Hepatic Morphology in Cardiac Dysfunction

A Clinicopathologic Study of 1000 Subjects at Autopsy

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Chronic passive congestion (CPC) and centrilobular necrosis (CLN) are well recognized pathologic changes, but their exact relationship to different forms of cardiac dysfunction is uncertain. We reviewed clinical data and hepatic, renal, and adrenal morphologic related to cardiac dysfunction in 1000 autopsy subjects at The Johns Hopkins Hospital where hearts had been studied after postmortem arteriography and fixation in distention. Fourteen pathologic variables, including body and organ size, and microscopic changes graded on a semiquantitative scale, and 18 clinical variables including congestive heart failure, shock, and cardiovascular disease, were analyzed statistically. Distinct patterns of cardiac dysfunction emerged for the two spectra of hepatic morphologic change. Among patients with variable CPC, but slight or absent CLN, the amount of CPC was predicted in a multivariate analysis by severity of right-sided congestive heart failure. CPC severity correlated with cardiac weight and chamber enlargement (P < 0.001). Among patients with variable CLN, but slight or absent CPC, CLN was predicted by profound hypotension and by renal failure. In addition, CLN, but not CPC, was significantly correlated with renal acute tubular necrosis (P < 0.001) and adrenal cortical medullary junction necrosis (P < 0.05), two lesions associated with shock. Among all 1000 patients CPC and CLN were highly significantly correlated (P < 0.001). The results show that hepatic CPC arises from conditions producing elevated systemic venous pressure but that CLN arises from reduced systemic arterial pressure, and the presence of one potentiates the development of the other. (Am J Pathol 1981, 104:159-166)

HEPATIC CHRONIC PASSIVE congestion (CPC) and centrilobular necrosis (CLN) are commonly encountered at autopsy and generally imply an abnormality of cardiac function. Chronic passive congestion is usually regarded as a consequence of right-sided heart failure, while centrilobular necrosis is considered a consequence of severe hypotension or shock. These two morphologic observations are often seen together, and some authors have emphasized the importance of synergistic processes.1,2 In the present study, we sought to clarify these relationships by correlating the clinical features of cardiac dysfunction with their morphologic manifestations at autopsy.

Materials and Methods

We reviewed the findings in 1000 consecutive adult (>15 years old) patients on whom autopsies were performed at the Johns Hopkins Hospital, whose hearts had been studied after postmortem coronary arteriography and fixation in distention.3 The autopsies took place between 1967 and 1977, and, in general, in the cases represented there had been clinical expectation of cardiac disease. This group comprised 19% of adult autopsies performed during this period. Eighteen clinical variables, including the duration and severity of right- and left-sided congestive heart failure, the duration and severity of shock, and features associated with cardiovascular disease, such

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as hypertension, diabetes mellitus, and chest pain, were abstracted from the patient's medical records. No attempt was made to reinterpret the diagnoses of the attending clinicians.

The clinical severity of left-sided congestive heart failure, right-sided congestive heart failure, and hypotension were each graded on a semiquantitative scale ranging from 0 (no disease) to 4+ (maximum severity). The degree of left ventricular failure was established on the basis of physical symptoms and clinically documented pulmonary vascular disease. The severity rating was a composite of these factors. For left-sided congestive failure, a severity of 1+ was assigned in the case of mild or episodic shortness of breath and dyspnea on exertion; a severity of 2+ was assigned for moderate shortness of breath and dyspnea on exertion. A rating between 2+ and 3+ was assigned if the moderate shortness of breath and dyspnea on exertion were accompanied by mild (3 pillow) orthopnea. A 3+ severity corresponded with the progression of these symptoms to shortness of breath at rest; acute respiratory distress; dyspnea following minimal exertion, such as climbing one flight of stairs or walking a few steps to one block; frequent nocturia; and paroxysmal nocturnal dyspnea.

Radiographic change in the pulmonary vasculature was assigned at least 2+ to 3+ left ventricular dysfunction. Findings of this degree included increased vascularity, Kerley B lines, and controllable pleural effusions. Manifestations of 3+ severity consisted of unremitting pleural effusions and pulmonary edema which responded to treatment. The rating of 4+ was assigned to intractable pulmonary edema.

