Effect of infusion of insulin into portal vein on hepatic extraction of insulin in anesthetized dogs

PHILIP E. HARDING, GAIL BLOOM, AND JAMES B. FIELD

Clinical Research Unit and Department of Medicine, University of Pittsburgh School of Medicine,
Pittsburgh, Pennsylvania 15261


Hepatic extraction of insulin was examined in anesthetized dogs before and after constant infusion of insulin (20 and 50 mU/min) with use of samples from the portal vein, mesenteric vein, left common hepatic vein, and the femoral artery. In 19 dogs, measurement of portal vein insulin concentration indicated an overall recovery of 110% of the insulin infused. The range varied from 9 to 303%, indicating the potential for serious error in sampling the portal vein. Equilibrium arterial insulin concentrations were achieved 20 min after starting the infusion. Prior to insulin infusion, hepatic extraction of insulin averaged 4.56 ± 0.43 mU/min, representing an extraction coefficient of 0.42 of the insulin presented to the liver. The proportion of insulin extracted by the liver did not change significantly during insulin infusion despite a 10-fold increase in portal vein insulin concentrations. During the infusion of insulin, a significant proportion of the extrahepatic clearance of insulin occurred in the mesenteric circulation. Infusion of insulin was associated with a significant increase in insulin extraction by tissues other than the liver and splanchic beds. Initially, hepatic glucose output averaged 36 ± 3 mg/min; by 20 min after insulin infusion, it was 16 ± 5 mg/min. Despite continuation of insulin infusion, hepatic glucose output returned to control values even though arterial glucose concentration continued to fall. Hepatic glucose output increased with termination of insulin infusion.

MATERIALS AND METHODS

Mongrel dogs (mean weight 21.6 kg) were fasted overnight and anesthetized with barbital (30 mg/kg). The surgical preparation and placement of electromagnetic flow probes on the portal vein and hepatic artery was as described by us previously (7), with the following modifications: a) hepatic venous blood was sampled from a catheter placed in the left common hepatic vein (LCHV) via the abdominal approach as described by Shoemaker et al. (20). In three preliminary experiments, two additional sampling catheters were placed in the interior vena cava (IVC) which was ligated immediately caudad to the hepatic veins so that it would contain only mixed-hepatic venous effluent. One of these catheters was placed, under direct vision, immediately opposite the entry of the hepatic veins, and the other, 2-5 cm cephalad and beyond a choker designed to constrict the IVC to 50% of its diameter and thus create turbulent mixing of the blood passing through to the upper catheter. The pressure gradient across this constriction was < 1 cmH₂O and hepatic blood flow was not reduced. Insulin concentrations in samples from these two catheters, termed high IVC and low IVC, were then compared with simultaneous LCHV samples. b) The portal...
vein flow probe was placed immediately caudal to the gastroduodenal vein, which was ligated. The portal vein sampling catheter, inserted via a peripheral mesenteric vein, was passed through the flow probe so that its multipurpose sampling tip lay immediately below the portal vein bifurcation. The flow probe was recalibrated in vitro for use under these geometric conditions and still gave an accurate linear response which was unaffected by changes in the hematocrit over the range 26 to 48%. c Catheters were also placed in a peripheral mesenteric vein tributary for sampling of mesenteric venous blood, and at the root of the cranial mesenteric vein, the principal tributary of the portal vein, for the infusion of insulin. The tip of the infusion catheter lay approximately 10 cm caudal to the portal vein sampling catheter. Although care was taken to site the mesenteric sampling catheter well away from the pancreatic venous drainage, mesenteric vein insulin concentrations during the control period may be spuriously high because of some contamination with pancreatic venous drainage.

Blood representative of that in the hepatic artery was sampled from a catheter in the femoral artery. The placement of all the catheters and flow probes in relation to the liver and the pancreatic venous drainage is illustrated in Fig. 1. At the end of each study, the catheter placements were checked and in no instance had displacement occurred.

In two preliminary experiments, transit time of insulin through the liver was estimated by collecting hepatic vein samples every 10 s following the rapid injection of a measured quantity of 125I-labeled insulin. As a result of these experiments, detailed below, hepatic vein samples were drawn 30 s after the simultaneous collection of all the other samples.

