Medical Progress

Cardiac Abnormalities in Liver Cirrhosis

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Cirrhosis is associated with several circulatory abnormalities. A hyperkinetic circulation characterized by increased cardiac output and decreased arterial pressure and peripheral resistance is typical. Despite this hyperkinetic circulation, some patients with alcoholic cirrhosis have subclinical cardiomyopathy with evidence of abnormal ventricular function unmasked by physiologic or pharmacologic stress. Florid congestive alcoholic cardiomyopathy develops in a small percentage, but the concurrent presence of cirrhosis seems to retard the occurrence of overt heart failure. Even nonalcoholic cirrhosis may be associated with latent cardiomyopathy, although overt heart failure is not observed. Tense ascites is associated with some cardiac compromise, and removing or mobilizing ascitic fluid by paracentesis or peritoneovenous shunting results in short-term increases in cardiac output. Cirrhosis also appears to be associated with a decreased risk of major coronary atherosclerosis and an increased risk of bacterial endocarditis. Small hemodynamically insignificant pericardial effusions may be seen in ascitic patients. The release of atrial natriuretic peptide appears to be unimpaired in cirrhosis, although the kidney may be hyporesponsive to its natriuretic effects.

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Let my liver rather heat with wine,
than my heart cool with mortifying groans.

WILLIAM SHAKESPEARE
The Merchant of Venice

Shakespeare's merchant, Antonio, may have been a shrewd businessman, but his medical knowledge was not sage, as he apparently failed to recognize that overheating his liver might "cool" his heart. During the past four decades, with the development of sophisticated techniques for measuring cardiac performance, much has been discovered about the cardiovascular abnormalities associated with liver disease. In fact, it is now clear that many facets of the circulation are deranged in patients with chronic liver disease: abnormal regional hemodynamics have been described in the splanchnic, hepatic, renal, and pulmonary vascular beds. Readers are referred to recent reviews of the alterations in these regional circulations.[1-5] In this review I will concentrate on the cardiac abnormalities found in chronic liver disease.

Hyperkinetic Circulation

Patients with liver disease have a hyperkinetic circulation: the cardiac output is increased, and arterial blood pressure and total peripheral resistance are decreased. The elevated cardiac output was first documented by Kowalski and Abelmann in 1953[6] and subsequently confirmed by numerous studies.[7-11] The increased output is due to augmentation of both stroke volume and heart rate. Not all patients show this abnormality, however; in the different series, 30% to 70% of cirrhotic patients have increased cardiac output. Nevertheless, the mean cardiac output of any group of patients with cirrhosis is invariably higher than that of a matched control group. Indeed, an intriguing observation is that the degree of circulatory hyperkinesis seems to be correlated with the degree of hepatocellular insufficiency—that is, the worse the liver function, the higher the cardiac output.[12-15] In one study, patients with Child-Pugh class A (best liver function), B, and C (poorest function) liver disease had mean cardiac indexes of 3.5, 4.0, and 4.7 liters per minute per m^2, respectively.[14]

The situation becomes yet more complicated by the observation that hepatocellular dysfunction is not even necessary for the development of a hyperkinetic circulation. Patients with portal hypertension due to portal vein obstruction, who have essentially normal liver function, will also have a hyperkinetic circulation.[16] Cirrhotic dogs without intrahepatic hypertension do not have a hyperkinetic circulation.[17] It thus appears that portal hypertension, rather than hepatic dysfunction, is prerequisite for the development of circulatory hyperkinesis. Studies in animals also support this conclusion: a hyperkinetic circulation develops in conscious rats[18] and rabbits[19] with prehepatic portal hypertension, as well as cirrhotic rats[20] and dogs.[21]

The etiology of this circulatory hyperkinesis is still obscure. It has been suggested that the development of portosystemic collateral vessels, an invariable consequence of portal hypertension, allows gut-derived vasoactive substances to bypass hepatic inactivation. These substances might then cause either direct cardiostimulation or peripheral vasodilatation. Vasoactive substances that could con-

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TABLE 1.—*Abnormal Cardiovascular Responses to Physiologic Stimuli in Patients With Cirrhosis*

