The Influence of Hepatic Venous Oxygen Saturation on the Liver's Synthetic Response to Metabolic Stress (44382)

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Abstract. **Hepatic oxygen consumption (HVO_2) and hepatic venous oxygen saturation ($S_{hv}O_2$) were assessed in the isolated perfused rat liver under conditions that mimic critical illness in an effort to assess their utility in predicting the functional status of the liver. Flow rates were adjusted over the physiologic range of oxygen transport as indicated by the hepatic venous O_2 saturation range of 10%–75%. HVO_2 was found to be transport (HDO_2) dependent only when perfusate conditions contained an increased counterregulatory hormone (glucagon, epinephrine, dexamethasone) stimulus or a high lactate concentration. In the absence of a metabolic load, (substrate and hormone-free perfusate), HVO_2 was transport independent even at an $S_{hv}O_2$ as low as 10%. Although transport dependency of HVO_2 is frequently used to infer tissue ischemia, hepatic oxygen consumption was poorly correlated with synthetic function under all conditions. In contrast, hepatic albumin production was directly related to $S_{hv}O_2$ at all levels of HDO_2 and under all perfusion conditions indicating that this metabolic process is particularly sensitive to reductions in oxygen availability, which is more reliably predicted by venous saturation measurements. However, glucose and urea synthesis were almost independent of $S_{hv}O_2$. These findings indicate that various hepatic processes are affected differentially by stress conditions and flow alterations that may exist during critical illness, and protein synthesis is particularly sensitive to oxygen deprivation. Additionally, hepatic venous oxygen saturation measurement, but not HVO_2, serves as a useful surrogate marker for hepatic albumin production suggesting that regional venous oximetry may play an important role in the detection of hepatic functional impairment.** [P.S.E.B.M. 1999, Vol 221]

Hepatic metabolism has received limited attention in the study of the stress response to trauma and critical illness. Further study of this organ system is warranted since evidence indicates that hepatic functional deterioration contributes to clinical morbidity, particularly *via* the impairment of its clearance and synthetic capacity and the permissive effects upon downstream organ dysfunction (1). Central nervous system abnormalities (2), pulmonary insufficiency (3), cardiac (4) and renal failure (5) have all been associated with acute and chronic hepatic failure. Despite the recognition that hepatic insufficiency may play a major role in the amplification of multiple organ dysfunction frequently observed following trauma and the Systemic Inflammatory Response Syndrome (SIRS) (6), routine diagnostic instruments to evaluate hepatic function are not readily available. This results from the lack of a generally accepted, rapid response tool that can provide liver-specific, physiologically relevant diagnostic information.

Regional ischemia/hypoxia is believed to be a major mechanism contributing to hepatic dysfunction in seriously ill patients (7). Consequently, the hepatic oxygen consumption/oxygen delivery balance has been studied in experimental models with the goal of identifying parameters that potentially may provide diagnostic information regarding functional status of the liver. Such reports have produced estimates of critical regional oxygen delivery below which

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hepatic functional activity is believed to become impaired (8, 9). In this light, we studied the isolated perfused rat liver under conditions that mimic critical illness. The major factors that acutely influence hepatic oxygen metabolism include oxygen availability, metabolizable substrate such as lactate and the ambient endocrine stimulus. We therefore evaluated the hepatic oxygen supply/demand relationship in response to increased concentrations of lactate or elevated counter-regulatory hormones including glucagon, epinephrine, and a glucocorticoid in order to determine whether these factors could induce functional changes. Furthermore, although study of the regional oxygen supply/consumption relationship in response to these factors is of interest, the application of these findings to clinical practice remains difficult since dynamic oxygen data are generally unavailable. Thus, hepatic synthetic capacity was also studied in relationship to hepatic venous oxygen saturation ($S_{hv}O_2$) since it is a clinically measurable index of liver oxygenation (10–12).

