Comparison of Peripheral and Portal Venous Insulin Administration on Postprandial Metabolic Responses in Alloxan-Diabetic Dogs

Effects of Identical Preprogrammed Complex Insulin Infusion Waveforms

U. FISCHER, R. A. RIZZA, L. D. HALL, R. E. WESTLAND, M. W. HAYMOND, A. H. CLEMENS, J. E. GERICH, AND F. J. SERVICE

SUMMARY

The optimal route for insulin administration by insulin infusion devices has not been established. To assess the differences between the peripheral venous and portal venous routes of insulin administration on postprandial metabolic responses, six alloxan-diabetic dogs were studied on four occasions. On the first, the insulin infusion rates given by the Biostator for disposal of a mixed meal were recorded electronically. On two subsequent occasions, these insulin infusion profiles were administered by a peripheral vein. On an additional occasion, the identical insulin infusion profile was given via the portal vein. No differences were observed in basal or peak plasma glucose, insulin, glucagon, branched chain amino acids, and lactate concentrations between portal and peripheral venous insulin administration. Furthermore, no differences in isotopically ([2-^{3}H]glucose) determined rates of systemic glucose appearance and disappearance were observed between the two routes. Although preprandial plasma alanine concentrations were greater when insulin was infused via the portal vein, the postprandial increments did not differ from those observed during infusion of insulin by a peripheral vein. These studies suggest that under the current experimental conditions, there appears to be no difference in the disposition of a mixed meal, measured as net whole body glucose appearance and disappearance rates, when insulin is administered in an open-loop fashion via either a peripheral or the portal vein. DIABETES *31*:579–584, July 1982.

It is not known whether optimal metabolic control of diabetes mellitus by open-loop devices necessitates administration of insulin into the portal vein. Since the liver plays a major role in the disposal of an oral glucose load,[1–4] secretion of insulin into the portal vein, which occurs under normal physiologic conditions, would be expected to have a primary effect on hepatic glucose disposal. In contrast, infusion of insulin into a peripheral vein, and the consequent relative peripheral hyperinsulinemia such as occurs with the use of closed-loop systems, may result in glucose uptake primarily in extrahepatic tissues.[5–7] Since the liver is more sensitive to changes in insulin concentrations than are the peripheral tissues, intraportal insulin delivery may result in glycemic control with smaller amounts of insulin than peripheral venous delivery and avoidance of peripheral hyperinsulinemia.[8]

Data supporting the above postulates are limited since measurements have generally been limited to plasma glucose concentrations without determining changes in glucose production and utilization. Several studies have demonstrated comparable decreases in glycemia when identical doses of insulin were given into the portal and a peripheral vein of man and animals.[4,9–13] Moreover, glycemic patterns, insulin infusion rates, and peripheral insulin concentrations were equivalent in diabetic dogs following an intravenous glucose challenge when insulin was infused into the portal or peripheral vein using a closed-loop system.[14] However, differences in the patterns of hepatic and extrahepatic glucose disposal between the portal and peripheral venous insulin administration would not be detected by measuring only peripheral venous plasma glucose concentration. Nevertheless, when pre- and postprandial glycemia was controlled by a closed-loop system using the peripheral and portal venous routes,[15] no difference in hepatic and extrahepatic glucose disposal was detected when insulin was infused by these two routes. In that study, the closed-loop system varied the insulin infusion in response to changes in plasma glucose concentrations. Thus, there is the possibility that subtle differences in insulin infusion rates during the portal and peripheral venous infusions may have obscured differences in glucose disposal. To test this hypothesis, rates of infusion of insulin

From the Endocrine Research Unit, Departments of Medicine, Pediatrics and Physiology, Mayo Medical School and Mayo Clinic, Rochester, Minnesota (R.A.R., L.D.H., R.E.W., M.W.H., J.E.G., F.J.S.); Life Science Instruments, Miles Laboratories, Inc., Elkhart, Indiana (A.H.C.); and Central Institute of Diabetes, Karlsburg, German Democratic Republic (U.F.).
Address reprint requests to Dr. F. J. Service, Mayo Clinic, Rochester, Minnesota 55901.
Received for publication 7 October 1981 and in revised form 18 February 1982.

by a closed-loop system for pre- and postprandial glucose control in alloxan-diabetic dogs were recorded on electromagnetic tape for each dog and readministered in an open-loop fashion to the same dog on three separate occasions before and after eating the same meal, twice via a peripheral vein and once via the portal vein. Plasma glucose, insulin, glucagon, lactate, and amino acid concentrations and rates of glucose appearance and disappearance were measured.