Nineteen dogs were studied according to the following protocol: after an equilibration period of 60 min following completion of the surgery, samples and flow measurements were taken 30, 20, 10, 5, and 1 min before insulin was infused into the portal vein at a rate of approximately 20 mU/min. Samples and measurements were then obtained after 2, 5, 10, 20, 30, 40, and 50 min; the infusion was then increased to approximately 50 mU/min and samples were obtained at similar intervals. The infusion was then stopped and samples were obtained 2, 5, 10, 20, and 30 min later. In 5 of the 19 dogs (dogs no. 25, 27, 32, 33, and 34) the infusion periods were 30 min duration only.

Since insulin and glucose were measured in plasma, the blood flow measurements were corrected to plasma flow (Q) by hematocrits obtained every 30 min during each study. The flux (F) of insulin (mU/min) or glucose (mg/min) was then determined for each vessel at each time point by multiplying Q (ml/min) by plasma concentration (mU or mg/ml). The hepatic vein plasma flow (QHV) was taken as the sum of the hepatic artery (QHA) and portal vein (QPV) plasma flows. No significant differences in hematocrit existed between arterial, portal venous, and hepatic venous blood. Hepatic insulin extraction (FE) and clearance (ml/min) and hepatic glucose balance (mg/min) were derived from these data as described previously (7), with the exception that in this study the coefficient of extraction (E) is expressed as a proportion of unity rather than as a percentage. The symbols and subscripts for plasma flows, fluxes, and extraction coefficients are as shown in the figure and illustrated in Fig. 3.

Extraction of insulin across the mesenteric vascular bed (Em) was calculated from the arterial (a) and peripheral mesenteric venous (m) insulin concentrations by the formula (a - m)/a. If the mesenteric vein sample is contaminated with pancreatic venous drainage, this will tend to diminish Em. The results, therefore, will be a minimum estimate of mesenteric extraction.

The difference between the plasma insulin concentrations in the portal vein catheter (p) and the mesenteric vein catheter (m), multiplied by Qm, yields Fp-m (mU/min) which is a direct measure of the rate of entry of insulin into the portal vein between the two catheters. During the basal state, this represents all endogenous insulin secretion subject to the limitations mentioned above in regard to the mesenteric vein insulin concentration (Fig. 1); during the infusion period, it represents the insulin infused into the cranial mesenteric vein plus the endogenous insulin secretion. Fp-m should, therefore, be equal to the known rate of insulin infusion in milliliters per minute when corrected for endogenous insulin secretion.

Porcine insulin (Eli Lilly and Company), at a concentration of 0.1 U/ml in physiological saline containing 1 mg/ml bovine serum albumin (Nutritional Biochemicals Corporation), was infused by a Harvard infusion pump at rates 0.2 and 0.5 ml/min. A portion of the insulin infusate from each study was retained and its insulin content was measured in the same assay as the experimental samples. Plasma insulin was measured by radioimmunoassay with dextrancoated charcoal, and plasma glucose, by the glucose oxidase method (Glucostat, Worthington Biochemical Corporation).

Pooled data are expressed as means ± standard errors of the mean unless otherwise indicated.

RESULTS

Hepatic insulin transit time. Following the injection of a bolus of 125I-labeled insulin into the portal vein, peak hepatic vein radioactivity was found at 20 and 30 s, respec
tively, in the two experiments performed. In each case the peak sample contained more than double the radioactivity of any other sample, suggesting a rapid and relatively homogeneous passage of insulin through the liver. A second smaller peak was observed at 70 s, possibly representing the first recirculation of the injected, labeled insulin.

Since the hepatic blood flow was measured and the volume of blood sampled from the LCHV was known, an estimate could be made of the amount of injected radioactivity recovered in the hepatic vein during the first 60 s. This was 51 and 23 %, respectively, in the two studies.