For right-sided congestive failure, a grade of 1+ indicated moderate jugular venous distention at an inclination of 45 degrees or less, or hepatomegaly with the liver edge palpable at one or two fingerbreadths below the right costal margin, but without overt edema. A value of 2+ was assigned for moderate jugular venous distention and hepatomegaly if minimal ankle or pretibial edema was also present. The severity was between 2+ and 3+ if, in addition to jugular venous distention and hepatomegaly, the edema was pitting in quality and extended to the knee, or if it involved both upper and lower extremities. Right ventricular failure of 3+ severity included jugular venous distention to the mandibular angle at 90 degrees, hepatomegaly ranging from 4 to 10 cm below the right costal margin, a positive hepatojugular reflux, ascites of cardiac origin, and pitting of the entire leg, with or without sacral edema. The 4+ rating was assigned for generalized anasarca. When central venous pressure (CVP) data were available, a level of 0 was assigned for a CVP of less than 15 cm H$_2$O; 1+ for 15-24 cm H$_2$O; 2+ for 25-34 cm H$_2$O; 3+ for over 35 cm H$_2$O. As for left-sided failure, the rating of right-sided congestive failure represented the combined information of many clinical features, and the presence of significant edema was necessary for a rating of 3+ or more. In the analysis of both left- and right-sided cardiac decompensation, values over 1+ or more represent those patients with a diagnosis of at least mild to moderate congestive failure. The duration of left- and right-sided heart failure was defined as the interval between the onset of symptoms of failure or the actual diagnosis of failure and the date of death.

The severity of hypotension during the terminal admission was graded according to the systolic pressures recorded in the clinical summaries and was classified as either sustained or episodic. A period over 1 hour was required for sustained shock. The terminal decline of blood pressure was not included in either the sustained or episodic category. Severity was classified as 0 for normotensive, 1+ for 90-99 mm Hg systolic, 2+ for 80-89 mm Hg, 3+ for 60-79 mm Hg, and 4+ for less than 60 mm Hg systolic. The duration of sustained shock in hours was noted. Episodic shock (lasting less than 1 hour) was graded as 0 for pressures ranging from normotensive to 100 mm Hg, 1+ for 90-99 mm Hg systolic, 2+ for 70-89 mm Hg, 3+ for 60-69 mm Hg, 3+ to 4+ for systolic pressures less than 60 mm Hg but without cardiac arrest, 4+ for ventricular fibrillation or asystole.

Fourteen pathologic variables, including body and organ sizes, cardiac chamber volumes and valve circumference, and histologic features in sections of liver, kidney, and adrenal, were examined. The histologic features were graded on a semiquantitative scale (0 to 4+). We identified chronic passive congestion and centrilobular necrosis on the basis of histologic changes. The features used to establish the presence of chronic passive congestion were atrophy of hepatic parenchymal cells, distention of sinusoids, and, in the severe grades, fibrosis, in the centrilobular areas (Figure 1). The presence of centrilobular necrosis was defined as necrosis of centrilobular hepatic parenchymal cells (Figure 2). In adrenals we determined the severity of two histologic features: cortical nodular hyperplasia and cortical medullary junction necrosis (Figure 3). Cortical nodular hyperplasia has a known association with hypertension, which was confirmed in our material, but there were no other significant correlations with manifestations of cardiac dysfunction. Cases with adrenal cortical medullary junction necrosis exhibited necrosis of variable numbers of cells, particularly involving the
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zona reticularis. Recent studies have shown a correlation of this histologic finding with shock, an observation which was also confirmed in the present series.\textsuperscript{4,5}

Sections of kidney were examined for the severity of acute tubular necrosis, a histologic finding associated with shock.\textsuperscript{6} The histologic features in acute tubular necrosis are quite variable, depending upon the severity of insult and the elapsed time until death. We used three separate features in determining this diagnosis: actual necrosis of the renal tubular epithelium; dilatation of renal tubules with proteinaceous casts; and the accumulation of nucleated cells in the vasa recta.\textsuperscript{7} All data were keypunched for computer processing and analyzed statistically by the use of Pearson's $r$ coefficient and stepwise multivariate regression analysis.\textsuperscript{8,9}

