Original Article

Clinical Evaluation and Hepatic Laboratory Assessment in Individuals with Congestive Heart Failure

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Summary

Objective: **To verify the clinical alterations and, in particular, hepatic laboratory alterations in patients in each of the heart failure (HF) functional classes.**

Methods: **The clinical and laboratory data – alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), bilirubin and coagulogram – of 50 patients admitted in 2002 to a tertiary hospital with the diagnosis of heart failure were researched by means of a cross sectional study. The patients were separated in accordance with their HF class and their data were compared statistically. Patients with hepatopathy of any etiology were excluded.**

Results: **Analysis of the mean transaminase values revealed a significant increase only for the Class IV patients. On the other hand, alkaline phosphatase and GGT presented a progressive increase in accordance with the HF class.**

Conclusion: **HF is characterized by a progressive cholestatic profile of laboratory alterations, while transaminase values are only elevated in advanced HF. It is of utmost importance to understand these alterations in order to avoid unnecessary hepatic investigations in individuals with heart failure.**

Key words: **Clinical evolution; liver; congestive heart failure; liver function tests.**

Introduction

Recent studies have classified liver complications associated with heart failure in three general groups: a) congestive hepatic fibrosis and cardiac cirrhosis; b) cardiogenic ischemic hepatitis; c) moderate liver function test alterations in congestive heart failure[1].

Cardiac cirrhosis and congestive hepatic fibrosis are characterized by collagen deposits in the lobules with and without the formation of regeneration nodules, respectively. Both represent reactions ranging from hepatic stroma to situations of increased venous pressure, hypoxia or hepatocyte necrosis. Nevertheless, while cardiac cirrhosis today is clinically defined by the triad of right sided heart failure in association with hepatomegaly, ascites with a high protein concentration and elevated serum-ascites-albumin gradient, congestive hepatic fibrosis remains clinically silent.

Cardiogenic ischemic hepatitis is characterized by the dramatic transaminase serum increase after an acute and serious drop in cardiac output. It usually occurs within 2 to 24 hours after the causal phenomenon. The initial symptoms are usually weakness and apathy, but occasionally it can cause mental confusion, jaundice, oliguria, flapping and hepatic coma. Laboratory alterations in addition to the transaminase serum increase include elevated LDH and bilirubin serum levels and an increased prothrombin time. For patients who survive the cardiogenic ischemic hepatitis episode, liver function test abnormalities peak within one to three days and return to normal within five to ten days after the onset of symptoms[1].

Most studies that include the clinical presentation of patients with cardiogenic ischemic hepatitis list cardiogenic shock as the causal factor for the drop in cardiac output[2-4]. Researchers, over the past few years, have been attempting to determine the relationship between this entity and the hepatic alterations it causes. This research has led to a better understanding of how the maximum degree of heart failure – cardiogenic shock affects the liver.

Nevertheless, very little is known in regard to moderate alterations in liver function tests resulting from lesser degrees of congestive heart failure, and even less is known about the clinical manifestations of liver dysfunction in these circumstances. It is known that the enzyme abnormalities improve with heart failure compensation and that one third of the patients present moderate jaundice[1].

The objective of this study was to establish a profile of both the clinical and laboratory alterations that the different degrees of congestive heart failure cause in the patient. Attention was focused on the liver and therefore major consideration was given to the liver function tests and symptoms that indicate liver damage or dysfunction.

Methods

The clinical and laboratory data of 50 individuals diagnosed with any degree of heart failure, including cardiogenic shock, were researched by means of a cross sectional study.

The study population was chosen from a sample of 337 patients admitted to a tertiary hospital, by tracking the International Classification of Diseases code for the diagnosis of heart failure (CID I500) and data collected from the patients' medical charts.

