Renal Glucose Production Compensates for the Liver During the Anhepatic Phase of Liver Transplantation

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The extent of the renal contribution to postabsorptive endogenous glucose production (EGP) in humans is controversial. We measured EGP in the absence of the liver during the anhepatic phase (AH) of liver transplantation in five patients (aged 46.4 ± 10.2 years, two women). Stable labeling of plasma glucose (PG) was achieved for a 2-h period before the AH by primed continuous infusion of di-deuterated 6,6[$^2H_2$]glucose (1.7 mg/min) and continued throughout the AH. PG was maintained above the fasting level (6.1 ± 2.73 mmol/l) with 5% dextrose labeled with 6,6[$^2H_2$]glucose throughout the AH (mean level during the AH 0.98 ± 0.45 mg · kg^{-1} · min^{-1}). Isotopic enrichment remained stable at 0.84 ± 0.21% atom percent excess throughout. EGP, calculated by use of a modified Steele equation, decreased from 2.6 ± 1.24 at baseline to 0.97 ± 0.9 mg · kg^{-1} · min^{-1} (36% baseline, P = 0.045) but recovered at ~30 min to reach 1.38 ± 0.83 mg · kg^{-1} · min^{-1} (54% baseline) by 60 min. Epinephrine, lactate, free fatty acid, and glycerol levels increased significantly (0.79 ± 0.74 to 3.65 ± 2.1 nmol/l, P = 0.005; 1.88 ± 0.43 to 3.46 ± 0.9 mmol/l, P = 0.024; 543.9 ± 215.5 to 705.5 ± 219.2 µmol/l, P = 0.012; 75.6 ± 30.2 to 139 ± 96.3 µmol/l, P = 0.003, respectively). These data show that postabsorptive nonhepatic glucose production in humans may contribute to greater than one-third of overall EGP, increasing when required, and that it is associated with a stress response and increased gluconeogenic substrate availability. We conclude that extrahepatic tissues, most notably those of the kidney, make a significant contribution to EGP in humans. *Diabetes* 49:450–456, 2000

The source of endogenous glucose production (EGP) in the postabsorptive state in humans is controversial. Although there is no doubt of the major role of the liver in supporting plasma glucose (PG) levels by gluconeogenesis and glycogenolysis, the possible contribution from other sources, particularly the kidneys, remains under debate. Early studies using net balance measurements concluded the renal contribution was trivial, except in stressed states and during prolonged fasting. More recently, a series of investigations combining isotopic tracer techniques with regional balance studies have estimated the magnitude of renal gluconeogenesis after an overnight fast in humans varied, with results ranging from 5% (1) to 25% (2,3). Glutamine appears to be the major substrate for renal gluconeogenesis with the kidney estimated in one study to account for 90% of glutamine gluconeogenesis (4). The discrepancies in the estimations of postabsorptive renal gluconeogenesis are difficult to resolve, but possible contributors include the lack of access to the portal vein in human studies, the small arteriovenous differences across the kidneys, and the use of different tracer infusions between apparently similar protocols.

The removal of the liver during the procedure of liver transplantation provides a unique opportunity to measure nonhepatic EGP in human subjects. We therefore set out to measure EGP in the absence of the liver throughout the anhepatic phase (AH) of liver transplantation by use of the tracer dilution technique in five patients with chronic liver disease who were undergoing whole-organ transplantation.

RESEARCH DESIGN AND METHODS

A study cohort of five patients (two women) with end-stage liver disease (three with primary biliary cirrhosis, two with alcoholic liver disease) who were aged 46.4 ± 10.2 years and were on the waiting list for liver transplantation were recruited. Their chronic hepatic failure was stable, and none of the patients were receiving parental nutrition or were on dietary restriction. Our unit does not encourage treatment with protein restriction or a high-carbohydrate diet, and food supplements are not used routinely. Only one patient was prescribed a liquid food supplement for poor appetite, and one patient was advised to change from a habitual once-daily meal pattern to smaller, more frequent meals. This patient was also advised to maintain a low-salt diet to prevent worsening of secondary hyperaldosteronism. All patients had normal pretransplant renal function tests (mean serum creatinine level 117 ± 4.6 µmol/l) and did not have diabetes (mean fasting blood glucose level <6 mmol/l). The patients were prescribed similar pretransplant medications for liver failure; these medications included spironolactone (3), 40 mg propanolol in the morning or twice a day (3), frusemide (2), 2.5 mg bendrofluazide (1), amlodipine (1), ranitidine (1), ursodeoxycholic acid (1), vitamin supplements (1), and antibiotics (1). None of the patients were on steroids, and none were ventilated presurgery. All of the patients were fully aware of their participation in the study. The study was approved by the Ethical Committee of King's College Hospital, and all of the subjects gave written informed consent.

