# Rapid Publications

# Splanchnic and Peripheral Disposal of Oral Glucose in Man

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**SUMMARY**

**Oral glucose (92 g) was administered to 22 healthy, young volunteers undergoing hepatic vein catheterization, and net splanchnic glucose output (SGO) was measured during the basal period and for 4 h after glucose ingestion. In the basal state, SGO averaged 1.90 ± 0.11 mg/min · kg. After glucose, SGO rose to a peak value of 6.65 ± 0.83 mg/min · kg at 30 min and returned to baseline by 3 h. Total SGO over 4 h was 69 ± 4 g; assuming complete absorption of the load, this amount represented 75% of the oral glucose.**

**In a subgroup of six subjects, leg glucose uptake was simultaneously quantitated by femoral vein catheterization and leg blood flow measurement. In the postabsorptive state, glucose uptake by one leg was 24 ± 8 mg/min and increased to a mean value of 76 ± 7 mg/min during the 4 h after glucose ingestion. Overall, 18 ± 2 g/4 h of glucose were taken up by one leg, which extrapolates to a total body muscle uptake of 65 ± 4 g over 4 h.**

**We conclude that in normal man, well over ⅔ of an oral glucose load escapes splanchnic removal, and that the peripheral tissues quantitatively play the dominant role in glucose disposal. DIABETES *32*:675–679, July 1983.**

The splanchnic area has long been recognized to play a central role in glucose homeostasis. A number of investigations, carried out in several animal species and using a variety of experimental techniques,[1–5] have suggested that the majority of a glucose load is eventually disposed of within the splanchnic bed; contrary evidence also has been reported.[6–8] It should be noted, however, that the aforementioned studies utilized indirect techniques in assessing glucose disposal. Felig and Wahren, using the hepatic vein catheterization technique in man, provided the first direct evidence to support the quantitatively predominant contribution of the splanchnic tissues in overall glucose disposal.[9] In the 10 normal subjects that they studied, they found that 40 g of an oral load of 100 g of glucose escaped splanchnic trapping in the 3 h after ingestion, from which it was concluded that 60% of the load was retained by the liver. In a series of studies performed in the same laboratory with the use of the hepatic vein catheter technique, we showed that intravenously administered glucose is taken up by the splanchnic bed to a very limited extent, even under rather unphysiologic conditions of hyperinsulinemia and hyperglycemia.[10] In subsequent studies we administered an oral glucose load after 1 h of sustained hyperglycemic hyperinsulinemia created by intravenous glucose administration (hyperglycemic clamp technique). Compared with intravenous glucose alone, combined oral/intravenous glucose administration resulted in a marked augmentation in splanchnic glucose uptake.[10] By comparing our results from intravenous glucose administration alone with our results from combined intravenous/oral glucose[10] and with previously published results using oral glucose alone,[9] we hypothesized the existence of a "gut factor" that specifically enhances the splanchnic uptake of oral glucose.[11,12] This idea has been challenged over the past few years[13,14] on the basis of results obtained in the dog. Although we too have accumulated evidence in our laboratory that in the dog oral and intravenous glucose are handled in a like manner [Barrett, E., Ferrannini, E., Gusberg, R., Bevilacqua, S., Reichard, G., and DeFronzo, R. A.: Hepatic and extrahepatic splanchnic glucose metabolism following intravenous and oral glucose administration in the dog. (In preparation.)], we thought that the controversy could only be resolved by reexamining *in man* the fate of oral glucose. We therefore undertook the present study in which a large number of healthy subjects underwent hepatic vein catheterization and received an OGTT. To further trace the disposition of the glucose escaping splanchnic retention, in a subgroup of subjects femoral vein catheterization was combined with the measurement of splanchnic glucose balance.