Results

One thousand adult autopsy subjects at The Johns CPC, no CLN or trivial CLN, and a mean liver weight examined. The patients ranged in age from 16 to 95 years (average 60 years), and 616 patients were male. The patient series included 409 with systemic hypertension, 203 with diabetes mellitus, 215 patients with angina pectoris, 187 patients with atrial fibrillation, and 435 patients with one or more myocardial infarcts. Table 1 shows the series of 1000 patients subdivided according to both chronic passive congestion (CPC) and centrilobular necrosis (CLN). A majority of patients ($650/1000 = 65\%$) had CPC or trivial CPC, no CLN or trivial CLN, and a mean liver weight 1634 g. With increasing CPC there was a tendency for liver weight to decrease ($r = -0.12, \ P < 0.001$). Centrilobular necrosis was not correlated with liver weight. In a statistical analysis of chronic passive congestion and centrilobular necrosis of the liver, distinct patterns of cardiac dysfunction emerged from the clinical and morphologic data. The correlation coefficients between chronic passive congestion and pathologic features for the entire group of patients

![Figure 1](https://example.com/figure1.png) - Chronic passive congestion of the liver. A – The hepatic parenchyma surrounding the portal areas is well preserved, while that around the central veins (arrows) shows atrophy of the liver cell plates and dilatation of the sinusoids. (H&E, $\times 100$) B – Junction of better preserved (top) and atrophic (bottom) parenchyma. In addition to sinusoidal dilatation, there is prominence of the space of Disse, which lies between the sinusoids and functions as a lymphatic. (H&E, $\times 600$) (With a photographic reduction of 9\%)
were significant at the 0.001 level for dilatation in all four cardiac chambers and for increased heart weight (Table 2). Chronic passive congestion also has a highly significant correlation with centrilobular necrosis, a fact that may tend to obscure some of the features associated with chronic passive congestion. We used a forward, stepwise multivariate regression analysis to determine which clinical variables would predict chronic passive congestion in the liver at the 0.001 level of significance (Table 3). In order to minimize the effect of associated centrilobular necrosis, we first analyzed the group of 786 patients with slight or no centrilobular necrosis (Table 1, column 1). Only one variable, the severity of right-sided congestive heart failure, entered the regression analysis. When all 1000 patients were analyzed and centrilobular necrosis was permitted to enter the list of dependent variables, again only one clinical variable, namely, right-sided congestive heart failure, entered the regression analysis as a predictor of chronic passive congestion, along with centrilobular necrosis. This clinical variable is associated with conditions producing elevated systemic venous pressure. As we shall see, centrilobular necrosis is associated with reduced arterial pressure.

The correlation coefficients between centrilobular necrosis and pathologic features for the entire group of patients were significant for adrenal cortical medullary junction necrosis ($P < 0.05$) and renal acute tubular necrosis ($P < 0.001$) (Table 4). The correlation coefficients for heart weight and chamber volumes compared with CLN were less than those compared with CPC, with the exception of left-ventricular volume. These adrenal and renal lesions have a known association with clinical shock, which was confirmed in our series of 1000 patients. Again, we observe the strong correlation between centrilobular necrosis and chronic passive congestion. We used multivariate regression analysis to determine which clinical variables would predict centrilobular necrosis in the liver at the 0.001 level of significance (Table 5). We first analyzed the group of 753 patients with slight or no chronic

*Figure 2—Centrilobular necrosis of the liver. A—The darker staining parenchyma around the portal areas is preserved. The majority of the tissue of the lobule surrounding the central veins (arrows) has undergone coagulation necrosis and stains pale. (H&E, × 100) B—Junction of preserved (top) and necrotic parenchyma (bottom). (H&E, × 600) (With a photographic reduction of 9%)
passive congestion (Table 1, row 1). Two variables, shock and renal failure, entered the regression analysis. When all 1000 patients were analyzed and chronic passive congestion was permitted to enter the list of dependent variables, the same two clinical variables, shock and renal failure, again entered as predictors of centrilobular necrosis, along with chronic passive congestion. The two clinical variables are associated with conditions producing reduced systemic arterial pressure, the pathologic variable with conditions producing elevated systemic venous pressure.