Assessment of portal vein sampling error. \( F_{p-m} \) representing pancreatic insulin secretion, averaged 5.1 ± 0.8 mU/min (0.24 mU/kg per min) during the control period in the whole group of 19 dogs. This is very similar to previous estimates of basal pancreatic insulin secretion in anesthetized dogs ([11–13] and unpublished observations). During the period 10–30 min after the cessation of insulin infusion, while arterial plasma glucose was still depressed, pancreatic insulin secretion was 3.4 ± 0.9 mU/min. As this change of 1.7 mU/min in pancreatic insulin secretion was small in relation to the amounts infused, the basal insulin secretion value in each experiment was deducted from the values of \( F_{p-m} \) obtained during insulin infusion, so that the corrected values would reflect only the infused insulin. These corrected values were then integrated with respect to time to yield the term \( \sum F_{p-m} \) in milliunits which is a recovery figure for the total amount of insulin infused.

Table 1 compares the value of \( \sum F_{p-m} \) with the measured amount of insulin infused in each of the 19 dogs. The mean \( \sum F_{p-m} \) was 3,917 mU and the mean insulin infused was 3,297 mU. The mean recovery in the 19 dogs was 110 %.

However, the standard deviation of the differences between the observed and expected figures in all the individual dogs was ±2.2 mU and the percent recovery ranged from 9 to 903 %, indicating a large random error in measuring the portal vein insulin concentration.

Assessment of hepatic vein sampling error. In three dogs in which the vena cava was ligated below the liver, insulin concentrations in the left common hepatic vein (LCHV) were compared with those found via catheters placed opposite the entry of the hepatic veins (Fig. 1, LOW IVC) and above this point (Fig. 1, HIGH IVC). The results of these observations during steady-state insulin infusion are depicted in Table 2. The LCHV values correspond closely to the high IVC, whereas the relationship of the low IVC to both other vessels is inconstant. In addition, the coefficients of variation for plasma insulin concentration in the LCHV and high IVC are 5.6 and 5.7 %, respectively, whereas for the low IVC it is 9.4 %.

Hepatic insulin extraction. The large portal vein sampling error found during insulin infusion precluded the use of this measurement in calculating \( E_h \). During infusion, therefore, the term representing the amount of insulin delivered to the liver by the portal vein was derived as \( F_p + \text{known infusion rate} \), in milliunits per minute (see Appendix). Four dogs were excluded from this calculation. In two (dogs 32 and 38), the values obtained for hepatic insulin extraction were negative throughout the control period, giving no valid basis for comparison. In a third (dog 43), hepatic vein insulin levels rose higher than either the measured or predicted portal vein insulin levels during infusion. The fourth dog (dog 36) showed no rise in hepatic vein insulin despite a rise in arterial levels. The values of \( E_h \) in the remaining 15 dogs are given in Table 3, together with the plasma flows, the insulin values in the femoral artery, the portal, hepatic, and mesenteric veins, and the absolute rate of insulin uptake by the liver in milliunits per minute. The changes in arterial insulin concentration and \( E_h \) during insulin infusion are also shown in Fig. 2; included for illustration are portal vein insulin concentrations for 10 of the dogs in which the sampling error was not large, as reflected by portal vein insulin recovery figures between 65 and 135 %. \( E_h \) values for these 10 dogs did not differ from the group as a whole. During the control period, basal insulin secretion for the group of 15 dogs was 5.5 ± 0.8 mU/min (0.25 mU/kg per min); arterial insulin, 16 ± 1 mU/ml; and mean \( E_h \) was 0.42 ± 0.2. During the first 30-min period of insulin infusion, 20.0 ± 1.4 mU/min were infused, and after 20 min the arterial insulin level had

<table>
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<th>Dog No.</th>
<th>∑ F&lt;sub&gt;p-m&lt;/sub&gt;, mU</th>
<th>Infused Insulin, mU</th>
<th>Observed - Expected</th>
<th>% Recovery of Infused Insulin</th>
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<tr>
<th>Dog No.</th>
<th>Insulin Concentration, μU/ml</th>
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<td>IVC (high)</td>
<td>IVC (low)</td>
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<td>31</td>
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Values are means ± SE of eight samples obtained at 10-min intervals. IVC = inferior vena cava. LCHV = left common hepatic vein.
Hepatic insulin extraction during insulin infusion

