

Pretibial Edema Strain Ratio Obtained by Elastography Can Be Used in Differential Diagnosis of Patients with Chronic Heart Failure and Nephrotic Syndrome

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ABSTRACT

Objective: Pretibial edema is a common examination finding in patients with both heart failure and nephrotic syndrome. We aimed to evaluate the utility of pretibial edema strain ratio obtained by strain elastography in the diagnosis of heart failure and nephrotic syndrome.

Materials and Methods: A total of 80 patients (40 patients with heart failure and 40 patients with nephrotic syndrome) were included in this study. Physical examination echocardiography and laboratory examinations were performed. Pretibial edema elastographic color grade and pretibial edema strain ratio measurements were performed in the pretibial edema region by strain elastography.

Results: Pretibial edema strain ratio and presence of pretibial edema elastographic color grade-I were found to be higher in heart failure. Tricuspid regurgitation pressure gradient, left ventricular diameters and volumes were significantly higher and left ventricular ejection fraction was significantly lower in heart failure. Left ventricular ejection fraction and pretibial edema strain ratio independently determined the presence of heart failure. The each-0.1 increase in pretibial edema strain ratio was being to the risk of heart failure by 29.1%. In predicting presence of heart failure, the area under the ROC curve was 0.827 for pretibial edema strain ratio. The cut-off value for pretibial edema strain ratio was taken as 0.70, it was determined the patients with heart failure disease with 80.0% sensitivity and 76.5% specificity. Pretibial edema strain ratio value was found to be closely related to tricuspid regurgitation pressure gradient, left ventricular ejection fraction and left ventricular volumes. The close relationship was found between pretibial edema strain ratio and tricuspid regurgitation pressure gradient.

Conclusion: In patients with heart failure, the pretibial edema strain ratio obtained by strain elastography is higher than in patients with nephrotic syndrome and can be used as an objective parameter for heart failure differential diagnosis in addition to conventional heart failure diagnostic methods.

Key words: Heart failure, nephrotic syndrome, pretibial edema stiffness

Received: 01 November 2019, Accepted: 20 December 2019,
Published online: 30 December 2019

INTRODUCTION

In patients with heart failure with reduced ejection fraction (HFrEF), jugular venous distention, liver enlargement, hepatojugular reflux and right-sided pleural effusion occur when right-sided heart failure (HF) or biventricular HF develops. In addition to these findings, bilateral pitting pretibial edema (PTO) is typically present and reflects both venous congestion and sodium and water retention. Edema is a cardinal manifestation of right-sided HF [1]. PTO is a nonspecific finding and edema duo to

HFrEF must be distinguished from edema related to medication (e.g. calcium-channel blockers, thiazolidinedione's, or nonsteroidal anti-inflammatory drugs), venous insufficiency, hypoproteinemia or hypoalbuminemia or myxedema [2]. In patients with bilateral PTO, 40% of the etiology is due to cardiac, 20% is due to bilateral venous disease, 20% is due to renal disease and especially to nephrotic syndrome (NS) and 20% is due to idiopathic edema [3]. Therefore, bilateral PTO is one of the minor criteria

for Framingham heart failure diagnostic criteria due to its low sensitivity to HF [4]. Also in patients with HF_{rEF}, PTO is commonly measured on a scale of 0 to 3+, but this system has marked intraobserver and interobserver variation.

NS is a glomerular disease caused by systemic or primary renal diseases. Generalized edema occurs due to hypoalbuminemia and decreased oncotic pressure. Initial swelling commonly occurs on the face (especially periorbital), as well as in the pretibial area.

When we evaluated the ultrasound (US) elastography studies performed in the last 1-decade; shear-wave elastography (SWE) in solid organ evaluation, strain elastography (SE) in the evaluation of superficial organs and tissues, tissue stiffness is measured and diagnosis and follow-up of many diseases are performed [5-14]. Although there is no evaluation of PTO stiffness in patients with HF and NS in the literature, there are studies related to the evaluation of tissue stiffness in patients with lymphedema and the use of tissue stiffness in diagnosis and follow-up [5, 15-19]. In one of these recent studies, it was reported that tissue stiffness was increased in lymphedematous limbs patients using acoustic radiation force impulse (ARFI) technique and this could be used as a non-invasive tissue stiffness evaluation [5]. In a similar study, SWE technique was used in patients with localized scleroderma, and increased tissue stiffness was closely associated with disease severity and progression [6].

HF_{rEF} and NS is a chronic disease of the heart and kidney with high mortality and morbidity. The pathophysiology of PTO, which is a common examination finding for both diseases, is different. In patients with HF_{rEF}, a harder PTO occurs and in patients with NS a soft PTO occurs. In physical examination, pitting edema is used to differentiate HF patients from NS patients, but it is a subjective finding. As a result of our experience and other studies in patients with NS and HF, we considered the hypothesis that PTO stiffness can be measured objectively with SE, and the obtained PTO strain ratio (PTO-SR) can be used as a more objective parameter in the differential diagnosis of HF_{rEF} and NS. Therefore, we aimed to evaluate the utility of PTO-SR obtained by SE method in differential diagnosis of HF and NS.

