The Role of Cardiovascular Hemodynamics and Liver Histology in Evaluating Bleeding Cirrhotic Patients

V. DICARLO, C. STAUDACHER, R. CHIESA, B. ANDREONI, M. CRISTALLO, E. RONCHETTI

Preoperative cardiovascular hemodynamics and percutaneous liver biopsies were used to evaluate the pathophysiologic factors determining the operative prognosis of patients with cirrhotic liver disease and bleeding esophageal varices. These studies confirm the observations of Siegel that the greater the magnitude of the peripheral abnormalities in vascular tone and oxygen consumption the better must be the capability of the ventricular function, if the cirrhotic is to survive emergency or urgent portal decompressive surgery. These studies also show that the cardiovascular hemodynamics are directly correlated with the nature and degree of the abnormalities in the liver biopsy, and that pathologic and physiologic features of this disease which impact on surgical prognosis can be expressed through the easily obtained Survival Index. Bleeding cirrhotic patients with poor quality hemodynamics and poor histologic characteristics should be treated non operatively, since the operative mortality appears greater than that produced by a strategy of medical supportive therapy and delayed surgery if stabilization occurs.

No other hemorrhage in the digestive tract poses such delicate therapeutic problems as those which complicate portal hypertension in cirrhotic patients. Hemorrhagic shock is more serious in such patients not only because of the amount of blood lost but also due to the relative insufficiency of physiologic compensatory mechanisms and to the hepatic decompensation which often occurs when blood is absorbed from the intestine. In the cirrhotic patients an abnormal hemodynamic situation exists which is capable of definitively conditioning the patients response to stress due to hemorrhage or to necessary decompressive surgery.

The knowledge of the different types of cardiovascular pathophysiologic responses provides a decisive basis for a more rational medical care, for deciding which patients should or should not be subjected to an emergency operation, for timing of elective surgery and for postoperative management.

Moreover, histological studies of the liver performed during active bleeding have outlined the influence of acute hyaline necrosis on mortality in patients not operated on and on mortality after emergency and elective portacaval shunt. These two parameters, cardiovascular hemodynamics and histological examination of the liver, are at present the most valid criteria for prognosis and rational treatment of the cirrhotic patients bleeding from esophageal varices. The purpose of this study was to examine in detail some of the physiologic abnormalities associated with massive hemorrhage and to integrate this information with histological results from percutaneous liver biopsies performed using a posterior approach, in an attempt to evaluate short-term prognosis and a more accurate prediction of postoperative survival. Hemodynamic changes were also correlated with the degree of liver damage.

Materials and Methods

Hemodynamic Measurements

Between June 1975 and December 1977, 66 patients with cirrhosis and portal hypertension, admitted to the Institute of Emergency Surgery of the University of Milan for massive bleeding from esophageal varices, underwent cardiovascular hemodynamics and oxygen consumption evaluation. The patients studied were selected from a larger group admitted to hospital during the same period on the basis of hemorrhage severity.

The source of bleeding was diagnosed by clinical, endoscopic and angiographic examination. Hemodynamic measurements were performed using a subclavian catheter positioned in the right atrium or a
7 F triple lumen Swan-Ganz catheter floated in the pulmonary artery; a Teflon catheter was inserted into the femoral artery percutaneously or into a surgically exposed radial artery. Pressures were measured using Bently Transee transducers and recorded on a MFE poligraph. Cardiac output was measured in fifty patients by the thermal dilution method (Output Computer, Edwards) and in 16 patients by the dye dilution method using indocyanine green and a Waters densitometer. Blood gas was determined using an ABL 1 Radiometer blood gas analyzer, and O₂ content in the arterial and mixed venous blood was measured by Lex O₂ Con (Lexington).