METHODS

Six adult mongrel (12–22.5 kg) alloxan-diabetic dogs were studied. They were fed a standard canine diet (Nutrena, Minneapolis, Minnesota) as one meal a day and were treated with two injections daily of intermediate-acting porcine insulin (Lente, Lilly, Indianapolis, Indiana). Each dog was shown not to augment plasma insulin concentrations following an intravenous injection of tolbutamide (0.5 g) and glucagon (0.25 mg). Under general anesthesia (pentobarbital sodium 28 mg/kg i.v.), a silastic catheter (Dow Corning Corp., Midland, Michigan) was inserted into a tributary of the splenic vein and advanced to the portal vein so that its tip lay approximately 1 cm distal to the porta hepatis. The catheter was filled with a dilute solution of heparin (120 U/ml: Abbott Laboratories, North Chicago, Illinois) and its distal end was ligated and placed in a subcutaneous pocket on the back in the paravertebral region. The intraportal location of the catheter was confirmed at postmortem examination after the conclusion of the series of experiments. The dogs were permitted a recovery period of not less than 2 wk before any studies were performed. On the day before the study, the intermediate-acting insulin was discontinued and the animals were treated with crystalline porcine insulin. On the morning of each study, short #18 gauge catheters (Jelco, Raritan, New Jersey) were placed percutaneously into two leg veins: one was used for infusion of isotope and insulin, the other for blood withdrawal for continuous glucose monitoring by the Biostator (Miles Laboratories, Elkhart, Indiana). A third catheter (Desert Pharmaceuticals, Sandy, Utah) was placed in a jugular vein and advanced to the superior vena cava for intermittent blood sampling. Euglycemia was achieved and maintained by the Biostator for at least 3 h before the test meal. During this period, a primed (5.5 μCi) continuous (0.05 μCi/min) infusion of [2-^{3}H]glucose (New England Nuclear, Boston, Massachusetts; specific activity 14.1 Ci/mM made up in 0.9% saline, 25 μCi/50 ml) was begun. Two hours were permitted for isotope equilibration. After collection of appropriate blood samples for baseline determinations, a standard liquid meal of 20 kcal/kg (50% CHO, 35% F, 15% P) in a volume of 20 ml/kg (Compleat B, Doyl Pharmaceuticals, Minneapolis, Minnesota) was consumed by each dog within 1 min. Additional blood samples were obtained at 15-min intervals for 210 min.

All dogs were studied on four occasions separated by at least 1 wk. Experiments were conducted in the following order.

Patterning. Closed-loop pre- and postprandial glycemic control was achieved by peripheral intravenous insulin infusion using the Biostator Glucose Controller (Miles Laboratories). During this experiment insulin was infused using feedback control, with the time, plasma glucose concentrations, and insulin infusion rates being recorded on magnetic tape. To accomplish this, a specially designed memory unit interfacing between the Biostator and the tape recorder was used.

First peripheral venous infusion (Pe 1). After euglycemia had been achieved and maintained for at least 2 h by the Biostator in the feedback mode, the prerecorded insulin infusion rates were initiated through a peripheral vein. The prerecorded insulin pattern was infused for 60 min before and for 210 min following meal ingestion. Administration of the meal was synchronized to that of the patterning study.

Portal venous infusion (Po). The design was identical to that of Pe 1 with the exception that the portal venous route was used for insulin infusion. During the initial achievement of euglycemia the distal end of the previously buried portal catheter was exposed through a skin incision under local anesthesia (2% lidocaine, Astra Pharmaceutical Products, Inc., Worchester, Massachusetts). The portal catheter was used for insulin administration starting 120 min before the meal ingestion.

Second peripheral venous infusion (Pe 2). The experiment was identical to Pe 1. This was done to evaluate whether the metabolic responses to the same insulin infusion administered by the same route was reproducible in each dog, weeks apart.

The animals' weights (17.6 ± 0.9, 17.9 ± 1.0, and 18.4 ± 0.7 kg) and prestudy hematocrits (38 ± 2%, 38 ± 1%, and 39 ± 1%) did not differ for Pe 1, Po, and Pe 2 studies, respectively.

LABORATORY METHODS

Samples for insulin[16] and glucagon[17] determinations were collected in chilled 4-ml tubes containing 17 mg EDTA (Sigma, St. Louis, Missouri). Blood for plasma glucose, lactate,[18] alanine,[19] leucine, isoleucine, valine,[20] and glucose specific activity was collected in NaF-oxalate tubes (Kimble-Terumo, Elkhart, Indiana). An aliquot of this plasma was used for duplicate determination of glucose concentration (Yellow Springs Instruments 23A, Yellow Springs, Ohio). Plasma 2-^{3}H glucose-specific activity was determined as previously described.[17] Triplicate 0.3-ml aliquots of deproteinized plasma were evaporated to dryness under vacuum to remove tritiated water. The residue was resuspended in 0.5 ml distilled water. After the addition of 10 ml Aquasol (New England Nuclear), its radioactivity was counted in a refrigerated liquid scintillation spectrometer. Correction for quenching was made using the method of external standard ratios. The calculated infusion rate of isotope was verified by measuring the volume of the [2-^{3}H]glucose before and after each experiment.