All studies took place in the operating theaters of the liver unit. All patients had been fasted as soon as they were aware of the availability of a donor organ (range 6–10 h). The study began in the anesthetics room adjacent to the operating theater. The anesthesiologist placed arterial and venous access catheters, including a central venous line. Before induction of anesthesia, a blood sample was taken for later measurement of background isotopic enrichment of glucose and estimation of fasting PG levels. A primed (170 mg) continuous infusion (1.7 mg/min) of di-deuterated 6,6[$^2H_2$]glucose (Cambridge Isotope, Woburn, MA)

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AH, anhepatic phase; APE, atom percent excess; EGP, endogenous glucose production; PG, plasma glucose.

was started via the central venous catheter, and a fixed infusion of 5% dextrose (Baxter Healthcare, Thetford, U.K.) was initiated concomitantly at a rate of 30–100 ml/h as specified by the Liver Unit operating protocol. This procedure was continued throughout the preoperative period and AH, and, in two cases, the infusion increased from 100 to 125 ml/h after the final baseline blood sample. The infusion was enriched with tracer at 8 mg/g of dextrose to maintain stable PG enrichment (5) subtracted from the calculated glucose rate of appearance in the calculations of EGP. Anesthesia was started at this time. A 90-min equilibration period was allowed to achieve steady-state tracer enrichment before taking five samples at –30, –20, –15, –10, and 0 min for determination of baseline levels of isotopic enrichment, catecholamine, free fatty acid, glycerol, lactate, insulin, and C-peptide. All subjects were thus assessed for EGP at least 8 h after their last food ingestion. However, operative procedures varied. The porta hepatis was dissected, the common bile duct and the lymphatics were ligated and divided, and the hepatic artery was clamped and divided. Subsequently, the portal vein was skeletonized, the liver lobes were mobilized, and the inferior vena cava were encircled above and below the liver. The sphighian veins were ligated, and then the portal and supra- and inferior cava were clamped, and a veno-venous bypass was initiated (femoroportal to axillary) to maintain venous return and circulating blood volume during the AH. The liver was removed. Blood samples at 0 min were taken immediately before clamping of the portal vein. Blood loss during surgery was minimized by using cutting and dissecting diathermy dissection. Estimated blood loss was replaced postoperatively, and no blood was given during AH.

Arterial PG levels were measured every 10 min during the 1-h AH. Additional arterial blood samples were withdrawn for later measurement of isotopic enrichment, intermediate metabolites, insulin, C-peptide, and catecholamine levels. Levels of PG and lactate were determined immediately in duplicate through use of glucose and lactate oxidase techniques, respectively (YSI, Yellow Springs, OH). Blood samples for the determination of levels of isotopic enrichment in terms of atom percent excess (APE) were collected in oxalate-fluoride tubes; blood samples for catecholamines were collected in lithium heparin tubes with sodium metabisulphate; and blood samples for insulin and C-peptide were collected in plain tubes. All samples were placed on ice and centrifuged within 30 min at 4°C. Except for samples to determine levels of catecholamines, which were stored at –70°C, all plasma was stored at –20°C until the time of the assay. Plasma [$_2H^2$]glucose enrichment was determined by gas chromatography-mass spectrometry (MSD 5971; Hewlett-Packard, Berkshire, U.K.) by use of selected ion monitoring of a glucose aldonitrile pentacetate derivative (6). The ions monitored were of molecular mass 187 and 189, representing [M-C_4H_9]$^+$ and the corresponding fragment enriched with two deuterium atoms, respectively. The within-assay coefficient of variation of isotopic enrichment was 2%. Plasma insulin and C-peptide levels were measured by radioimmunoassay (BPC-dpc, Llanberis, Wales). Free fatty acid (Alpha Labs, Hampshire, U.K.) and glycerol (Randox Labs, Crumlin, Northern Ireland) were measured by enzymatic assay (7,8). Epinephrine and norepinephrine were measured by high-pressure liquid chromatography with electrochemical detection (9).