MATERIALS and METHODS

Study Population

This cross-sectional study included 40 patients with

newly diagnosed HF_{rEF} and 40 patients with newly diagnosed NS. Patients with HF_{rEF} had left ventricular ejection fraction (LVEF) < 40% as a result of echocardiography examinations and did not meet the criteria for NS. Patients with NS also consisted of newly diagnosed NS with LVEF values > 50% on echocardiographic examination. Severe renal failure (eGFR < 30 ml/kg/1.73m²), history of known acute or chronic liver disease, congenital heart disease, acute or chronic respiratory problems, proximal venous or lymphatic obstruction (lymphedema), hematologic diseases, rheumatoid arthritis, active thyroid disease and pretibial myxedema, histories of tibial trauma, cancer and/or pregnancy suspicion, active infections or thrombophlebitis, musculoskeletal disease, immobility problems, peripheral vascular and cerebrovascular diseases and patients who did not wish to be included in the study were excluded. The study was conducted according to the recommendations of the Human Subjects Biomedical Research Helsinki Declaration, and the institutional ethics committee approved the protocol (decision/protocol number of your ethics committee approval was 2018/262). Voluntary consent forms were explained in detail to all patients, written informed consent was obtained from all of the patients.

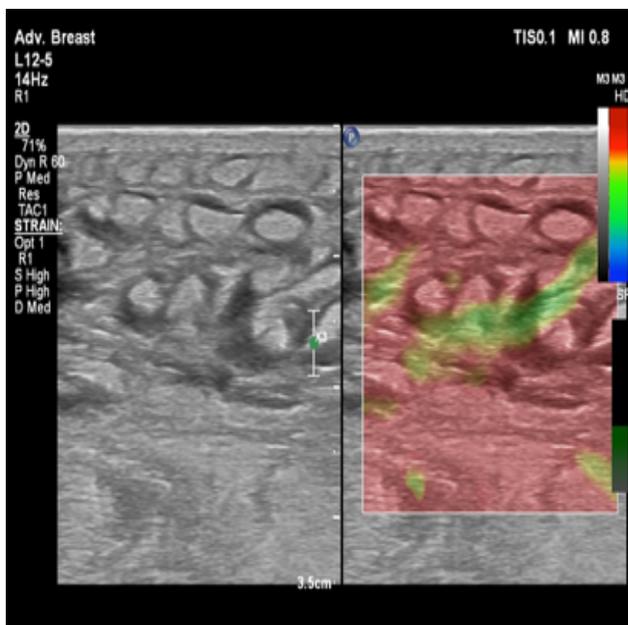
After all patients were included in the study, detailed medical history was taken and physical examination was performed. Subsequently, basal demographic characteristics of all groups were questioned for age, gender, presence of diabetes mellitus, hypertension, active smoking and hypercholesterolemia. Heart rate, systolic blood pressure and diastolic blood pressure were recorded. Height and weight was measured. Patients were rested for 20 minutes in the supine position and after that blood samples were taken from an antecubital vein. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid. Complete blood count test was performed. At study entry glucose, blood urea nitrogen (BUN), creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and NT-proBNP levels were also measured using an automated chemistry analyzer (Abbott Aeroset, MN, USA) with appropriate commercial kits (Abbott).

Pretibial Edema Ultrasonography

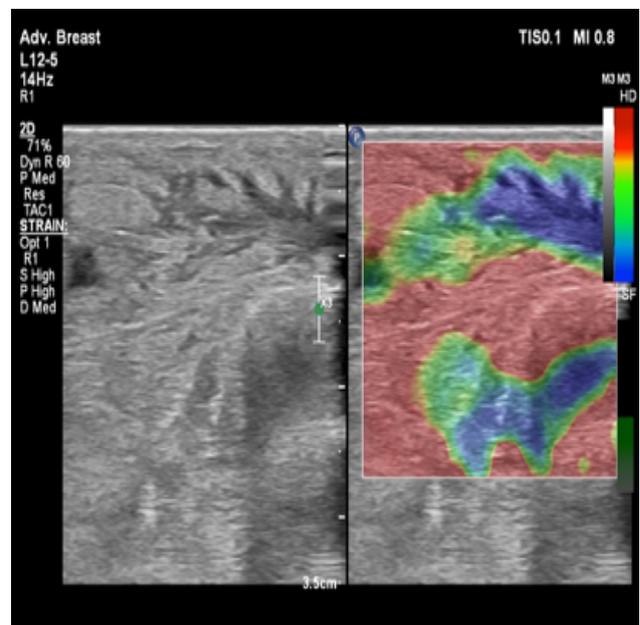
The PTO US examinations were performed by two experienced radiologists using a high-resolution ultrasound Doppler system (Philips EPIQ 7 Philips Health Care, Bothell, WA, USA) equipped with a

