Liver stiffness increases in patients with severe pericardial effusion, especially in the presence of cardiac tamponade

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Abstract

Aims: Liver stiffness (LS) is associated with central venous pressure and pericardial effusion (PE) may be associated with these increased pressures. The aim of this study was to investigate the change in LS obtained by liver elastography (LE) in patients with severe PE and its usefulness for the diagnosis of cardiac tamponade. Materials and methods: Forty-patients with severe-PE were included in this study. All patients underwent LE examination in addition to echocardiography. Patients were divided into 2 groups: with and without cardiac tamponade. Results: In patients with cardiac tamponade, LS values, inspiratory-expiratory vena cava inferior (VCI) diameters and presence of <50% inspiratory-VCI collapse was significantly higher. LS value and inspiratory-VCI diameter before pericardiocentesis independently determined the risk of cardiac tamponade. Each 1kPa increase in LS value and 1mm increase in inspiratory-VCI diameter increased the risk of cardiac tamponade by 4.9-times and 40.8%, respectively. When the cut-off value of 10kPa for LS was analyzed, it determined the presence of cardiac tamponade with ≥90% sensitivity and specificity. The higher LS before pericardiocentesis and the decrease in LS after pericardiocentesis (Δ-Liver stiffness of 5.91±1.79 kPa in first group and 2.31±1.25 kPa in the second group) was interpreted to be directly related to the pathophysiology of systemic congestion due to PE. Conclusion: In all patients with severe PE, and especially in patients with cardiac tamponade, the LS is significantly increased and this modification can be explained by the systemic congestion. However, this being the first study to evaluate LS in patients with severe PE and cardiac tamponade, the data should be confirmed by multicenter prospective studies. Keywords: pericardial effusion; cardiac tamponade; liver stiffness

Introduction

The pericardium is a fibro elastic membrane surrounding the heart and contains a thin layer of fluid. The definition of pericardial effusion (PE) is accepted when the accumulated fluid exceeds the normally small amount of fluid. PE develops rapidly (acute) or more progressively (subacute or chronic) and increases intrapericardial pressure. When PE is severe (>500 ml or >20 mm), the increased intrapericardial pressure prevents cardiac filling producing cardiac dysfunction and finally cardiac tamponade occurs [1]. The diagnosis of cardiac tamponade is based on history, physical examination, electrocardiogram (ECG) and chest x-ray, but the definitive diagnosis is based on the echocardiographic detection of advanced PE and also information that effusion reaches the hemodynamic significance and prevents the right ventricular (RV) diastolic filling [1]. Computed tomography (CT) and magnetic resonance imaging (MRI) are used in differential diagnosis of PE and suspected cases rather than the diagnosis of tamponade.

There is no use of liver ultrasonography (US) in the diagnosis and follow-up of pericardial tamponade and is not recommended by the guidelines. One of the diagnos-
tic criteria for cardiac tamponade is the presence of vena cava inferior (VCI) dilatation (>25mm) and less than 50% reduction in inspiratory VCI (Ins-VCI) diameter in patients with PE [1]. Since this finding can be detected by echocardiography, liver US is not required. In recent years, liver stiffness (LS) measured by liver elastography (LE), has been shown to increase with acute and chronic right heart pressure and the central venous pressure (CVP) increases due to hepatic congestion [2-10].

To the best of our knowledge, there is no clear data on the change in LS value obtained by LE in patients with cardiac tamponade and its use in clinical practice. Some patients with severe PE (>20 mm) have cardiac tamponade clinically and echocardiographically, while others do not. The most important critical information in these patients is that intrapericardial pressure exceeds RV diastolic filling pressure. In this case, cardiac tamponade develops, the right atrial (RA)–CVP–VCI pressures increase and hepatic congestion develops [2-4].

We hypothesized that the non-invasively obtained LS may be associated with intrapericardial pressure. Therefore, in this study, we aimed to investigate the change of LS value obtained by LE in patients with severe PE and its use for the diagnosis of cardiac tamponade.