Stimulus	*Expected or Normal Response*	*Observed Response*	*Source*
Exercise	↑ Cardiac output; no change in pulmonary wedge pressure	Blunted inotropic response	Gould et al, 1969[41]; Kelbaek et al, 1984[42]
		↑ Pulmonary wedge pressure	Gould et al, 1969[41]
Eating	↑ Splanchnic blood flow; no change in cardiac output	Earlier onset of splanchnic hyperemia; decreased cardiac output	Lee et al, 1988[43]
Upright tilting	Tachycardia; stable blood pressure	Blunted tachycardiac response	Lunzer et al, 1975[44]; Bernardi et al, 1983[45]
		Fluctuations in blood pressure	Lunzer et al, 1975[44]
Valsalva maneuver	Bradycardia	Blunted bradycardiac response	Lunzer et al, 1973[46]
Deep respirations	Physiologic sinus arrhythmia	No change in heart rate	Decaux et al, 1986[47]
Cold stimulation	Bradycardia	Blunted bradycardiac response	Lunzer et al, 1975[44]

↑=increased

TABLE 2.—*Abnormal Cardiovascular Responses to Drug Infusions in Patients With Cirrhosis*

Drug	*Expected or Normal Response*	*Observed Response*	*Source*
Angiotensin II	↑ Stroke work index (SWI); no change in pulmonary wedge pressure	Blunted ↑ SWI; ↑ pulmonary wedge pressure	Limas et al, 1974[48]
Tyramine	↑ Blood pressure	Blunted pressor response	Mashford et al, 1962[9]
Isoproterenol hydrochloride	Tachycardia	Blunted tachycardiac response	Lenz et al, 1985[49]; Ramond et al, 1986[50]
Dobutamine	↑ Stroke volume	No change in stroke volume	Mikulic et al, 1983[51]
Ouabain	↑ Ventricular contractility	No change in contractility	Limas et al, 1974[48]

↑=increased

ceivably play this role include glucagon,[22,23] histamine,[24] serotonin,[25,26] and vasoactive intestinal polypeptide.[27] Added support for this hypothesis comes from the observation that creating a portosystemic shunt, such as a portocaval shunt, even in animals with normal livers, results in an increased cardiac output and decreased peripheral resistance.[28,29] In patients with cirrhosis, creating similar portocaval shunts increases the cardiac output even further.[30,31] Construction of a peripheral arteriovenous anastomosis will increase the cardiac output,[32] but if these anastomoses are created in the splanchnic bed, thus interposing the liver in the circuit, the cardiac output remains unchanged.[33] An alternative explanation, however, may be purely hemodynamic—that is, that surgically or naturally occurring portosystemic anastomoses allow blood from the splanchnic venous bed to bypass the liver resister and shunt directly into the central compartment.

The cardiac output can be increased by an augmentation of the plasma volume, and this is known to occur in cirrhosis.[7,8,34,35] A substantial portion of the volume appears to be sequestered in the capacitance vessels, however, and the circulation behaves as if there were a decrease in the actual circulating volume. This phenomenon has been termed the decreased "effective blood volume."[36(p288)] Unfortunately, because this effective volume cannot be quantified in any way, it is difficult to substantiate or refute this hypothesis. Cardiac output is not correlated with plasma volume expansion in cirrhotic patients,[8,11,37] and currently the weight of opinion is against the view that volume expansion is a major contributory factor in the pathogenesis of the hyperkinetic circulation.

Hypoxemia can also occur in patients with cirrhosis. Most patients, however, have arterial oxygen pressures in the normal range and therefore no sign of overt tissue hypoxia. Nevertheless, some of these patients show a subtle sign of tissue hypoxia: an abnormal oxygen supply dependency.[38] In other words, whole body oxygen uptake appears to be directly linked to oxygen transport. Normally, above a critical threshold value increasing oxygen availability by increasing oxygen transport does not result in increased oxygen uptake. In states of tissue hypoxia, however, such as the adult respiratory distress syndrome, increasing oxygen delivery to tissues results in proportional increases in oxygen consumption, suggesting that the tissues are actually in an oxygen-deficient state.[39] Based on these observations, it has been suggested that a state of subclinical or latent tissue hypoxia also occurs in cirrhosis.[38] Furthermore, it has been opined that in both acute[40] and chronic liver failure,[38] cardiac output increases as a homeostatic compensatory mechanism to increase tissue oxygen transport and thereby relieve the latent tissue hypoxia.