high-resolution linear probe (12-5). PTO B-mode US evaluation was performed while the patients were placed in supine position. The PTO SE evaluations were performed in the same position. Minimal amount of pressure was applied to avoid compression. Short repetitive manual compressions were applied to the PTO with care to avoid anisotropy. The compression amount and uniformity were standardized using pressure graphics. After at least 3 compression-relaxation cycles, the SE calculations were performed based on the best images. The color scales and predefined PTO-SR elastographic findings were used. The PTO stiffness was graded automatically by our USG device. These grades were as follows: Grade 1: red to yellow (hardest or hard tissue, Figure 1); Grade 2: green (intermediate tissue); and Grade 3: blue (soft tissue; Figure 1). Local PTO-SR calculations were performed on the same

images. PTO-SR measurements were performed from the middle part of lower limb and this calculation was compared with a reference tibialis anterior muscle located at the posterior of subcutaneous fat tissue. To avoid anisotropy, all scans were performed perpendicular to the long axis of limbs (at the transverse section) and the US probe was placed perpendicular to skin surface. The default size of the region of interest (ROI) was 2.0 x 2.5 cm. The first ROI (A) was placed in the reference muscle tissue, and the other ROIs were placed on the subcutaneous fat tissue (B). The strain ratio (B/A) was automatically calculated (Figure 2). The PTO-SR was compared with an adjacent reference tissue and semi quantitatively evaluated. Three consecutive measurements were made for each PTO, and mean values were calculated from the results from both limbs.

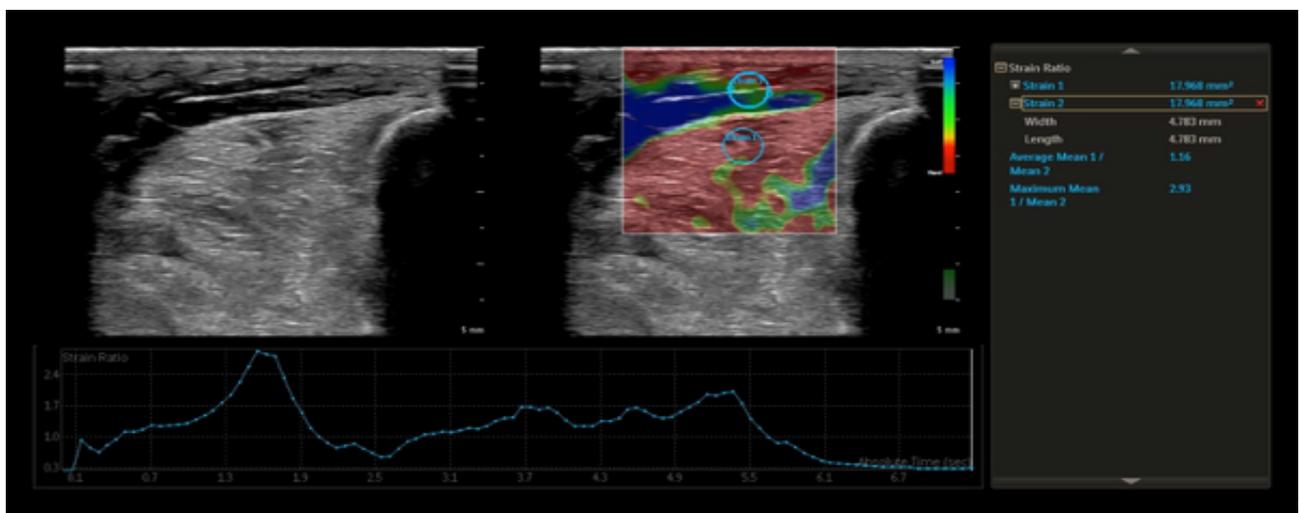


(a)

