

Cardiac Hepatopathy: Clinical, Hemodynamic, and Histologic Characteristics and Correlations

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Cardiac hepatopathy, hepatic injury caused by cardiac dysfunction, is a common entity but has been characterized incompletely, particularly the relationship between hemodynamics and histology. We aimed to describe the clinical, biochemical, hemodynamic, and histologic characteristics of this disorder. Eighty-three patients from 2 tertiary referral centers were studied. Patients were divided into 3 groups based on the duration of cardiac dysfunction: (1) acute (n = 12); (2) chronic (n = 53); and (3) acute on chronic (n = 18). Results showed that serum aminotransferase levels were increased typically, particularly in the acute group (median aspartate aminotransferase level was 30.2 times the upper limit of normal [range, 1-100]; $P < .0001$ vs. the chronic group). The most salient hemodynamic features were elevated right atrial (14 mm Hg [range, 1-29]), and hepatic venous pressures (wedged: 18 mm Hg [range, 5-35]; free: 15 mm Hg [range, 2-30]). The hepatic venous pressure gradient was normal in most (81%), correlated moderately with the aminotransferase levels (aspartate aminotransferase level: $r = .59$; $P < .0001$), and associated with the presence of centrilobular necrosis and inflammation, periportal necrosis, and stainable hepatic iron ($P < .05$ for all comparisons), but not fibrosis. Sinusoidal dilatation was associated with higher right atrial ($P = .047$) and free hepatic venous pressures ($P = .06$). Although cirrhosis was rare (n = 1), centrilobular fibrosis was common (74%) and not associated with any hemodynamic measurement. In conclusion, cardiac hepatopathy has diverse clinical, hemodynamic, and histologic manifestations that vary with the temporal course of cardiac dysfunction. Hepatic fibrosis is common, but does not correlate with systemic or hepatic hemodynamics. (HEPATOLOGY 2003;37:393-400.)

Hepatic injury as a consequence of cardiac disease is a relatively common, but often poorly recognized, syndrome.¹⁻⁹ Sherlock's⁴ classic work, published in 1951, still stands as the standard reference on

the syndrome now called *cardiac hepatopathy*. Further reports since then have defined the natural history,¹⁰⁻¹³ diagnostic tests,¹²⁻¹⁴ and histologic findings^{3,15-19} of this condition. Surprisingly, given the dramatic circulatory disturbances associated with this syndrome, few hemodynamic studies have been reported.^{5,6,20,21} No prior study has examined both hepatic and systemic hemodynamics, or the correlation between hemodynamics and histology. In addition, the current spectrum of cardiac hepatopathy may be greatly different from that described in earlier reports, due to a shift in etiology from predominantly rheumatic valvular disease^{3,4,18} to ischemic cardiomyopathy, as well as major advances in the treatment of heart failure. Patients with this condition may present to a wide variety of physicians including hepatologists, gastroenterologists, cardiologists, and internists. In this study, we present the clinical, hemodynamic, and histologic data of 83 patients with cardiac hepatopathy assessed in the hepatic hemodynamics units of the Hôpital Beaujon and the University of Calgary.

Abbreviations: RAP, right atrial pressure; FHVP, free hepatic venous pressure; WHVP, wedged hepatic venous pressure; HVPG, hepatic venous pressure gradient; ALT, alanine aminotransferase.

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This article is dedicated to the memory of Dame Sheila Sherlock, one of the founders of modern hepatology, and author of the first complete study of cardiac hepatopathy a half-century ago.

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Patients and Methods

All patients were diagnosed consecutively between 1980 and 2001; the charts of the first 63 patients were

reviewed retrospectively whereas the remaining 30 were studied in a prospective fashion. The cases were roughly evenly distributed during the 2 decades of study. All patients were referred for hepatic vein catheterization studies and/or transjugular liver biopsy to investigate hepatic dysfunction (usually biochemical test abnormalities) or disease. In most cases, there was previous suspicion of cardiac disease, and the referring physician specifically requested systemic hemodynamic measurements. In selecting the cases, the diagnostic criteria were: (1) a liver biopsy compatible with cardiac hepatopathy,^{3,15-19} and (2) at least one of the following abnormal hemodynamic measurements: right atrial pressure (RAP) greater than 10 mm Hg, mean pulmonary arterial pressure greater than 25 mm Hg, pulmonary capillary wedge pressure greater than 15 mm Hg, cardiac index less than $2.2 \text{ L/min} \cdot \text{m}^{-2}$; or (3) clinically overt circulatory shock or congestive heart failure. Additional causes of liver disease including hepatitis B infection, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson disease, and α 1-antitrypsin deficiency were excluded carefully based on conventional clinical, biochemical, serologic, and histologic criteria. Patients with excessive alcohol consumption ($\geq 30 \text{ g/d}$ in women and $\geq 50 \text{ g/d}$ in men) also were excluded. The study was performed according to the principles of the Helsinki Declaration and all patients gave witnessed informed consent.