It is possible that many of the aforementioned factors are involved in the pathogenesis of the hyperkinetic circulation. Because cirrhosis is the end result of diverse insults to the liver, it is possible that the pathogenesis of hyperkinesis is indeed multifactorial. Further research is needed to elucidate these mechanisms.

Cirrhotic Cardiomyopathy

Paradoxically, despite the existence of a hyperkinetic circulation, an uncertain but probably substantial percentage of patients with cirrhosis have overt or subtle evidence of impaired ventricular contractile function (Tables 1 and 2).[41–51] The issues are complicated by the fact that in western countries, alcohol use represents one of the commonest causes of both cirrhosis and cardiomyopathy. Thus, separating the effects of alcohol and the possible effects of liver disease on ventricular function is sometimes difficult. Despite the tendency of patients with cirrhosis, particularly alcoholic patients, to be malnourished, true beriberi cardiomyopathy appears to be relatively rare, as the great majority of cirrhotic patients with cardiomyopathy fail to respond to thiamine supplementation.[52,53]

Over the past two decades, many studies have investigated the problem of cardiac dysfunction seen in alcoholic patients and those with alcoholic cirrhosis.[41,42,48,53–58] It ap-

pears that this dysfunction encompasses a spectrum ranging from asymptomatic patients with a hyperkinetic circulation and evidence of abnormal ventricular contractility only with stress, to patients with end-stage, dilated, low-output cardiomyopathy. In the former group, the peripheral vasodilatation and reduced systemic vascular resistance can affect cardiac function. This decrease in afterload may not only mask signs of overt ventricular failure but probably protects the heart from florid decompensation until late in the disease course. Many studies have shown normal or hyperdynamic resting ventricular contractility, with subsequent abnormal responses that only manifest themselves if the ventricle is physiologically or pharmacologically stressed. Gould and coworkers catheterized patients with chronic alcoholic liver disease and found resting cardiac outputs to be increased with normal left ventricular filling pressures.[41] On exercise, however, all patients had increased left ventricular end-diastolic and pulmonary artery pressures but the stroke index fell or remained the same; this pattern represents a clearly abnormal ventricular response. Limas and colleagues studied patients with alcoholic cirrhosis and no clinical evidence of heart disease.[48] They found, in the resting state, a high cardiac output, low peripheral vascular resistance (mean, 825 dynes per second per cm^{-5}), and normal pulmonary capillary wedge pressure. Infusing the vasoconstrictor angiotensin in doses sufficient to "normalize" the peripheral vascular resistance to 1,140 dynes per second per cm^{-5} doubled the pulmonary wedge pressure, but the cardiac output remained unchanged. Kelbaek and associates studied asymptomatic patients with alcoholic cirrhosis.[42] In the resting state, echocardiographic systolic time intervals and radionuclide ventricular ejection fractions were not different from those of age-matched controls. With exercise, the left ventricular ejection fraction increased only 6% in cirrhotic patients versus 14% in controls, a significant difference. In a study of patients with predominantly alcoholic cirrhosis, even a physiologic stimulus of a liquid meal produced small but substantial decreases in cardiac output.[43]

Because alcoholic cirrhosis and cardiomyopathy share a common cause, the two conditions might frequently be expected to coexist in the same patient. Studies, however, support the clinical impression that the combination of the two is relatively rare.[11,52-54] Perhaps this represents underdiagnosis—that is, there may be some substance to the cardiologists' opinion that hepatologists cannot hear gallop rhythms and the hepatologists' suspicion that cardiologists rarely examine anything below the diaphragm. Two other factors are likely much more important in explaining this apparent rarity of concurrence. One is Berkson's bias. In 1947 Berkson's statistical analyses suggested that any two lethal diseases will show a negative association at autopsy.[59] Subsequent testing of his hypothesis has confirmed this artifactual negative association for diseases such as cirrhosis and hepatic metastases as well as brain tumor and myocardial infarction.[60,61] The second and probably most important factor is the previously mentioned protective effect of low peripheral resistance in unloading the ventricles. A patient will probably die of cirrhosis before overt congestive cardiomyopathy can develop.