Materials and Methods

Isolated Perfused Liver Preparation. Liver perfusions were conducted *in situ* using male Sprague-Dawley rats(250–300 g) after an overnight fast. Previous studies have indicated that 90% of liver glycogen is depleted in this model, thereby minimizing functional changes due to glycogenolysis (13). Animals were anesthetized with i.m. ketamine (50 mg/kg) and xylazine (5 mg/kg) and placed in an incubated (37°C) environment. The portal vein was cannulated and perfused with a blood perfusate that was prepared from a modified Krebs-Henseleit bicarbonate buffer containing 3% bovine serum albumin, 5 m*M* glucose, and washed, fresh bovine red cells compounded to a hemoglobin of 7.5 g/dl. Previous studies have indicated that a sanguinous perfusate maintains hepatic oxygen consumption at a higher level compared to red cell–free perfusates (14). The suprarenal vena cava and hepatic artery were ligated, and the hepatic venous outflow was directed to the return reservoir *via* a cannula introduced into the suprahepatic vena cava through the right atrium; all other tissue beds were totally excluded from the perfusion circuit. Perfusions were conducted using a recirculating system containing a 250-ml reservoir that was oxygenated with a 95% O_2/5% CO_2 gas mixture. Endogenous rat blood washout was performed with the initial 10–20 ml of the perfusate that was wasted prior to establishing the recirculating system. Thereafter, blood sampling could be accomplished immediately prior to the portal vein and just after blood exited the hepatic veins. Pre- and post-hepatic samples were removed every 15 min during a 2-hr perfusion to determine hepatic oxygen consumption. Hemoglobin values were determined with each blood gas measurement, and they remained constant during the perfusion experiments. Metabolite (glucose, urea, albumin) production rates were determined by measuring their accumulation in the perfusion circuit over time.

Perfusate conditions were modified to mimic substrate and endocrine conditions that exist during critical illness (15). Although *in vivo* hormone concentrations are typically present in the 1–10 n*M* range, glucagon and epinephrine were added in excess to accommodate their hepatic clearance over the perfusion cycle. Additionally, previous studies have demonstrated that a physiologically relevant hepatic response is observed at these doses (16). Shortly after baseline blood sampling, sufficient lactate/pyruvate or glucagon/epinephrine were injected into the substrate and hormone free perfusion reservoir (Control; Group I) to make it 20 n*M* glucagon/1 μ*M* epinephrine (Group II) or 5 m*M* lactate/1 m*M* pyruvate (Group III). Substrate and hormone additions were made to the system within 1–3 min of initiating the perfusion. All reagents were diluted in perfusion buffer, and the added volumes did not exceed 1.0 ml. Animals that were used for the hormone stimulation studies were also pretreated with dexamethasone (15 mg/kg i.m.) given in two divided doses 16 and 4 hr prior to liver perfusion. Dexamethasone was omitted from the liver perfusate. Nonetheless, glucocorticoid pretreatment, using a dose comparable to the one used here, has been previously shown to maximize the gluconeogenic capacity of the liver *via* its ability to induce pyruvate carboxylase and phosphoenolpyruvate carboxykinase activity that is sustained over the ensuing 8–12 hr (16). This provided a counter-regulatory hormonal milieu similar to that which is present in the posttraumatic period (triple hormones) (15, 17). Each liver was evaluated at a constant flow rate for a 2-hr period. Flow rates were varied in different livers to evaluate rates ranging from 2.5 to 12 ml/min. The highest and lowest flows corresponded to a hepatic venous oxygen saturation level of ≈10% and 75%, respectively, which is considered a clinically relevant range of oxygenation.

Analytical Measurements. Hepatic oxygen consumption (HVO_2) and delivery (HDO_2) were determined by measuring the pre- and post-hepatic oxygen content gradient every 15 min multiplied by the flow rate that was measured volumetrically at the completion of each experiment. Blood flow was controlled by a Harvard peristaltic pump during the experiment. Oxygen consumption measurements were integrated over time so that each data point represents a complete experiment for a single liver. Blood oxygen content was determined using a Radiometer (Westlake, OH) blood gas system calibrated with bovine blood containing perfusate. The pH of the perfusate was stable at 7.30–7.35 over the experimental period. Liver synthetic function was assessed by measuring albumin, glucose, and urea accumulation in the perfusate over time. Concentration measurements, determined at 15-min intervals, were plotted against time, and production rates were calculated from a linear regression analysis of these data. These production rates were also plotted against the hepatic venous oxygen saturation measured following system stabilization after substrate or hormone additions. Albumin concentration was determined using agarose immunoelectrophoresis, with monospecific anti-rat albumin antibody generated in the

rabbit (Cappel, West Chester, PA). Rat native albumin was used for creation of the standard curve (Sigma, St. Louis, MO). Glucose concentrations were determined using a coupled chromogenic assay based upon glucose oxidase (Trinder Assay, Sigma Co.). To minimize glycolytic activity in collected samples (1.0 ml), specimen tubes contained 10 μmole of sodium fluoride and were cooled in crushed ice immediately after sampling. No corrections were applied for glucose consumption by the perfusate red cell mass. Urea was determined spectrophotometrically using an assay system based on the Bertholot reaction (Sigma Co.).