All patients had free hepatic venous pressure (FHVP), wedged hepatic venous pressure (WHVP), and RAP recorded. Among the first 63 cases, cardiac output, pulmonary capillary wedge pressure, and mean pulmonary arterial pressure were measured sporadically at the discretion of the referring physician or physician performing the catheterization either to confirm a suspicion of underlying heart disease or in cases of elevated RAP. The 30 patients studied prospectively had uniform hepatic and systemic hemodynamic measurements.

Hepatic venous and systemic hemodynamic measurements and transjugular liver biopsy were performed in all patients, as described previously.^{22,23} The hepatic venous pressure gradient (HVPG), which is correlated closely with the intrahepatic contribution to portal pressure,^{24,25} was calculated as the difference between the WHVP and FHVP. Pressures were measured with a Statham P23 pressure transducer (Gould Instruments, Valley View, OH) connected to a recorder. The external zero reference level was set 5 cm below the sternal angle. Cardiac output and right heart pressures were measured by using a Swan-Ganz thermodilution catheter.

Clinical, biochemical, hemodynamic, and histologic information were recorded on a structured data collection

instrument. Underlying cardiac diagnoses were classified as cardiomyopathy (*e.g.*, acute myocardial infarction), valvular (*e.g.*, rheumatic heart disease), hemorrhagic shock, pericardial (*e.g.*, constrictive pericarditis), pulmonary (*e.g.*, cor pulmonale due to chronic pulmonary disease), or mixed. For the purpose of the main analysis, patients were divided into 3 groups based on the duration of their cardiac disease: (1) acute: symptoms less than 2 weeks duration and no prior cardiac disease; (2) chronic: known, compensated cardiac disease; and (3) acute on chronic: prior cardiac disease with acute decompensation over the preceding 2 weeks. Biochemical variables including serum aspartate and alanine aminotransferase (ALT) levels, alkaline phosphatase levels, total bilirubin levels, albumin levels, and prothrombin time (as percentage of normal clotting activity) also were recorded. Histologic variables including an assessment of hepatic architecture (normal or fibrotic), centrilobular features (centrilobular and sinusoidal dilatation, necrosis, atrophy, inflammation, and fibrosis), periportal characteristics (necrosis, atrophy, inflammation, and fibrosis), steatosis, cholestasis, and the presence of stainable iron also were recorded. Histologic lesions were graded on a semiquantitative scale (0 = none; 1 = mild; 2 = severe); the histopathologist was unaware of the biochemical or hemodynamic values.

Statistical Analysis. Statistical comparisons were made using Spearman-rank correlations, Fisher exact test, and 2-sided *t* tests and the Wilcoxon rank-sum test for normally and nonnormally distributed variables, respectively. *A priori* hypotheses were made that patients with abnormal architecture would have elevated hepatic venous pressures and HVPG, reflective of increased portal pressure, and those with sinusoidal dilatation would have elevated FHVP and RAP.¹⁵ As a result, 1-sided tests were used for these comparisons. A *P* value of less than .05 was considered statistically significant. All analyses were performed using NCSS 2001 statistical software (NCSS, Kaysville, UT).

Results

Clinical Features. Ten of 93 eligible patients were excluded from the analysis because of excessive alcohol consumption ($n = 5$), concomitant hepatitis B virus infection ($n = 3$), and lack of a liver biopsy and therefore inability to confirm the diagnosis ($n = 2$). The median age of the remaining patients ($n = 83$) was 55 years (range, 14-84 y) and the majority (80%) were men; there were no significant differences in demographics between groups (Table 1). Fifty-one percent of the patients had cardiomyopathies, with fewer cases of valvular dysfunc-