Materials and methods

Study design and patient population

In this cross-sectional study, 20 patients (mean age: 57.6±14.9 years, male/female: 9/11) admitted to the coronary intensive care unit of our hospital with severe PE and newly diagnosed cardiac tamponade and 20 patients (mean age: 54.1±16.6 years, male/female: 14/6) similarly newly diagnosed with severe PE without cardiac tamponade were included in the study. All patients were evaluated and treated using the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases [1]. Mild-moderate PE (<20 mm), end stage renal disease (eGFR<30 mL/kg/1.73 m²), chronic cardiac disease and cardiac failure, other congenital heart disease, acute or chronic pulmonary embolism, acute or chronic liver diseases, patients with hepatitis, alcohol consumption (>20 gr/day), serious heart valve diseases, rheumatologic disorders, active hematologic diseases, thyroid diseases, cancer and/or pregnancy suspicion and patients unwilling to participate in the study were excluded. The regional ethics committee approved the study; all patients included in the study were informed about the study and a revised consent form was signed.

Detailed medical history was taken and physical examinations of all patients were performed. Demographic characteristics and clinical parameters of all patients were recorded. Height and weight were measured and body mass index was calculated. Cardiac tamponade diagnosis was made according to the clinic of the patients. Systolic blood pressure (BP), diastolic BP and heart rate were measured. Presence or absence of pulsus paradoxus (a reduction in systolic blood pressure greater than 10 mmHg during inspiration) was evaluated. Electrocardiography was performed in all cases.

Clinical tamponade was considered when heart beats were ≥100 beat/min, and documented evidence of systolic BP <90mmHg. Cardiac tamponade was confirmed by two dimensional and Doppler echocardiographic findings: RA or RV collapse, IVC plethora without inspiratory collapse, and exaggerated respiratory variation of mitral/tricuspid early filling velocity [1]. Blood urea nitrogen, creatinine, sodium, potassium, aspartate aminotransferase, alanine aminotransferase (ALT), NT-proBNP, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, uric acid and hs-CRP levels were measured using automated laboratory methods and using appropriate commercial kits.

Echocardiographic evaluation

Two dimensional and Doppler echocardiography were performed with EPIQ 7 (Philips Healthcare Andover MA, USA). All echocardiography procedures were performed by two echocardiographers. M-mode examination in parasternal long-axis showed left ventricular diastolic (LVd) dimension ad LV systolic (LVs) dimension.

The LV ejection fraction was calculated by the modified Simpson method from apical four and two chambers [9]. The widest measure of PE circumferential for the presence of severe PE (>20 mm) was measured in patients with PE. Echocardiographic confirmation of cardiac tamponade was confirmed by 2D echocardiography. RA collapse >1/3 of cardiac cycle, RV collapse in ventricular diastole and the presence of respiratory flow variations in ventricular diastole and mitral/tricuspid flows was recorded and these findings were morphologically associated with cardiac tamponade [1].

Liver ultrasonography

All of the patients underwent liver ultrasound (US) screening using a high-resolution US device (Philips EPIQ 7), with a 1-5 MHz high-resolution convex probe before and after pericardiocentesis. Inspiratory IVC (Ins-IVC) and expiratory IVC (Exp-IVC) diameters were measured by using liver US in hepatic long-axis by placing the probe in the subxiphoid region. At least three IVC diameter measurements were taken and their average was calculated. Point shear-wave elastography (pSWE) technique was used for LS measurements. The patients were in lateral decubitus position. During the liver US
assessment, the least possible compression was applied. During the elastography, participants were asked to stop breathing for a few-seconds to minimize with the motion artifact during respiration. First, regular US images were obtained, then the radiologist determined the target area and the region of interest (ROI) was positioned at least 1 cm depth of the liver capsule. ROI was positioned perpendicular to the liver capsule, to a line parenchyma area containing no bile ducts and vascular structures or space occupying lesions. In our study, the maximum ROI target distance was 8 cm, with a constant ROI box dimension of 1 cm - 0.5 cm. Least possible, the compression was maintained during the imaging, to avoid mechanical pressure on the liver parenchyma. In each participant, 10 valid measurements from different segments of hepatic parenchymal were obtained and their average was calculated. During the LS measurements, when the measurement has low reliability and if there is a patient or operator condition that affects the measurement value, the measurement was accepted as 0.00kPa and the mean measurement was not taken into account and another measurement which was reliable was obtained again.