The studies reported here were approved by the Institutional Review Board of Wayne State University for the care of animal subjects, and the care and handling of the animals were in accord with National Institutes of Health guidelines.

Statistics. Results were presented as two-dimensional linear plots. The mean slopes of these plots (± SEM) were compared using multiple *t*-test comparisons (ANOVA) with significance being determined by the Student-Newman-Keuls test. Differences were considered significant at $P<0.05$.

Results

The relationship between HVO_2 and HDO_2 in the isolated perfused liver is demonstrated in Figure 1. Group I (control, no metabolic load, $n = 31$) exhibited a constant HVO_2 over a 3-fold HDO_2 range (i.e., the regression slope was essentially zero). Even at the lowest end of the HDO_2 range where oxygen extraction is greater than 90% (Fig. 2), oxygen consumption was not found to be transport dependent. On the other hand, when an exogenous metabolic demand was placed on the liver (Groups II, $n = 20$, and III, $n = 31$), HVO_2 declined progressively as HDO_2 was increasingly restricted. Neither of these latter two groups exhibited an apparent inflection point or plateau region in the HVO_2/HDO_2 relationship. Figure 2 demonstrates that these oxygen exchange measurements were conducted over the clinically relevant hepatic venous saturation range indicating that if an inflection point exists, it occurs outside of this range, or it may result from a summation of different metabolic influences in whole-animal models.

Of interest, at high levels of HDO_2 (e.g., 200 ml/min/g in Figure 1), both Groups II and III achieved higher levels of HVO_2 (78.7 and 73.3 ml/min/g, respectively) compared to Group I(56.8 mL/min/g) indicating that oxidative metabolism is substantially augmented provided that oxygen availability is adequate under conditions of a metabolic demand. Correspondingly, the rate of HVO_2 vs. HDO_2 decline is greater in the livers exposed to the triple hormone combination (Group II) relative to the lactate loaded livers (Group III). The regression slope of the hormone treated livers is greater than the lactate group by a factor of 1.65 suggesting that counterregulatory hormones effect a greater oxidative demand stimulus than a substrate load. However, these slopes (Group II vs. Group III) are not statistically