Table 1. Clinical Characteristics of 83 Patients With Cardiac Hepatopathy

Characteristic	All Patients (n = 83)	Acute (n = 12)	Acute on Chronic (n = 18)	Chronic (n = 53)
Age, y	55 (14-84)	52 (31-64)	57 (22-77)	58 (14-84)
Male sex	66 (80%)	8 (67%)	14 (78%)	44 (83%)
Cardiac Condition				
Cardiomyopathy	42 (51%)	7 (58%)	9 (50%)	26 (49%)
Valvular	15 (18%)	0 (0%)	3 (17%)	12 (23%)
Hemorrhagic shock	3 (4%)	3 (25%)*	0 (0%)	0 (0%)
Pericardial	12 (15%)	1 (8%)	2 (11%)	9 (17%)
Pulmonary	6 (7%)	1 (8%)	0 (0%)	5 (9%)
Mixed	5 (6%)	0 (0%)	4 (22%)†	1 (2%)
Hepatomegaly	62 (75%)	10 (83%)	12 (67%)	40 (76%)
Jaundice	23 (28%)	6 (50%)*	11 (61%)†	6 (11%)
Ascites	47 (57%)	5 (42%)	6 (33%)†	36 (68%)
Encephalopathy	8 (10%)	3 (25%)*	4 (22%)†	1 (2%)
Splenomegaly	10 (11%)	1 (8%)	1 (6%)	8 (15%)
Esophageal varices	6 (7%)	0 (0%)	2 (11%)	4 (8%)

NOTE. All data are medians (range) and proportions.

* $P < .05$ for comparison of acute versus chronic groups.

† $P < .05$ for comparison of acute on chronic versus chronic groups.

tion (18%) and pericardial disease (15%). In general, the etiology of cardiac disease was similar between groups, with the exception of a predominance of hemorrhagic shock in the acute group ($P = .005$ vs. the chronic group), and mixed etiologies in the acute on chronic group ($P = .01$ vs. the chronic group).

Physical examination findings commonly included hepatomegaly (75%) and ascites (57%). Whereas ascites tended to be more prevalent in those with chronic disease ($P = .11$ vs. the acute, and $P = .01$ vs. the acute on chronic groups), those with an acute element of cardiac dysfunction had a higher frequency of jaundice and encephalopathy (acute: $P \leq .001$, and acute on chronic: $P = .003$ vs. the chronic group, respectively). Splenomegaly (11%) and esophageal varices (7%) were infrequent.

Biochemistry. The biochemical features are outlined in Table 2. Both aspartate aminotransferase and ALT levels were elevated frequently, particularly in the acute and acute on chronic groups versus those with chronic disease. Elevations in alkaline phosphatase concentration were less

frequent, and not significantly different between groups. Liver function was reduced moderately; median serum bilirubin and albumin levels were 23 $\mu\text{mol/L}$ (range, 6-323 $\mu\text{mol/L}$) and 35 g/L (range, 25-50 g/L), respectively. The median prothrombin time was moderately prolonged at 55% of normal clotting activity (range, 10 to 100). Bilirubin levels were lower and prothrombin times were less prolonged in those with chronic disease than the other groups.

Hemodynamics. There were several notable differences in hemodynamics between groups (Table 3). Patients with chronic disease had a lower cardiac index and a higher RAP, and mean pulmonary arterial pressure and hepatic venous pressures than the other groups, reflective of more severe congestive heart failure. The WHVP (normal, 4-13 mm Hg) and FHVP (normal, 2-10 mm Hg) were elevated frequently (73% and 67%, respectively), due to caudad transmission of elevated right atrial pressure. In contrast, the HVPG was normal (≤ 4 mm Hg) in the majority (81%). The HVPG was significantly lower

Table 2. Biochemical Characteristics of Patients With Cardiac Hepatopathy

Variable (Reference Range)	All Patients (n = 83)	Acute (n = 12)	Acute on Chronic (n = 18)	Chronic (n = 53)
AST (X ULN)	1.3 (1-150)	30.2 (1-100)*	7.5 (1-150)†	1.0 (1-8)
ALT (X ULN)	1.0 (1-150)	18.5 (1-120)*	8.0 (1-150)†	1.0 (1-6)
Alkaline phosphatase (X ULN)	1.3 (0.5-13)	1.9 (1-7.5)	1.2 (0.5-6)	1.5 (1-13)
Total bilirubin ($\mu\text{mol/L}$)	24 (6-323)	41 (14-323)*	58 (14-310)†	18 (6-119)
Albumin (g/L)	35 (25-53)	37 (33-42)	33 (25-50)	35 (25-48)
Prothrombin time (% of normal activity)	55 (10-100)	53 (10-89)	35 (10-100)†	60 (26-100)

NOTE. All data are medians (range).

