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The Physiologic Basis for Nutritional Support in Hepatic Failure

John J. Fath, MD, MPH*

Hepatic failure is often perceived as a unidimensional progression from near normal clinical function (Child's class A) to overt clinical failure (Child's class C). As this view fails to distinguish between patients who are capable of using exogenous protein and those who cannot, it hinders the nutritional support team in determining protein supplementation. This report addresses the physiologic basis for variable findings in hepatic failure and proposes a simple definition of hepatic failure based upon ability to utilize amino acids. (Henry Ford Hosp Med J 1990;38:229-34)

Chronic hepatic failure is often viewed as a unidimensional failure of hepatic organ function related solely to loss of hepatic parenchymal volume. While perhaps correct for certain aspects of hepatic function, this view fails to account for the complex nature of the hepatic role in the body's responses to different metabolic or nutritional settings. Such a limited view may lead to inappropriate restriction of protein intake. What follows is an attempt to place the complex nature of hepatic failure into a framework of metabolic responses. By depicting the hepatic role in the body's normal responses to certain metabolic or nutritional settings, it hopefully will be easier to understand the body's responses to the failing liver.

Hepatic Use of Nutritional Substrates

The liver has many different pathways available for the metabolism of any particular substrate. How it uses substrates depends on the hormonal control over these pathways (1). In general, the pathways tend to lead either to storage or acute use. The carbohydrate pathways, potentially the simplest, become complex as the available precursors change. For example, in the fed state, sufficient glucose is available to allow glycogen formation and to supply glucose for peripheral use. Fasting leads to glycogenolysis, and glucose presenting to the liver via the arterial or portal system during fasting tends to be exported for peripheral use. In starvation, precursors for glucose production become scarce, and amino acids (from protein degradation) or glycerol (from fat metabolism) become the main gluconeogenic precursors. The pathways for fat metabolism are similarly controlled but made more complex by the need to coordinate formation of both triglyceride and transport proteins to allow storage at the peripheral lipocytes.

Control over protein metabolism is different in that there is no storage site for protein comparable to glycogen or fat. Muscle becomes a repository of intracellular free amino acids and expendable protein (2,3). In fed states, muscle takes up free amino acids. Muscle protein is made not for storage but as a response to exercise. In injury or sepsis, amino acids are released and muscle protein is catabolized (Table). In starvation, organ protein from the kidney, gut, and liver is catabolized to a greater extent while muscle protein is catabolized at a slower rate (1). The liver's role in these metabolic states is governed by complex hormonal interactions which are not yet well understood.

Normal Metabolic States

The various alternate pathways for hepatic substrate are present to allow adaptation to the different environmental settings organisms face. One example is the fed versus fasting state. Fed animals use nutrients for current needs and shunt the remainder to storage. Fasting animals use glycogen and free amino acids and begin mobilizing fat stores. A shift away from a glucose-intensive metabolism does not occur until starvation ensues.

Starvation and hibernation are two examples of long-term metabolic states (4). Both are fat-dependent and attempt to spare muscle protein. Hibernation actually increases lean body mass

Table

| Relative Rates of Metabolic Processes in Sepsis/Injury, Starvation, and Hibernation |
|-----------------------------------|-----------------|-----------------|-----------------|
| Metabolic State                    | Sepsis/Injury   | Starvation      | Hibernation     |
| Muscle protein catabolism          | ++              | +               | —               |
| Visceral protein catabolism        | +               | ++              | —               |
| Gluconeogenesis                    | +++             | +               | ++              |
| Lipolysis                          | +               | +++             | ++              |
| Protein synthesis                  | ++              | +               | +               |

Note: The number of "+" markings indicate the rate of that process relative to the other metabolic states. The "—" markings signify an increase in lean body mass.

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as a means to prevent urea formation. The metabolic states of starvation and hibernation both tend to preserve stores as much as possible.

In contrast, the response to fear is a mobilization state (5). Glucose and amino acids are rapidly released to provide acute energy for brain and muscle. The response to provide energy for short-term muscle reaction in times of extraordinary need is shifted after injury to provide short-term energy for reparative processes (1, 6). The response to injury is not a conservative one and never shifts to a fat-based metabolism. Although fat is used, glycerol and amino acids are necessary to maintain gluconeogenesis. Muscle protein catabolism fuels gluconeogenesis and provides for hepatic synthesis of acute phase proteins. The response to injury and sepsis becomes a nitrogen-wasting metabolism at the expense of muscle protein despite high hepatic synthesis rates (3, 5). It is also directed toward an anaerobic reparative process at the local wound level. The systemic effects of hormonal messengers released to guide the local repair process may partially explain the oxidative metabolic "defect" (7) seen in sepsis and hepatic failure. From the standpoint of hepatic involvement in such processes, its capacity to respond is large. Hepatic response is likely related to the level of hormonal stimulation rather than to parenchymal mass.