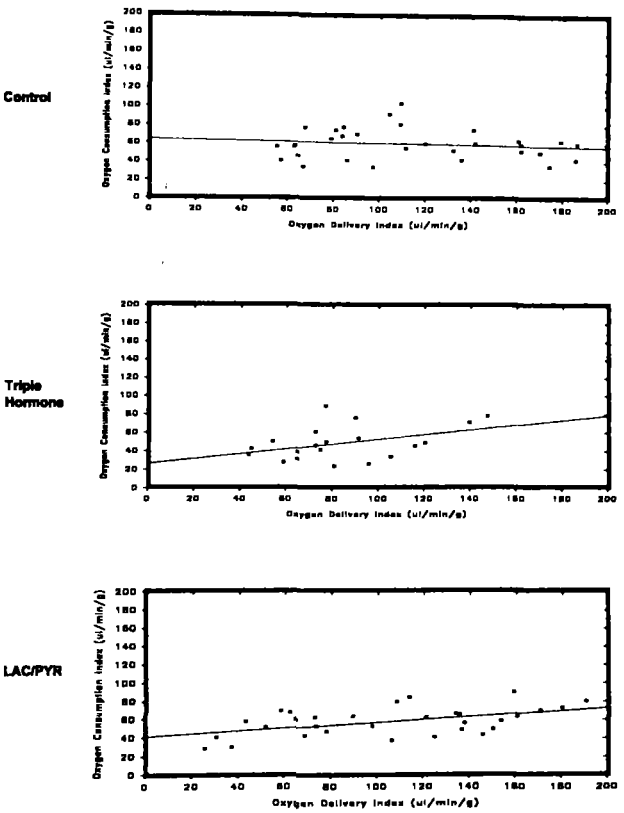

Figure 1. Hepatic oxygen consumption is plotted against oxygen delivery for the isolated perfused rat liver. Livers were perfused with a substrate- and hormone-free perfusate [control; y = −0.035 (± 0.072)x + 63.8 (± 8.76), r = 0.09, P = 0.07, n = 31] a triple hormone containing perfusate [y = 0.26 (± 0.14)x + 26.7 (± 12.1), r = 0.41, P = 0.07, n = 20] or a perfusate containing 5 mM lactate/1 mM pyruvate [y = 0.16 (± 0.05)x + 41.3 (± 6.0), r = 0.49, P = 0.005, n = 31]. An HVO_2 effect due to a restriction of HDO2 is observed only in livers perfused with an extrahepatic metabolic load. Variance is expressed as (± SEM).

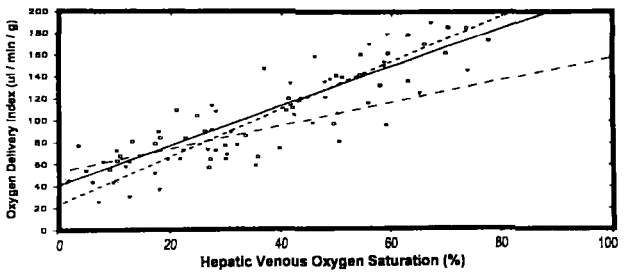

Figure 2. Hepatic oxygen transport is related to hepatic venous oxygen saturation in control o—o ($r = 0.91$, $P = 0.001$), triple hormone treated ●—● ($r = 0.66$, $P = 0.002$) and lactate/pyruvate treated △—△ ($r = 0.90$, $P = 0.001$) livers.

different. Although the overall *P*-value for the analysis of variance of all three groups is $P = 0.025$, only Group III is statistically different from the control population ($P < 0.05$).

Despite the importance commonly ascribed to oxygen consumption as an index of functional status, the relationship observed between HVO_2 and hepatic synthetic capacity under all three study conditions was poor. Albumin was not significantly correlated with HVO_2 in any group (Group I: $r = -0.19$, $P = 0.30$; Group II: $r = 0.04$, $P = 0.88$; Group

III: $P = 0.35$, $P = 0.07$). Furthermore, a similarly poor correlation was noted for hepatic glucose and urea production except under two circumstances – Group III glucose production: $r = 0.41$, $P = 0.02$; Group II urea production: $r = 0.78$, $P = 0.001$. In contrast, Figure 3 shows that albumin synthesis in all three groups is directly related to $S_{hv}O_2$, which is a clinically assessable monitoring parameter. Slope differences among all three curves were not significant ($P = 0.22$).

Hepatic glucose output for the different groups is displayed in Figure 4. Even in the absence of glucogenic substrate, hepatic glucose output is positive in this model. Following the pretreatment of these rats with dexamethasone and administration of glucagon and epinephrine (triple hormone; Group II), glucose production increased by 5–10-fold. Administration of lactate alone to the perfusate augments hepatic glucose production by 2–4-fold relative to control. Probably the most significant aspect of hepatic glucose production in all three groups was that it is essentially independent of hepatic venous oxygen saturation, a distinctly different situation from the albumin synthetic response of the liver. Similarly, hepatic urea production (Fig. 5) is almost unaffected by the progressive decline in HDO_2 in all groups.