**TABLE 3. Hepatic insulin extraction \( (E_h) \) during insulin infusion**

<table>
<thead>
<tr>
<th>Min</th>
<th>Plasma Insulin, ( \mu U/ml )</th>
<th>Plasma Flow, ( \text{ml/min} )</th>
<th>( E_h )</th>
<th>Hepatic Insulin Uptake, ( \mu U/min )</th>
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<td>Femoral artery</td>
<td>Portal vein</td>
<td>Hepatic artery</td>
<td>Portal vein</td>
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**First infusion**

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<th>Min</th>
<th>Plasma Insulin, ( \mu U/ml )</th>
<th>Plasma Flow, ( \text{ml/min} )</th>
<th>( E_h )</th>
<th>Hepatic Insulin Uptake, ( \mu U/min )</th>
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**Second infusion**

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<th>Plasma Insulin, ( \mu U/ml )</th>
<th>Plasma Flow, ( \text{ml/min} )</th>
<th>( E_h )</th>
<th>Hepatic Insulin Uptake, ( \mu U/min )</th>
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**Postinfusion**

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<th>Plasma Insulin, ( \mu U/ml )</th>
<th>Plasma Flow, ( \text{ml/min} )</th>
<th>( E_h )</th>
<th>Hepatic Insulin Uptake, ( \mu U/min )</th>
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Values are means \( \pm SE \). Four of the 19 dogs have been excluded from these data (see Results).

risc to a plateau of 50 \( \pm 1 \) \( \mu U/ml \). The values for \( E_h \) during infusion were compared with the mean control values by the paired \( t \) test. Significant elevations were found at 2 min following the commencement of infusion (0.66 \( \pm 0.07 \), \( P < .001 \)) and at 5 min (0.53 \( \pm 0.07 \), \( P < .025 \)). During the remainder of the first period of insulin infusion, \( E_h \) was consistently above control, but the differences were not significant. The elevation of \( E_h \) at the 2- and 5-min points is felt to be due to failure to account fully for dead space within the infusion system, so that the anticipated concentration of insulin has not yet been achieved in the portal vein. This source of error does not apply to the remainder of the experiment when the infusion is running continuously. The 2- and 5-min values have, therefore, been omitted from the data in Fig. 2. During the second stage of infusion, 50.8 \( \pm 1.7 \) \( \mu U/ml \) were infused, and once again a plateau of arterial insulin concentration was reached between 20 and 50 min at a level of 175 \( \pm 8 \) \( \mu U/ml \). \( E_h \) did not differ significantly from control, the mean value between 20 and 50 min being 0.39 \( \pm 0.03 \). However, this value was significantly lower than the value of 0.46 \( \pm 0.03 \) found during the plateau of the first infusion period (\( t = 2.702 \), \( P < .01 \)). During the 30 min following the cessation of insulin infusion, arterial insulin levels fell rapidly with an initial disappearance half-time over the first 10 min of 4 min. The log concentration disappearance, however, was not linear with respect to time, suggesting the presence of an additional slower component. \( E_h \) fell markedly to a nadir of 0.15 \( \pm 0.08 \) between 10 and 20 min after the infusion was stopped. The values were significantly below control at 5 min (\( P < .05 \)) and at 10, 20, and 30 min (\( P < .025 \)) following the cessation of the infusion, so that control values were not reestablished by the end of the experiment.

Mesenteric insulin extraction. In 7 of the 15 dogs, control mesenteric vein insulin levels (\( I_m \) in Appendix) were slightly above arterial, making the calculation of control \( E_m \) impossible. As mentioned previously, this presumably reflects contamination with pancreatic blood. During steady-
state infusion, this was not a factor since arterial insulin concentrations exceeded those of the mesenteric vein in all 15 dogs (Table 3). $E_m$ averaged $0.33 \pm 0.02$ for the first period and $0.43 \pm 0.01$ for the second. However, after the cessation of infusion the mesenteric vein insulin in eight dogs was $127 \pm 37\%$ of the arterial value at 20 min post-infusion and $147 \pm 54\%$ at 30 min, indicating an average net efflux of insulin from the mesenteric circulation. This was not felt to reflect contamination with pancreatic venous blood, as these dogs did not exhibit mesenteric vein insulin concentrations greater than arterial during the control period.