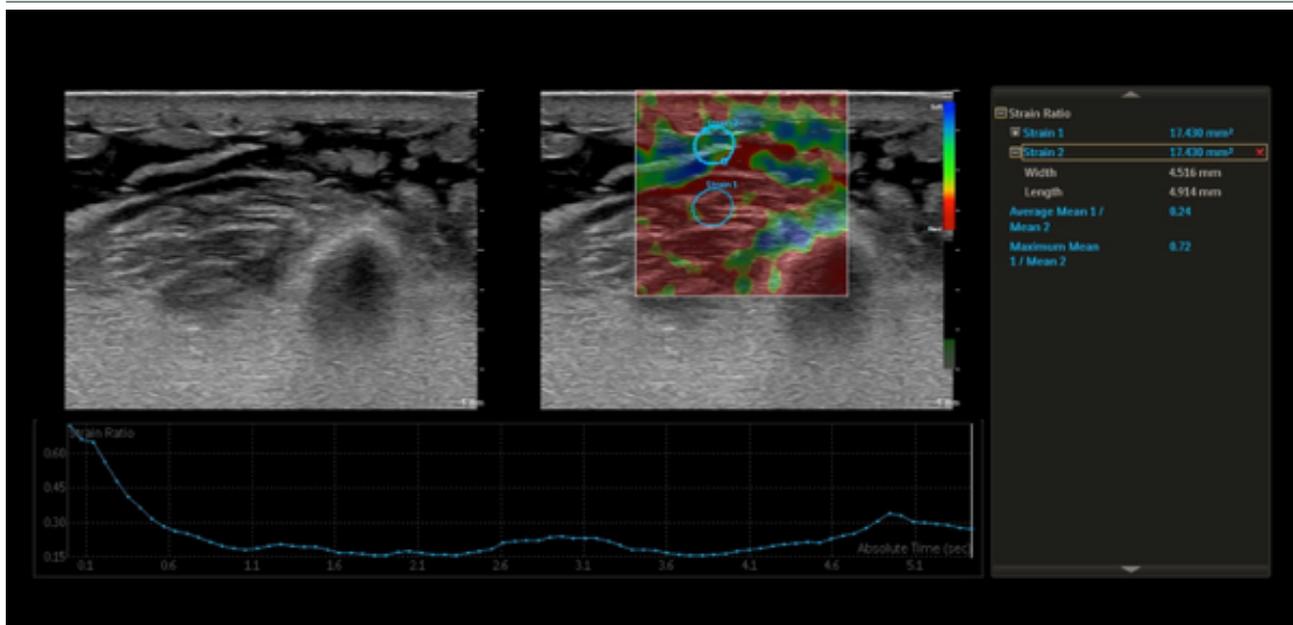


(b)

Figure 1. Different elastography color grades of the pretibial edema. (a), grade 1: red to yellow (hardest or hard tissue). (b) grade 3; blue (soft tissue).



(a)



(b)

Figure 2. Pretibial edema strain ratio measurement by strain elastography. The strain ratio was measured at the level of the medial malleolus (region of interest) and the reference region (Kager's fat pad, posterior wall of the AT) (a) a patient with heart failure and (b) a patient with nephrotic syndrome. Ultrasound device software was used to calculate the strain ratio.

Echocardiographic Evaluation

Two-dimensional (2-D) and Doppler echocardiography examinations were done with EPIQ 7 (Philips Healthcare Andover MA, USA). Images were taken according to the guidelines of the American Echocardiography Society when the patients were monitored and left-sided, a standard short and parasternal long axis was obtained, as well as apical 5, 4 and 2 chambers and at least 3 consecutive cycles [20]. Two echocardiographers who were experienced in HFrEF performed all echocardiography procedures. Echocardiographers were selected from physicians who had at least 1000 echocardiography examinations per year and worked in echocardiography laboratory for at least 5 years. Parasternal long-axis M-mode examination revealed LV diastolic and systolic dimensions, volumes and left atrial (LA) diastolic dimension. The LVEF was calculated by the modified Simpson method from apical four and two chambers [20]. Tricuspid regurgitation pressure gradient (TRPG) was calculated by the Bernoulli equation over the peak flow rate of tricuspid regurgitation.

Statistical Analyses

For all analyses SPSS 22.0 statistical software pack (Chicago, IL, USA) was used. The variables were divided into groups: continuous and categorical. Kolmogorov-Smirnov test was used for normal distribution of the continuous variables. Continuous

variables were expressed as mean \pm standard deviation if they were normally distributed. Categorical variables were expressed as numbers and percentages. Continuous variables that showed normal distribution were compared using the Student's t-test, whereas the Mann-Whitney U test was used for non normally distributed samples. The chi-square (χ^2) test was used to compare categorical variables. The kappa coefficient was used to examine the interobserver, intraobserver variability of echocardiography and US parameters. Parameters associated with PTO-SR were determined with univariate Pearson's and Spearman's correlation analyses. Statistically significant parameters were included in a linear regression analysis, and the parameters having the closest association with the PTO-SR were identified. In univariate analyses, a logistic regression analysis was performed to determine the independent markers among patients with HFrEF. In logistic regression analysis, ROC curve analysis was performed for parameters that independently determined HFrEF. A p level of < 0.05 was considered statistically significant.

RESULTS

Successful PTO US measurements and PTO-SR were obtained from all the patients who were included in the study. Cohen kappa values that evaluate the intraobserver and interobserver variability were over

90% for all echocardiographic and US measurements. Mean, median, minimum and maximum PTO-SR in patients with HF were 0.99 ± 0.61 , 0.80, 0.38 and 3.52, respectively. Mean, median, minimum and maximum PTO-SR values in patients with NS were 0.57 ± 0.32 , 0.50, 0.12 and 1.42, respectively. Study data were divided into 2 groups as HF and NS.