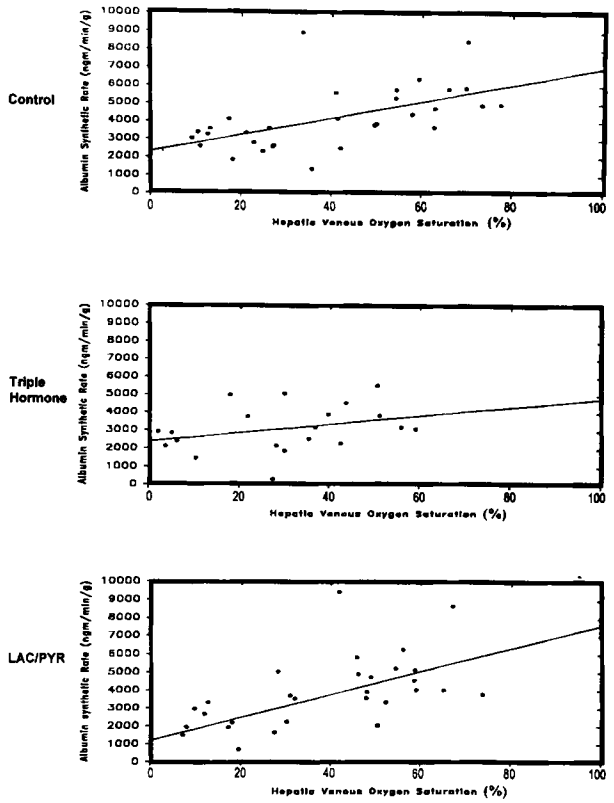

Figure 3. Albumin production is directly related to hepatic venous oxygen saturation in control [$y = 46.9$ (± 12.4)$x + 2315$ (± 564), $r = 0.57$, $P = 0.001$, $n = 31$], triple hormone treated [$y = 24.2$ (± 16.1)$x +$ 2378 (± 558), $r = 0.34$, $P = 0.15$, $n = 20$] and lactate treated [$y = 64.3$ (± 16.6)$x + 1191$ (± 709), $r = 0.58$, $P = 0.001$, $n = 31$] livers. Variance is expressed as ($\pm$ SEM).

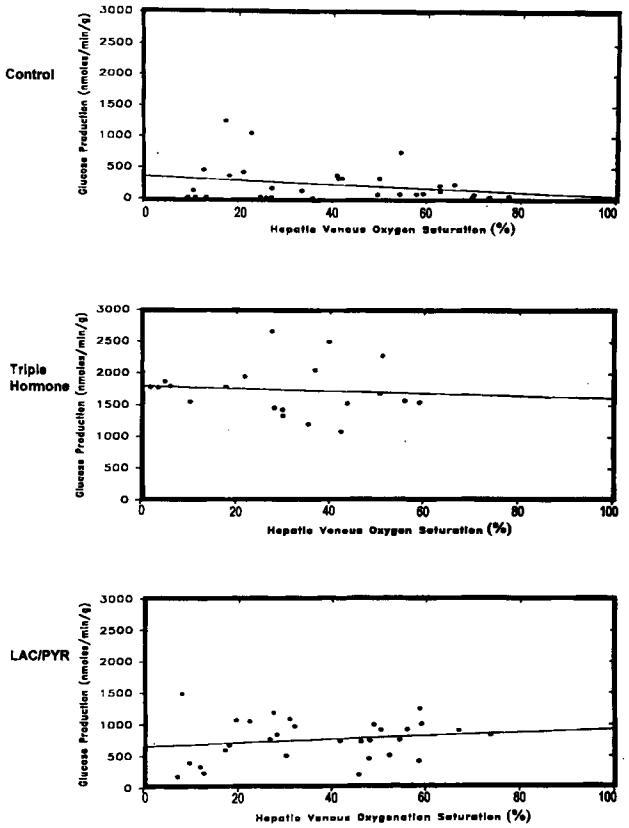

Figure 4. Hepatic glucose production is essentially unaffected by reductions in perfusate flow that was varied over the physiologic range of hepatic venous oxygen saturation.

Discussion

Previous reports have focused on the finding that hepatic oxygen consumption exhibits a biphasic relationship with respect to oxygen delivery (8, 9). At high levels of HDO_2 where oxygen availability is nonlimiting, hepatic oxygen consumption is transport independent but at low levels, these two variables are directly related. These studies have identified the critical HDO_2 to be in the range of 28–50 μl/g-min with a critical oxygen extraction fraction of 68%. Below this critical delivery range, HVO_2 becomes transport dependent, and the liver becomes an organ exhibiting a progressively declining redox state. Doubtless, these studies have provided important experimental descriptors of hepatic function that should serve as groundwork for predicting metabolic events. However, although these observations are of considerable physiologic interest, they are difficult to utilize from the clinical perspective. Notably, regional/visceral oxygen transport data are generally unavailable, and hepatic substrate gradients are essentially unmeasurable under usual clinical circumstances. Furthermore, the relationship of organ oxygen consumption to synthetic ability has not been clearly defined. Thus, the applicability of these findings to decision-making and general care of the critically ill patient remains unclear. Consequently, this study was undertaken to further characterize hepatic oxygen dynamics under stress-like conditions and evaluate the clinical utility of $S_{hv}O_2$ measurements.