Glucose production and utilization rates were calculated by the non–steady-state Steele's equation (10). This model has been shown to perform adequately when EGP is the major source of glucose entering the circulation and when tracer concentration in plasma is maintained (11). Before calculation of glucose turnover, PG concentrations and glucose enrichment curves were smoothed using optimal segments technique analysis (12). Data up to the end of the AH, but not including measurements made after connection of the donor liver, were incorporated. EGP was calculated by subtracting the contribution of the labeled 5% exogenous glucose infusion from the total rate of glucose appearance. A volume of distribution of 200 ml/kg and a pool fraction of 0.65 were used, but the calculated volume of distribution during the AH was adjusted using the ratio of body weight–to–recipient liver weight instead of body weight alone. If this was not done, estimated total rates of glucose appearance would have varied by ~2%.

Data in the text are presented as means ± SD. The figures show SE for clarity. Data at baseline were compared with those during the AH by using pair-wise comparisons with Student's t test. A P value of <0.05 was considered statistically significant.

RESULTS

PG, isotopic enrichment, insulin, and C-peptide concentrations. The mean level of PG at induction of anesthesia was 6.1 ± 2.7 mmol/l; it increased to 8.2 ± 1.9 at baseline (–30 to 0 min pre-AH) and decreased to 7.46 ± 2.26 mmol/l during the AH, despite continued exogenous-labeled glucose infusion at 0.98 ± 0.45 mg · kg^{-1} · min^{-1} (Fig. 1). Despite exogenous glucose infusion and removal of the liver, there was minimal intrasubject variability in isotopic enrichment throughout the AH. It remained stable at a mean of 0.84 ± 0.21% APE with an intra-subject coefficient of variation of 2.0 ± 0.4%. There were slight but nonsignificant changes in plasma insulin (30.4 ± 40.9 at baseline, maximum 80.1 ± 71.3 mU/l during the AH and 29.5 ± 21.2 mU/l [P = 0.30 and 0.88, respectively, vs. baseline]) and C-peptide levels (baseline value of 1,376 ± 354 to 1,197.9 ± 463.5 pmol/l at the end of the AH [P = 0.36]) (Fig. 2).

Catecholamines and metabolic substrates. Plasma catecholamine and all metabolic substrate levels measured increased during the AH (Figs. 3 and 4). Epinephrine levels increased significantly from 0.79 ± 0.74 nmol/l at baseline to 3.65 ± 2.1 nmol/l by the end of the AH (P = 0.005). Norepinephrine levels also increased significantly during the AH (7.1 ± 6.4 vs. 12.4 ± 7.3 nmol/l, baseline vs. AH, P = 0.01). Plasma free fatty acids, glycerol, and lactate levels increased significantly during the AH (543.9 ± 215.5 vs. 705.5 ± 219.2 µmol/l, P = 0.012; 75.6 ± 30.2 vs. 139 ± 96.3 µmol/l, P = 0.003; 1.9 ± 0.43 vs. 3.46 ± 0.9 mmol/l, P = 0.024; baseline vs. AH, respectively).

EGP and glucose disposal. Mean baseline EGP was 2.61 ± 1.24mg · kg^{-1} · min^{-1}. The start of the AH was associated with a decrease in EGP to a nadir of 36.4 ± 33.3% of baseline at 30 min (P = 0.045 vs. baseline) (Fig. 5). EGP subsequently recovered, achieving a 53.7 ± 31.9% baseline by the end of the 1-h AH, which was not significantly different from baseline (P = 0.14 vs. baseline). Glucose disappearance and mean glucose clearance rate remained stable throughout the AH (Fig. 6). The baseline value of the glucose disappearance rate (2.73 ± 1.12 mg · kg^{-1} · min^{-1}) matched the baseline total rate of glucose appearance plus the small exogenous glucose infusion.

DISCUSSION

We have shown that EGP does not fall to zero in the absence of the liver during the anhepatic phase of liver transplantation. All of our patients had whole-organ transplantation and yet maintained EGP as the whole liver was removed, initially at 36% of baseline and increasing over time.

In theory, any nonhepatic tissue might contribute to the measured glucose entry into the circulation during the AH of the study. Extrahepatic splanchnic tissue is one possibility, but the leading candidate for extrahepatic EGP must be the kidneys (13). Glucose in muscle is stored primarily as glycogen and is used up during anaerobic (glycolysis) and aerobic metabolism (14). The enzymatic capability for gluconeogenesis is not present in the myocyte or adipocyte, because they lack significant amounts of glucose-6-phosphatase (15). In contrast, the cells of the renal proximal tubule possess enormous potential for glucose production from metabolic substrates (16). Studies in humans that use a combination of isotope dilution, arteriovenous difference measurements, and estimation of renal blood flow have shown renal glucose production to rise in healthy people by 100% during epinephrine infusion studies (3). In our study, epinephrine levels increased significantly to double baseline values during the AH. This rise in epinephrine would be the stimulus for increased renal gluconeogenesis during the AH and increased generation of gluconeogenic precursors from fat and muscle.