**Percutaneous pericardiocentesis**

Percutaneous pericardiocentesis was performed in the coronary care unit or catheterization laboratory. After checking the pericardial effusion using echocardiography, a needle was inserted percutaneously into the pericardial space and was then replaced with a drainage pigtail catheter using a guide wire. The catheter was mounted and the pericardial effusion was removed by first applying negative pressure and then by gravity. The pigtail catheter was removed from the pericardial region after pericardial effusion drainage <25 mL per day.

**Statistical analysis**

All analyzes were performed using the SPSS 22.0 (Chicago, IL, USA) statistical software package. Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was normal. Continuous variables in-group data were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. Student’s t-test was used to compare the continuous variables between groups. However, Mann-Whitney U test was used for the evaluation of without normal distribution parameters. The categorical variables were compared by the chi-square (χ²) test. Logistic regression analysis was used to determine the parameters that independently determined patients with cardiac tamponade. In addition, LS and Ins-VCI diameter Receiver Operating Characteristic (ROC) curve analysis were performed to determine patients with cardiac tamponade. A p <0.05 was considered statistically significant.

**Results**

Echocardiography and liver US were performed in all patients with severe PE. Cohen kappa values that evaluate interobserver and intraobserver variability were over 90% for all echocardiography and US parameters. The patients with severe PE were divided into two groups with and without cardiac tamponade and all parameters were compared between the two groups.

When the demographic and clinical data of all groups were examined, it was found that SBP, DBP and heart rate were significantly higher in patients with pericardial tamponade (Table I). Other demographic and clinical data were similar between the two groups. All laboratory data except serum ALT level were found to be similar between the two groups. When the echocardiography data of the study groups were examined, the RA systolic collapse, RV diastolic collapse and mitral and tricuspid respiratory flow variations were found only in patients with pericardial tamponade. Maximum circumferential PE was higher in patients with pericardial tamponade (Table II).

LS values, Δ-Liver stiffness (liver stiffness before pericardiocentesis - liver stiffness after pericardiocentesis) value, presence of <50% Ins-VCI collapse, Ins-VCI and Exp-VCI diameters were higher in patients with pericardial tamponade. The mean, median, minimum and maximum LS values of the patients with cardiac tamponade before pericardiocentesis were 14.2±2.41, 14.1, 9.70 and 18.80 kPa; the mean, median, minimum and maximum LS values of patients without cardiac tamponade before pericardiocentesis were 8.20±1.52, 7.86, 5.70 and 10.90 kPa, respectively (fig 1).

![Fig 1. The Boxplot graphic showed that liver stiffness values were higher in patients with cardiac tamponade than in patients without cardiac tamponade](image-url)
Table I. Demographic, clinic and laboratory findings in patients with and without cardiac tamponade

|                      | Patients with cardiac tamponade (n=20) | Patients without cardiac tamponade (n=20) | p   |
|----------------------|----------------------------------------|------------------------------------------|-----|
| Age (year)           | 57.6±14.9                              | 54.1±16.6                                | 0.481|
| Sex (male/female)    | 9/11                                   | 14/6                                     | 0.200|
| Hypertension, n (%)  | 5 (25%)                                | 6 (30%)                                  | 0.723|
| Diabetes mellitus, n (%) | 2 (10%)                              | 2 (10%)                                  | 1.000|
| Current smoker, n (%) | 7 (35%)                                | 6 (30%)                                  | 0.739|
| Systolic blood pressure (mmHg) | 83.1±6.9                             | 118±12                                   | <0.001|
| Diastolic blood pressure (mmHg) | 45.2±7.89                             | 77.7±9.2                                 | <0.001|
| Pulse (bpm)          | 124±9.2                                | 85±11                                    | <0.001|
| Body mass index (kg/m2) | 26.3±3.6                              | 26.8±5.3                                 | 0.729|
| Blood urea nitrogen (mg/dL) | 45.7±19.3                             | 45.8±21.7                                | 0.993|
| Creatinine (mg/dL)   | 0.98±0.28                              | 0.93±0.26                                | 0.532|
| Sodium (mg/dL)       | 137±4.2                                | 136±4.8                                  | 0.553|
| Potassium (mg/dL)    | 4.60±0.60                              | 4.18±0.80                                | 0.065|
| Aspartate aminotransferase (u/L) | 36.4±20.4                             | 27.3±17.3                                | 0.137|
| Alanine aminotransferase (u/L) | 39.2±16.1                            | 23.7±16.2                                | 0.004|
| Total cholesterol (mg/dL) | 177±62                                 | 176±62                                   | 0.930|
| LDL cholesterol (mg/dL) | 117±42                                 | 114±43                                   | 0.835|
| HDL cholesterol (mg/dL) | 37±15                                  | 36±14                                    | 0.938|
| Triglycerides (mg/dL) | 232±168                                | 229±170                                  | 0.950|
| Uric acid            | 6.82±2.32                              | 6.14±2.05                                | 0.333|
| NT-proBNP (pg/mL)    | 682±1079                               | 671±1771                                 | 0.616|
| hs-CRP (mg/dL)       | 2.31±2.42                              | 1.94±2.25                                | 0.985|

