Echocardiographic Correlates of Abnormal Liver Tests in Patients with Exacerbation of Chronic Heart Failure

Grzegorz Styczynski, MD, PhD, Aleksandra Milewska, MD, Małgorzata Marczewska, MD, Piotr Sobieraj, MD, Magdalena Sobczynska, MD, Michal Dabrowski, RN, Agnieszka Kuch-Wocial, MD, PhD, and Cezary Szmigielski, MD, PhD, *Warsaw, Poland*

Background: Elevated total bilirubin (TB) and transaminases are frequently reported in patients with heart failure and are related to their worse prognosis. On the basis of hemodynamic data from previous studies, the investigators hypothesized that elevated bilirubin and transaminases are associated with different patterns of cardiac remodeling and dysfunction in patients with heart failure (i.e., elevated bilirubin with predominantly right-heart dysfunction and elevated transaminases with predominantly left-heart dysfunction). Therefore, the aim of this study was to evaluate prospectively echocardiographic correlates of elevated TB and transaminases on admission in patients with exacerbation of chronic heart failure.

Methods: The following echocardiographic parameters were prospectively analyzed in 150 patients (mean age, 75 years; 59% men): right ventricular end-diastolic diameter, right atrial area, tricuspid regurgitation, right ventricular systolic pressure, tricuspid annular plane systolic excursion, tricuspid lateral annulus systolic velocity, estimated right atrial pressure, portal vein pulsatility index (PVPI), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction, and cardiac index.

Results: Elevated TB was found in 61 patients (41%) and elevated transaminases in 46 patients (31%). In univariate logistic regression analysis, right ventricular end-diastolic diameter, right atrial area, tricuspid regurgitation, estimated right atrial pressure, tricuspid annular plane systolic excursion, tricuspid lateral annulus systolic velocity, PVPI, left ventricular ejection fraction, and cardiac index were significant predictors of elevated TB ($P < .05$ for all). LVEDD indexed to body surface area, right ventricular end-diastolic diameter, and systolic blood pressure on admission were significant predictors of elevated transaminases ($P < .05$ for all). In a multivariate regression model, only PVPI remained a significant predictor of elevated TB and LVEDD indexed to body surface area of elevated transaminases. Sensitivity, specificity, and positive and negative predictive values of PVPI > 0.5 in the prediction of elevated TB were 81%, 87%, 82%, and 87%, respectively.

Conclusion: Several echocardiographic indices of right-heart dysfunction and low cardiac index are related to elevated TB, with an increased PVPI having the best predictive value. A weak statistically significant association was found between elevated transaminase levels and left ventricular end-diastolic diameter indexed to body surface area. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: Heart failure, Total bilirubin, Transaminases, Echocardiography, Portal vein

Elevated serum total bilirubin (TB) and transaminase levels (aspartate transaminase [AST] and alanine transaminase [ALT]) are frequently reported in patients with acute or chronic heart failure and are related to their worse prognosis.[1-7] On the basis of hemodynamic studies, it is assumed that elevated bilirubin results from hepatic venous congestion caused by elevated right atrial pressure (RAP), while elevated transaminases are due to a decrease in cardiac output.[7-10] At the level of the hepatic lobule, increased venous pressure and distension of hepatic sinusoids are thought to cause compression or obstruction of biliary canaliculi, leading to elevated serum bilirubin.[11,12] In contrast, elevated transaminases most likely result from hepatic cell necrosis due to inadequate perfusion and hypoxia.[11,12] Invasive studies are rarely performed in patients hospitalized with exacerbation of heart failure. However, noninvasive echocardiography is usually accessible and can help in choosing the optimal treatment for patients with heart failure. Correlations between abnormal liver function test results in patients with heart failure and echocardiographic parameters are rarely reported in the scientific literature. Only one previous study demonstrated a significant positive correlation between serum bilirubin level and degree of tricuspid regurgitation (TR).[13] We hypothesized that elevated bilirubin and transaminases are associated with different patterns of cardiac remodeling and dysfunction in patients with heart failure (i.e., elevated bilirubin with predominantly

From the Department of Internal Medicine, Hypertension and Angiology, Medical University of Warsaw, Warsaw, Poland.

Reprint requests: Grzegorz Styczynski, MD, PhD, Medical University of Warsaw, Department of Internal Medicine, Hypertension and Angiology, Banacha 1a, 02-097 Warsaw, Poland (E-mail: *grzegorz.styczynski@wum.edu.pl*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2015.09.012

Abbreviations

ALT = Alanine transaminase

AST = Aspartate transaminase

AUC = Area under the curve

BSA = Body surface area

CI = Cardiac index

IVC = Inferior vena cava

LVEDD = Left ventricular end-diastolic diameter

LVEF = Left ventricular ejection fraction

PVPI = Portal vein pulsatility index

RAA = Right atrial area

RAP = Right atrial pressure

RVEDD = Right ventricular end-diastolic diameter

RVVTI = Tricuspid lateral annular systolic velocity

TAPSE = Tricuspid annular plane systolic excursion

TB = Total bilirubin

TR = Tricuspid regurgitation

Vmax = Maximal velocity

Vmin = Minimal velocity

right-heart dysfunction and elevated transaminases with predominantly left-heart dysfunction). Therefore, we decided to correlate several selected, prospectively acquired echocardiographic parameters with serum TB and transaminases in patients hospitalized with exacerbation of chronic heart failure.

