40-2 (4-0)</td>
<td>33-5 (3-1)</td>
<td>27-4 (1-9)</td>
</tr>
<tr>
<td>Protein</td>
<td>27-4 (0-8)</td>
<td>36-0 (2-3)</td>
<td>37-6 (2-5)</td>
<td>37-6 (4-4)</td>
<td>34-3 (2-0)</td>
</tr>
<tr>
<td>Iso-osmolar saline</td>
<td>25-2 (0-8)</td>
<td>26-6 (2-0)</td>
<td>26-2 (1-2)</td>
<td>24-3 (1-1)</td>
<td>25-4 (1-7)</td>
</tr>
</tbody>
</table>

Sham feeding caused only a small increase in SMABF over basal values (Fig 1).

**Discussion**

In this study, the effects of various components of food on human SMABF were investigated by perfusing isocaloric, isovolemic, and isosmolar loads of carbohydrate, fat, protein, and a test meal into the duodenum on different days in the same group of healthy volunteers. The results were compared with the SMABF responses after oral intake of liquid and solid test meals and with modified sham feeding. The results of the study can be summarised as follows:

1. **SMABF increased significantly after liquid and solid meals. The maximal responses were of similar magnitude.**

2. **Modified sham feeding did not affect SMABF.**

**Figure 1:** Doppler calculated volume flow through the superior mesenteric artery before and after intake of a liquid test meal (n=6), a solid meal (n=4), a liquid test meal perfused to the duodenum (n=6), and after modified sham feeding (n=4) in healthy subjects. Volume flow is expressed as percentage of the fasting value (mean (SEM)). Basal superior mesenteric artery blood flow ranged from 318 to 505 ml/minute (median: 389 ml/minute) and did not significantly differ in the various experiments.

**Figure 2:** Superior mesenteric artery blood flow response to intraduodenal perfusion of different food components or saline in six healthy subjects. Doppler calculated volume flow is expressed as percentage of the fasting value (mean). Basal superior mesenteric artery blood flow ranged from 336 to 466 ml/minute (median: 393 ml/minute).
(3) Intestinal perfusion of the liquid test meal induced an increase in SMABF of similar magnitude to that observed with oral intake.

(4) SMABF increased significantly after iso-caloric and iso-osmotic loads of intraduodenal carbohydrate, fat, and protein meals. The maximal responses were of similar magnitude after the test meal, fat, and protein, but significantly less after carbohydrate. Two different osmolar loads of saline did not affect SMABF.

Little is known about the regulatory mechanisms of human intestinal blood flow dynamics because of the practical and technical difficulties involved in measuring splanchnic blood flow in man. Thus, it is not surprising that only a limited number of papers have been published on this subject. An increased awareness of the role of intestinal circulation in the pathogenesis of gastrointestinal diseases has led to a greater emphasis on the development of techniques adaptable for intestinal blood flow measurements in humans. Transcutaneous Doppler ultrasound is one of the newly applied techniques for measuring blood flow in the major gastrointestinal arteries. The method is reproducible and can detect changes in blood flow after physiological stimuli such as food intake or exercise. Accurate measurements with this technique require, firstly, precise measurements of the diameter of the vessel of interest by real time ultrasonography. Secondly, precise determination of mean blood flow velocity depends on accurate adjustment of the sample volume of the pulsed Doppler beam in the vessel of interest to minimise and correct the angle between the incident Doppler beam and the long axis of the vessel. In vitro and in vivo calibrations of this method have, however, indicated an acceptable level of accuracy. Two papers describing the potential sources of error in the intestinal vascular bed have recently been published by Moneta et al. and the Bologna study group. Both groups conclude that duplex ultrasound provides us with a non-invasive method of serially examining splanchnic arterial blood flow in humans and that the technique should be extremely helpful in investigating the physiological control of the human mesenteric circulation.

In this study, we have shown that food in the upper small intestine accounted for most of the mesenteric response to ingestion of the same meal. Furthermore, modified sham feeding did not change SMABF, suggesting that a cephalic phase of SMABF is not operative in healthy human subjects. Also, as less than 2% of the marker was recovered from the stomach in the various perfusion experiments, it is unlikely that the observed stimulation is the result of a gastric phase of reflux of perfused nutrients into the stomach. These findings suggest that the duodenum and the small intestine play a major, perhaps even predominant, role in regulating postprandial SMABF in humans. The results are, in principal, similar to observations in conscious animals where the anticipatory phase of digestion does not alter intestinal blood flow, but a significant increase in flow is observed 30 to 90 minutes after ingestion of a meal, suggesting that the upper small bowel mainly regulates postprandial blood flow.

The effect of the chemical nature of nutrients on postprandial mesenteric hyperaemia has been studied before and the results have been contradictory. In 1955, Brandt et al reported that splanchnic blood flow increased after a protein meal, but not after glucose. In contrast to these early results, Norryd et al showed a significant increase in SMABF after perfusion of glucose into the jejunum of normal subjects. Recently, different groups have studied oral ingestion of various food components on SMABF in man by using non-invasive, transcutaneous Doppler ultrasound to quantify the responses. The results of these studies indicated that the chemical nature of the meal rather than its volume determines the magnitude of the postprandial mesenteric hyperaemia. In both studies, the different food components were given orally. As the authors did not assess gastric emptying, nothing can be said about the various phases regulating the postprandial mesenteric response. SMABF increased significantly after iso-caloric, isoosmotic, and iso-osmolar loads of carbohydrate, fat, and protein perfusion. The responses after fat and protein were comparable, whereas the response to glucose was significantly lower. Neither iso-osmolar nor hyperosmolar saline increased SMABF. These findings indicate that the chemical nature of the meal and not the osmolality is responsible for the postprandial increase in mesenteric hyperaemia. The findings of the previous studies have to be interpreted in the light of the present studies. Qamar and Read reported similar maximal mesenteric blood flow responses to carbohydrate, fat, and protein, but responses to fat and protein were significantly slower than the response to carbohydrate. As the different meals were given orally and not controlled for gastric emptying, their results probably reflect to some degree differences in gastric delivery of food components to the duodenum or differences in digestive breakdown of the test meals. In our experiments, the caloric load was identical, the solutions were isotonic, and the perfusion rate equal, giving identical volumes perfused to the duodenum. The observed differences between the responses to glucose on one side and protein and fat on the other reflect the chemical nature of the various food components.

In conclusion, the intestinal phase seems to play a major role in determining postprandial mesenteric blood flow in healthy human subjects. Furthermore, the chemical nature of the food induces the pattern of the mesenteric response. Further experiments are required to define the mediators of these effects.

We thank Mrs Carita Frei for editorial assistance and for typing the manuscript. The study was supported by grants of the Schweizerische Stiftung fuer Kardiologie, the Swiss National Science Foundation (grant 3.890-0.88), and the Stanley Thomas Johnson Foundation. Part of this study was presented at the American Gastroenterological Association Meeting (Washington, May 1989).

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