Control Over Metabolism

The orchestration of these various metabolic states is controlled by several systems which are responding to stimuli on different fronts (1). The portal system allows simple feedback control over insulin and glucagon release during cycles of feeding or fasting. The triggers for hibernation are not clear but most likely are related to steroid hormonal control. The neuroendocrine axis initiates the flight/fight response (5). Hepatic involvement in the various metabolic responses requires sensitivity to multiple control stimuli (1). The liver has a direct autonomic nervous system innervation. Direct neural responses are immediate as in the "flight or fight" response. Arterial plasma brings classic neuroendocrine hormones, catecholamines, and lymphokines. Portal flow brings pancreas and gut hormones as well as neurotransmitters released to guide the local repair process. The systemic effects of hormonal messengers released to guide the local repair process may partially explain the oxidative metabolic "defect" (7) seen in sepsis and hepatic failure. From the standpoint of hepatic involvement in such processes, its capacity to respond is large. Hepatic response is likely related to the level of hormonal stimulation rather than to parenchymal mass.

Control Over Portal System

The liver is not a passive component in the network of metabolic control. It commands the venous exit site from the portal system and effectively isolates portal venous circulation from systemic circulation. Appropriate interaction between the two environments, portal and systemic, is dependent upon hepatic function. Sometimes hepatic function entails reducing high concentrations of portal substrates to levels tolerated by the organ of systemic circulation. At other times the liver controls the systemic levels of a substrate by synthesis. Systemic glucose levels are a common example of hepatic control, but levels of most circulating substrates are controlled by the liver in one way or another. Hepatic control over plasma levels of substrates provides feedback to systemic hormonal control systems. Failure of the liver to control portal circulation output can alter the body's metabolic state by disrupting these feedback mechanisms.

Immune Functions

The liver can exert metabolic control indirectly through Kupffer cell interactions. Immunologic functions of the Kupffer cell system include local control over portal system bacteremias and some processing of peritoneal and systemic antigens. White cell mediated activation of the stress response can thus affect the liver through local or systemic action (8). Laboratory data support a direct Kupffer cell action upon adjacent hepatocytes, with potentially destructive or inhibitory action as well as activation of stress metabolism (9). The potential systemic effects of portal blood shunting away from the Kupffer cell system have not been well studied but could be responsible for activating the immune system on a systemic level.

Testing Hepatic Function

Current hepatic function tests do not assess the various control systems which influence hepatic function. Determining how well the liver is performing in any metabolic state is difficult without knowing the degree of stimulus for any single function. Some hepatic functions are not extensively supported and, like ethanol metabolism, are readily saturated (10). Other functions are concentration gradient phenomena and can be altered by simple changes in hepatic blood flow (11). Detoxification of some drugs is linearly related to blood flow or parenchymal mass. Several clearance tests have been purported to be for hepatic function, but they either lack specificity or fail to distinguish between parenchymal mass and blood flow changes. Clinically, such tests do not provide information regarding hepatic ability to recover from or tolerate stress. While metabolic clearance tests, such as plasma amino acid clearance, have demonstrated good correlation with hepatic function in severe stress (12-15), they do have limitations. For example, plasma amino acid clearance is useful only in the late stages of hepatic failure. Because of the varied functions of the liver, any single test is unlikely to provide all the information that clinicians may require for an accurate prognosis.

Complex Versus Basic Functions

Complex functions, such as those described above, represent the controlling aspects of hepatic metabolism. Basic functions, such as gluconeogenesis, protein synthesis, amino acid uptake and triglyceride production, are the controlled functions. Such a categorization of functions has value in that the capacity for basic hepatic functions is well supported within the parenchymal mass and requires extensive loss of parenchyma to reach dangerous levels.
Amino Acid Chance m
Child’s A Child’s B Child’s C Survived • Died

mg of N / 9 hrs/kg
(A)

Central plasma amino acid clearance rates of patients undergoing operative procedures. Patients are classified by Child’s class and by their survival postoperatively. Note that survival was related to an increased ability to use amino acids as the clinical hepatic failure worsened. (Data from Pearl et al [12].)

A third category, intermediate functions, includes functions that are neither directly involved in stress metabolism nor a part of the controlling process. For example, functions such as drug detoxification and bile metabolism may be sensitive to changes in blood flow or enzyme induction (11), but they are not necessarily the determining factors in survival when altered during stress metabolism.