Rates of glucose appearance and disappearance were calculated employing the equations of Steele et al.[21] as modified by De Bodo et al.[22] The validity of the use of [2-^{3}H]glucose has been previously discussed in detail.[23] Although [2-^{3}H]glucose slightly overestimates glucose flux rates due to futile cycling between glucose-6-phosphate and fructose-6-phosphate, its label is lost during glycogenesis and glycogenolysis, thereby avoiding the artifact resulting from recycling of label through glycogen.[23]

All the data in the text and figures are expressed as mean ± SEM, and their statistical significance was evaluated using Student's two-tailed paired t test.[24]

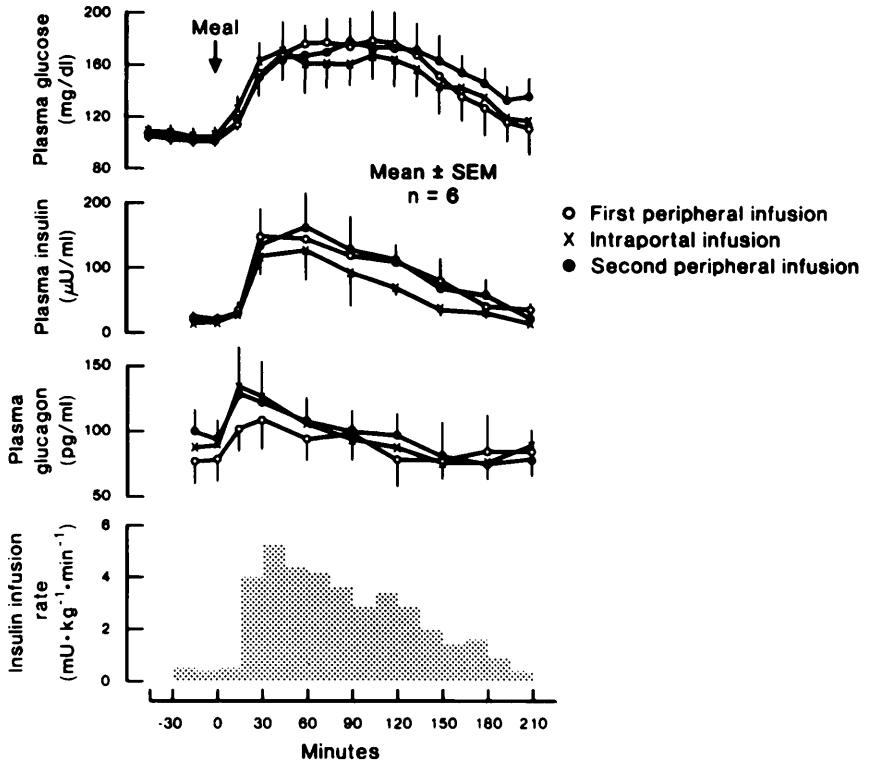


FIGURE 1. Comparison between portal venous and peripheral venous infusions of the identical pre- and postprandial insulin waveform in alloxan-diabetic dogs on plasma glucose, insulin, and glucagon. The mean insulin infusion rates are also shown.

RESULTS

Effects of portal and peripheral venous insulin infusions on postprandial plasma glucose, insulin, and glucagon concentrations (Figure 1). Plasma glucose concentrations before the initiation of each experiment were comparable (323 ± 35, 341 ± 26, and 338 ± 26 mg/dl for Pe 1, Po, and Pe 2, respectively). Plasma glucose concentrations 90 min before the test meal (104 ± 6, 112 ± 4, and 108 ± 4 mg/dl) and at the initiation of the meal (101 ± 4, 104 ± 7, and 102 ± 3 mg/dl) were not different for Pe 1, Po, and Pe 2, respectively. In addition, peak postprandial plasma glucose concentrations (178 ± 25, 170 ± 22, and 176 ± 28 mg/dl) and total increment above baseline (10,400 ± 2800, 9,210 ± 2060, and 11,000 ± 2900 mg · dl^{-1} · min^{-1}) did not differ for Pe 1, Po, and Pe 2, respectively.

Plasma insulin concentrations before each experiment (12 ± 1, 12 ± 1, and 13 ± 1 μU/ml) and immediately before meal ingestion (19 ± 4, 15 ± 2, and 18 ± 3 μU/ml) were not different for Pe 1, Po, and Pe 2, respectively. The increment in plasma insulin concentrations during preprandial insulin infusions (7 ± 3 and 5 ± 2 μU/ml for Pe 1 and Pe 2) were not significantly different from that observed during portal infusion (3 ± 2 μU/ml). Postprandial increases above basal values were the same for both peripheral infusions (15,000 ± 4000 μU · ml^{-1} · 210 min^{-1}, Pe 1; and 15,600 ± 3300 μU · ml^{-1} · 210 min^{-1}, Pe 2). Although these increases were 50% greater than those observed during the portal infusion (10,600 ± 3200 μU · ml^{-1} · 210 min^{-1}, the difference did not reach statistical significance.