NT-proBNP: N-terminal probrain natriuretic peptide, hs-CRP: High sensitive C reactive protein

Table II. Liver ultrasound and echocardiographic findings in patients with and without cardiac tamponade

|                      | Patients with cardiac tamponade (n=20) | Patients without cardiac tamponade (n=20) | p   |
|----------------------|----------------------------------------|------------------------------------------|-----|
| LVd dimension (mm)   | 48.0±7.8                               | 50.1±6.6                                 | 0.325|
| LVs dimension (mm)   | 31.3±7.34                              | 34.4±7.5                                 | 0.197|
| LVEF (%)             | 58.8±10.3                              | 56.7±8.9                                 | 0.497|
| RA collapse >1/3 of cardiac cycle, n (%) | 19 (95%)                             | 0(0%)                                    | <0.001|
| RV collapse, n (%)   | 20 (100%)                              | 0 (0%)                                   | <0.001|
| Respiratory flow variations, n (%) | 19 (95%)                             | 0 (0%)                                   | <0.001|
| Maximum circumferential PE size (mm) | 32.1±4.81                             | 28.2±3.59                                | 0.004|
| Liver stiffness before pericardiocentesis (kPa) | 14.2±2.41                             | 8.20±1.52                                | <0.001|
| Ins-IVC diameter before pericardiocentesis (mm) | 21.6±2.88                             | 12.5±1.88                                | <0.001|
| Exp-IVC diameter before pericardiocentesis (mm) | 29.9±4.76                             | 22.3±2.86                                | <0.001|
| Presence of < 50% Ins-VCI collapse, n (%) | 15 (75%)                              | 2 (10%)                                  | <0.001|
| Liver size before pericardiocentesis (mm) | 14.7±1.88                             | 14.0±1.99                                | 0.293|
| Liver stiffness after pericardiocentesis (kPa) | 8.33±1.36                             | 5.72±1.12                                | <0.001|
| Δ-Liver stiffness (kPa) | 5.91±1.79                              | 2.31±1.25                                | <0.001|

Exp-IVC: Expiratory inferior vena cava, Ins-IVC: Inspiratory inferior vena cava, LVd: Left ventricular diastolic, LVEF: Left ventricular ejection fraction, LVs: Left ventricular systolic, PE: Pericardial effusion, Δ-Liver stiffness: Liver stiffness before pericardiocentesis - liver stiffness after pericardiocentesis

Table III. Multivariate regression analysis of independent risk factors for occurrence of cardiac tamponade

|                      | Odds Ratio | 95% Confidence Interval | p   |
|----------------------|------------|-------------------------|-----|
| Liver stiffness (1 kPa) | 4.896      | 1.453–16.504            | 0.001|
| Inspiratory inferior vena cava diameter (1 mm) | 1.408      | 1.072–1.849             | 0.014|
In addition to echocardiographic parameters, the laboratory and liver US variables, which were different in patients with and without cardiac tamponade in univariate analysis, were evaluated by multivariate analysis and independent variables were determined. Pre-pericardiocentesis LS value and Ins-VCI diameter independently determined the risk of cardiac tamponade in patients with severe PE (Table III). Each 1 kPa increase in LS value and 1 mm increase in Ins-VCI diameter increased the risk of cardiac tamponade by 4.9 times and 40.8% respectively.