In patients with nonalcoholic cirrhosis, florid low-output congestive cardiomyopathy has not been described in the absence of hypertension, ischemia, or some other known cause of heart failure. Nevertheless, there are reasons to believe that cirrhosis per se may be associated with subtle evidence of abnormal contractile function. First, on theoretic grounds, hyperkinetic circulatory changes may induce a high-output cardiac failure resembling a chronic volume overload of the heart.[52,53] Second, cirrhosis of any cause is associated with high serum catecholamine levels,[62] and long-term cardiac exposure to elevated catecholamines is known to result in cardiomyopathy.[63] Third, necropsy series of patients with predominantly alcoholic or predominantly nonalcoholic cirrhosis show similar cardiac pathologic findings: mild diffuse fibrosis, subendocardial edema, nuclear and cytoplasmic vacuolation, and ventricular dilatation and hypertrophy.[64,65] Fourth, there is good evidence that jaundice itself, regardless of the cause, may exert some cardiodepressant effects.[66] Finally, some animal models of nonalcoholic liver disease also show abnormal cardiac responsiveness. Volume infusion in rats with carbon tetrachloride-induced cirrhosis causes acute ventricular failure with a 50% decrease in cardiac output.[67] Rats with prehepatic portal hypertension[68] as well as biliary cirrhosis[69] display impaired chronotropic responses to the β-adrenergic agonist isoproterenol. Ventricles from the latter group were recently found to have diminished β-adrenergic-receptor density, thus indicating that the catecholamine hyposensitivity was associated with receptor downregulation.[69] Similar β-receptor downregulation has been found in ventricles from failing human hearts.[70]

Myocardial membrane receptor studies of human cirrhosis have not been done, presumably owing to the difficulty in obtaining cardiac tissue in vivo. Lymphocyte β_2-receptors, however, correlate well with the predominantly β_1-receptors in ventricles,[71] and in a subgroup of patients with decompensated cirrhosis, Gerbes and colleagues found reduced lymphocyte β-receptor density.[72] Clearly, further research in receptor and cellular pathophysiology in cirrhotic cardiomyopathy is needed.

What are the treatment options in patients with cardiac decompensation? In alcoholic patients, abstinence could be expected to improve or at least slow the rate of deterioration of hepatic and cardiac function.[52,53,73,74] Prolonged bed rest was helpful in one study of alcoholic cardiomyopathy, although this may have been due to the effects of abstinence.[75] As for active treatment in all types of cirrhotic patients, those with normal resting cardiac function should not need drug therapy. Those with more overt heart failure should have careful drug treatment to change cardiac loading conditions.[76,77] Studies in cirrhotic patients with latent ventricular dysfunction[48] and in jaundiced dogs[78] showed that cardiac glycosides were completely ineffective in improving ventricular contractility, so at present, any possible role for digitalis compounds remains speculative.

Ascites

Ascites is a common complication of hepatic sinusoidal portal hypertension. To discuss all the hemodynamic derangements associated with ascites is not the intent of this review, but certain aspects of ascitic fluid accumulation and resolution are worth noting, as they bear directly on cardiac function. Massive ascites can affect the measurement of cardiac performance indexes directly and also artifactually. The latter refers to a misleading calculation for the cardiac index, which is obtained by dividing the cardiac output by the body surface area. Because the surface area is usually derived from tables or nomograms based on height and weight, it is