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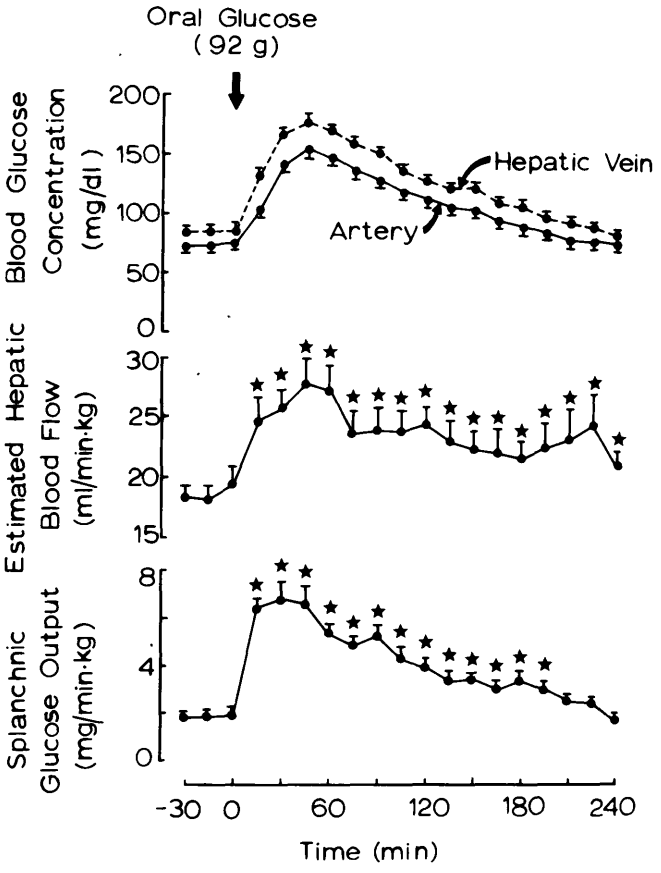


**FIGURE 1. Time course of blood glucose concentration, estimated hepatic blood flow, and net splanchnic glucose output in 22 normal subjects after the ingestion of an oral glucose load. Vertical bars indicate SEM. Stars denote that the mean values are significantly different ($P < 0.05$ or less) from the mean basal values (paired *t* test).**

## MATERIALS AND METHODS

**Subjects.** Twenty-two healthy volunteers, 7 women and 15 men, participated in the study. Their ages ranged from 19 to 33 yr (mean ± SEM = 23 ± 1 yr), their body weight was 69 ± 1 kg (ideal body wt = 104 ± 3% according to the Metropolitan Life Insurance Co. Tables, 1959). All subjects were consuming a weight-maintaining diet containing at least 200 g of carbohydrate per day for 3 days before the study. No subject had a positive family history for diabetes mellitus or other endocrine or organ system disease; none were taking any medication. The purpose, nature, and potential risks of the study were explained in detail to all subjects before obtaining their written consent to participate. The study protocol was reviewed and approved by the Human Investigation Committee at Yale University School of Medicine.

**Experimental protocol.** All studies were performed at 8 a.m., after a 10–12-h overnight fast. Under local anesthesia with 1% lidocaine, the femoral artery was punctured with an 18-gauge thin-wall needle, and a 3.7 or 4.0 French Teflon catheter was introduced. The catheter tip was positioned fluoroscopically at the level of the inferior end of the sacroiliac joint, so that it remained distal to the origin of the internal iliac artery. The catheter was connected to a high-pressure infusion bag to maintain patency. The femoral vein was similarly punctured, and a 6.5 French polyethylene catheter was advanced via the inferior vena cava into the right-sided hepatic vein under fluoroscopic control. The catheter was advanced into a wedge position and then withdrawn 1–2 cm. The hepatic catheter had an end-hole and a single side-hole proximal to the tip. One milliliter of contrast medium was injected to visualize the tip of the catheter and to ensure that it was positioned in an area of adequate blood flow. The catheter was kept open by a slow drip of isotonic saline.

Hepatic blood flow was estimated in all experiments by a primed-continuous infusion of indocyanine green (Hynson, Westcott and Dunning, Baltimore, Maryland) as previously described.[9] The dye infusion was started via an antecubital vein 75 min before glucose ingestion, and continued throughout the study. Blood was sampled simultaneously from the artery and the hepatic vein at 10-min intervals starting 45 min after the beginning of green dye infusion. At time zero, all subjects ingested 300 ml of a 30% aqueous glucose solution (Dextol, American Scientific Products, McGaw Park, Illinois) over 5 min; the glucose content was checked on every individual drink, and was found to average 92 ± 1 g. Arterial and hepatic venous blood was then sampled at 15-min intervals for 4 h after glucose ingestion.