*Systemic insulin extraction.* The appendix describes a mathematical model of the kinetics of insulin secretion and its extraction by vascular beds. This model is depicted in Fig. 3. Equation 4 of this model yields $E_s$, the mean coefficient of insulin extraction in the systemic circulation. This is derived from the hepatic artery and portal vein plasma flows, hepatic vein ($I_V$) and systemic arterial ($I_a$) insulin concentrations, and the systemic plasma flow ($Q_s$). All these parameters are measured in the present study with the exception of $Q_s$, which is the ascending aorta flow minus hepatic and mesenteric flow. Dedichen and Schenk (4) measured the distribution of cardiac output using electromagnetic flow probes in ventilated, barbital-anesthetized mongrel dogs of weights similar to our dogs'. Their value for total hepatic blood flow of $21.2\, ml/kg per min$ corresponds closely to ours of $23.7\, ml/kg per min$. Assuming the same distribution of cardiac output in the two groups of dogs, a mean value for $Q_s$ of $1,085\, ml per min$ may be derived for the present study. It should be noted that $Q_s$ is a simple inverse determinant of $E_s$, and its value, therefore, only determines the magnitude of $E_s$ rather than the relative magnitude of any changes. Using this value for $Q_s$ together with the mean values from the 15 dogs studied for the other parameters, we can calculate values for $E_s$. During the control period, $E_s$ averaged $0.107 \pm 0.009$; whereas between 20 and 50 min of the first infusion, it was $0.135 \pm 0.012$. This latter was significantly ($P < 0.05$) different from the control value. During the second infusion period, $E_s$ was $0.059 \pm 0.004$.

*Hepatic glucose output (HGO).* During the control period, hepatic glucose output averaged $36 \pm 3\, mg/min$ when the arterial plasma glucose was $106 \pm 3\, mg/100\, ml$. The changes in both these parameters during the insulin infusion are shown in Fig. 4. HGO fell to a nadir of $16 \pm 5\, mg/min 20\, min$ after the onset of insulin infusion. The values at 10, 20, and 30 min were significantly ($P < 0.025$) below control. After this time, however, HGO returned toward control values. The higher rate of insulin infusion was not associated with as marked a fall, and during the last 30 min of the infusion, HGO had returned to control values although arterial glucose levels continued to fall to a nadir of $60 \pm 4\, mg/100\, ml$ at the end of the infusion. Following cessation of insulin infusion, HGO increased and was still rising at the end of the period of observation, when it was $67 \pm 12\, mg/min$.

**DISCUSSION**

Direct measurement of the quantities of insulin entering and leaving the liver affords the most accurate estimate of hepatic removal of insulin from the circulation. Ideally, a representative sample should be obtained from the same segment of blood as it first enters the liver and then leaves it. To approach this, hepatic vein samples were obtained 30 s after portal vein samples. In two experiments, recovery as a single sharp peak in the hepatic vein within 60 s of 5 and 23% of the $^{125}$I-labeled insulin injected suggested that this peak represents unaltered insulin not extracted by the liver.

The wide variation in recovery (9–303\%) from the portal vein sampling catheter of insulin infused some 10 cm upstream emphasizes the difficulties involved in obtaining representative portal vein insulin samples necessary for the measurement of insulin balance across the liver, at least under the conditions of our experiments. The finding of an overall recovery of 110\% with an equal proportion of anomalously high or low values suggests random variations in lamination of blood flow relative to the position

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**Fig. 3.** Model for insulin secretion and extraction by various vascular beds (see appendix for legend).