The increase in gluconeogenic substrate levels during the AH certainly provides for increased uptake and incorporation into glucose by the kidneys. Studies in humans have suggested these metabolites to be the main renal gluconeogenic precursors (13,16,17). Cersosimo et al. (18) demonstrated that lactate

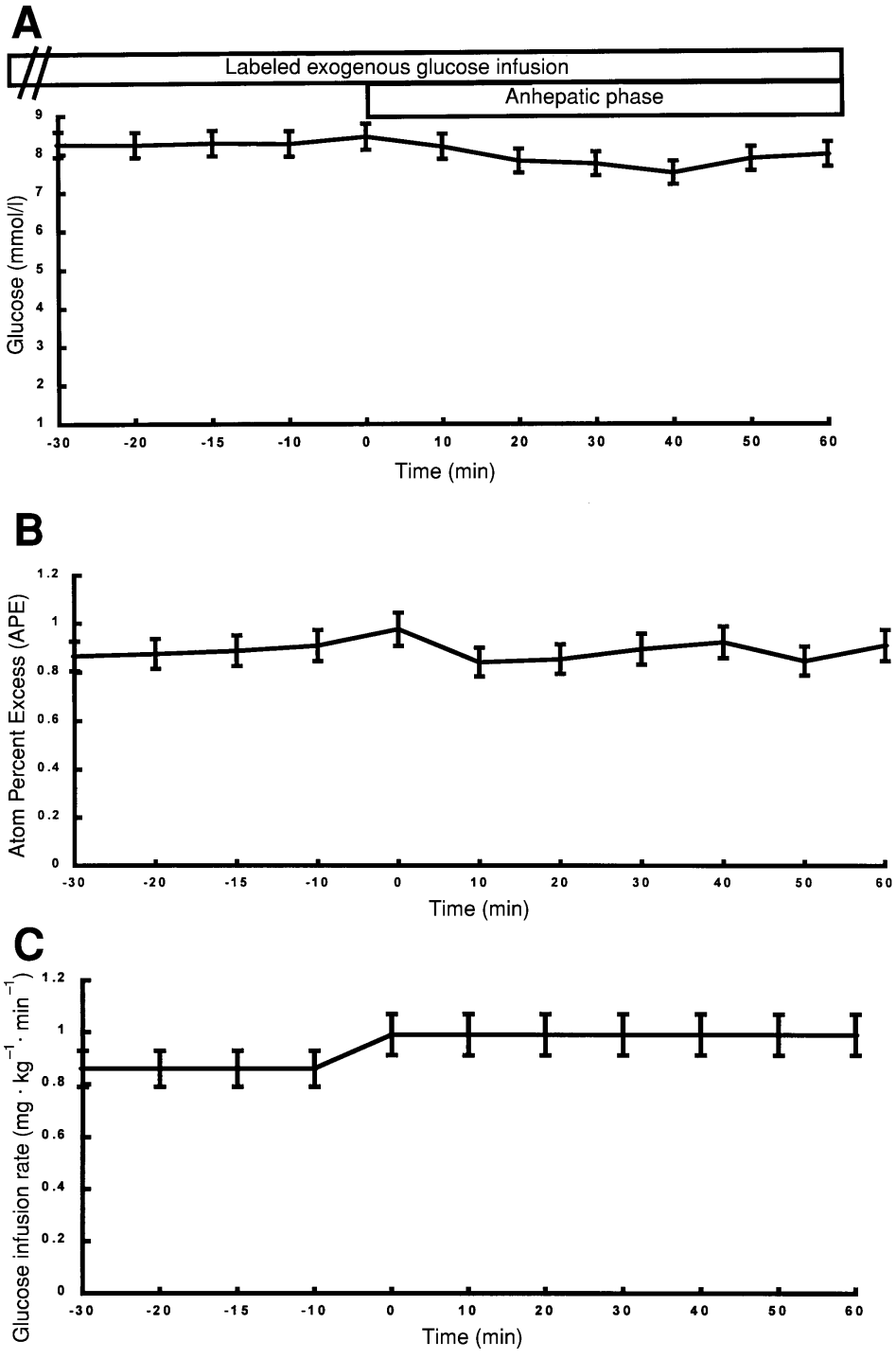

FIG. 1. Glucose profiles (*A*), labeling of PG by di-deuterated glucose (*B*), and glucose infusion rates (*C*) before and during the AH of whole-organ liver transplantation in five human subjects. In all three panels, AH denotes the time between cross-clamping the recipient liver and the initiation of the AH. Data are means ± SE.