Data analyzed from each medical chart included: a) clinical signs of liver failure such as hepatic encephalopathy, jaundice, coagulopathy, hypoglycemia, metabolic acidosis, pruritus, ascites and telangiectasias; b) laboratory signs of hepatic cellular lesion, liver dysfunction and cholestasis (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], alkaline phosphatase [AP], direct bilirubin [DB], indirect bilirubin [IB] and total bilirubin [TB], albumin, coagulation factors and coagulogram [R and RNI]). The laboratory data were collected within a maximum timeframe of four days after decompensation, a period in which possible alterations are usually observed. The reference numbers used for the research are as follows (Table1):

Table 1 – Reference laboratory values adopted upon admission to the hospital	
AST	Male – up to 37 U/l Female – up to 31 U/l
ALT	Male – up to 40 U/l Female – up to 30 U/l
AP	Male – 40 to 129 U/l Female – 35 to 104 U/l
GGT	Male – up to 269 U/l Female – up to 239 U/l
DB	Up to 0.2 mg/dl
IB	Up to 0.8 mg/dl
TB	Up to 1.0 mg/dl
R	Up to 1.3
RNI	Up to 1.25

The heart failure classes were obtained from the medical histories in accordance with the criteria prepared by the New York Heart Association (NYHA): class I (patients with heart disease however asymptomatic during ordinary activities), class II (slight limitation of physical activity; ordinary activity results in fatigue, palpitation, dyspnea or chest pain), class III (marked limitation of physical activity; less than ordinary activity causes symptoms) and class IV (symptoms at rest).

For the patients who had an echocardiogram, the ventricular ejection fraction (EF) values (Teichholtz method) were obtained for later correlation with the heart failure level.

Patients with a history of any type of hepatitis, noncardiogenic shock, hepatic tumor, hepatic trauma, alcoholism, noncardiogenic cirrhosis of the liver or other liver or bile duct diseases were not analyzed. Patients with any type of bone disease as well as neoplasias or metastases in any location were excluded due to the possibility of increased alkaline phosphatase. Patients who were admitted for acute myocardial infarction were also excluded due to the possibility of increased aspartate aminotransferase serum levels.

Comparisons of the patients' laboratory data for the different heart failure classes were conducted using the Student's t-test with a significance level of $p < 0.05$.

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Comparisons of the patients' laboratory data for the different heart failure classes were conducted using the Student's t-test with a significance level of $p < 0.05$.

Results

From the 337 patients, the medical charts of 175 (51.93%) were analyzed. From these, 125 (71.43%) had one of the exclusion factors and the remaining 50 (28.57%) fulfilled the requirements for the study.

In relation to gender, 32 were female (64%). In regard to skin color, 33 (66%) were white, 10 (20%) mulattos, and seven (14%) negro. In relation to age groups, there were no patients between the ages of zero and ten years; one patient (2%) between 11 and 20 years ; one patient between 21 and 30 years; 2 patients (4%) between 31 and 40 years; 5 patients (10%) between 41 and 50 years; 9 (18%) between 51 and 60 years; 17 (34%) between 61 and 70 years; 12 (24%) between 71 and 80 years and 3 (6%) older than 81 years.

In regard to causal diagnoses of congestive heart failure, the main cause was systemic hypertension in 31 patients (62%), followed by acute myocardial infarction, affecting 15 (30%), and Chagas disease in 13 (26%). Six had valvular heart disease (12%) and three had stable angina (6%). Systemic sclerosis, atrial fibrillation, hyperthyroidism, hypothyroidism and obesity were each presented by one patient.

From the 50 patients in the study, six (12%) had class I heart failure, 10 (20%) class II, 18 (36%) class III, and 16 (32%) class IV.

During the decompensation phase, 47 patients (94%) presented dyspnea, 25 (50%) edema in the lower extremities, 15 (30%) nocturnal paroxysmal dyspnea, 13 (26%) orthopnea, 7 (14%) fatigue, and 4 (8%) anasarca. Chest pain, tachycardia, nocturia, oliguria, loss of appetite and lethargy were each presented by two patients. One patient

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presented abdominal pain and nausea. Four patients (8%) suffered from cardiogenic shock. At the conclusion of the hospital admission timeframe chosen for analysis purposes there had been seven deaths (14%).

The results of the laboratory data are as follows (Table 2):

and the standard deviation 5.65. The lowest value was 8 U/L and the highest 23 U/L. The class II patients had a median of 18 U/L, and the standard deviation was 14.29. The lowest value was 9 U/L and the highest 56 U/L. Among the class III patients the median was 19 U/L and the standard deviation 22.09. The