The computations of hemodynamic data were made with a portable computer (HP 97 Hewlett Packard) and using a cardiovascular program developed by Siegel et al.* The following parameters were calculated: cardiac index (CI), left ventricular stroke work (SW), total peripheral resistance (TPR), oxygen consumption/square meter (O₂ cons/m²) and effective O₂ transport (EOT). For a graphic representation of these parameters which provides a physiologic frame of reference to previously studied patient groups including normal and patients in various pathophysiologic states of compensation, we have utilized the four diagrams proposed by the same authors. These plots represent the following functions: Vascular Tone, Effective Oxygen Transport, Relative Peripheral Shunting and Ventricular Function. From the Relative Peripheral Shunting Index and Ventricular Function Index a Survival Index was calculated which has been shown to express the probability of survival for the cirrhotic patient from major hemorrhage or following surgical portal decompression.

**Histological Study**

Percutaneous liver biopsy was performed using a posterior approach. Under local anesthesia and with the patient recumbent in a prone position, the needle (Tru-Cut, Travendo) was introduced at the level of the superior margin of the 11th rib about 6–7 cm from the median line. This method offers the advantage of penetrating the liver across the extraperitoneal space through the coronary ligament without the danger of biliary injury or hemorrhage (Fig. 1). A previous coagulation study is not required. Histological results are available within 18 hours. Histological findings were classified in four groups (I–IV Table 1). On the basis of the degree of necrosis and of degenerative lesions, group IV was subdivided into two subgroups with moderate changes (IVm) and severe changes (IVs) respectively. Between 1975 and 1977, 156 successful liver biopsies were performed on patients with portal hypertension: 93 in actively bleeding patients and 63 in patients studied during a period remote in time from previous episodes of hemorrhage.

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**Table 1. Histologic Classification of the Liver Lesions**

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Normal aspect of the liver (prehepatic portal hypertension)</td>
</tr>
<tr>
<td>II</td>
<td>Structural alterations without active flogosis or degenerative lesions or important necrosis of the liver (inactive cirrhosis, post-necrotic cirrhosis, congenital fibrosis).</td>
</tr>
<tr>
<td>III</td>
<td>Structural alterations with important activity of chronic liver process, but with slight liver tissue lesions (chronic active hepatitis, chronic alcoholic liver disease with fibrotic evolution).</td>
</tr>
<tr>
<td>IV</td>
<td>Structural alterations with important degenerative lesions and parenchymal necrosis (chronic liver disease with important alcoholic or viral or ischemic reactivation).</td>
</tr>
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</table>
Results

Hemodynamic Findings

Cirrhotic patients with bleeding from esophageal varices show a very different hemodynamic pattern from that observed in patients with bleeding due to other causes. The difference in pattern is more evident 48 hours after hemorrhage when the blood volume is replaced.

We have studied and analyzed the following four functions.12

Vascular tone. Vascular tone (Fig. 2) is a means of gaining insight into the degree of net vasoconstriction or vasodilatation of the vascular tree.11 In this relationship the peripheral vascular resistance is evaluated as a function of flow (cardiac index) to provide a comparison with values obtained from other individuals. In this figure the values from cirrhotic patients were compared to the mean slopes of vascular tone relations previously determined for patients with septic, and non septic shock, and for normals.11 The use of these lines derived by Siegel11,12 in this, and the other physiologic figure provides a coordinate system whereby the abnormal physiologic characteristics found in cirrhotic patients can be compared to previously studied cirrhotics and other types of serious disorders of physiologic compensation. This is especially im-

portant to the understanding and quantification of the cirrhotic abnormalities, since as previously shown, cirrhotic patients with portal hypertension have a decrease in vascular tone equal to or greater than that seen in severe septic shock.11

The vascular tone changes in these 66 patients are strikingly similar to those reported by Siegel.11 However, some important new facts should be ascertained from these data. Hemorrhage produced an important change in vascular tone. After replacement of the blood lost all the patients except 18 became hyperdynamic (CI > 3 l/min/m²), while the peripheral vascular resistance decreased to clearly lower levels than those observed in cirrhotic patients with portal hypertension but no recent hemorrhage.

Vascular tone was lower than normal in all patients (Fig. 2); this abnormality may have prognostic significance. Patients who died are clearly divisible from septic patients. Also, patients who remained hypodynamic or normodynamic after blood volume replacement had a high mortality rate (14 deaths in 18 patients). When peripheral resistance was lower than 550 dyne/sec/cm² no patient survived. Emergency surgery had poor results if patients showed serious abnormality in vascular tone (8 out of 15 died).