could account for 40% of postabsoprtive renal glucose production and for 60% during hypoglycemia. Our data therefore suggest that the rise in gluconeogenic substrates sustains the increase in renal glucose production during the AH.

Postabsorptive studies in animals and healthy humans indicate that renal glucose release accounts for up to 25% of glucose released into the circulation (2,3). If we assume all of the EGP measured in our study during the absence of the liver to be renal, our higher values (of the order of 36%) should be explored.

One possibility is that some of our subjects were not truly postabsorptive. Liver transplantation is scheduled as an emergency when a suitable donor becomes available, and it is possible that the preoperative fast was not as long as 10 h, leaving some contribution to apparent EGP from residual food absorption. The mean PG level at the initiation of anesthesia was slightly high in these nondiabetic patients. However, we believe that this is unlikely for the following reasons: *1*) the stability of the PG enrichment during the last 30 min of the preoperative tracer infusion does not suggest a changing entry of unlabeled glucose into the circulation; *2*) the estimated nonhepatic EGP fell rapidly upon removal of the liver and then began to rise, suggesting a reliance on endogenous mechanisms alone initially, followed by a compensatory exaggeration of those mechanisms; and *3*) although the minimal time

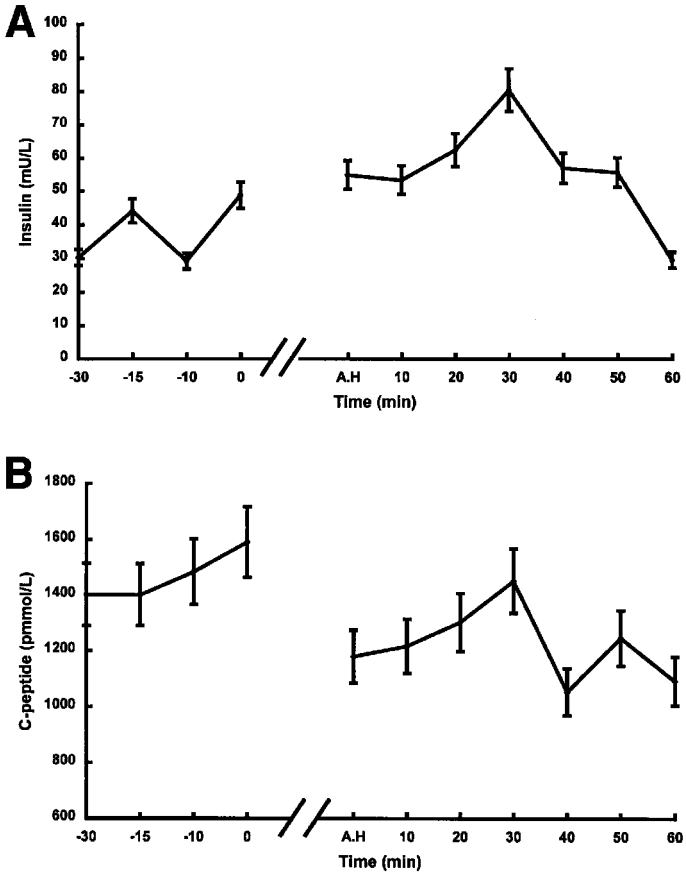

FIG. 2. Circulating insulin (*A*) and C-peptide (*B*) levels before and during the AH of whole-organ transplantation. Data are means ± SE.