evident that the presence of as much as 20 to 25 kg of ascitic fluid will lead to an underestimation of the cardiac index unless an estimated "dry" body weight is used. Tense ascites may directly impair the cardiac performance by a hydrostatic pressure on the diaphragm, with consequent increased intrathoracic and intrapleural pressures and a decrease in the cardiac transmural filling pressure. In addition, many patients have small diaphragmatic lymphatic channels, which allow ascitic fluid to track up into the pleural cavity and thereby impair cardiac function by the same mechanism. If these hypotheses are correct, then withdrawing ascitic fluid should result in an increased cardiac output. Indeed, most studies on the hemodynamic effects of paracentesis have found significant increments in cardiac output following the procedure.[79-81] In other studies, no changes in the cardiac output were found,[82,83] but this may be related to differences in the amount of fluid removed, the timing of the cardiac output measurement after paracentesis, and whether or not albumin was concurrently infused. It appears that ascitic fluid quickly starts reaccumulating, and if peripheral interstitial edema is absent, the reaccumulation will be at the expense of the intravascular fluid compartment. Thus, remeasuring the cardiac output several hours after a paracentesis may be too late to detect the initial hemodynamic changes.

Ascitic fluid can also be removed from the peritoneal cavity by a peritoneovenous shunt such as a LeVeen or Denver shunt. In this case, however, the fluid is shunted directly into the central veins. Thus, the cardiac output would be expected to rise in the immediate postoperative period because of a decrease in intra-abdominal pressure and a direct increase in venous return. Blendis and colleagues have shown this to be the case: the cardiac output rose from a mean of 7 liters per minute to 10 liters per minute in such patients.[84] If the cardiac reserve was borderline, such a volume challenge might have precipitated pulmonary congestion, but pulmonary wedge pressures did not change, indicating a normal cardiac response. Two weeks to two months after shunt insertion, cardiac output values had returned to the preoperative levels,[84,85] suggesting a "resetting" of cardiac output controls to adjust to the long-term hemodynamic changes of peritoneovenous shunting.

Coronary Atherosclerosis

There is a pervasive view among physicians that cirrhosis, particularly alcoholic in origin, protects against the development of ischemic heart disease. The evidence in favor of this notion derives from several sources. Autopsy studies of large numbers of cirrhotic patients reveal a lower prevalence of both significant coronary atherosclerosis and myocardial infarctions.[86-88] For example, one study showed that 3.3% of cirrhotic patients died of myocardial infarction whereas the corresponding figure in patients without cirrhosis was 11.4%.[88] Other evidence comes from coronary arteriography, which in persons with chronic alcoholism usually shows no major atherosclerotic lesions.[89] Finally, epidemiologic data indicate that a modest daily alcohol intake—about two drinks per day—is associated with a decrease in the incidence of coronary ischemic events.[90,91]

Although Berkson's bias could again partly account for these observations, it is unlikely to be the sole factor. The most plausible explanation is that cirrhosis, especially alcoholic cirrhosis, modifies two of the major risk factors for coronary atherosclerosis. First, the pathophysiologic effects of alcoholism and chronic liver disease on lipids are complex. The previously mentioned protective effect of modest alcohol intake on atherosclerosis may be related to increases in high-density-lipoprotein cholesterol levels,[92] as it seems that this form of cholesterol somehow hinders arterial atherogenesis. With increasing alcohol intake and the consequent development of chronic liver disease, however, the lipoprotein profiles are further modified in patterns that are not yet fully determined. An example of the complexity of the situation is the lipid pattern of patients with primary biliary cirrhosis. Despite the high lipid levels leading to xanthomas, ischemic vascular events are distinctly rare. The likely explanation lies in the observation that in the early to middle stages of the disease, very-low-density-lipoprotein levels are normal while those of high-density lipoprotein are high. Only in the advanced stages do very-low-density-lipoprotein levels increase while the high-density-lipoprotein levels fall.[93]

The second factor may be that cirrhosis is associated with a fall in the arterial pressure. While it is now clear that alcohol abuse per se aggravates arterial hypertension, once alcoholism has led to the development of cirrhosis, the hypotensive effect of the liver disease outweighs the hypertensive effect of alcohol.[94,95] Furthermore, established cirrhosis of any cause is associated with peripheral vasodilatation and reduced arterial pressure. Such hypotension thus removes a major risk factor for coronary atherosclerosis.