When demographic data were compared, gender and age were found to be similar in two groups. Except heart rate, other demographic and clinical parameters were similar (Table 1). Resting heart rate was higher in patients with HF. BUN, total protein, albumin, NT-proBNP and hemoglobin levels were significantly higher in HF patient group (Table 1). Also, creatinine level was also significantly lower in HF patient group. Other laboratory data were similar in two groups.

Table 1. Clinical and laboratory characteristics of the study groups

	Patients with HF n=40	Patients with NS n=40	P
Age (years)	68.0 ± 12.8	69.9 ± 10.1	0.284
Gender (male)	24	20	0.500
Office systolic BP (mmHg)	130 ± 20	131 ± 17	0.831
Office diastolic BP (mmHg)	83 ± 13	81 ± 16	0.610
Heart rate (beat/min)	86 ± 10	80 ± 8.1	0.003
Weight (kg)	76 ± 9.1	77 ± 6.7	0.809
Height (cm)	167 ± 6.9	168 ± 9.4	0.733
Smoking n, (%)	11 (27.5%)	8 (20.0%)	0.243
Hypertension n, (%)	23 (57.5%)	24 (60.0%)	0.950
Diabetes mellitus n, (%)	14 (35.0%)	17 (42.5%)	0.370
Hypercholesterolemia n, (%)	56 (40.6%)	8 (17.4%)	0.647
Glucose (mg/dL)	158 ± 90	150 ± 42	0.633
Blood urea nitrogen (mg/dL)	61.9 ± 5.56	52.4 ± 6.14	<0.001
Creatinine (mg/dL)	1.22 ± 0.52	1.93 ± 0.65	<0.001
Alanine aminotransferase (u/L)	31.6 ± 39.3	28.6 ± 10.1	0.644
Aspartate aminotransferase (u/L)	46.3 ± 36.1	38.3 ± 15.9	0.466
Total protein (mg/dL)	6.19 ± 0.59	5.24 ± 0.61	<0.001
Albumin (mg/dL)	3.41 ± 0.44	2.59 ± 0.69	<0.001
NT-proBNP (pg/mL)	13478 ± 10227	3534 ± 2244	<0.001
White blood cell count (1000/mm ³)	9.9 ± 3.1	9.6 ± 4.3	0.965
Hemoglobin (g/dL)	12.4 ± 2.13	10.8 ± 1.70	<0.001

Comparing PTO US findings according to study groups, PTO elastographic color grade and PTO-SR were found to be significantly different between two groups (Table 2). Having PTO elastographic color grade 1 incidence was found to be higher in HF patient group (Table 2). Similarly, PTO-SR was significantly higher in HF patient group (Table 2).

When the echocardiographic parameters of patients were compared, all echocardiographic data were significantly different between two groups. LV diastolic and LV systolic diameters and volumes, LA diastolic dimension and TRPG were found to be higher in HF patients group (Table 2). LVEF value was found to be the lower in HF patient group (Table 2).

Table 2. Echocardiographic and strain elastography imaging findings according to study groups

	Patients with HF n=40	Patients with NS n=40	P
PTO elastographic color grade I-II-III (n)	16-14-10	6-12-22	<0.001
PTO strain ratio	0.99 ± 0.61	0.57 ± 0.32	<0.001
Left ventricular diastolic dimension (mm)	62.1 ± 5.6	52.2 ± 5.2	<0.001
Left ventricular systolic dimension (mm)	48.7 ± 7.4	34.4 ± 5.9	<0.001
Left ventricular diastolic volume (mL)	116 ± 17	78 ± 10	<0.001
Left ventricular systolic volume (mL)	80.0 ± 9.2	41.1 ± 7.8	<0.001
Left ventricular ejection fraction (%)	31.2 ± 6.7	54.6 ± 5.8	<0.001
Left atrial diastolic dimension (mm)	45.2 ± 4.1	38.4 ± 5.9	<0.001
Tricuspid regurgitation pressure gradient (mmHg)	43.6 ± 8.1	30.8 ± 7.5	<0.001

When logistic regression analysis was performed to determine the value of PTO strain elastography data for the diagnosis of HF, it was found that PTO-SR independently determined the presence of having HF (Table 3). According to this analysis each 0.1 increase in PTO-SR increased the probability of having HF by 29.1%. A similar analysis was performed with the ROC curve and found that the area under the ROC curve was 0.827 (95% CI 0.740 – 914, $p < 0.001$ and Figure 3) for PTO-SR. According to this analysis, when the cut-off value for PTO-SR was taken as 0.70, it was determined the patients with HF disease with 80.0% sensitivity and 76.5% specificity.

Table 3. Independent risk factors for the presence of heart failure according to multivariate regression analysis.