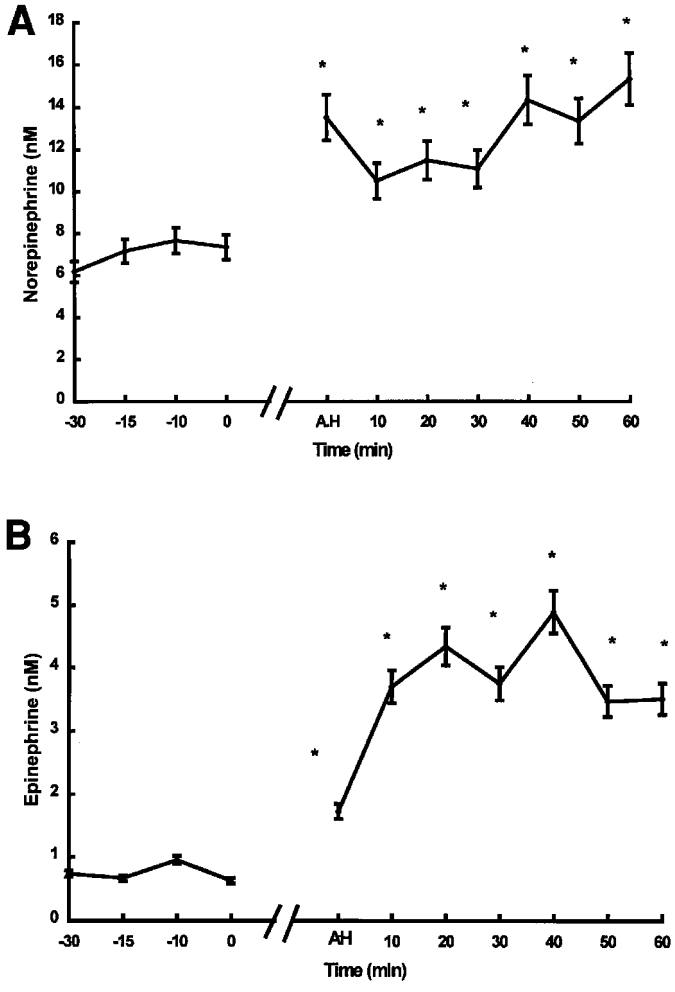

FIG. 3. Circulating norepinephrine (*A*) and epinephrine (*B*) during the AH of whole-organ transplantation. Data are means ± SE. *Significantly different from baseline.

between the last meal and induction of anesthesia was 6 h, the patients remained fasted with only minimal infusion of exogenous glucose for a further 2 h, at least until baseline measurements were made. Therefore, the slightly high overall basal EGP of our subjects is probably a response to the stress of preparing for surgery and is reflected by the high basal epinephrine levels (normal postabsorptive values are usually in the order of 0.15 nmol/l [19]). These elevated epinephrine levels would be expected to increase renal and hepatic glucose production with the further increase in catecholamine levels during the AH, further driving renal gluconeogenesis.

It is possible that the pretransplant chronic liver disease of our subjects made them more dependent on renal gluconeogenesis in the preoperative state. In one study in rats, residual hepatic tissue maintained baseline EGP with a stable contribution from the kidneys after 70% hepatectomy, suggesting that hepatocytes can make major compensations in EGP (20). However, in end-stage human disease with substantial disorganization of liver architecture, it is likely that hepatic EGP was reduced at baseline (21). Nevertheless, substantial hepatic compensation is suggested by the significant decrease in EGP after hepatectomy with the extrahepatic gluconeogenesis making an acute response. Finally, the insulin-resistant state of chronic liver disease (22) and the stress of the surgical procedure could both contribute to the higher value of renal glucose production obtained by our methods.

We did not obtain measurements of EGP in a control group. The anesthetic procedures for liver transplantation are specific, and measurements made in other abdominal surgeries would be different in aspects other than hepatectomy alone. It is possible, therefore, that the absolute values for renal glucose production obtained in our study were influenced by other aspects of the operation, such as anesthetic drugs. There are few reports of EGP estimations during surgery, although there is evidence that certain anesthetic agents can increase EGP (23), and the extent of the postoperative rise in EGP is proportional to the time the peritoneal cavity is open (24). Neither of these factors is likely to have influenced the relative changes seen in our subjects; regardless of what was driving EGP during the AH, the source of the glucose remained unequivocal, and the time of operation was remarkably stable. The failure to see any significant change in insulin or C-peptide levels during the AH may seem surprising: one might have expected a stress-related increment initially and/or a reduction in insulin clearance with removal of the liver. A type 2 error is possible, but no significant changes were seen in the glucose disappearance or mean clearance rates, and no changes in portal insulin were observed in Nakamura's rat model of acute hepatectomy (25).