**Fig. 4.** Effect of insulin infusion on arterial plasma glucose concentration and hepatic glucose output. Values are means ± SF for 15 dogs.
of the catheter tip in the transverse plane of the vessel. The literature contains previous examples of such lamina-
tion of flow in the portal vein. We have reported an experi-
ment (7) in which, during glucose stimulated insulin secre-
tion, hepatic vein and arterial insulin levels rose before 
those in the portal vein. Erwald et al. (5) explained portal 
vein insulin levels inappropriate to the prevailing systemic 
levels in several of their subjects on the basis of lamination 
of portal vein flow. Kanazawa et al. (9) found that India 
ink injected into the portal vein via the superior pan-
creaticoduodenal vein was distributed in a selective and 
inconstant pattern among the various hepatic lobes. Further-
more, in four of six experiments in which hepatic blood 
samples were obtained from each lobe, there was evidence 
that pancreatic insulin secretion was distributed in the 
same pattern as the India ink. Our use of a catheter with 
multiple holes did not overcome the sampling errors 
produced by this phenomenon, and caution should be 
exercised in interpretation of studies based on portal vein 
insulin concentrations.

Selective distribution of insulin to the different hepatic 
lobes will also result in differential insulin concentrations 
within the hepatic venous bed, as found by Kanazawa and 
his colleagues (9). Therefore, hepatic vein sampling is 
another possible source of error in these studies. The oc-
casional inappropriate finding of hepatic vein insulin 
levels lower than systemic has been reported by others 
(4, 9, 15) and ourselves (7), when we catheterized blindly 
the hepatic vein from the inferior vena cava. However, in 
the present study, hepatic vein samples were obtained 
from the left common hepatic vein, which carries approxi-
mately 40% of hepatic venous blood (20). Evidence that 
such samples adequately reflect mixed hepatic venous insulin 
concentration was obtained in three experiments in which 
the IVC was ligated immediately below the hepatic veins. 
Mean steady-state concentrations in the LCHV over a 
70 min period were 83, 97, and 99% of the corresponding 
samples taken from the vena cava at a point farthest away 
from the liver where most mixing is presumed to have 
ocurred (Table 2). The greater variation in vena caval 
insulin levels taken opposite the entry of the hepatic veins 
(low IVC) suggests that this catheter was more liable 
to sample small streams from lobes being perfused with 
variable insulin concentrations. No obvious abnormality 
of catheter placement was found in the two dogs excluded 
from the study because of clearly erroneous hepatic vein 
results. In the remainder of the dogs, whereas there were 
occasional time points when the hepatic vein insulin con-
centration was less than arterial, there were no cases in 
which such an anomaly was consistent.

Therefore, calculation of $E_0$ from the arterial, mesenteric 
vein, and left common hepatic vein plasma insulin con-
centrations, together with the known insulin infusion rate 
and hepatic artery and portal vein plasma flows, constitutes 
the most valid measurement during steady-state infusion. 
This does not apply to the measurements immediately 
following the start of the infusion, in which the increased 
extraction demonstrated appears to be artifactual.

The control $E_0$ of 0.42 ± 0.02 corresponds closely to 
our previously reported value (7) and to those of other 
investigators (10, 19, 14, 19). Although the slight rise in 
$E_0$ during the first infusion period (Fig. 2) is not statistically 
significant, some increase in tissue extraction, either in the 
arterial or portal veins, appears to be necessary to account for 
the 20 min taken for arterial insulin levels to rise to a steady 
level consistent with the abrupt fourfold increase in insulin 
"secretion" produced by the infusion. Blackard and Nelson 
(2) found a sharp peak of portal vein insulin occurred at 
1 min after glucose infusion in man whereas the peripheral 
levels peaked at 5 min. It seems unlikely that this lag is 
due to transit time, which should not be grossly different 
from our value of 30 s determined in the dog; it would be 
consistent with a transient increase in tissue extraction. 
Also, in our previous report (7), hepatic insulin clearance 
increased within 5 min of the onset of glucose-induced 
insulin secretion. The transitory increase in the proportion 
of insulin leaving the blood during passage through the 
hepatic veins may represent equilibration of a tissue insulin 
compartment or compartments within the liver to the higher 
plasma concentrations. This equilibration may in part be 
attributable to the binding of insulin to vascular endothe-
lin, as has been postulated by Rasio and Conard (17). 