The results show that when the hepatic lesions are considered separately, chronic passive congestion arises from conditions producing elevated systemic venous pressure, whereas centrilobular necrosis arises from conditions producing reduced systemic arterial pressure. When the hepatic lesions are considered together, there is a highly significant association between chronic passive congestion and centri-

Table 1—Distribution of Liver Weights in 1000 Autopsy Subjects

<table>
<thead>
<tr>
<th>Chronic passive congestion</th>
<th>None or trivial</th>
<th>Mild-moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Liver wt*</td>
<td>n</td>
<td>Liver wt*</td>
</tr>
<tr>
<td>None or trivial</td>
<td>650</td>
<td>1634 ± 20</td>
<td>63</td>
<td>1631 ± 72</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>85</td>
<td>1503 ± 55</td>
<td>44</td>
<td>1439 ± 60</td>
</tr>
<tr>
<td>Severe</td>
<td>51</td>
<td>1593 ± 75</td>
<td>30</td>
<td>1167 ± 80</td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td>1617 ± 19</td>
<td>137</td>
<td>1525 ± 44</td>
</tr>
</tbody>
</table>

* Mean ± standard error, in grams.
lobular necrosis, suggesting that the presence of one may potentiate the other.

**Discussion**

Chronic passive congestion (CPC) and centrilobular necrosis (CLN) frequently appear together in the liver during cardiac dysfunction. However, the pathogenesis of these lesions in this situation is yet uncertain, particularly the factors responsible for CLN. In a recent review article, it was suggested that hypoxia sufficient to cause CLN can be generated by an increase in hepatic venous pressure.\(^1\) CLN is associated with at least a moderate degree of hepatic congestion, and it is further suggested that perisinusoidal edema arising secondary to increased venous pressure may reduce oxygen diffusion to a critical level. Using 50% occlusion of the inferior vena cava, both CPC and CLN were produced, possibly duplicating the changes seen in clinical CHF.\(^10\) However, the assumption that the pressures obtained by such manipulations are representative of central venous pressure in clinical CHF has been questioned. In fact, there is a lack of correlation between right atrial pressure and the amount of hepatocellular necrosis.\(^11\) The capacity of prolonged CPC in RCHF to produce CLN has been claimed without supporting pathologic data.

Hypoxia in the centrilobular areas can also be created by diminished hepatic perfusion, but there is disagreement as to what level of hypoperfusion is required in order to exceed hepatic oxygen extraction. Some authors suggest that the addition of fever or exercise in a setting of CPC is sufficient to precipitate CLN.\(^1\) Others have considered the most frequent etiology of hepatocellular necrosis linking central veins as "congestive heart failure,"\(^12\) implying that the extent of hypoperfusion should correlate with diminished cardiac output. In contrast, Sherlock\(^11\) has noted the lack of a significant correlation between lowered cardiac output and the extent of centrilobular necrosis. In summary, the frequent appearance of CLN in cases of cardiac dysfunction is evidence for circulatory alterations producing a lowered oxygen tension. Hypoxia sufficient to produce CLN is thought to be adequately explained by the contributions of CPC or low cardiac output, or both.

The present study of 1000 autopsy subjects demonstrates that hypoxia sufficient to produce CLN requires the presence of shock. Centrilobular necrosis, occurring regardless of the presence of CPC, correlates significantly (P < 0.001) with the severity of sustained or episodic hypotension in the patient's course. Similarly, clinically evident renal failure, often precipitated by shock, is also a strong predictor of hepatic CLN. Pathologically, CLN is associated with adrenal cortical medullary junction necrosis (CMJN) (P < 0.01) and renal acute tubular necrosis (ATN) (P < 0.001). While shock as a cause of renal ATN has been established, the recognition of hypotension as the cause of CMJN is a more recent devel-

**Table 2—Correlation of Chronic Passive Congestion With Other Pathologic Variables in 1000 Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart weight</td>
<td>0.25</td>
<td>0.001</td>
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<tr>
<td>Right atrial volume</td>
<td>0.28</td>
<td>0.001</td>
</tr>
<tr>
<td>Right ventricular volume</td>
<td>0.16</td>
<td>0.001</td>
</tr>
<tr>
<td>Left atrial volume</td>
<td>0.19</td>
<td>0.001</td>
</tr>
<tr>
<td>Left ventricular volume</td>
<td>0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Centrilobular necrosis</td>
<td>0.32</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 4—Correlation of Centrilobular Necrosis With Other Pathologic Variables in 1000 Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular volume</td>
<td>0.14</td>
<td>0.001</td>
</tr>
<tr>
<td>Adrenal cortical-medullary junction necrosis</td>
<td>0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>0.15</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronic passive congestion</td>
<td>0.32</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 3—Prediction of Chronic Passive Congestion of the Liver by Multivariate Regression Analysis**

Clinical variables* in 786 patients with slight or absent centrilobular necrosis

CPC (0-4+) = 0.21

+ 0.33 RCHF (0-4+) SE = 0.33 r = 0.47

Centrilobular necrosis and clinical variables* in all 1000 patients

CPC (0-4+) = 0.17

+ 0.36 RCHF (0-4+) SE = 0.03 + 0.24 CLN (0-4+) SE = 0.03 r = 0.52

* Entered to a significance level of P < 0.001.