Finally, the models used to calculate EGP may have become unreliable during the removal of the host liver. The

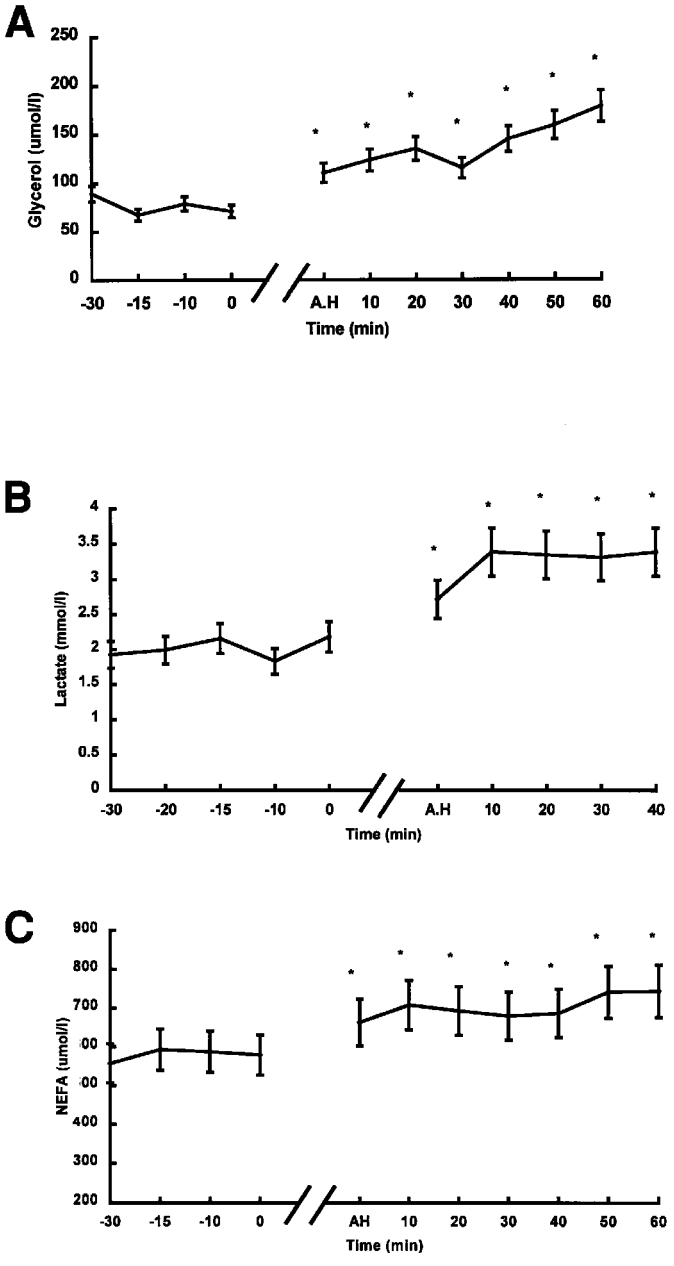

FIG. 4. Circulating glycerol (*A*), lactate (*B*), and nonesterified fatty acids (*C*) before and during the AH of whole-organ liver transplantation. Data are means ± SE. *Significantly different from baseline.

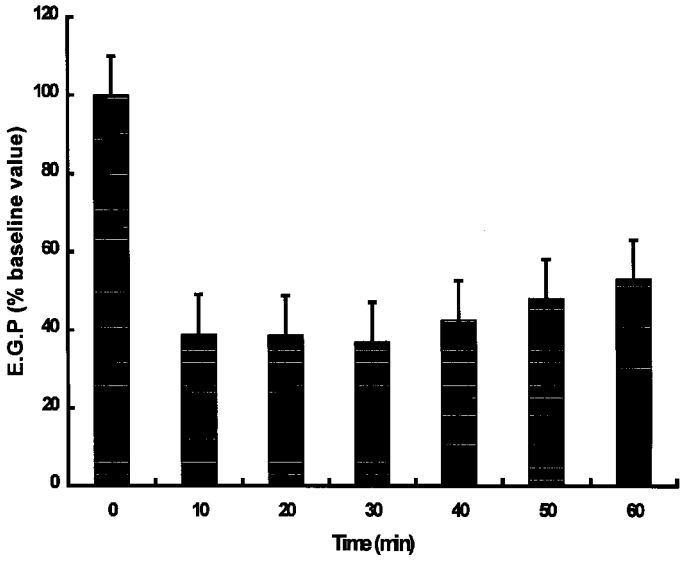

FIG. 5. EGP levels expressed as the percentage of change from baseline before and during the AH of whole-organ liver transplantation. Data are means ± SE.