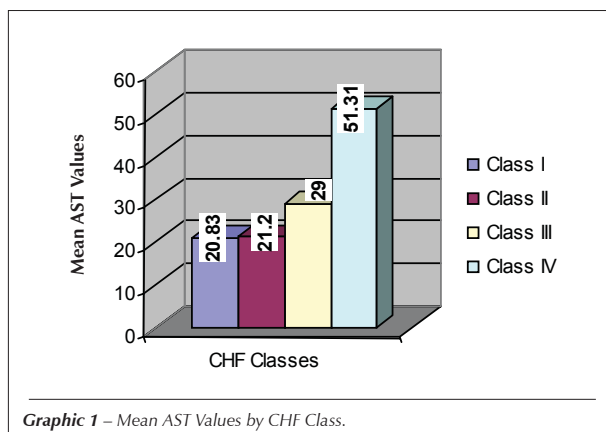| Table 2 – Individual evaluation of the study variables						
	Patients	Lowest value	Highest value	Mean	Median	Standard deviation
AST (U/l)	50	7	158	34.08	24.5	28.18
ALT (U/l)	50	2	264	36.14	19	44.07
AP (U/l)	33	124	572	249.75	205	101.26
GGT (U/l)	30	12	883	119	75.5	162
DB (mg/dl)	14	0.1	2.3	0.55	0.4	0.58
IB (mg/dl)	14	0.2	3.0	0.67	0.4	0.72
TB (mg/dl)	14	0.4	5.3	1.22	0.7	1.29
R	35	0.85	1.64	1.15	1.12	0.18
RNI	35	0.95	2.72	1.29	1.2	0.33
Echo (%)	21	17.30	50.80	34.48	35.25	9.79

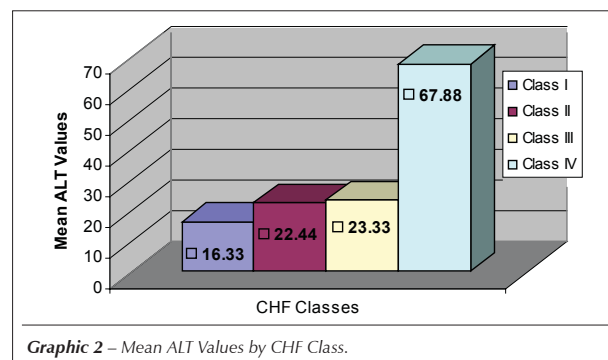Bivariate analysis was used for the CHF class and hepatic enzymes, revealing the following results.

AST - Among the six patients with class I heart failure, the lowest value was 13 U/L and the highest 30 U/L. The standard deviation was 6.85 and the median 20.5 U/L. Among the 10 class II patients, the standard deviation was 6. The lowest value was 11 U/L and the highest 30 U/L. The median was 20.5 U/L. The highest AST value among the patients with class III congestive heart failure was 158 U/L and the lowest 13 U/L. The standard deviation was 32.67 and the median was 20.5 U/L. Among the 16 patients with class IV HF the standard deviation was 28.05 and the median 54. The lowest value was 7 U/L and the highest 126 U/L (graphic 1). Analysis of the mean AST values using the Student's t-test was statistically significant only when the class IV mean value was compared to the other averages.

ALT - Among the patients in class I, the median was 16 U/L

lowest value was 3 U/L and the highest 100 U/L. Among the class IV patients the lowest value was 2 U/L and the highest 264 U/L. The median was 61 U/L and the standard deviation was 63.80 (graphic 2). Analysis of the mean ALT values using the Student's t-test was statistically significant only when the class IV mean value was compared to the other averages.


Graphic 2 – Mean ALT Values by CHF Class.

AP - Among the class I patients the median was 193 U/L and the standard deviation was 23.89. The lowest value was 149 U/L and the highest 202 U/L. The class II patients had a median of 216.5 U/L, and the standard deviation was 58.53. The lowest value was 139 U/L and the highest 344 U/L. Among the class III patients the median was 195 U/L and the standard deviation 127.90. The lowest value was 124 U/L and the highest was 572 U/L. Among the class IV patients the lowest value was 171 U/L and the highest was 461 U/L. The median was 293.5 U/L and the standard deviation was 109.87 (graphic 3). The analysis of the mean AP values using the Student's t-test was statistically significant only for comparisons between

Graphic 1 – Mean AST Values by CHF Class.

classes I and III and between classes I and IV.