Effective oxygen transport. Oxygen consumption/min/m² is a critical determinant of metabolic adequacy in the cirrhotic patient, and cirrhotic patients with portal hypertension and low Effective Oxygen Trans-
port (EOT) have been shown to have poorer operative 
prognosis than those with normal or increased EOT. 
The nature of this abnormality is similar to that found 
in sepsis and Figure 3 shows the grid lines relating 
flow and oxygen consumption developed by Siegel\textsuperscript{11} 
which permit this function to be defined by regions of 
different flow; \(O_2\) consumption relations. In the present 
study when oxygen consumption was evaluated as a 
function of total blood flow (Fig. 3), it was seen that 
about 80% of our patients had an oxygen extraction 
abnormality similar to that found by Siegel et al.\textsuperscript{11-14} 
in both hyperdynamic septic or cirrhotic patients. They 
required a higher peripheral flow at each level of 
oxigen consumption than that required by patients in other 
groups. All seven patients who could not maintain an 
oxigen consumption higher than 70 ml/min/m\(^2\) died. 

Relative peripheral shunting. The relative peripheral 
shunting function which relates the level of oxygen 
consumption as a function of the total peripheral 
resistance is perhaps the most important physiologic 
relationship expressing the adequacy of peripheral 
perfusion.\textsuperscript{11,12} It is an attempt to demonstrate to what 
extent the diminished vascular tone is functionally 
related to the reduced oxygen consumption. Again, 
the use of the coordinate system developed by Siegel 
using the different physiologic limits seen in septic 
and non septic shock states, and applied by him to the 
study of patients with cirrhosis and portal hyperten-
sion\textsuperscript{11-12} is used to delineate the physiologic region of 
greatest risk. The data in the present physiologic studies 
of our Italian patients confirm the previous American 

The study of the correlation between effective oxy-
gen transport and total peripheral resistance (Fig. 4) 
shows that 48–72 hours after hemorrhage the cirrhotic 
patients develop a progressive increase in peripheral 
shunting. The further decreased the index is compared 
to the mean slope for patients in septic shock, the 
higher was the cirrhotic patients mortality. The area 
of greatest risk was delimited by EOT \(\leq 30\) ml/l and 
TPR \(\leq 700\) dyne/sec/cm\(^2\) \(10\) patients out of 13 died). 

Ventricular function. When left ventricular stroke 
work is plotted against central venous pressure (Fig. 5), 
it can be seen that in more than half the cirrhotic pa-
tients myocardial function is depressed (fair and poor 
range). All patients in the Poor range died, while mor-
tality was 75% in the Fair range and 27.2% in the Good 
range. These data suggest that the level of ventricular 
function has the major prognostic significance. 

**Histological Findings**

Of the 66 patients comprising the above study, 19 
belonged to the histological Group II, 8 to III, 22 to 
IV moderate, 17 to IV severe. Progressive lethality 
occurring with increasing severity in liver damage. The 
mortality rate was 21% in Group II, 37% in III, 68.1% 
in Group IVm and 82.3% in IVs. Eight of the 15 patients
Table 2. Influence of the Degree of Liver Lesions on Mortality and on Causes of Death Following Emergency and Elective Portacaval Shunt

<table>
<thead>
<tr>
<th>Histologic Groups</th>
<th>Emergency Surgery</th>
<th>Delayed Surgery</th>
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<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Deaths</td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>IV moderate</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>IV severe</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>18</td>
</tr>
</tbody>
</table>

operated urgently died. Among them 6 belonged to the Group IV, one to II and one to Group III. The survivors were 2 patients from Group II, 4 patients from Group III and only one patient from group IVm.

Table 2 illustrates the influence of the grade of histologic alteration of the liver to the postoperative mortality, in a larger series of patients operated during the same period of study. It was comprised of cases who had undergone hepatic biopsy before the elective intervention. In patients belonging to Group IV, urgent surgery gives poor results (87%), but the mortality is high (33%), even in elective operations.