	Odds Ratio	95% Confidence Interval	P
Left ventricular ejection fraction (each %1 decrease)	0.329	0.110– 0.989	0.001
Pretibial edema strain ratio (each 0.1 increase)	1.291	1.111– 1.500	0.012

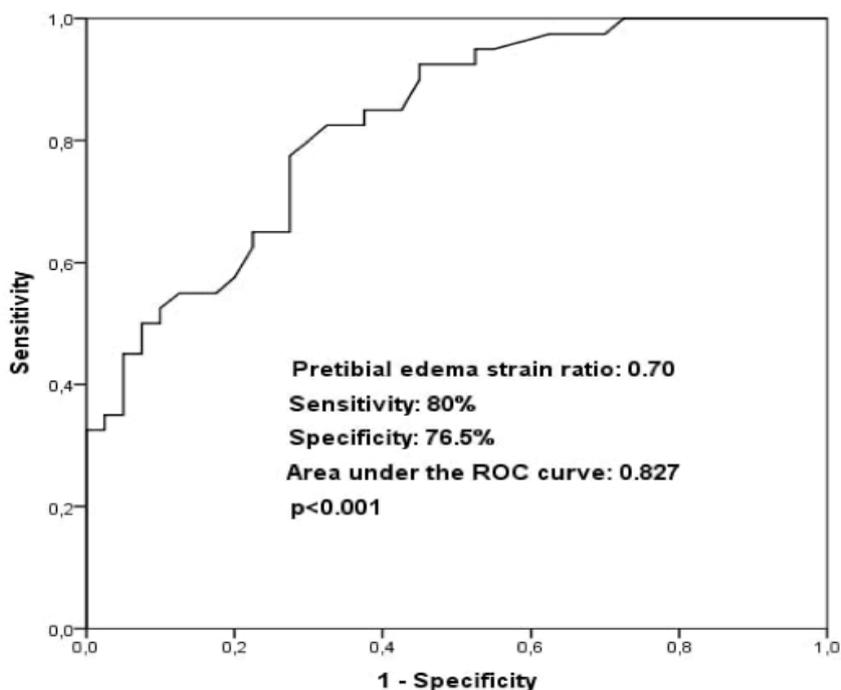


Figure 3. ROC curve analyses of the usefulness of the pretibial edema strain ratio for predicting heart failure

The demographic, clinical, laboratory and echocardiographic parameters associated with PTO-SR in the univariate analysis are summarized in Table 4. Linear regression analysis was performed with these parameters significantly related to PTO-SR (Table 4). PTO-SR values were found to be closely related to TRPG, LVEF and LV diastolic volume (Table 4). The close relationship between PTO-SR and TRPG was shown in Figure 4.

Table 4. The parameters associated with pretibial edema strain ratio in all patients

	Univariate analysis		Multivariate analysis	
	p	r	p	β
Heart rate (beat/min)	0.004	0.320	0.258	0.131
Albumin (mg/dL)	0.039	0.231	0.567	0.067
NT-proBNP (pg/mL)	0.021	0.260	0.545	0.080
Left ventricular diastolic dimension (mm)	0.003	0.331	0.478	0.120
Left ventricular systolic dimension (mm)	0.001	0.371	0.706	0.042
Left ventricular diastolic volume (mL)	<0.001	0.495	0.016	0.378
Left ventricular systolic volume (mL)	<0.001	0.451	0.845	0.042
Left ventricular ejection fraction (%)	<0.001	-0.412	0.026	0.379
Left atrial diastolic dimension (mm)	0.001	0.378	0.946	0.032
Tricuspid regurgitation pressure gradient (mmHg)	<0.001	0.639	<0.001	0.665

R_{Adjusted}²=0.704 in multivariate analyses.