GGT - Among the class I patients the median was 24 U/L and the standard deviation was 12.83. The lowest value was 12 U/L and the highest 40 U/L. The class II patients had a median of 56 U/L and standard deviation of 70.93. The lowest value was 22 U/L and the highest 218 U/L. The median among the class III patients was 77 U/L and the standard deviation was 252.50. The lowest value was 18 U/L and the highest was 883 U/L. Among the class IV patients the lowest value was 18 U/L and the highest was 334 U/L. The median was 116 U/L and the standard deviation was 88.58 (graphic 4). Analysis of the mean GGT values using the Student's t-test was statistically significant only when the class I averages were compared with the other classes.

Graphic 3 – Mean AP Values by CHF Class.

Graphic 4 – Mean GGT Values by CHF Class.
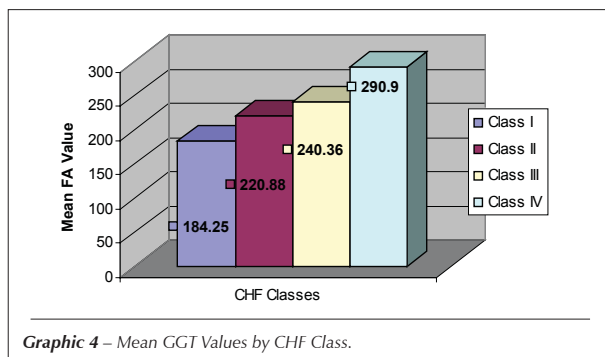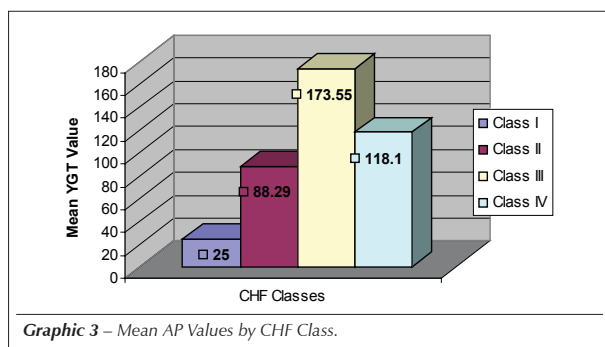
Analysis of the mean GGT values using the Student's t-test is represented by the p-value shown in each of the following graphics.

CHF class versus deaths - There were no deaths among the class I and II patients. Among the 18 class III patients there were two deaths (11.11%) and among the class IV patients there were five deaths (31.25%).

Discussion

In regard to age groups, the results obtained agreed with those in medical literature, showing that the incidence of congestive heart failure increases with age. It is known that the prevalence doubles with every decade of life and that it is found in roughly 40% of the people above age 70[5].

One possible explanation for this age distribution can be found by analyzing the incidence rates of the factors involved in the genesis of most heart failure cases such as acute myocardial infarction and hypertension that tend to appear in older individuals.

Contrary to the adult population, whose CHF prevalence is relatively consistent throughout the world[6], the number of children affected by this condition varies considerably according to the region being studied[7]. In the present project, only one of the 50 patients studied (or in other words, 2%) was in the pediatric age group.

As mentioned earlier, among the 50 patients selected for the study there were 18 males and 32 females. Nevertheless, this should not be considered as a true proportion of heart failure cases between the two genders since the selection was biased and the exclusion factors predominated in the male gender. In the group of 175 patients that were considered for the study, 91 (52%) were men and 84 (48%) were women. From the 125 patients that did not participate in the study due to some exclusion factor, 74 (59.2%) were males and 51 (40.8%) were females.

The best manner found to establish gender distribution for this paper was the study of the initial group of 337 patients. From these, 186 (55.20%) were male. The higher incidence of congestive heart failure and deaths among the male gender agrees with documented data in medical literature. Most studies indicate that the disease is found less often in women and when it is found it is not as severe[8,9] due to the better cardiac remodeling characteristic of this gender. The underlying reasons responsible for this reality are not yet firmly established, nevertheless, it is believed that female hormone differences and myocardiocytes with greater resistance to apoptosis are contributing factors.

In regard to hormonal differences, estrogen seems to play an essential role. Many of its effects on cardiovascular system cells are known and considered beneficial. It is estimated that close to 5% of the proteins produced by the myocardiocytes are regulated by estrogen including the endotelina-1 receptor expression[10].

As expected, the two most common CHF etiologies found in this study were systemic hypertension and acute myocardial infarction. However, the importance of these two diseases conflicted with the findings of various studies that indicate coronary artery disease as the most common cause of heart failure[11,12]. Valvular heart disease, that in the past was the main etiology, is becoming less prevalent. In this study, it was the fourth main etiology, presented by 12% of the patients.