Abbreviations: AST, aspartate transaminase; ULN, upper limit of normal.

* $P < .05$ for comparison of acute versus chronic groups.

† $P < .05$ for comparison of acute on chronic versus chronic groups.

Table 3. Hemodynamic Characteristics of Patients With Cardiac Hepatopathy

Hemodynamic Variable (Reference Range)	All Patients (n = 83)	Acute (n = 12)	Acute on Chronic (n = 18)	Chronic (n = 53)
HR (50-90 beats/min)	85 (57-133)	93 (58-130)*	97 (61-133)*	82 (57-117)
MAP (60-110 mm Hg)	88 (53-150)	93 (68-125)	83 (60-119)	94 (53-150)
RAP (0-5 mm Hg)	14 (1-29)	5 (1-25)*	9 (3-23)†	16 (4-29)
MPAP (10-18 mm Hg)	33 (9-60)	18 (15-37)*	31 (9-50)	35 (16-66)
PCWP (6-12 mm Hg)	18 (4-38)	9 (4-33)‡	18 (7-30)	19 (6-38)
CI (2.5-3.9 L/min/m ²)	2.5 (1.4-6.1)	3.4 (2.4-6.1)*	2.6 (2.0-4.7)	2.4 (1.4-4.1)
SVRI (2,000-2,400 dyne-s-cm ⁻⁵ -m ²)	2,796 (1,420-5,577)	2,135 (1,639-3,244)*	2,449 (1,420-3,657)†	3,252 (1,922-5,577)
WHVP (4-13 mm Hg)	18 (5-35)	14 (5-25)*	15 (7-32)	19 (9-35)
FHVP (2-10 mm Hg)	15 (2-30)	7 (2-22)*	9 (3-23)†	17 (5-30)
HVPG (1-4 mm Hg)	2 (0-25)	4 (1-13)*	4 (1-25)†	2 (0-7)

NOTE. All data are medians (range).

Abbreviations: HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVRI, systemic vascular resistance index.

* $P < .05$ for comparison of acute versus chronic groups.

‡ $P = .06$ for comparison of acute versus chronic groups.

† $P < .05$ for comparison of acute on chronic versus chronic groups.

in the chronic group compared with the other 2 groups ($P = .0004$ vs. the acute and $P < .0001$ vs. the acute on chronic groups).

Liver Histology. Liver histology is outlined in Table 4. Fibrosis severe enough to distort the normal microscopic architecture was evident in 19% of the patients, but only one patient with mitral valvulopathy had cirrhosis. Fibrotic architecture was absent in the acute group. Centrilobular and periportal fibrosis specifically, were more frequent in the chronic and acute on chronic groups; however, differences did not reach statistical significance.

Centrilobular and sinusoidal dilatation were common, but did not differ between the groups. Approximately one third of the patients had centrilobular necrosis, inflammation, or hemorrhage. These findings were more frequent in the 2 acute groups. The degree of centrilobular necrosis was correlated with centrilobular inflammation ($r = .47$, $P \leq .0001$) and hemorrhage ($r = .26$, $P = .02$), periportal necrosis ($r = .52$, $P \leq .0001$), and the intensity of iron staining ($r = .36$, $P = .0007$). Periportal necrosis, present in only 8% of patients, was more common in the acute and acute on chronic groups ($P = .02$ and $P = .047$ vs. the chronic group, respectively). Centrilobular atrophy