Assessment of Hepatic Function
Most liver function tests that clinicians use do not assess the capacity of the basic hepatic metabolic system. As a result, tests such as serum bilirubin or hepatic enzymes may suggest hepatic failure when the parenchymal mass is adequate for metabolic function. Pearl et al (12) reported that patients with the same Child’s classification often had markedly different capacities to use amino acids. (Child’s classification is a clinical categorization of patients based upon presence of ascites and hepatic encephalopathy, the patient’s nutritional status, and values for serum bilirubin and albumin. A Child’s class C patient may have uncontrolled ascites, muscle wasting, marked hepatic encephalopathy, serum bilirubin > 3.0 g/dL, and serum albumin < 3.0 g/dL.) These authors noted that postoperative survival related more to the body’s ability to use amino acids rather than the patient’s Child’s classification (Fig 1). What has “failed,” then, is the control over metabolism. Instead of the standard metabolic patterns, a different metabolism appears due to alterations in the more complex control systems.

The cause of such failure is not known, but several mechanisms are possible. Shunting of portal blood to a systemic pool may allow toxins, usually cleared by hepatic systems, to stimulate peripheral immune cells and set up a systemic stress response. Portal hormones which normally are cleared by the liver may pass to the systemic circulation and alter the hormonal balance. In turn, peripheral hormonal instructions may be interpreted incorrectly by the compromised liver. Complex functions of the liver may be related to parenchymal mass, yet it is more likely that the balance of hormonal control from portal and systemic input becomes deranged. The result is a maladaptive metabolism that approximates the stress response in its hemodynamic characteristics (16-18) and in the hypermetabolic protein wasting that occurs. Clinically, the ability to estimate the level of metabolic stress and changes in the controlling milieu is currently limited to nitrogen excretion studies (19). Hormonal and amino acid levels have been used in categorization schemes but are seldom available clinically.

Definition of Two Stages of Hepatic Failure
The above definitions allow breakdown of hepatic failure into two simple stages: early hepatic failure and late hepatic failure. Early hepatic failure involves progressive impairment of complex and intermediate functions. Alteration of the complex liver functions leads to a stress-style metabolism. Swart et al (20) have demonstrated increased protein synthesis and rapid protein breakdown in patients with hepatic failure when compared to control subjects. This increase was noted in patients on protein supplemented diets (1 g/kg) (Fig 2A) as well as in those on protein-restricted diets (Fig 2B). These data suggest that many pa-
patients with hepatic failure actually have increased hepatic protein metabolism when compared to patients with normal hepatic function. Clinical assessment of amino acid clearance demonstrates increased clearance by patients with hepatic cirrhosis compared to nonstressed patients (12,15). A shift to a metabolism that is less effective at oxidative function makes total body oxidative metabolism flow-dependent (18). Failure to maintain such increased basic functions bodes poorly for the patient, indicating the beginning of late hepatic failure. Early hepatic failure includes decreased ability to control complex functions and a shift to stress-style metabolism. Such a metabolism actually increases the rate of many basic functions but does so in the context of a peripheral protein-wasting stress-style metabolism.

Prolongation of such a metabolism leads to many of the signs attributed to chronic hepatic failure. Decreased bile synthesis leads to poor fat absorption and loss of calories and fat-soluble vitamins (21-23). Protein synthesis, although increased, is accompanied by a rapid proteolysis (20). Muscle mass is consumed, as in sepsis, and albumin levels fall. Hormonal imbalances are seen, with high aldosterone and renin levels (24) (Fig 3). Sodium and water dynamics shift, leading to ascites formation.

Nutrition During Early Hepatic Failure

Complications during early hepatic failure are mainly due to the effects of malnutrition and portal hemodynamics (25-28). Nutritional support of patients during this period is essential to prolonging survival. Although most concur about supplementation of calories in the form of carbohydrate and fat, much controversy exists over the use of protein. Two areas of protein metabolism complicate our understanding of the process. It is known that the liver handles amino acids differentially (2). Branched-chain amino acids are readily metabolized by both hepatic and nonhepatic cells. In the altered metabolism of stress and hepatic failure, branched-chain amino acids may enter the cellular energy pathways and be oxidized (7). Some amino acids, which are used more for protein synthesis and less for oxidative energy, are often present in higher concentrations than in normal plasma. These high levels indicate that protein breakdown releases amino acids faster than they can be used, whereas the low plasma levels of branched-chain amino acids indicate that their oxidation is delivery-dependent. This differential metabolism makes more apparent the rationale for high quantities of branched-chain amino acids and lower quantities of aromatic amino acids in the nutritional supplementation of patients with hepatic failure. Supporting the energy metabolism of both peripheral cells and hepatocytes aids in protein synthesis but may not decrease the catabolic activity. Protein support does allow positive nitrogen balance to occur. Some studies suggest that branched-chain amino acid enriched solutions support nitrogen retention better than standard amino acid content nutritional solutions (29,30). The role of branched-chain amino acid solutions in reducing encephalopathy is less clear (19,31-38).