Plasma glucagon concentrations before each experiment (224 ± 38, 237 ± 70, and 231 ± 33 pg/ml), before meal ingestion (78 ± 16, 88 ± 18, and 93 ± 15 pg/ml), and postprandial peaks (108 ± 22, 134 ± 30, and 139 ± 31 pg/ml) were not significantly different for Pe 1, Po, and Pe 2, respectively.

Effects of portal and peripheral venous insulin infusions on postprandial rates of glucose appearance and disappearance (Figure 2). Glucose appearance (3.3 ± 0.2, 3.4 ± 0.4, and 3.5 ± 0.1 mg · kg^{-1} · min^{-1}) and disappearance (3.4 ± 0.2, 3.4 ± 0.4 and 3.3 ± 0.2 mg · kg^{-1} · min^{-1}) before meal ingestion were not different for Pe1, Po, and Pe 2, respectively. In addition, peak postprandial rates of glucose appearance (13.1 ± 1.8, 12.6 ± 0.9, and 12.6 ± 1.3 mg · kg^{-1} · min^{-1}), disappearance (12.9 ± 1.6, 12.5 ± 1.8, and 13.5 ± 1.3 mg · kg^{-1} · min^{-1}), and increment above baseline for glucose appearance (1212 ± 170, 1227 ± 99, and 1238 ± 84 mg · kg^{-1} · min^{-1}) and disappearance (1191 ± 167, 1216 ± 80, and 1305 ± 94 mg · kg^{-1} · min^{-1}) did not differ for Pe 1, Po, and Pe 2, respectively.

Effects of portal and peripheral venous insulin infusions on branched chain amino acids (Figure 3). Preprandial (107 ± 17, 92 ± 16, and 60 ± 10 versus 121 ± 15, 105 ± 16, and 64 ± 8 mmol/L) and peak postprandial (177 ± 12, 151 ± 21, and 99 ± 10 versus 171 ± 22, 153 ± 30, and 83 ± 12 mmol/L) concentrations of valine, leucine, and isoleucine were not significantly different for Pe 1 and Po, respectively.

Effects of portal and peripheral venous insulin infusions on plasma lactate and alanine concentrations (Figure 4). Preprandial (1.02 ± 0.2, 1.23 ± 0.23 mmol/L) and peak postprandial (2.95 ± 0.28, 3.08 ± 0.46 mmol/L) plasma lactate concentrations did not differ for Pe 1 and Po, respectively. Preprandial alanine concentrations were significantly greater ($P < 0.05$) during portal insulin infusion (243 ± 37 mmol/L) than during peripheral venous insulin infusion (144 ± 18 mmol/L). However, the total increments above

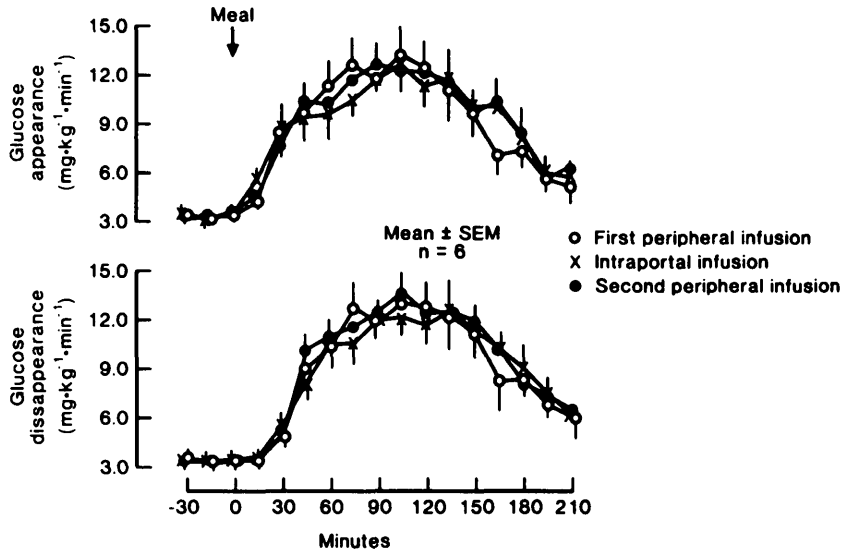


FIGURE 2. Comparison between portal venous and peripheral venous infusions of the identical pre- and postprandial insulin waveform in alloxan-diabetic dogs on glucose appearance and disappearance using [2-^{3}H]glucose.

basal (30,279 ± 4347 versus 27,483 ± 4428 mmol · L^{-1} · 210 min^{-1}) were not different for Po and Pe 1, respectively.