Table 4. Histologic Findings in Patients With Cardiac Hepatopathy

Histologic Feature	All Patients (n = 83)	Acute (n = 12)	Acute on Chronic (n = 18)	Chronic (n = 53)
Abnormal architecture (distortion by fibrosis or cirrhosis)	16 (19%)	0 (0%)	4 (22%)	12 (23%)
Centrilobular features				
Dilatation	30 (36%)	5 (42%)	4 (22%)	21 (40%)
Sinusoidal dilatation	62 (75%)	9 (75%)	11 (61%)	42 (79%)
Necrosis	24 (29%)	8 (67%)†	11 (61%)‡	5 (9%)
Atrophy	34 (41%)	1 (8%)†,§	10 (56%)	23 (43%)
Inflammation	33 (37%)	6 (50%)	10 (56%)‡	14 (26%)
Hemorrhage	25 (30%)	5 (42%)	10 (56%)‡	10 (19%)
Fibrosis	61 (74%)	6 (50%)	14 (78%)	41 (77%)
Periportal features				
Necrosis	7 (8%)	3 (25%)†	3 (17%)‡	1 (2%)
Inflammation	27 (33%)	4 (33%)	9 (50%)	14 (26%)
Fibrosis	42 (51%)	4 (33%)	10 (56%)	28 (53%)
Steatosis	28 (34%)	6 (50%)	5 (28%)	17 (32%)
Cholestasis	8 (10%)	1 (12%)	4 (22%)	3 (6%)
Stainable iron	9 (11%)	3 (25%)†	4 (22%)‡	2 (4%)

NOTE. All data are proportions.

* $P = .10$ for comparison of acute versus chronic groups.

† $P < .05$ for comparison of acute versus chronic groups.

‡ $P < .05$ for comparison of acute on chronic versus chronic groups.

§ $P = .02$ for comparison of acute versus acute on chronic groups.

Table 5. Relationship Between Hemodynamics and Liver Histology

Histologic Feature	Hemodynamic Variable	Pressure (mm Hg)		P Value
		Histologic Feature Absent	Histologic Feature Present	
Architecture*	WHVP	17 (5-35)	21 (11-34)	.01
Centrilobular features				
Sinusoidal dilatation	FHVP	10 (3-30)	16 (2-27)	.06
	HVPG	4 (0-13)	2 (0-25)	.01
	RAP	8 (1-29)	15 (1-26)	.047
Necrosis	FHVP	17 (3-30)	7 (2-22)	<.0001
	HVPG	2 (0-10)	4 (0-25)	<.0001
	RAP	16 (3-29)	7 (1-25)	<.0001
	MPAP	35 (15-60)	22 (9-50)	.02
Inflammation	FHVP	16 (3-30)	14 (2-24)	.02
	RAP	15 (2-29)	12 (1-23)	.01
	MPAP	35 (15-60)	24 (9-50)	.008
	PCWP	18 (4-38)	12 (6-30)	.02
Fibrosis	CI	2.6 (1.5-6.1)	2.5 (1.4-4.7)	.35
Atrophy	HR	90 (58-133)	78 (57-120)	.02
Periportal necrosis	FHVP	15 (3-30)	6 (2-17)	.01
	HVPG	2 (0-25)	6 (2-15)	.003
	RAP	15 (2-29)	5 (0-12)	<.001
	MPAP	31 (13-60)	11 (9-20)	.008
	CI	2.5 (1.4-6.1)	4.3 (3.4-5.3)	.05

NOTE. All data are medians (range). Reference values for pressure measurements are reported in Table 3.

Abbreviations: MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; HR, heart rate.

*Histologic feature absent = normal architecture; histologic feature present = fibrosis or cirrhosis.

was less frequent in the acute than the acute on chronic ($P = .02$) and chronic groups ($P = .04$).

Relationship Between Hemodynamics and Liver Biochemistry and Histology. When patients were classified according to their duration of cardiac dysfunction, there were no significant correlations between hepatic or systemic hemodynamics and alkaline phosphatase level, albumin level, or prothrombin time. Total bilirubin was correlated strongly with the HVPG in patients with acute cardiac dysfunction only ($r = .83$, $P = .01$). In these patients, ALT level was correlated highly with RAP ($r = .72$, $P = .01$), FHVP ($r = .77$, $P = .005$), and WHVP ($r = .68$, $P = .02$), but not the HVPG or cardiac index. In the acute on chronic group, ALT level was correlated negatively with the WHVP only ($r = -.52$, $P = .03$). In patients with chronic cardiac dysfunction, only a weak correlation between ALT level and RAP ($r = -.29$, $P = .06$) was observed.

Table 5 shows the relationship between selected systemic and hepatic hemodynamics and liver histology. As hypothesized, patients with fibrotic architecture had higher WHVP reflective of increased portal pressure ($P = .01$). Patients with sinusoidal dilatation had higher FHVP ($P = .06$) and RAP ($P = .047$); however, there was considerable overlap between groups, making the determination of threshold values difficult. The median HVPG was higher in those with centrilobular necrosis ($P < .0001$), inflammation ($P = .01$), periportal necrosis ($P = .003$),

and stainable hepatic iron ($P = .003$). Patients with centrilobular ($P = .06$) and sinusoidal dilatation ($P = .01$) had lower HVPG than those without these histologic features. The HVPG was not associated with fibrosis in either the centrilobular ($P = .43$) or periportal regions ($P = .88$).