In six subjects, the above procedure was modified to allow simultaneous sampling from the femoral vein. At the time of the femoral vein puncture, a 7.0 French dilator, surrounded by a thin plastic sheath 12 cm in length with a sidearm, was introduced. An adjustable washer at the external end of the sheath prevented leakage of blood or entrance of air between the dilator and the sheath. The dilator was then removed and the hepatic vein catheter was introduced through the sheath and advanced into the hepatic vein as described above. The tip of the sheath was positioned in the external iliac vein, peripheral to the termination of the internal iliac vein. Both the hepatic vein catheter and the sidearm of the sheath were perfused with isotonic saline to maintain patency of the lumina. A small plastic cannula was inserted into an antecubital vein to allow quantitation of recirculating green dye. Blood was drawn simultaneously from the femoral artery, hepatic vein, and the femoral vein every 15 min. Leg blood flow was estimated every 60 min as described by Jorfeldt and Wahren.[15] Leg volume was calculated as previously described.[16]

Blood glucose concentration was measured by the glucose-oxidase method using a Yellow Springs Analyzer Model 23A (Yellow Springs, Ohio). Plasma insulin concentration was measured by radioimmunoassay as previously described.[10] Plasma green dye levels were measured spectrophotometrically.

**Calculations.** Hepatic plasma flow was calculated by dividing the green dye infusion rate by the arteriohepatic venous dye concentration difference. A space correction was applied for changes in arterial green dye levels. Hepatic blood flow was estimated by dividing hepatic plasma flow by (1 − hematocrit). Splanchnic glucose output (SGO) (or net splanchnic glucose balance) was calculated as the product of estimated hepatic blood flow and the arteriohepatic venous blood glucose concentration difference. The cumulative net output of glucose from the splanchnic area was computed as the integral of SGO between time zero and

240 min. Integration was performed by the trapezoidal rule. Similar calculations were carried out to quantitative leg glucose uptake.

All data are expressed as the mean ± SEM. Mean values were compared by *t* test analysis, paired or unpaired as appropriate.

## RESULTS

The fasting blood glucose concentration was 75 ± 1 mg/dl. After glucose ingestion, it rose to a peak of 156 ± 6 mg/dl at 45 min, and by the end of the study had returned to basal values (77 ± 4 mg/dl).

Mean basal plasma insulin concentration was 14 ± 1 μU/ml. After glucose, arterial insulin levels increased eightfold, reaching peak values at 45 min. The mean arterial insulin concentration during the entire absorptive period was 70 μU/ml ($P < 0.001$ versus basal).

Blood glucose levels were higher in the hepatic vein than in the artery at all timepoints, both in the basal state and after glucose ingestion (Figure 1). Estimated hepatic blood flow averaged 18.8 ± 1.2 ml/min · kg (or about 1300 ml/min) in the postabsorptive state, rose to a peak value of 28.0 ± 2.3 ml/min · kg at 45 min (a 50% increase), and remained significantly elevated throughout the study (Figure 1). Splanchnic glucose output rose from a basal value of 1.9 ± 0.11 mg/min · kg to a peak value of 6.65 ± 0.83 mg/min · kg at 30 min ($P < 0.001$), and it was not until 3 h after glucose ingestion that it had returned to baseline (Figure 1). The mean total SGO over 4 h was 69 ± 4 g (Table 1).

In the six subjects undergoing simultaneous hepatic vein and femoral vein catheterization, the splanchnic glucose balance data were similar to those of the whole group of volunteers. Basal SGO was 1.93 ± 0.31 mg/min · kg and over the course of the 4 h after glucose ingestion the cumulative SGO was 61 ± 7 g. In the postabsorptive state, leg blood flow averaged 54.6 ml/min · kg leg wt and showed no significant change after glucose ingestion. Glucose levels in arterial blood exceeded those in the femoral vein at all time intervals (Figure 2). From these data, basal leg glucose uptake was calculated to be 24 ± 8 mg/min; this value rose fourfold 30 min after oral glucose, and remained significantly elevated above basal throughout the study (Figure 2). The total glucose uptake by one leg over the 4 h after glucose was 18 ± 2 g. Leg volume averaged 11.6 ± 0.45 L.