DISCUSSION

The current studies demonstrate that comparable pre- and postprandial plasma glucose concentrations and patterns of glucose disposal occurred when identical insulin infusion profiles were given by a peripheral vein and the portal vein. These results agree with our previous observations that portal and peripheral insulin administration by means of a closed-loop insulin infusion system resulted in an equivalent hepatic and extrahepatic contribution to disposition of a mixed meal.[15] They are also consistent with the report by Botz et al.[14] that comparable clearance of an intravenous glucose load occurred when insulin was given using a closed-loop system by a peripheral vein and the portal vein.

Since both of the latter studies used closed-loop systems, it was possible that subtle differences in insulin infusion rates may have obscured differences in metabolic control between the peripheral venous and portal venous routes. This possibility was eliminated in the current studies since identical preprogrammed complex insulin waveforms were infused on each occasion. This was accomplished by recording the insulin infusion rates given by a closed-loop device in response to a mixed meal on magnetic tape. These prerecorded insulin infusion rates were readministered on each subsequent occasion to the same dogs by either a peripheral or the portal vein. To ensure that a difference between the peripheral venous and portal venous routes was due to the route used rather than random experimental variation, the peripheral venous insulin infusion study was performed on two occasions, once before and once following the portal infusion study.

The lack of difference in glycemic control between portal and peripheral insulin infusions observed in the current study is in apparent contrast to earlier reports.[25] However, in those studies higher insulin infusion rates given by an open-loop device to pancreatectomized dogs pre- and postprandially were used for peripheral rather than portal infusion.[25] In addition, the significance of these observations is difficult to assess since they were not paired studies, the prandial insulin infusion rates were arbitrarily set at seven times the

FIGURE 3. Comparison between portal venous and peripheral venous (Pe 1) infusions of the identical pre- and postprandial insulin waveform in alloxan-diabetic dogs on branched chain amino acids.

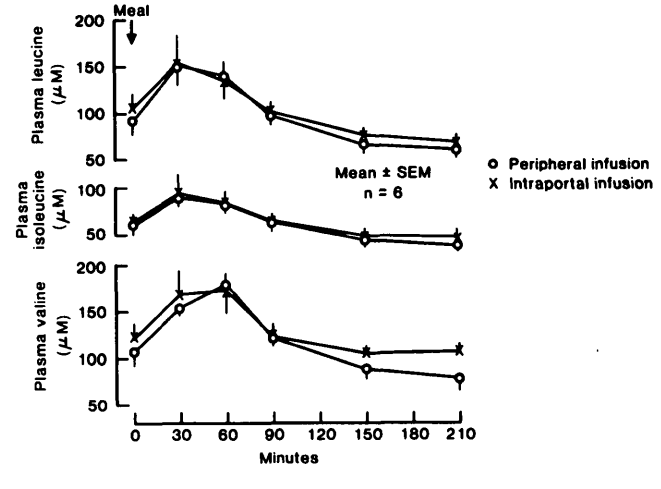
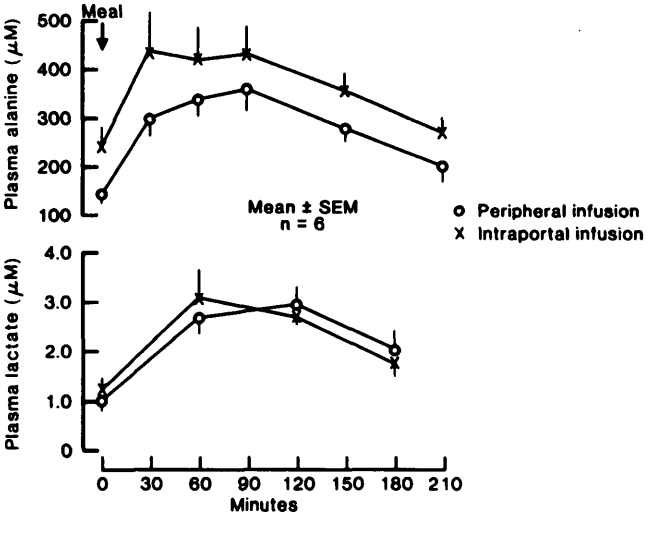


FIGURE 4. Comparison between portal venous and peripheral venous (Pe 1) infusions of the identical pre- and postprandial insulin waveform in alloxan-diabetic dogs on plasma alanine and lactate.



basal rates, and glucose concentrations were not equivalent during the portal and peripheral insulin infusions.