METHODS

Patients

Echocardiography was performed in 150 patients admitted to the Department of Internal Diseases, Hypertension and Angiology with exacerbation of heart failure who fulfilled the following criteria: (1) blood samples for TB and transaminases were taken on admission or <12 hours after admission, (2) time from admission to echocardiographic study was <24 hours, (3) patients had no known active liver disease on the basis of history and the clinical judgment of the physician in charge, (4) patients were not current chronic alcohol users, and (5) patients were not on respiratory or inotropic support. All patients admitted to our department with exacerbation of heart failure who fulfilled these criteria were included in the study, except those admitted between Friday afternoon and Sunday morning, who were not eligible because of the time criterion (>24 hours from admission). The diagnosis of heart failure was based on clinical, laboratory, and echocardiographic features: typical symptoms and findings on physical examination, elevated N-terminal pro–brain natriuretic peptide (>450 pg/mL), and significant structural abnormalities on echocardiography. Ninety-one percent of patients had been previously hospitalized for heart failure or had significant cardiac disease diagnosed in the past. In 9% of patients, heart failure was diagnosed for the first time, with gradual progression of symptoms, that had started ≥4 weeks before the current admission. Therefore, we diagnosed our patients as having exacerbation of chronic heart failure. Because of the "noninvasive cardiology" profile of our department, we did not admit and include patients with cardiogenic shock or acute heart failure due to acute myocardial infarction, myocarditis, or acute valvular insufficiency. All patients underwent chest radiography on admission. Eighty-five percent of patients had radiologic signs of pulmonary congestion, and 56% of patients had signs of pleural effusion on chest radiography. All patients were in New York Heart Association functional class III or IV. There were eight in-hospital deaths (5%). The mean length of hospitalization was 12.5 days.

There were 41% women and 59% men. The mean age of the population was 75 ± 11 years. Etiologies of cardiac failure included coronary artery disease (54%), chronic valvular disease (11%), tachycardiomyopathy due to atrial fibrillation or flutter with fast ventricular rate (19%), arterial hypertension (7%), dilated cardiomyopathy (7%), hypertrophic cardiomyopathy (0.7%), restrictive cardiomyopathy (0.7%), and anthracycline-induced cardiomyopathy (0.7%). In this group, no constrictive pericarditis etiology (as a potential cause of liver dysfunction) was suspected on the basis of clinical and echocardiographic assessment. It included the presence of known causes of patients' clinical status, dilatation of the ventricles in most patients, and lack of echocardiographic findings suggestive of constrictive pericarditis, especially abnormal ventricular septal motion, distortion of ventricular contours, and thickening of the pericardium. The clinical characteristics of the whole study group, with division into subgroups with reduced and preserved left ventricular systolic function, are presented in Table 1. Echocardiographic and laboratory characteristics are presented in Table 2. The study was approved by the local ethics committee, and patients gave written informed consent to participate in the study.

Biochemistry

Serum TB, AST, and ALT as well as other routine biochemistry parameters were collected on admission or <12 hours after admission and analyzed in the central laboratory of an academic hospital using an integrated chemistry system (Dimension Xpand; Siemens Healthcare, Erlangen, Germany). Serum concentration of TB ≥1.2 mg/dL, AST >40 U/L, and ALT >56 U/L were considered abnormal.

Transthoracic Echocardiography

Two-dimensional echocardiography (Vivid 9; GE Healthcare, Little Chalfont, United Kingdom) was performed <24 hours after admission by a single experienced physician. The mean time between blood testing and echocardiography was 15.3 hours. Examinations were stored on a workstation (EchoPAC; GE Healthcare) and analyzed offline by the same dedicated physician, who was blinded to patients' laboratory results. The following right-heart functional parameters were analyzed: right ventricular end-diastolic diameter (RVEDD) measured from the apical four-chamber view, just above the level of the tricuspid annulus; right atrial area (RAA) measured from the apical four-chamber view just before the opening of the tricuspid valve; degree of TR on the basis of vena contracta diameter (>7 mm for severe TR, >3 and ≤7 mm for moderate TR); estimated right ventricular systolic pressure; tricuspid annular plane systolic excursion (TAPSE; mean value of five consecutive cycles); tricuspid lateral annular systolic velocity (RVVTI) by tissue Doppler (mean value of five consecutive cycles); estimated RAP on the basis of end-expiratory dimension and respiratory collapsibility of the inferior vena cava (IVC), according to the 2010 American Society of Echocardiography guidelines[14]; and portal vein pulsatility index (PVPI). The portal vein was visualized between the ribs at the right costal angle, with the patient in a supine position. First it was identified in two-dimensional mode as a large vessel entering the liver, with slightly hyperechogenic walls, then with color Doppler showing antegrade flow in red (using a 2.5-MHz echocardiographic probe with general abdominal preset) (Figure 1), and then the portal vein Doppler waveform was recorded with pulsed-wave Doppler. Because of respiratory movement of the liver, only expiratory cycles, and in patients with the Cheyne-Stokes respiration pattern only apneic cycles, were analyzed. The pulsatility index was calculated as