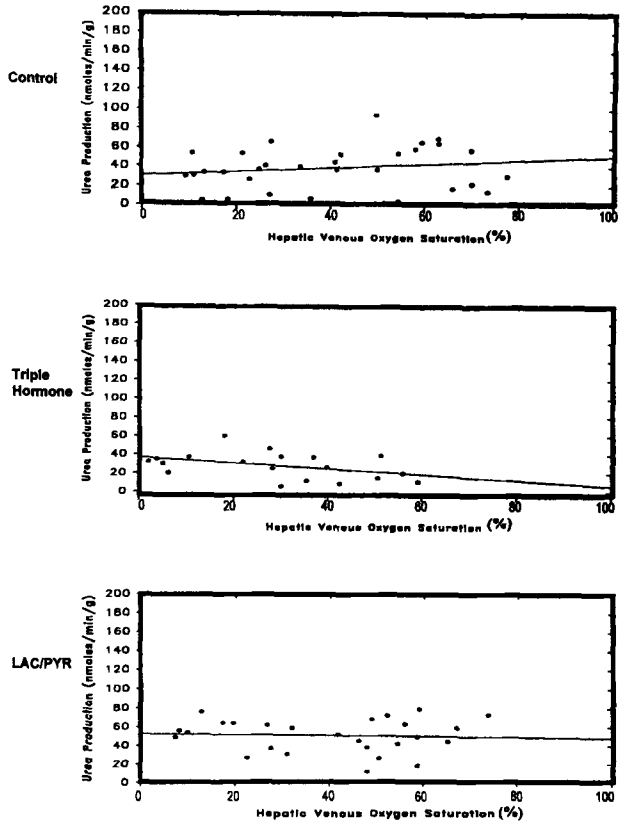

Figure 5. In a manner similar to hepatic glucose production, urea production is influenced by flow reductions to a very limited degree.

The present studies demonstrate that HVO_2 in the isolated perfused liver becomes transport dependent only in the presence of an extra hepatic metabolic demand such as an increased substrate availability (Fig. 1). The counterregulatory stimulus to oxygen utilization similarly influences the HVO_2-versus-HDO_2 relationship although statistical significance under these conditions was not achieved when compared to control or lactate-treated livers. However, the counterregulatory hormones would probably exhibit an even greater effect *in vivo* as a result of the availability of plasma amino acids and ammonia, which could substantially augment the oxygen demand associated with hormone-driven ureagenesis (18). Collectively, the different patterns observed in the groups studied here suggest that previously described biphasic VO_2-versus-DO_2 curves determined *in vivo* or using cross circulation models (8, 9) may not reflect a single phenomenon but may be a composite of different extra-hepatic stimuli occurring at various points on the oxygen transport/consumption relationship.

The inability of the current studies to identify a plateau (oxygen transport independent) portion to the HVO_2-versus-HDO_2 relationship in the hormone and lactate-loaded groups was unexpected. This observation suggests the presence of hypoxic regions in the liver even at the highest oxygen transport rates studied here. Such a hypothesis would be in concert with a previous report by Iles *et al.* (19) who used perfusate characteristics comparable to those used in this report. That study indicated that peak HVO_2 was not reached until hepatic blood flows were raised to greater than twice the flows studied here. Also, Kizaki and Thurman (20) showed a similar HVO_2 dependence upon flow in the glucagon-stimulated, isolated, perfused liver; however, these authors used an asanguinous perfusate making comparisons with the present model difficult. Additional studies using *in vivo* hepatic surface oxygen tension measurements under unstressed conditions have demonstrated that approximately 6%–8% of random determinations exhibited a surface pO_2 in the 0–5 torr range indicating the potential presence of hypoxic regions even under normal resting conditions (21). If minor hypoxic regions indeed exist naturally in the unstimulated liver, they may not become significant until an increased metabolic demand is superimposed upon preexisting sublobular and/or intracellular oxygen gradients present along the course of the hepatic acinus. This hypothesis is supported by reports showing the presence of intracellular oxygen gradients *within* individual hepatocytes (22) and a reduced HVO_2 responsivity to lactate and glucagon in downstream (oxygen-depleted) acinar hepatocytes at a time when upstream cells are fully augmentable (23). Furthermore, induced hepatic ischemia can be demonstrated using three-dimensional fluorescence redox scanning studies of the perfused liver that reveal a marked decline of the centrilobular redox state following the provision of an exogenous metabolic load under normal flow conditions (24).