The estimated contribution of the liver to the clearance of an oral glucose load has varied with the technique used for its assessment. Most studies have suggested that between 40 and 60% of the load is disposed by the liver.[2,3,26,27] These figures are in close agreement with the results observed in the present study: approximately 1.2 g/kg of glucose entered the extrahepatic space when a total of 2.4 g/kg of carbohydrate was administered orally. This disposal of a glucose load was due to both a suppression of endogenous glucose production and to extraction of enterally absorbed glucose by the liver. The techniques used in the current study that measure net glucose appearance do not permit differentiation between these two components.[26] It has been suggested that insulin administered intraportally may be more effective in decreasing hepatic glucose production than the same amount of insulin administered by a peripheral vein but that intraportally infused insulin may have less of an effect on peripheral tissue glucose uptake than the same amount of insulin infused by a peripheral vein.[11,12] The latter effect would not be surprising since the same quantity of insulin administered intraportally would be expected to result in lower plasma insulin levels in the peripheral circulation due to hepatic extraction of insulin.[28–30] The lack of difference in the amount of glucose entering the circulation following the mixed meal in the current studies between the peripheral and portal venous routes may have been due to several factors. First, maximally effective insulin concentrations may have been rapidly achieved with both routes of insulin administration. Suppression of hepatic glucose production in man occurs with an increase in insulin concentrations of approximately 40–50 μU/ml with half-maximal suppression occurring with an increase of insulin concentrations of about 20 μU/ml. In contrast, an increase in insulin concentrations of approximately 50 μU/ml is required for half-maximal stimulation of utilization of glucose with maximal utilization occurring at insulin concentrations of 200–500 μU/ml.[8] The rapid increases in insulin concentrations during both peripheral and portal venous insulin infusions may have resulted in insulin concentrations exceeding those needed for maximal hepatic effects; differences between the two routes of insulin administration on hepatic glucose disposal, therefore, would not be detected. This conclusion is consistent with a recent report of a similar degree of inhibition of hepatic glucose production when insulin was infused at a rate of 0.05 U $\cdot$ kg^{-1} $\cdot$ h^{-1} by peripheral and portal venous routes into hyperglycemic dogs. This infusion produced peripheral venous insulin concentrations of approximately 40 μU/ml.[31]

Second, recent experiments have suggested that changes in plasma glucose concentrations are the primary regulators of hepatic glucose production with insulin merely altering the sensitivity of the liver to glucose.[32] Thus, an increase in both glucose and insulin, as occurs following meal ingestion, might influence hepatic glucose metabolism to a greater degree than an increase of insulin alone. An increase in arterial glucose concentration of only 19 mg/dl in the presence of arterial insulin concentrations of 20 μU/ml has been reported to produce an 85% reduction in hepatic glucose production.[33] Since postprandial glucose concentrations in the portal vein can be assumed to be similar regardless of the route of insulin administration, the net hepatic disposal of the nutrient load would be expected to be similar.

Third, the infusion of insulin into the portal vein results in streaming and nonuniform perfusion of the liver.[34,35] A portal venous infusion of insulin may therefore perfuse only a portion of the liver, with the rest of the liver being exposed on a second pass such as would occur from a peripheral insulin infusion.

Although portal venous insulin concentrations were not measured because of the technical difficulty of performing simultaneous portal venous sampling and portal insulin infusion, the portal vein insulin concentrations were undoubtedly greater than when insulin was infused by a peripheral vein. The postprandial peripheral venous insulin concentrations were less, although not significantly so, when insulin was infused portally compared with peripheral infusion of insulin. The small differences in peripheral insulin concentrations between these two routes may have been due to a reduction in hepatic insulin extraction with increasing portal concentrations of insulin and glucose.[36,37] This postulate is consistent with the observation that the peripheral insulin concentrations during both portal and peripheral insulin infusions were greater than those in nondiabetic dogs following a mixed meal (unpublished observations).

Complete or partial correction of abnormal plasma concentrations of lactate, pyruvate, free fatty acids, triglycerides, ketone bodies,[38] and glucagon,[39] characteristic of diabetes, have been reported with the use of closed-loop devices employing the peripheral venous route. In contrast, excessive decreases in the concentrations of branched chain and essential amino acids[39] have been reported. In the current study postprandial changes in glucagon, lactate, and branched chain amino acids were equivalent when insulin was administered portally and peripherally. Preprandial plasma alanine concentrations were higher during portal insulin infusion than during peripheral insulin infusion. Since alanine flux was not measured, we cannot determine whether this was due to decreased hepatic alanine extraction as a result of portal hyperinsulinemia or to accelerated alanine production due to peripheral hypoinsulinemia. Since preprandial peripheral insulin concentrations were identical, the latter explanation is unlikely.

The current studies demonstrate that when identical preprogrammed complex insulin infusion rates are given in an open-loop fashion to alloxan-diabetic dogs to control a mixed meal, there is no difference in glucose disposal between the portal and peripheral venous routes. Except for basal alanine, there were also no differences in concentrations of amino acids pre- and postprandially. Since the algorithms used with both the peripheral venous and portal venous routes resulted in peripheral venous hyperinsulinemia, the current studies do not address the question whether exquisitely regulated changes in pancreatic insulin secretion and portal insulin concentrations that occur in normal man selectively modulate hepatic response to ingestion of a mixed meal. In summary, under the current experimental condition there appears to be no advantage of portal venous insulin over peripheral venous insulin administration by an open-loop technique on the disposition of a mixed meal measured as the net whole body glucose appearance and disappearance rates.