The causes of death are different, based on the variation of histologic groups. Fourteen of the 16 patients belonging to group IV who died were comatose, while the causes of death in the other groups were sepsis, rebleeding and renal failure. The histological results have also been correlated to the Survival Index (Fig. 6).12

**Survival Index**

In previous studies11,16 it was shown that the preoperative patterns of cardiovascular hemodynamics and oxygen consumption could be used to predict the probability of survival after portal decompression surgery. The best synthesis of these data into an information rich graphic display was achieved by developing an algorithm which enabled the plotting of the Ventricular Function Index (Fig. 5) as a function of the index of Relative Peripheral Shunting (Fig. 4).12

This is seen in Figure 6 which also shows the three prognostic survival regions (Good > 50%, Fair > 20% < 50%, and Poor < 20%) derived by Siegel and Williams.12 In physiologic terms, the interpretation of this relationship is that to survive, a cirrhotic patient whose peripheral abnormalities of vascular tone and oxygen extraction are small (as measured by the Relative Peripheral Shunting Index), does not require as good a level of Ventricular Function, as a patient whose peripheral abnormalities are great.

This hypothesis is confirmed by our data which shows a 72% survival for patients whose lowest preoperation study placed them in the Good (G) region, a 55% survival for patients in the Fair (F) region, but only an 11% survival for patients in the Poor (P) region. However, our data extend their observations12 by clearly demonstrating that the hemodynamic and metabolic abnormalities reflected in the Survival Index are directly correlated with the nature and magnitude of the histologic pathology seen on liver biopsy. This is also shown in Figure 6 where the group IV histologic grade biopsied patients (open circles) are seen to lie almost exclusively in the F and P regions and the combination
of poor histology and poor physiology (histologic group IV and Survival Index in Poor region) produced the highest mortality.

Discussion

The value of emergency surgery in the treatment of bleeding from esophageal varices continues to be a matter of debate. Many of the criteria used to evaluate cirrhotic patients have shown no significant correlation with survival. Child's classification, based on clinical and laboratory data, still provides a good basis for patient selection for elective surgery, but it is not very useful for evaluating the bleeding patient. Also, a better knowledge of the hemodynamics of the splanchnic circulation has not helped to improve patient selection in terms of better survival rates.10 These considerations led Orloff et al.10 to perform emergency operations on all patients with bleeding varices due to alcoholic cirrhosis, his only contraindication to emergency portacaval shunt being the combined presence of ascites, icterus, encephalopathy and severe muscle wasting. However, this approach resulted in an unacceptable mortality rate.

The study of cardiovascular hemodynamics and liver biopsy appear to be a more valid criteria for surgical prognosis and thus for rational treatment of cirrhotic patients bleeding from esophageal varices. Systemic manifestations of hepatic cirrhosis have been studied by Del Guercio6 and Siegel;11 these authors have shown that some cardiovascular aspects assume remarkable prognostic significance for hemorrhage and stress due to surgery.

Recent observations by Siegel et al.12,13 have extended the description of the hyperdynamic states that characterize the circulatory response patterns in cirrhotic liver disease. Three types of hyperdynamic responses exist. In stable patients with good liver function there is only a slight increase in the cardiac index with minimal alterations in vascular tone (R state). In patients under greater stress from hemorrhage with some acute hepatic decompensation there is a great increase in cardiac index and heart rate, with minimal decrease in mean blood pressure, which signifies a reduction in peripheral vascular tone. However, arteriovenous oxygen extraction is normal, so that total oxygen consumption is increased and a physiological correlation exists between oxygen supply and demand (A state or balanced hyperdynamic response).

In the third group of cirrhotic patients the distinguishing features consist of the narrowing of the arteriovenous oxygen content difference and the corresponding rise of the mixed venous oxygen tension. Although the increase in cardiac index is large, vascular tone is markedly decreased and the resultant increase in peripheral flow is not able to compensate for reduced \( O_2 \) extraction and total oxygen consumption falls (B state or unbalanced hyperdynamic response). A small group of the B state patients may also manifest a decompensated pattern and transition into a state of respiratory insufficiency (C state). There is also a great tendency for the B state patient with abnormal vascular tone and low oxygen consumption to develop a state characterized by myocardial failure similar to that seen in patients with cardiogenic shock (D state), at which point cardiac output falls and death frequently ensues unless major inotropic therapy can be used.