Increasing the insulin infusion rate to 50.8 mU/min did not 
significantly increase $E_0$ (Fig. 2), and arterial insulin 
levels rose more abruptly. By 2 min the mean rise was 
40 μU/ml (89% above the previous value), whereas 2 
min after the onset of the first infusion, the mean rise was 
only 4 μU/ml (24%). As arterial insulin concentration 
rise to a plateau between 20 and 50 min, $E_0$ tended to fall 
slightly, but not significantly. However, during this time, 
arterial arterial insulin levels were proportionately greater 
relative to the infusion rate than during the first 
infusion period. During the control period, the ratio of 
arterial insulin to insulin secretion was 2.9; during the first 
infusion (20 50 min), 1.9; during the second infusion, 3.1. 
This ratio should remain constant provided there is no 
change in either blood flow or tissue extraction coefficients. 
As blood flows were unchanged (Table 3), the reduction 
of this ratio during the "equilibrium" portion of the first 
infusion period must be due to a persisting increase in 
arterial insulin levels. Although the rise in $E_0$ at this time achieved 
statistical significance, variations in $E_0$ are more effective 
in modifying systemic insulin levels than are changes in $E_0$ 
because of the higher concentrations of insulin presented to 
the liver. Figure 5 plots the relationship between the total 
amount of insulin presented to the liver and the arterial 
insulin concentration, which should also remain constant 
if extractions do not change. Figure 5, which used all the 
individual time plots for each dog during the control and 
20- to 50-min periods of each infusion, demonstrates that 
during the equilibrium period of the first infusion, the 
rise in arterial insulin levels was less commensurate with 
the increased amounts of insulin presented to the liver. 
The time course of this divergence from linearity is similar to 
that observed when intraduodenal glucose was admin-
istered to dogs (7). Five minutes after glucose was given, 
the ratio of arterial plasma insulin to total insulin delivered 
to the liver decreased and remained below the control 
ratio for 60 min. After this time, the ratio was the same as 
during the control period. The return of this relationship 
to control values, and not below, during the infusion of 
50.8 μU/min of insulin, achieving arterial levels averaging
The peripheral plasma insulin response to an abrupt increase in pancreatic insulin secretion will be modulated by a slight increase in hepatic insulin uptake and by a more pronounced increase in peripheral tissue uptake requiring approximately 1 h for equilibration. Such a mechanism was postulated in general terms by Kanazawa et al. (9) to account for their observation that peripheral plasma insulin curves were not a simple reflection of those found in the pancreaticoduodenal vein. Upon cessation of insulin infusion, a rapid decrease in percent uptake of insulin was observed in each vascular bed with, in some instances, a net efflux of insulin being demonstrated. This washing out of insulin may be due to displacement of insulin bound to capillaries as demonstrated by Rasio (16) and could affect the time course of the disappearance of insulin from the plasma. Variations in the rate of this washout from tissues with different rates of perfusion might contribute to the nonlinearity of the log concentration-disappearance curve of insulin which was observed in this study.

The fall in hepatic glucose output from a control value of 36 ± 3 mg/min to a nadir of 16 ± 5 mg/min at 20 min after the onset of insulin infusion is similar to that observed by Madison et al. (11) in dogs with portocaval shunts. However, in their studies, a progressive fall of HGO was observed during the infusion of 46 mU/min of insulin, so that after 70 min it had fallen to 7.4 mg/min compared with a control value of 43.3 mg/min. In the present study, control values had been regained by this time. The essential difference between their preparation and ours is the intact portal circulation in our dogs which ensures that the liver received high portal vein levels of glucagon, should this hormone be secreted in response to hypoglycemia. Studies currently in progress indicate that a significant rise in dog portal vein glucagon levels occurs in response to the hypoglycemia found during the first period of insulin infusion in the present study. Madison et al. (11) stressed the importance of avoiding profound hypoglycemia in the assessment of hepatic response to insulin. In the present study, however, HGO started to increase toward control values 30 min after the start of insulin infusion when the arterial plasma glucose had fallen to only 90 ± 4 mg/100 ml from a mean control value of 106 ± 3 mg/100 ml (Fig. 4). Despite this, arterial plasma glucose continued to fall to a nadir of 60 ± 4 mg/100 ml at the end of the infusion when HGO was back to control values. This suggests that increased peripheral glucose utilization is the major factor in maintaining insulin-induced hypoglycemia. In this connection, the persistent increase in $E_h$ found during insulin infusion may have physiological significance. When the insulin infusion was stopped a prompt rise in HGO occurred, suggesting that insulin still exerted an inhibitory effect on this function even though the value had returned to control level during the infusion.