model we used to calculate EGP was designed to examine the non–steady state. It is possible that more frequent sampling during this turbulent time might have altered the findings. We think that this is unlikely. The raw data did not "bounce" excessively. The most likely relevant disturbance might be a change in the volume of distribution of tracer by removal of the liver. We believe that this effect is negligible. The operative procedure is designed to minimize blood loss at removal of the liver by draining the liver into the rest of the circulation immediately before hepatic removal. We did adjust the volume of distribution for the loss of the liver, but this made a negligible impact on the estimates of the total rate of glucose appearance. We also applied the Mari model (26), which uses two compartments, to our data and found the same patterns of EGP response (data not shown). Most reassuring was the stability of PG enrichment throughout the study, achieved in the presence of an infusion of exogenous glucose labeled in a model-driven anticipation of the need, which makes it unlikely that the removal of the liver significantly affected the performance of the model. The model has, of course, performed well in other situations of non–steady state, such as progressive hypoglycemia (27).

The clinical implications of our findings are varied. Severe hypoglycemia has been described in nondiabetic patients with renal failure (28,29). The usual explanation for this has been the reduced clearance of insulin in the presence of renal failure (30). Our data suggest that the absence of the significant contribution of renal glucose production to net EGP is an alternative explanation. Renal glucose production has recently been shown to increase during hypoglycemic clamp studies in humans (31,32), suggesting a role for the kidney in glucose counterregulation to hypoglycemia. Furthermore, renal glucose production is insulin sensitive (2), and suppression of renal gluconeogenesis may contribute to the high risk of hypoglycemia that is associated with peripherally-delivered insulin of conventional subcutaneous therapy versus intraperitoneal insulin delivery (33).

We conclude that renal glucose production makes a significant contribution to net EGP in the absence of the liver and that an increase in the concentration of epinephrine and gluconeogenic precursors is essential to sustaining the rise in renal glucose output. These findings are relevant to the narrow setting of treating diabetic patients who have nephropathy and to our understanding of glucose homeostasis, its derangement in diabetes of all types, and its treatment.

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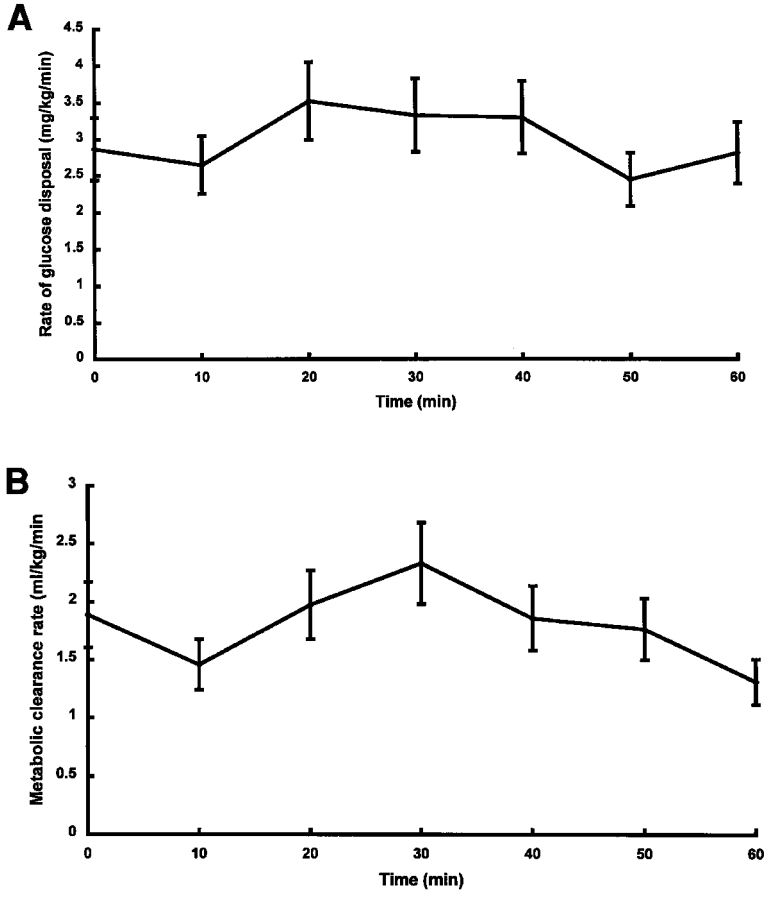

FIG. 6. Rate of glucose disposal (*A*) and metabolic clearance rate (*B*) during the AH of whole-organ liver transplantation. Data are means ± SE.

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