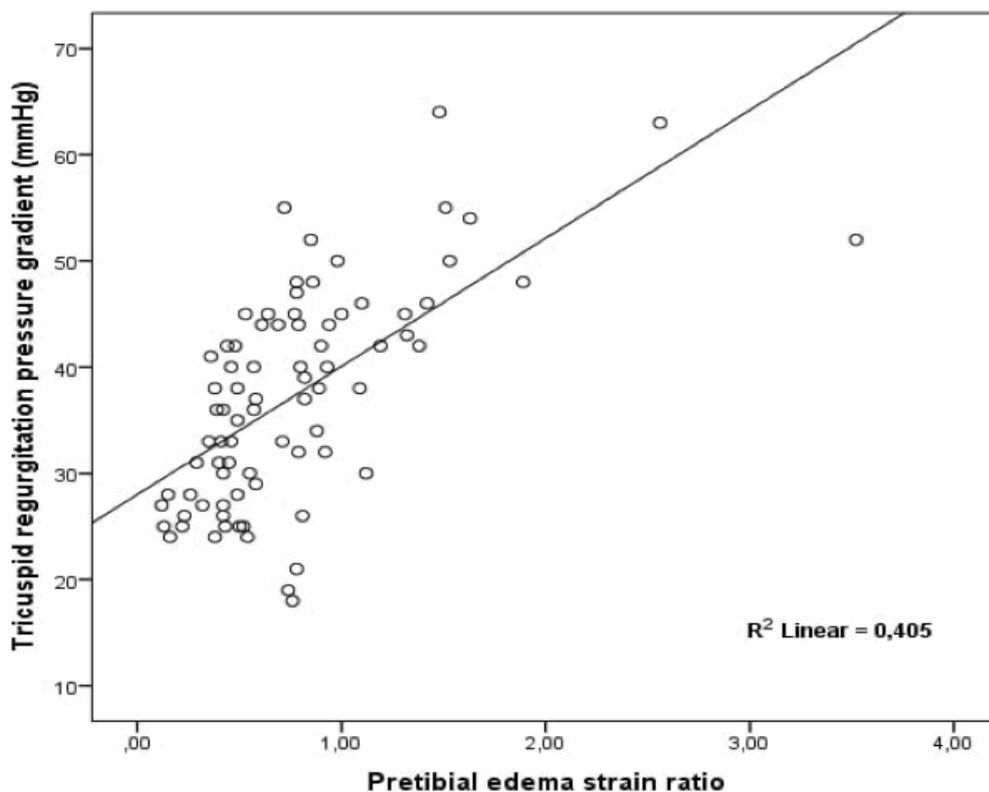


Figure 4. Scatter plot diagram of the relationship between tricuspid regurgitation pressure gradient and pretibial edema strain ratio

DISCUSSIONS

This study has 3 main findings. The first of these; PTO-SR value is significantly higher in patients with HFrEF than in patients with NS. Secondly; increased PTO-SR assessed by SE independently predicts the presence of HFrEF. When cut-off value of > 0.7 was taken for PTO-SR, this could be able to predict the presence of HFrEF with an acceptable sensitivity and specificity. Another important finding is; PTO-SR is closely related with TRPG. To the best of our knowledge, this is the first study to evaluate the tissue stiffness in patients with HFrEF and NS.

Elastography is an examination that evaluates the elastic properties of tissue and where tissue stiffness is obtained objectively, its usage is increasing every day in our clinic and many centers [5-14]. Elastography can be performed using two major modalities: SE and SWE. The SE examination is generally used for the assessment of superficial tissue stiffness. During this examination, a relative strain ratio is obtained by referring to the target tissue and the muscle or adipose tissue that is close to the target tissue and whose stiffness is standard. At the same time, during the examination, color scale of the target tissue is obtained and information about tissue hardness is obtained [12, 21]. However, this is an operator-dependent examination and may not give a clearer result than the SWE examination. The most important problem is the difference in stiffness value that can occur with the compression of the US probe to the target tissue. For this reason, two experienced ultrasonographers who have experience in SE and have done many studies carried out our study.

There is no study in the diagnosis and follow-up of PTO-related diseases by measuring tissue stiffness from PTO or ankle edema regions in diseases causing bilateral PTO in the literature. However, in several studies, the mechanical properties of edematous tissues were evaluated by US elastography. [5,6,15-19]. In the majority of these studies, the cause of PTO is usually lymphedema [5, 15-17, 19]. Lymphedema occurs frequently in patients undergoing surgery for breast cancer. Studies using the SE method, which included patients with breast cancer, have been shown to be able to objectively diagnose and monitor parenchymal breast edema or lymphedema in these patients [15]. A recent study using the ARFI technique in patients with limb lymphedema demonstrated that cutaneous and subcutaneous tissue stiffness increased in patients

with lymphedematous limb relative to the intact leg [5]. For this reason, it has been reported that elastography examinations are non-invasive and easy to evaluate for the determination of the stiffness of the patients with lymphedema and follow-up of the treatment of these patients [5]. Another study evaluating edematous tissue by elastography was performed in localized scleroderma patients [6]. In patients with localized scleroderma, skin stiffness is increased in the affected areas and it is reported that non-invasively normal abnormal skin separation can be made by elastography in patients with localized scleroderma [6].

Fluid-electrolyte balance is very important in patients with NS and end-stage renal diseases. When fluid overload or fluid depletion occurs in these patients, the necessary treatment should be performed immediately. Because the initial peripheral edema can cause life-threatening congestive HF in later stages. Similarly, peripheral edema that occurs in patients with right-sided HF should be treated at the appropriate time and in an appropriate manner, usually with hospitalization. Peripheral edema in patients with HFrEF and NS can be evaluated by non-invasive and invasive methods. Non-invasive evaluations included jugular venous distention, liver enlargement, hepatojugular reflux, pleural effusion and PTO as determined by physical examination, liver enlargement, ascites and increased liver stiffness in abdominal US evaluation. In the invasive evaluation, right atrial pressure or central venous pressure is measured by central catheterization. Both disease groups are treated appropriately as a result of these invasive and non-invasive assessments. Unfortunately, all the evaluations obtained in the physical examination are related to the experience of the physician, especially whether the PTO is pitting or not, and the PTO grade varies between intraobserver and interobserver. In recent years, there have been studies on the determination of liver stiffness by liver elastography in the evaluation of peripheral congestion in patients with HF. In these studies, it was reported that liver stiffness value increased in patients with HF and this was positively related with right atrium mean pressure and NYHA class [7, 9].