Discussion

The patients reported in this series show the diverse clinical, hemodynamic, and histologic manifestations of cardiac hepatopathy. Whereas previous reports emphasized rheumatic valvular disease,^{3,4,18} our series had a higher proportion of patients with cardiomyopathy, largely ischemic in nature. The most striking biochemical feature of this disorder was a marked elevation of the aminotransferase levels, often greater than 2,000 IU/L, particularly in patients with acute cardiac dysfunction. In our chronic group, on the other hand, the aminotransferases, which are independent predictors of mortality in this population,¹² were elevated only minimally. The alkaline phosphatase concentration was increased modestly. With respect to tests of liver function per se, abnormalities in cardiac hepatopathy were moderate.^{20,21} However, significant elevations in bilirubin and prothrombin time were seen, particularly in patients with acute cardiac dysfunction. Many patients in all groups presented with signs of portal hypertension and jaundice.

Ascites and edema, in particular, had no relation to the extent of hepatic damage, and are likely a function of elevated right-sided cardiac pressures. The frequency of ascites and jaundice may reflect some selection bias, but nonetheless, these were not uncommon modes of presentation. Indeed, the presenting clinical features of several patients were indistinguishable from typical noncardiac liver diseases, such as alcohol-induced hepatitis or cirrhosis. Only on hemodynamic testing did the correct diagnosis become apparent, underscoring the importance of a high index of suspicion for cardiac causes of liver disease, particularly in patients with a history of cardiac dysfunction.

No previous studies have examined systemic and hepatic hemodynamics in patients with cardiac hepatopathy completely. In our series, the hemodynamic patterns were distinct and virtually pathognomonic in the case of right heart or biventricular failure. Backward failure, as reflected in high right atrial pressure, was transmitted clearly to the hepatic and portal venous circulations, resulting in a tracing of the WHVP that often was pulsatile instead of the usual flat line. It has been shown that WHVP reflects the portal pressure, whereas the HVPG reflects the intraparenchymal (sinusoidal) contribution to portal pressure.^{24,25} Despite frequently elevated WHVP, caused by elevated FHVP, the HVPG was normal in the majority (81%) of our patients. Although logical enough, we did not find this observation of normal HVPG in cardiac hepatopathy reported in the English-language literature.

The correlation between systemic hemodynamics and liver biochemistry has been reported in only 2 studies.^{20,21} In 65 pediatric patients with congenital heart disease, Mace et al.²⁰ found several correlations suggesting that biochemical abnormalities are associated with the severity of heart failure, findings confirmed in adults with stable, dilated cardiomyopathy.²¹ We found similar results in our patients with acute cardiac dysfunction, in whom the aminotransferases were correlated strongly and positively with the right-sided cardiac and hepatic venous pressures. This finding mirrors the common clinical scenario of the patient presenting with acute heart failure and markedly elevated aminotransferase levels. In contrast to previous reports, we did not find significant associations between liver biochemistry and the severity of cardiac dysfunction in patients with chronic disease. This discrepancy may relate to the small sample size of our study. Alternatively, heterogeneity of the cardiac diagnoses within these groups caused by our temporal classification system may be implicated. With respect to other liver biochemical tests including alkaline phosphatase, bilirubin, prothrombin time, and albumin, significant correlations with the sys-

temic and hepatic hemodynamic measurements were not observed. Thus, although these parameters may alert the clinician to an underlying cardiac hepatopathy in an at-risk individual, they cannot be considered in isolation for predicting the severity of cardiac or hepatic disease.