ACKNOWLEDGMENTS

This research was supported in part by grants AM 8-2218, AM 00648, AM 20411, AM 20837, and AM 5827 from the National Institutes of Health, NIAMDD. Dr. Fischer was a recipient of an IREX travel grant.

REFERENCES

[1] Madison, L.: Role of insulin in the hepatic handling of glucose. Arch. Intern. Med. *123*:284–92, 1969.

[2] Jeffcoate, S., and Moody, A.: The role of the liver in the disposal of orally administered 14-C-glucose in the normal rat. Diabetologia *5*:293–98, 1969.

[3] Felig, P., Wahren, J., and Hendler, R.: Influence of maturity-onset diabetes on splanchnic glucose balance after oral glucose ingestion. Diabetes *27*:121–26, 1978.

[4] Madison, L., and Unger, R.: The physiologic significance of the secretion of endogenous insulin into the portal circulation. 1. Comparison of the effects of glucagon-free insulin administered via the portal vein and via a peripheral vein on the magnitude of hypoglycemia and peripheral glucose utilization. J. Clin. Invest. *37*:631–39, 1958.

[5] Pfeiffer, E., Beischer, W., and Kerner, W.: The artificial endocrine pancreas in clinical research. Horm. Metab. Res. *96* (Suppl. 7):95–114, 1977.

[6] Santiago, J., Clemens, A., Clarke, W., and Kipnis, D.: Closed-loop and open-loop devices for blood glucose control in normal and diabetic subjects. Diabetes *28*:71–81, 1979.

[7] Rizza, R. A., Gerich, J. E., Haymond, M. W., Westland, R. E., Hall, L. D., Clemens, A. H., and Service, F. J.: Control of blood sugar in insulin-dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion and intensified conventional insulin therapy. N. Engl. J. Med. *303*:1313–18, 1980.

[8] Rizza, R. A., Mandarino, L. J., and Gerich, J. E.: Dose-response characteristics for effects of insulin on production and utilization of glucose in man. Am. J. Physiol. *240*:E630–39, 1981.

[9] Erdwald, R., Hed, R., Nygren, A., Rojdmark, S., and Weichel, K.: Comparison of the effect of intraportal and intravenous infusion of insulin on blood glucose and free fatty acids in peripheral venous blood of man. Acta Med. Scand. *195*:351–57, 1974.

[10] Starzl, T., Scalan, W., Yarouf, H., Thornton, F., Wendel, R., Stearn, B., Lazarus, R., McAllister, W., and Shoemaker, W.: A comparison of the hypoglycemic effect of insulin with systemic venous and portal venous administration. J. Surg. Res. *36*:293–95, 1963.

[11] Stevenson, R., Parsons, J., and Alberti, K.: Insulin infusion into the portal and peripheral circulation of unanesthetized dogs. Clin. Endocrinol. *8*:335–47, 1978.

[12] Baruth, S.: The physiologic significance of portal vs peripheral injection of insulin in man. Am. J. Med. Sci. *269*:25–35, 1975.

[13] Poulsen, J. S. D., Smith, M., Deckert, M., and Deckert, T.: Comparison of intraperitoneal, intraportal and intravenous insulin infusions. Acta Endocrinol. *95*:500–504, 1980.

[14] Botz, C., Leibel, B., Zingg, W., Gander, R., and Albisser, A.: Comparison of peripheral and portal routes of insulin infusion by a computer-controlled insulin infusion system (artificial endocrine pancreas). Diabetes *25*:691–700, 1976.

[15] Rizza, R. A., Westland, R. E., Hall, L. D., Patton, J., Haymond, M. W., Clemens, A. H., Gerich, J. E., and Service, F. J.: Peripheral versus portal venous administration of insulin on postprandial hyperglycemia and glucose turnover in alloxan diabetic dogs. Mayo Clin. Proc. *56*:434–38, 1981.

[16] Herbert, V., Lau, K., Gottlieb, C., and Bleicher, S.: Coated charcoal immunoassay of insulin. J. Clin. Endocrinol. Metab. *25*:1375–84, 1965.

[17] Rizza, R. A., Cryer, P., and Gerich, J. E.: Role of glucagon, catecholamine and growth hormone in human glucose counterregulation. Effect of somatostatin and combined alpha and beta adrenergic blockade on plasma glucose recovery and glucose flux rates after insulin-induced hypoglycemia. J. Clin. Invest. *64*:62–71, 1979.

[18] Lowry, O. H., Passonneau, J. V., Hasselberger, F. X., and Schulz, D. W.: Effect of ischemia on known substrates and cofactors of the glycolytic pathway in brain. J. Biol. Chem. *239*:18–30, 1964.