At this time it should be emphasized, that the 16 patients included in the study with New York Heart Association functional classes I and II were not admitted to the hospital for congestive heart failure. The reasons were very diverse – decompensation of chronic kidney failure was the most common, cellulite in the lower limbs, atrial fibrillation, etc. – however none of them were comorbidities considered in the study exclusion criteria.

The transaminase results revealed a significant increase only in the class IV heart failure patients. Nevertheless, it was a slight increase and was not consistent with the ischemic hepatitis profile, where values 10 to 20 times higher than the normal limits are expected[1]. These data demonstrate that

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serious circulation problems such as shock are not necessary for the development of hepatic cellular lesions, even though they would be much more evident in this situation. They also reveal that congestion and diminished hepatic perfusion in class I, II and III heart failure patients are not sufficient to cause hepatocyte lesions.

These results are compatible with those obtained in a study that sought to relate cardiac output and liver function abnormalities[13]. The patients were divided in three groups according to cardiac output. Significant increases of AST and ALT were only observed in the group with the worst output (less than or equal to 1.5 L/min/m^2).

Analysis of the alkaline phosphatase and gamma glutamyl transpeptidase (GGT) results revealed a distinct profile in relation to the transaminases. Generally, the serum levels of these enzymes increased progressively with the more severe heart failure classes. Comparison of the averages of the class II, III and IV patients with those of the class I patients, confirmed that these increases were more significant in the more advanced classes. Only two situations did not follow this trend. Comparison of the mean alkaline phosphatase values between the class I and II patients, presented a p-value of 0.07834. Even though this value is not statistically significant, it is very close and with a larger study group it could have been significant. The other situation is the drop in the mean gamma glutamyl transpeptidase value from class III to class IV instead of the expected increase. This can be explained by the discrepant and significantly elevated GGT value (883 U/L) of one class III patient that raised the average.

Based on these data it can be said that heart failure is characterized by a cholestatic profile of laboratory alterations with increased levels of alkaline phosphatase and GGT, and that the seriousness of the cholestasis correlates with the CHF class. Considering that alkaline phosphatase is produced by the hepatocytes and GGT by the bile duct epithelial cells, this could indicate that the hepatocytes and the bile duct epithelia are the main hepatopathy targets in these patients[14] as there is a certain degree of intrahepatic biliary obstruction even with the most moderate levels of heart failure.

In a prospective study to evaluate the relation between the degree of tricuspid regurgitation observed on an echocardiogram with hepatic laboratory alterations[14] this cholestasis profile was also present and progressed in accordance with the degree of regurgitation. Furthermore, increased bilirubin levels and hepatic synthesis function abnormalities were also recorded as indicated by the hypoalbuminemia found. These results were not seen in the present study since the bilirubin and albumin serum levels close to the date of the decompensation episode, were not recorded on most of the patients' medical charts.

Alkaline phosphatase and GGT are located in the bile duct and are elevated in situations where the biliary canaliculi suffer some type of damage. Elevated levels of these enzymes in congestive heart failure patients indicates that there are other mechanisms responsible for liver failure in CHF in addition to the traditional mechanisms that associate ischemia and congestion with hepatocellular lesions (elevated AST and ALT levels). One of these models[15] is based on increased mechanical pressure within the hepatic sinusoids that is associated with sinusoid endothelial cell lesions and consequent direct pressure transmission to the hepatocytes and their tight junctions. With this increased pressure, the tight junctions, that are responsible to separated the extravascular matrix from the biliary canaliculi, would rupture causing a fistula between these two compartments. These alterations have been proven by microscopic assessment of rats submitted to hepatic venous return obstructions. Similar alterations have been reported in humans with extrahepatic cholestasis.

Nevertheless, the conflicting opinions and studies in medical literature demonstrate that the profile of hepatic laboratory alterations in heart failure is not yet established. Some consider the predominant transaminase increase to be typical while others defend the cholestatic or mixed model[13-15]. Still others, do not believe that there is a specific pattern. The understanding of these alterations is of utmost importance in order to avoid unnecessary hepatic investigations in heart failure patients. Patients that exhibit a moderate increase of AP and GGT, for example, could receive intensive heart failure therapy before other liver disease examinations have been performed so as to avoid delaying the diagnosis and submitting the patients to invasive procedures such as liver biopsies.

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