APPENDIX

Figure 3 is a schematic representation of insulin kinetics under steady-state conditions. The body has been divided into hepatic (h), mesenteric (m), and remaining systemic (s) vascular beds, each of which removes insulin from the circulation with a coefficient of extraction, $E_i$, which is the percent extraction by that vascular bed expressed as a proportion of unity. The vessels connecting these beds each carry an insulin flux ($F_i$, mU/min) which is the product of
plasma flow (Q, ml/min) and plasma insulin concentration (I, \( \mu U/ml \)) times 10\(^{-3} \). Input of insulin into the system representing pancreatic insulin secretion plus or minus insulin infused into the portal vein is expressed as S (mU/min). The flow and fluxes and insulin concentrations are designated by the following subscripts (see Fig. 3): a, ascending aorta; ha, hepatic artery; m, mesenteric supply entering mesenteric bed including the spleen; s, remaining systemic arterial flow; v, systemic venous return; hv, hepatic vein; p, portal vein, cv, pooled venous return.

It is assumed that no extraction occurs across the cardiopulmonary circuit and the spleen is considered a representative part of the mesenteric-portal circuit. The following equations may then be derived.

\[
I_a = I_{ha} = I_m = I_v
\]

in which \( I_p \) is the insulin concentration in portal vein prior to entry of S from pancreas and is equivalent to the insulin concentration in the mesenteric vein. In Table 3 the portal vein insulin concentration includes insulin secreted by the pancreas or infused during the experiment and is not equivalent to \( I_p \) in the following equations.

\[
E_m = \frac{Q_s (I_a - I_p)}{Q_s I_a} \quad (1)
\]

insulin extracted by the liver

\[
- Q_{ha} I_a + Q_{pl} + S - I_{hv} (Q_{ha} + Q_p)
\]

and

\[
E_h = \frac{Q_{ha} I_a + Q_{pl} I_p + S - I_{hv} (Q_{ha} + Q_p)}{Q_{ha} I_a + Q_{pl} I_p + S}
\]

insulin extracted systemically = \( Q_s (I_a - I_v) \)

and

\[
E_s = \frac{Q_s (I_a - I_v)}{Q_s I_s}
\]

total plasma flow \( Q = Q_{ha} + Q_s + Q_v \)

Since the amount of insulin entering and leaving the heart is the same

\[
I_a (Q_{ha} + Q_p + Q_d) = I_{hv} Q_{hv} + I_v Q_s
\]

\[
= I_p (Q_{ha} + Q_p + Q_d) = I_{hv} (Q_{ha} + Q_p) + I_v Q_s
\]

\[
E_v = \frac{I_p (Q_{ha} + Q_p + Q_d) - I_{hv} (Q_{ha} + Q_p)}{Q_v}
\]

or

\[
E_v = \frac{I_p (Q_{ha} + Q_p + Q_d)}{Q_v} + 1 - I_{hv} \left( \frac{Q_{ha} + Q_p}{Q_v} \right)
\]

Substituting for \( I_v \), in equation 3 gives

\[
E_s = \frac{Q_s I_h - Q_s \left( \frac{Q_{ha} I_a + Q_{pl} I_p + I_v - I_{hv} Q_{ha} - I_{hv} Q_p}{Q_{ha} I_a + Q_{pl} I_p + S} \right)}{Q_s I_h}
\]

\[
E_s = \frac{I_{hv} (Q_{ha} + Q_p) - I_v (Q_{ha} + Q_p)}{Q_s I_h}
\]

\[
E_s = \frac{(Q_{ha} + Q_p) (I_{hv} - I_v)}{Q_s I_h}
\]

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Present address of P. E. Harding: Endocrine Unit, Royal Adelaide Hospital, Adelaide, Australia.

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