Gut metabolism of protein may produce different portal substrates depending on the type and amino acid mix of the protein. Blood or red meat protein is poorly tolerated by patients with hepatic failure; equal amounts of nitrogen delivered as plant protein are much better tolerated (33). Protein supplementation studies are still incomplete and no conclusive data have been obtained. While many studies support the use of special amino acid mixtures for patients with hepatic failure, others do not (19,31-38). What should be apparent is that the liver’s basic metabolic function is still intact enough to use calories and protein, because it is still producing more protein than a nonstressed liver. In an attempt to reduce the complications of protein synthesis and malnutrition, patients should receive protein dietary supplements. The type of supplementation is determined mainly by the risk of encephalopathy. Some patients tolerate standard supplementation well, whereas others do not. For the latter group, the cost and risks of high branched-chain solutions are justified. When branched-chain amino acid formulations are used, a carbohydrate-based nutrition plan should be followed. Some of the conflicting reports regarding efficacy of branched-chain amino acid preparations may be related to use of fat-based plans (19).

Late Hepatic Failure

In the above staging system, early hepatic failure is depicted as that period when the complex and intermediate hepatic functions are impaired, yet the capacity of the liver to perform the basic functions is actually stimulated. Late hepatic failure begins when the liver’s capacity to perform basic functions deteriorates. Unless the events responsible for deterioration to late hepatic failure (such as sepsis or toxins) can be reversed, an inexorable progression of complications leading to death will ensue. Hypoglycemia and marked hyperaminoacidemia are poor prognostic signs. What confounds the study of hepatic failure is the ability of sepsis, hepatitis, dietary indiscretion, or gastrointestinal bleeding to push a patient into the late stage of hepatic failure (39). Treatment of the inciting event can often lead to recovery. Acute fulminant hepatic failure is an example of a rapid progression from early to late hepatic failure which can sometimes be reversed. Single laboratory tests become useless in determining outcome. Death from hepatic failure is seldom solely related to loss of hepatic function. In chronic hepatic failure, complications of portal hypertension and infection can overwhelm these poorly tol-ien patients.
Summary

The liver is a complex organ which has acquired several layers of functions during its evolution. The metabolic aspects of hepatic function are crucial regarding patient survival following injury or infection. The liver’s metabolic functions are under extensive control by several systems which are responsive to different stimuli. In early hepatic failure, complex hormonal control is altered into a maladaptive state of stimulated basic functions in a pattern similar to the response to sepsis and injury. Intermediate functions which are sensitive to loss of parenchymal mass and changes in blood flow or which require support of specific protein synthesis may become progressively impaired. The metabolic response to early hepatic failure is termed maladaptive because it leads to a progressive malnutrition due to extensive catabolism, impaired absorption of nutrients, and shifts in the patterns of protein synthesis. Such a state diminishes the body’s ability to tolerate additional insult from injury, infection, or hemorrhagic shock. Nutrition must be supported, yet differential handling of proteins and the risk of encephalopathy demand caution during nitrogen supplementation. Although studies are not conclusive, a prudent approach to early hepatic failure would include trials of standard formulas, reserving branched-chain supplemented formulas for those whose preadaptation to early hepatic failure precludes the use of standard diets.

References


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Liver transplantation has improved survival in the past decade and new techniques for liver transplantation are constantly evolving. Criteria for transplantation have become more stringent. Increased knowledge of complications and improved surgical techniques have led to a decreased mortality and the increased survival of patients who in the past were considered inoperable.

Debility, often associated with liver failure, continues to be a major problem in the management of these patients. Nutritional support is becoming an increasing issue. The purpose of nutrition support in patients with liver disease is to maintain or improve nutritional status, to maintain organ function, to reduce complications, and to improve survival.

Nutritional Support in Hepatic Failure—Part I

Jeanette F. Tiersten, MD

In order to achieve the nutritional requirements of a patient with liver disease, they must be individualized. The assessment of energy requirements occurs during the evaluation of the liver transplant patient. It is important to consider the usual calorie needs and the tumor. These include the primary diagnosis, nutritional status, serum albumin, and the body weight.