A major acute stress such as hemorrhage is usually the stimulus for a change from one compensation state to another. The hypovolemic phase of an acute hemorrhage produces a low cardiac output acutely, but after resuscitation the characteristic hyperdynamic response states are seen as a function of the degree of acute and chronic liver injury. In this phase a clear deterioration of the hemodynamic and metabolic parameters occurs with a marked reduction in vascular tone, the appearance of a reduced arteriovenous oxygen extraction, and a worsening of ventricular function. In this phase the hemodynamic study acquires precise prognostic significance, and there are clear cardiovascular differences between patients who die and those who survive (Figs. 2–6). The cardiac function pattern seems particularly useful for prognosis: mortality is significantly different in the three areas of the ventricular function graph (Fig. 5); in our study 27% in “Good,” 75% in “Fair” and 100% in “Poor.” These data confirm that myocardial adequacy is a key factor in the cirrhotic patients in overcoming stress due to hemorrhage.11 This becomes more important in proportion to the seriousness of the combined vascular tone and oxygen consumption abnormalities in the peripheral tissues (Fig. 4) and the vascular and myocardial abnormalities can be accurately quantified by the Survival Index (Fig. 6).12

Because of the great perfusion demands imposed by the marked reduction in vascular tone (Fig. 2), if the total blood flow cannot be maintained high by good cardiac function, the prognosis becomes grave. In our case histories, the patients who remained hypodynamic or normodynamic after 48 hours had a very high mortality rate (14 deaths in 16 patients). As previously shown12 heart failure can occur even with a high cardiac output. This motivates our usage of inotropic agents (digoxin or a combination of isoproterenol and glucagon given by continuous intravenous infusion as proposed by Siegel et al.13) in all cirrhotic patients with a reduced arterial–venous oxygen content, given that their chance for survival depends on an adequate myo-
cardiac function. With regard to timing of surgery it is evident that progressive deterioration, despite medical support, of vascular tone, oxygen extraction and myocardial function, represents a strict contraindication to emergency portal decompression, since when all of these factors are combined the mortality approaches 100% (Fig. 6).

The second aim of our study was to investigate whether a preoperative liver biopsy is an important factor in determining the prognosis and indications for surgery, and whether correlations exist between the degree of liver changes and hemodynamics. Previous reports from Mikkelsen, are consistent with the presence of acute hyaline necrosis in the hepatocyte adversely influences survival after portocaval shunt in cirrhotic patients. These authors recommend that a percutaneous liver biopsy must precede consideration of either an emergency or an elective shunt.

The standard anterior method of liver biopsy is not thought possible in all bleeding patients due to the problems imposed by coagulation deficits. For this reason we have executed needle-biopsy using an approach which is shown to be safer. The posterior approach permits an extraperitoneal liver biopsy through the costal-diaphragmatic sinus, the diaphragm, and the right coronary ligamentum. This technique can be utilized not only in the patient with ascites but also when intense jaundice and grave coagulation deficits are present, since the connective tissue at the level of the insertion of the coronary ligament of the diaphragm is very compact and does not permit the outflow of an eventual bile or hemorrhagic collection.

Our microscopic study of the liver differs from that of Mikkelsen, in that histologic aspects other than hyaline necrosis are considered. Indeed, hyaline necrosis represents only 30% of the alterations found in histologic Group IV. In this group are seen three different histologic aspects of the same level of gravity. These correspond to acute alcoholic hepatitis, acute viral hepatitis and hepatitis of ischemic type which is observed in major hemorrhage.

The first histologic pattern is that described by Mikkelsen et al. It is characterized by the hyaline necrosis, typical Mallory bodies, and grave steatosis with a polymorphonuclear leucocytic infiltration (Fig. 7).

The second pattern shows extensive necrosis of the hepatic parenchyma, Councilman bodies, grave cellular pleomorphism, and eosinophilic degeneration of the hepatic cells. The third pattern seen in acute ischemic hepatopathology is characterized by necrosis of an eosinophilic type with cytoplasmic retraction, a loss of cellular limits and intense perisinusoidal edema (Fig. 8).