With respect to the prediction of hepatic synthetic activity, this study focuses on albumin secretion, glucose, and urea production. These three metabolites are commonly evaluated in clinical practice and are representative of major synthetic energy consuming processes in the liver. Each of these processes individually can account for as much as 30%–50% of the total energy consumption of the liver depending upon its metabolic state (7, 18, 25). Significantly, HVO_2 correlated poorly with synthetic function, which was an unexpected finding. We also related these processes to hepatic venous oxygen saturation measurements since this latter parameter has previously been related to hepatic secretory protein synthesis (13), and it can potentially be monitored routinely as a predictive guide of hepatic function as well as an index of resuscitation (10, 26). Venous oximetry, as it is generally used in clinical practice, has been criticized because it only reflects global oxygen exchange dynamics in the central circulation and cannot identify regional oxygen imbalances. On the other hand, hepatic venous oximetry has been advocated as a reliable predictor of hepatic hypoxic injury in both experimental and clinical studies (10–12, 26, 27). If hepatic function can indeed be related to such a clinically measurable parameter, it would offer an indirect means of dynamic hepatic functional assessment. In this study, dynamic hepatic synthetic capacity was evaluated over the physiologic range of venous oxygen saturation in all three groups (Fig. 2). As demonstrated by Figure 3, $S_{hv}O_2$ can be used as a correlative index of hepatic secretory protein production abnormalities. Substantial re-

ductions in albumin synthesis will occur if the $S_{hv}O_2$ declines below approximately 50%. Therefore, it appears that even relatively minor reductions in $S_{hv}O_2$ may have a negative influence upon hepatic albumin secretory capacity.

A similar finding has been previously noted for the substrate and glucagon-induced depression of hepatic fibringen secretion (13). This influence of $S_{hv}O_2$ upon albumin production is consistent with previous findings demonstrating that hepatic acinar albumin synthesis is less zonal in distribution than other metabolic processes. All hepatocytes in the hepatic acinus produce albumin in contrast to the primarily periportal disposition of gluconeogenesis and ureagenesis (28). In fact, after an overnight fast, perivenous hepatocytes have been found to be more active than periportal cells in albumin synthesis (29) making them more susceptible to the oxygen-consuming influences of upstream processes. Although reduced plasma albumin during critical illness is believed to result from numerous mechanisms, a depressed synthetic rate on the basis of hepatic venous desaturation has been reported as a contributing factor (7) that would be consistent with the current observations. Notably, hepatic venous desaturation is commonly observed in critically ill patients (30, 31). Therefore, this suggests a contributing mechanism to the commonly observed refractoriness of plasma albumin concentration changes despite vigorous nutritional repletion over extended periods. Continued or intermittent centrilobular desaturation may impair the liver's ability to maintain a satisfactory albumin production rate. This inhibitory influence on hepatic protein production, however, may not extend to all liver-derived plasma proteins since synthesis of some proteins such as the acute phase reactants may occur predominantly in the periportal region of the liver lobule thereby avoiding centrilobular hypoxic effects (32). The observations that hepatic glucose and urea production remain essentially unaffected by the progressive decline in $S_{hv}O_2$ (Figs. 4 and 5) is also consistent with the heterogeneous nature of the hepatic acinus in which these two metabolic processes exhibit a predominantly periportal distribution (28, 33). It is notable that hypoglycemia is uncommonly observed in critically ill patients, and liver glucose production is usually markedly augmented under acute circumstances, primarily due to the periportal influences of glucagon (33, 34).

In summary, this study indicates that the biphasic nature of oxygen transport/consumption relationships may be derived from a multiplicity of factors including endogenously produced endocrine and substrate factors. More importantly, hepatic protein synthesis, which carries a high priority with respect to host survival during critical illness, may be impaired in a subclinical fashion since protein kinetics are not measured in clinical practice. In addition, HVO_2 appears to be an insufficiently sensitive indicator to predict the stability of important metabolic functions of the liver such as albumin production. Therefore, the use of hepatic venous oximetry may offer a marker for hepatic functional assessment that would permit the timely identification of insufficient regional oxygen transport.

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