## DISCUSSION

In the healthy volunteers in the present study, a total of 69 ± 4 g of glucose over 4 h (and 56 ± 3 g over 3 h) escaped splanchnic retention after the ingestion of 92 g. This result

TABLE 1
Splanchnic glucose output (SGO) in 22 normal subjects in the basal state and following glucose ingestion

| SGO | Mean ± SEM |
|---|---|
| Basal | 1.90 ± 0.11 mg/min · kg |
| | 31 ± 2 g/4 h* |
| Total over 4 h | 4.19 ± 0.26 mg/min · kg |
| | 69 ± 4 g/4 h |

*Assuming that basal SGO remained unchanged during the 4-h study period.

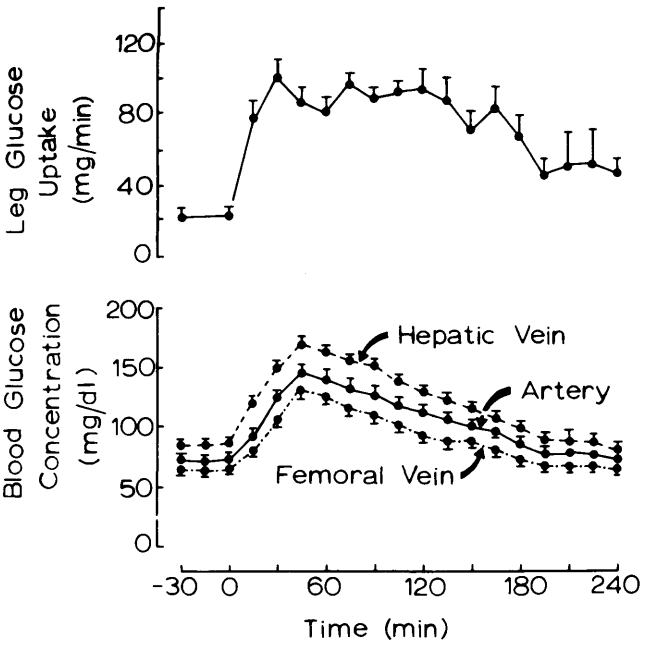


**FIGURE 2. Time course of leg glucose uptake and blood glucose concentration from the hepatic vein, femoral artery, and femoral vein in six subjects after the ingestion of an oral glucose load. Vertical bars indicate SEM. All mean values for leg glucose uptake were significantly different ($P < 0.05$ or less) from the mean basal values (paired *t* test).**

is remarkably different from that in the study by Felig and Wahren[9] where only 40 ± 2 g of a 100-g glucose load were recovered in the hepatic vein during 3 h. The reasons for this discrepancy are not clear, but may be partly related to interindividual variation in glucose absorption and to the small number of subjects in the previous study.[9] The previous authors also used a commercially available glucose solution, which most likely contained only 90–92 g of glucose (not 100 g). In addition, the study duration (2½–3 h) was short and it is likely that a significant portion of the oral glucose load was not absorbed.[22,23] If we assume that only 90 g was administered and of this only 70% was absorbed, then it can be calculated that approximately 36% of the oral glucose load was retained within the splanchnic bed (63 g ± 40 g/63 g × 100). The result is quantitatively more similar to the present findings.

The subjects in the present study were young, healthy volunteers of normal body weight. The experimental design, the amount of glucose given, and the techniques for blood sampling and hepatic blood flow estimation were similar to previous studies.[9,17,18] Special care was taken in the present investigation that the volunteers not be stressed; splanchnic measurements were begun 90 min after the insertion of the catheters, when subjects were lying comfortably on a bed out of the catheterization room, reading, sleeping, or chatting with one of us.

The present data with oral glucose alone (small splanchnic glucose uptake) also are different from our previous results[10,12] using combined intravenous/oral glucose administration (large splanchnic glucose uptake). To ensure that the observed difference in splanchnic glucose disposal did not result from differences in experimental technique, we