Endocardial and Pericardial Disease

Because the liver acts as a "filter" for the gut circulation, a diseased liver may have difficulty in properly removing bacteria from the portal vein. This impaired ability to process gut bacteria, with a consequent "spillover" into the systemic circulation, is thought to be a major reason for the polyclonal gammopathy characteristically seen in chronic liver disease.[96] In addition, liver failure is associated with immune system defects in chemotaxis, opsonization, and phagocytosis.[97,98] A cirrhotic patient would therefore theoretically be at risk for bacterial endocarditis. The only study to address this issue is that of Snyder and co-workers.[6] On reviewing the records of 41,151 hospital admissions, they found the incidence of endocarditis in patients with cirrhosis to be 0.34% versus 0.1% in noncirrhotic patients. Cirrhotic patients, therefore, are apparently susceptible to the development of endocarditis, although the overall risk is still fairly low.

Although it is well known that constrictive pericarditis can cause cardiac cirrhosis, the converse, cirrhosis causing pericardial disease, is practically unstudied. In rare cases, fibrinous pericarditis in the acute renal failure of the hepatorenal syndrome has occurred.[99,100] In an autopsy review of 220 cases of alcoholic cirrhosis, fibrinous pericarditis was found in 18 patients.[101] Although 15 of the 18 patients had overt azotemia, 3 had evidence of only mild renal impairment. Interestingly, no pericarditis was found in 71 patients with nonalcoholic hepatitis or cirrhosis. Because all 28 patients described in the three series have been alcoholic, it has been suggested that a synergistic effect of alcoholism and mild or overt uremia may somehow predispose to the development of fibrinous pericarditis.

A recent echocardiographic study of 27 patients with alcoholic cirrhosis documented small pericardial effusions in 63%, all associated with gross ascites.[102] The pericardial

effusions regressed with effective treatment and resolution of the ascites. No patient had evidence of cardiac tamponade or notable hemodynamic impairment. Because small pericardial effusions can be seen in other edematous states such as the nephrotic syndrome, these observations are not surprising.

Cardiac Endocrine Function

The only hormone known to be secreted by the heart is atrial natriuretic peptide, or atriopeptin.[103] Human atriopeptin is a 28-amino acid peptide stored in and released from atrial granules, with natriuretic and vasoactive properties. Currently much interest is being focused on this peptide in the sodium and water retention of cirrhosis. A discussion of this issue is inappropriate for this review, and readers are referred to recent reviews.[103,104] Suffice it to say that in patients with cirrhosis, serum levels are elevated,[104-106] the kidney appears to be desensitized to its effects,[104,105] and the atrial release of this hormone appears to be unimpaired.[106]

Conclusions

The heart and liver are closely interrelated, with disease processes in one affecting the function of the other. Although the systemic and regional circulations become hyperkinetic in cirrhosis of the liver, the pathogenetic mechanism for this is still unclear. Despite basal hyperkinesis, some patients have evidence of overt or latent cardiomyopathy. Almost all the investigation in these areas up till now has been merely descriptive or phenomenologic. With the recent emergence of advanced in vitro techniques such as membrane receptor assays and methods to characterize postreceptor membrane function, further insights into the biochemical and cellular pathophysiology of cardiac dysfunction in cirrhosis should be forthcoming. In the meantime, many questions remain. Is nonalcoholic cirrhosis in humans associated with cardiomyopathy? Are cirrhotic patients truly protected from vascular atherosclerosis, and, if so, by what mechanisms?

Another important issue is that of orthotopic liver transplantation. Many chronic liver diseases with a formerly bleak prognosis, such as primary biliary cirrhosis, can be treated with transplantation. The disappearance or regression of signs such as ascites, bounding peripheral pulses, and resting tachycardia in a stable allograft recipient suggests that many of the cardiovascular complications of cirrhosis are wholly or partially reversible. Research in this area may help elucidate the fundamental pathophysiology of circulatory disturbances in liver disease.

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