In multivariate analysis, ROC analysis was performed for LS and Ins-VCI that were independently associated with cardiac tamponade. As a result of this analysis, the area under the ROC curve was significantly higher for both parameters (Table IV). According to the result of this analysis, the LS value had more ROC area under the curve than the Ins-VCI. In determining the presence of cardiac tamponade in patients with severe PE; 10 kPa for LS and 20 mm for Ins-VCI had ≥90% sensitivity and specificity (Table IV).

**Discussion**

The main finding of our study was that the LS values obtained by pSWE were significantly higher in patients with severe PE and cardiac tamponade and LS was found to be significantly higher in patients with cardiac tamponade than in patients with severe PE alone. In addition, a significant decrease in LS value was found in patients with and without cardiac tamponade after pericardiocentesis.

In the presence of severe PE, patients should be closely monitored for cardiac tamponade. The diagnosis of cardiac tamponade is based on clinical and imaging evidences. Electrical alternans and microvoltage on ECG and cardiomegaly on chest x-ray are important findings, but the diagnosis is confirmed by the detection of severe PE and impaired RV diastolic filling on echocardiography [1].

Liver US examination is not routinely performed in patients with cardiac tamponade or severe PE. The hypothesis that LS may be associated with mean RA pressure in patients with chronic or acute liver disease was first shown in 2013 [4]. In the last few years it has been reported that in patients with acute and chronic heart failure, the high CVP and right heart pressures are related to the increased LS and this situation can be used especially for non-invasive volume and pressure monitoring [2,3,5-8]. An enlarged VCI and <50% reduction in Ins-VCI diameter are signs of systemic congestion in cardiac tamponade. In patients with advanced PE, especially in patients with cardiac tamponade, the filling of RA and RV decreases in relation with high intra-pericardial pressure, secondary producing high intravascular pressure in the central and peripheral venous system. The hepatic venous congestion explains the higher LS in these cases. We found also significantly increased LS in patients with severe PE, with and without cardiac tamponade. The limit value of 7 kPa for LS is considered suggestive for liver pathologies [3,8,12-14]. In our study, the LS value was >10 kPa in most patients with cardiac tamponade. In addition, after pericardiocentesis, Δ-LS value decreased significantly in patients with severe PE with and without cardiac tamponade. In this finding, LS was interpreted to be directly related to the pathophysiology of systemic congestion due to PE.

This study has some important limitations. We included a relatively small number of patients, but still our findings showed that LS was significantly increased in patients with cardiac tamponade. The study could be more meaningful if done prospectively and with more patients. Therefore, it should be supported by randomized, multicenter studies involving more patients. Another important limitation is the lack of evaluation of the relationship between CVP and LS due to the fact that we did not evaluate CVP in all patients.

**Conclusion**

The LS value increases in all patients with advanced PE, with more prominence in the patient group with cardiac tamponade and this modification is related directly to the pathophysiology of systemic congestion. Using a non-invasive, simple, easily accessible and objective imaging technique for LS evaluation, some of the pathophysiological mechanisms related to severe PE might be reinterpreted. However, this being the first study to evaluate LS value in patients with severe PE and cardiac tamponade, the data should be supported by multicenter prospective studies.

| Table IV. ROC curve analysis of liver stiffness and inspiratory inferior vena cava diameter for predicting cardiac tamponade |

| Variable                                         | AUROC         | p       | Cut-off value | Se (%) | Sp (%) |
|--------------------------------------------------|---------------|---------|---------------|--------|--------|
| Liver stiffness before pericardiocentesis (kPa)   | 0.988 (0.964–1.000) | <0.001  | 10.0          | 95.0   | 90.0   |
| Inspiratory inferior vena cava diameter (mm)     | 0.911 (0.803–1.000) | <0.001  | 20.0          | 90.0   | 90.0   |

AUROC: Area under the Receiver Operating Characteristic, Se: Sensitivity, Sp: Specificity
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Conflict of interest: there is no conflict of interest.

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