**Table 5—Prediction of Centrilobular Necrosis of the Liver by Multivariate Regression Analysis**

Clinical variables* in 753 patients with slight or absent chronic passive congestion

CLN (0-4+) = 0.14

+ 0.09 Shock (0-4+) SE = 0.02 r = 0.25

+ 0.32 Renal Failure SE = 0.07

(0 = No, 1 = Yes)

Chronic passive congestion and clinical variables* in all 1000 patients

CLN (0-4+) = 0.13

+ 0.11 Shock (0-4+) SE = 0.02

+ 0.30 Renal Failure SE = 0.06

(0 = No, 1 = Yes)

+ 0.28 CPC (0-4+) SE = 0.03 r = 0.41

* Entered to a significance level of P < 0.001.
Hypotension, previously these levels however, increases pathogenesis, increases of degrees with other thrombosis occlusion,22,23 venous pressure elevated,24,1 histologically has chamber gross significant onary artery with right-sided,25 left-sided,26 and renal failure,27,28 acute with other conditions producing elevated venous pressure. Among the entire group of patients, however, an association exists between CPC and CLN. This indicates that local alterations resulting from one lesion may enhance the underlying pathologic features of the other lesion.

The correlation in 1000 patients between CLN and shock and between CPC and elevated venous pressure are at variance with other reported series.20,21 In patients with CLN, there was no evidence of hypotension (or RCHF) at presentation. Biopsies revealed significant numbers of erythrocytes accompanying the CLN and replacing hepatocyte cords. This lesion histologically has been associated with elevated venous pressure, as it has been noted in experimental venous occlusion,22,23 Jamaican veno-occlusive disease,24,25 the Budd-Chiari syndrome, and hepatic vein thrombosis with other causes.26 Because varying degrees of left-ventricular decompensation were present in these patients, it was concluded that LCHF was the cause of the CLN. Elevated serum transaminase levels in these patients were cited in support of this pathogenesis, increases in SGOT levels having previously been reported in cases of myocardial injury;27 however, these levels were uniformly associated with significant hypotension, which was absent in these patients. LCHF as the appropriate cause of the CLN in these reports is controversial at the present time.

While CPC and CLN have distinct hemodynamic causes when considered separately, they frequently occur together. The correlation coefficient analysis indicates that the presence of one lesion predicts the other (r = 0.32, r < 0.001). This suggests that although the origins of CPC and CLN may be different, the local alterations resulting from one lesion may enhance pre-existing morphologic features of the other. CPC may contribute to the development of the morphologic features of CLN, exacerbating the effect of a depressed arterial pressure. Hepatocellular atrophy and stagnation of sinusoidal flow may pre-dispose the centrilobular region to necrosis. In addition, Safran and Schaffner27 have demonstrated the active deposition of perisinusoidal collagen in CPC. CLN, on the other hand, may potentiate the local effects of elevated venous pressure. Congestion of the sinusoids and central vein frequently accompany necrosis, although there may be little or no inflammatory response.28 Some authors14 have regarded this concomitant congestion as a criterion for CLN. Secondly, the accumulation of stromal connective tissue following hepatic necrosis, in contrast to CPC, occurs by both passive reticulin condensation as well as active deposition.29 This reciprocal potentiation between CPC and CLN, based on local effects of the lesions, may account for the frequency of their simultaneous appearance in cardiac dysfunction.

Chronic passive congestion and centrilobular necrosis are the pathologic manifestations of distinct systemic vascular conditions. Statistical analysis of 1000 patients permitted a separation of the two lesions. CLN was associated with shock and with clinical and pathologic sequelae of hypotension, but not with left-sided CHF. CPC was associated with right-sided CHF and other conditions producing elevated systemic venous pressure. Among the entire group of patients, however, an association exists between CPC and CLN. This indicates that local alterations resulting from one lesion may enhance the underlying pathologic features of the other lesion.

References
26. Reynolds TB, Peters RL: Budd-Chiari syndrome,10 pp 1402–1411