The overall mortality in the 66 patients series considered in this study was directly proportional to the gravity of hepatic lesions. That is 21% for Group II patients, 37.5% for Group III and 68.1% and 82.3% for patients belonging to histologic alteration groups IV moderate and IV severe respectively.

In Group IV patients any surgical program is contraindicated. The already gravely injured liver cells cannot support any further damage produced by surgical trauma, by anaesthetics or by hemodynamic changes due to surgical shunts. As can be seen in Table 2,
such patients do poorly after emergency operations, 13 out of 15 Group IV patients (87%) died, but mortality was also high (33%) in elective operations. Moreover, all Group IV patients died in hepatic coma, while the causes of death in the other histologic groups were sepsis, rebleeding or renal insufficiency. In non-operated bleeding patients in Group IV the mortality rate was also 71.8%, but with time the lesion can be reversible and the survivors will then be better operative candidates.

The final aspect of this study takes account of the relationship existing between the hemodynamic alterations and histologic aspects. Consideration of the more important aspects of the physiologic response to hemorrhage in the cirrhotic patient, the relative peripheral shunt and the ventricular function shows that there exists a major difference in the pattern of physiologic response in patients of histologic Group IV compared to those in Groups II and III. The Group IV patients have a lower vascular tone and a reduced oxygen extraction, thus a greater index of relative peripheral shunting than patients with more favorable histology. However, most important in the group IV patients is the fact that cardiac function (the ventricular function index) is significantly more depressed with respect to the patients in the other two histologic groups. This disproportionate reduction in myocardial capacity with respect to the degree of abnormality in relative peripheral shunting is reflected in the lower values of Survival Index (SI) (Fig. 6) observed in these patients (SI ≤ 0 > 50 equaled 35% survival, SI ≤ −50 equaled 11% survival).

These findings confirm the utility of hemodynamic staging in the preoperative evaluation of cirrhotic patients with bleeding esophageal varices as a critical predictor of the short-term survival prognosis and as a means following the improvement in post operative course. They also confirm the premise that the adequacy of liver function plays the fundamental role in conditioning the gravity of the cardiovascular and metabolic abnormalities found in the cirrhotic patient. The true mechanical shunting of portal blood plays a role of minor importance in hemodynamic compensation, as demonstrated by patients with pre-hepatic block and normal liver histology in whom the hemodynamic alterations do not even reach the gravity observed in stable cirrhotic patients without variceal hemorrhage.

Summary

The adequacy of cardiovascular hemodynamics and the degree of normality of the histological study of the liver are the most valid criteria for survival prognosis and rational treatment of the cirrhotic patient bleeding from esophageal varices. These criteria were applied to the study of 66 cirrhotic patients during hemorrhage, 15 of whom underwent emergency portal decompression. The time course evaluation of hemodynamic parameters was made using the method of cardiovascular evaluation developed by Siegel and associates. Within 48 hours after the onset of hemorrhage and following volume replacement the hemodynamic and metabolic pattern changes noticeably and acquires
precise prognostic significance. There is a marked reduction of Vascular Tone which relates cardiac index and peripheral resistance, a narrowing of the arteriovenous oxygen content difference and a worsening of Ventricular Function which relates cardiac stroke work and right atrial pressure. The pattern of cardiac function viewed in the light of the peripheral abnormalities in vascular function (Survival Index) is particularly useful for prognosis.

Percutaneous needle biopsies were also done in all patients in whom hemodynamics were evaluated, using a posterior extraperitoneal approach. As a result of the histological studies of the liver, the cirrhotic patients were classified into four groups (I, II, III, IV) of increasing pathologic abnormality. Group IV was characterized by severe degenerative lesions and parenchymal necrosis (chronic liver disease with important acute superimposition of alcoholic, viral or ischemic injury). Almost all patients in Group IV who underwent emergency surgery died during the postoperative period with liver failure. In nonoperated Group IV patients the mortality was 71%, but with time these acute histologic lesions are reversible and survivors will then be good operative candidates, similar to patients in the other histologic groups. A strong positive correlation exists between the extent of the pathologic changes in the liver biopsy and the degree of hemodynamic impairment.

References