Our series represents the largest to date of histology in living patients with cardiac hepatopathy. The most common histologic features included sinusoidal dilatation, and centrilobular and periportal fibrosis. Other common findings were centrilobular necrosis, atrophy, hemorrhage, inflammation, and periportal necrosis. These changes varied with the temporal course of cardiac dysfunction. In particular, patients with acute cardiac dysfunction were more likely to show centrilobular damage, presumably reflecting the vulnerability of this region to acute ischemic insult. In contrast, there was a trend toward increased fibrosis and distorted hepatic architecture in those with long-standing cardiac dysfunction, in accordance with an autopsy series reported 6 decades ago.²⁶

The relationship between hemodynamics and histology in cardiac hepatopathy previously has not been examined. Not surprisingly, patients with distorted hepatic architecture caused by fibrosis had higher WHVP reflective of increased portal pressure. Fibrosis per se was not associated significantly with any hemodynamic variable. Dilatation of the central veins and sinusoids, classic features of cardiac hepatopathy, were associated with higher filling pressures. Arcidi et al.,¹⁵ in an autopsy series, reported a similar association between chronic passive congestion and increased right atrial size. Finally, patients with centrilobular and periportal damage had higher HVPGs. This finding is in agreement with previous studies in other necroinflammatory conditions including acute alcohol-induced^{27,28} and viral hepatitis,²⁹ and likely relates to hepatocyte swelling.²⁷⁻²⁹ The resultant sinusoidal compression presumably elevates portal pressure by increasing hepatic vascular resistance.^{25,27-29} The presence of stainable hepatic iron was an additional predictor of the HVPG. We hypothesize that this finding reflects the correlation between iron deposition and centrilobular necrosis and hemorrhage, rather than undiagnosed genetic hemochromatosis. Although HFE testing was not available in the majority of our patients to definitively exclude this diagnosis, conventional clinical, biochemical, and histologic criteria were used. Moreover, the pattern of iron deposition was not consistent with hereditary iron overload in any patient, and the prevalence of fibrosis did not differ according to the presence of stainable iron (data not shown).

In agreement with others,^{4,19} we found a high frequency of steatosis in our patients with cardiac hepatopathy. This may relate to alcohol consumption or

comorbid conditions including diabetes, hyperlipidemia, and obesity, which predispose to ischemic heart disease, the predominant cardiac diagnosis in our series. In a review of necropsies in patients with heart failure, Lefkowitz and Mendez¹⁹ described regenerative hyperplasia, including the nodular variant, in 23% of patients. In our 83 antemortem biopsies, no such lesions were identified. We therefore speculate that these regenerative lesions¹⁹ represent agonal changes associated with severe hypoperfusion before death.

Cardiac cirrhosis continues to be a rare condition.^{2,4,19} In our series, despite centrilobular fibrosis in three quarters of the patients, only one case of cirrhosis was identified. Although false-negative transjugular liver biopsies must be considered, it appears that with newer methods of treatment of heart failure, cardiac hepatopathy rarely progresses to this severe stage, and/or patients die of their cardiac condition before the development of cirrhosis.^{11,13} As noted previously,³⁰ esophagogastric varices are uncommon in this condition. Because varices represent collateral vessels from the high-pressure portal circulation to the low-pressure systemic venous bed, they are unlikely to form in cardiac hepatopathy in which pressures generally remain high along the entire path of venous return to the right atrium. Based on these pathophysiologic considerations, it is possible that the varices observed in a few patients represent either false-positive endoscopies or undetected concomitant disease such as portal vein thrombosis.

Our study has several limitations that must be acknowledged. First, the mixed retrospective-prospective sample collection makes it difficult to draw any conclusions regarding prevalence/incidence. Second, inclusion of only patients with a compatible liver biopsy may have introduced a selection bias because patients referred for biopsy may have had greater alterations in liver function. This may account for the high prevalence of ascites and jaundice in our patient population. Third, our classification system based on the temporal course of cardiac dysfunction is limited by heterogeneity in the underlying cardiac diagnoses within groups. We chose this classification because of its ease of definition, clinical applicability, and to minimize the number of groups and maximize the amount of information available from this study. Moreover, although we carefully excluded other causes of liver disease, hepatitis C virus infection could not be definitively ruled out in patients studied during the 1980s. Finally, numerous between-group comparisons were made without correcting for multiple comparisons, mainly due to the small sample size of our study. As a result, type I errors cannot be excluded and confirmatory studies are warranted.

In summary, the patients described herein show the diverse manifestations of cardiac hepatopathy, and represent the most rigorously studied population to date. Elevated right-sided cardiac pressures transmitted caudad to the hepatic and portal venous circulations, and a typically normal hepatic venous pressure gradient, are the most salient hemodynamic features. Because the clinical manifestations of this disorder may mimic those of common hepatic conditions, a high index of suspicion is required, particularly in patients with a previous history of cardiac dysfunction.

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