[19] Karl, I. E., Pagliara, A. S., and Kipnis, D. M.: A micro fluorometric enzyme assay for the determination of alanine and pyruvate in plasma and tissue. J. Lab. Clin. Med. *80*:434–41, 1971.

[20] Dickinson, J. C., Rosenblum, H., and Hamilton, P. G.: Ion exchange chromatography of free amino acids in the plasma of infants under 2500 gm at birth. Pediatrics *45*:606–13, 1970.

[21] Steele, R., Wall, J., De Bodo, R., and Altszuler, N.: Measurement of size and turnover rate of body glucose pool by the isotope dilution method. Am. J. Physiol. *187*:15–24, 1956.

[22] De Bodo, R., Steele, R., Altszuler, N., Dunn, A., and Bishop, J.: On the hormonal regulation of carbohydrate metabolism: studies with C^{14} glucose. Recent Prog. Horm. Res. *19*:445–88, 1963.

[23] Altszuler, N., Barkai, A., Bjerkness, C., Gottlieb, B., and Steele, R.: Glucose turnover values in dog obtained with various species of labeled glucose. Am. J. Physiol. *229*:1662–67, 1975.

[24] Zar, J.: Biostatistical Analysis. Englewood Cliffs, N.J., Prentice Hall, 1974.

[25] Goriya, Y., Bahoric, A., Marliss, E. B., Zinman, B., and Albisser, A. M.: The metabolic and hormonal responses to a mixed meal in unrestrained pancreatectomized dogs chronically treated by portal or peripheral insulin infusion. Diabetologia *21*:58–64, 1981.

[26] Radziuk, J., McDonald, T. J., Rubenstein, D., and Dupre, J.: Initial splanchnic extraction of ingested glucose in normal man. Metabolism *27*: 657–69, 1978.

[27] Issekutz, B., Issekutz, T. B., Elahi, D., and Borkow, I.: Effect of insulin infusion on the glucose kinetics in alloxan-streptozotocin diabetic dogs. Diabetologia *10*:323–28, 1974.

[28] Field, J. C.: Insulin extraction by the liver. *In* Handbook of Physiology, Section 7: Endocrinology. Vol. 1. Greep, R. O., and Astwood, E. B., Eds. Washington, D.C., American Physiology Society, 1972, pp. 505–13.

[29] Berger, W., Groeschke, H., Moppert, J., and Kuenzli, H.: Insulin concentrations in portal venous and peripheral venous blood in man following administration of glucose, galactose, xylitol and tolbutamide. Horm. Metab. Res. *5*:4–8, 1973.

[30] Lund, B., Schmidt, A., and Deckert, T.: Portal and cubital serum insulin during oral, portal and cubital glucose tolerance test. Acta Med. Scand. *197*:275–81, 1975.

[31] Stevenson, R. W., Parson, J. A., and Alberti, K. G. M. M.: Comparison of the metabolic responses to portal and peripheral infusions of insulin in diabetic dogs. Metabolism *30*:745–52, 1981.

[32] Bergman, R. N., and Bucolo, R. J.: Interaction of insulin and glucose in the control of hepatic glucose balance. Am. J. Physiol. *227*:1314–22, 1974.

[33] Felig, P., and Wahren, J.: Influence of endogenous insulin secretion on splanchnic glucose and amino acid metabolism in man. J. Clin. Invest. *50*:1702–11, 1971.

[34] Copher, G. H., and Dick, B. M.: Streamline phenomena in the portal vein and the selective distribution of portal blood in the liver. Arch. Surg. *17*:408–19, 1928.

[35] Haln, P. F., Donald, W. D., and Grier, R. C., Jr.: The physiological bilaterality of the portal circulation. Streamline flow of blood into the liver as shown by radioactive phosphorus. Am. J. Physiol. *143*:191–97, 1945.

[36] Tranberg, K.-G., and Thorell, J.: Variation in the disappearance of unlabeled insulin from plasma. Studies with portal and peripheral infusions. Diabetes *28*:846–51, 1979.

[37] Rojdmark, S., Bloom, G., Choi, M. C. Y., Jaspan, J. B., and Field, J. B.: Hepatic insulin and glucagon extraction after their augmented secretion in dogs. Am. J. Physiol *235*(1):E88–96, 1978.

[38] Zinman, B., Stokes, E. F., Albisser, A. M., Hanna, A. K., Minuk, H. L., Stein, A. N., Leibel, B. S., and Marliss, E. B.: The metabolic response to glycemic control by the artificial pancreas in diabetic man. Metabolism *28*:511–18, 1979.

[39] Hanna, A. K., Zinman, B., Nakhooda, A. F., Minuk, H. L., Stokes, E. F., Albisser, A. M., Leibel, B. S., and Marliss, E. B.: Insulin, glucagon and amino acids during glycemic control by the artificial pancreas in diabetic man. Metabolism *29*:321–32, 1980.