have studied three young healthy subjects in New Haven using the same experimental protocol as employed in Sweden.[10] After 1 h of sustained hyperglycemic hyperinsulinemia (+125 mg/dl hyperglycemic clamp), an oral glucose load was administered and subjects were followed for an additional 4 h. We calculated that 55 ± 7% of the oral glucose load was retained within the splanchnic bed. This is twice as great as the 25% observed in the present study. We interpreted these data to indicate that the oral route of glucose administration had a specific effect to enhance splanchnic glucose disposal.[10–12] We also acknowledged the possibility that incomplete gastrointestinal absorption could alter the interpretation of our results.[12] Thus, if preexisting hyperglycemia and/or hyperinsulinemia were to inhibit glucose absorption during our intravenous/oral studies,[10] the contribution of the splanchnic tissues to overall glucose disposal would be overestimated. To resolve this question would require portal vein catheterization. Whether or not there is enhanced splanchnic glucose uptake after combined intravenous/oral glucose administration, the present results clearly indicate that when glucose is ingested under postabsorptive conditions peripheral, not splanchnic, tissues play the predominant role in glucose disposal.

The values for estimated hepatic blood flow and basal splanchnic output in the current experiments are superimposable with those reported in other studies using the hepatic vein catheterization technique.[9,16–20] With regard to the effect of oral glucose on SGO, Bratusch-Marrain et al. reported a cumulative splanchnic glucose output of 40 g after 2 h in one study,[17] and of 56 g after 2½ h in another study[18] after the ingestion of 100 g in young volunteers. Although the latter results match ours quite well (38 g over 2 h, and 50 g over 2½ h in the present experiments), they have been interpreted as indicative of predominant splanchnic disposal of oral glucose.[17] The rationale for this conclusion has been that, if total SGO amounts to 40 g, of which 15 g is basal, then only 25 g escape splanchnic trapping while the remainder of the load (100 − 25 = 75 g) is retained. This calculation would be correct if basal SGO continued at unchanging rates throughout the absorptive period and if absorption of the oral load from the gastrointestinal tract were complete within 2–3 h. Neither of these conditions appears to be satisfied. Splanchnic glucose release has long been known only to be partly inhibited by glucose-induced portal hyperinsulinemia;[21] this inhibition has been estimated to average 60% over the 4 h after the ingestion of 100 g of glucose in healthy man.[22,23] Glucose absorption from the intestine, on the other hand, has not been measured in any human studies that have employed the hepatic vein catheterization technique. However, tracer experiments[22] have indicated that complete absorption of a large oral load of glucose may take considerably longer than 2–3 h. Recent studies using indirect calorimetry[24] are in agreement with these tracer studies. The implication of these observations is that, if a significant portion of the oral glucose load is not absorbed, then the "percentage" of the glucose load retained within the splanchnic bed will be grossly overestimated. It should be emphasized that the hepatic vein catheter technique only measures a *net* balance across organs that receive glucose at variable rates (from the circulation and from the intestine) and concomitantly secrete glucose at changing rates (residual hepatic production).

In the present experiments, splanchnic glucose output was followed for a long period (4 h) in an attempt to ensure that the majority of the oral glucose load was absorbed. The results unequivocally indicate that the splanchnic tissues play a lesser quantitative role than the peripheral tissues in the disposal of oral glucose. In our subjects, 75% of the ingested glucose went to the periphery. If one assumes that hepatic glucose production was continuing at a rate that averaged about half that of basal (15 g/4 h) during the absorptive period,[21] still 60% (69 − 15/92)* of the oral load would be disposed of by extrasplanchnic tissues. Direct confirmation of these data is provided by the concurrent measurements of leg glucose uptake in six subjects in the present study. Leg glucose uptake was significantly stimulated above basal values throughout the absorptive period (Figure 2). If one assumes that most of the glucose taken up by leg tissues in man occurs in muscle,[25] leg glucose uptake can be extrapolated to total body muscle uptake assuming that muscle represents 64% of leg volume[26] and total muscle is 40% of body weight.[25] We can thus calculate that in our volunteers a total of 65 ± 4 g of glucose (or 71% of the ingested load) was eventually taken up by peripheral tissues (primarily muscle) during the 4 h after glucose ingestion. This estimate fits well with the net amount of glucose escaping the splanchnic bed in the same subjects.

In summary, the hepatic and femoral vein catheterization results are internally consistent and indicate that peripheral, not splanchnic, tissues play the predominant role in the disposal of an oral glucose load.

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*Where 92 g = ingested glucose load; 69 g = net amount of glucose appearing in the hepatic vein over 4 h; 15 g = residual hepatic glucose production over 4 h post glucose ingestion.

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