Similar to increased liver stiffness due to peripheral congestion in patients with HFrEF, we thought that increased fluid output in the PTO area and changes in the subcutaneous tissue could increase stiffness in these tissues. Considering the pathophysiology of PTO in patients with NS and HFrEF, different

mechanisms are known to cause PTO. The main problem in patients with HF is increased peripheral hydrostatic pressure. Oncotic pressure may be normal or decreased in this disease. As a result, an interstitial fluid accumulates in the perivascular areas, usually similar to the patient's serum characteristics, and forms PTO. This results a pitting edema in physical examination. The main cause of PTO in patients with NS is the decreased oncotic pressure due to hypoalbuminemia. Hydrostatic pressure may be reduced, normal or rarely increased. This is related to the hydration status of the patient. Therefore, a protein-poor interstitial edema occurs. As a result, tissue stiffness may be increased in patients with HFrEF in the PTO area compared to patients with NS. Tissue stiffness was measured by SE technique in a patient who was newly diagnosed with HFrEF or NS for the first time in the literature. Tissue stiffness in the PTO region is objectively demonstrated by calculating the PTO-SR. As a result of our study, it was found that PTO-SR value in patients with HFrEF was significantly higher than patients with NS. In addition, PTO-SR may be used in the diagnosis of patients with HF. In addition, PTO-SR was found to be very close and positively correlated with TRPG, an elevated right-sided pressure indicator known to be associated with peripheral congestion. Both SWE and SE examinations are a non-invasive method that can be performed in a short period of time and for many diseases. Therefore, it may help conventional diagnostic methods to differentiate NS and HFrEF in patients with PTO. In addition, the PTO-SR value, which can be measured non-invasively in patients with HFrEF, can be considered as an indicator of right-sided pressures.

This study has some important limitations. One of them was the number of patients included in our study and only patients with HFrEF and NS were included as having PTO. It could be more meaningful if more patients and all of the diseases causing bilateral PTO were included in the study. Another limitation was only the newly diagnosed patients for both NS and HFrEF were included. Therefore, the effect of

drugs on PTO-SR could not be evaluated. In a recent study, subcutaneous tissue US, subcutaneous tissue echogenicity and subcutaneous eco-free area were successfully evaluated for differentiation of lymphedema and venous insufficiency edema [18]. We did not evaluate these findings in our study. Our study is not a follow-up and prognosis study. The association of PTO regression with treatment and prognosis of the disease has not been evaluated. By including more patients, follow-up and prognosis studies can be performed only in patients with isolated HFrEF.

CONCLUSION

PTO-SR was significantly increased in patients with HFrEF. An independent association was found between the PTO-SR and the presence of HFrEF, and the PTO-SR can be easily detected by SE. Increased PTO-SR value is closely related to increased TRPG. The PTO-SR is thus considered to be a simple, inexpensive, noninvasive, reproducible, and objective parameter for the prediction of HFrEF. In patients with PTO, we think that PTO-SR evaluations should become a part of conventional US assessments in patients who are at a high risk of HFrEF. Moreover, patients with PTO-SR > 0.7 should be closely followed for possible HFrEF. Our study is the first study in which patients with PTO have undergone SE examination and a limited number of patients have been included. Therefore, we thought that multicenter studies involving more patients should be performed in order to use the PTO tissue stiffness routinely.

ACKNOWLEDGEMENTS

We thanks to Dr. Ayse Selcan Koc for her contribution.

CONFLICT of INTEREST

We have no conflict of interest for this study.



REFERENCES

- [1] Clark AL, Cleland JG. Causes and treatment of edema in patients with heart failure. *Nat Rev Cardiol* 2013; 10: 156-70.
- [2] O'Connor CM, Rogers JG. Heart Failure: Pathophysiology and Diagnosis. *Goldman-Cecil Medicine* 58, 298-305.e2
- [3] Lee Goldman. Approach to the Patient with Possible Cardiovascular Disease. *Goldman-Cecil Medicine* 51, 248-257. e1.
- [4] Mahmood SS, Wang TJ. The epidemiology of congestive heart failure: The Framingham Heart Study perspective. *Glob Heart* 2013; 8: 77-82.
- [5] Chan WH, Huang YL, Lin C, et al. Acoustic Radiation Force Impulse Elastography: Tissue Stiffness Measurement in Limb Lymphedema. *Radiology* 2018; 289: 759-65.
- [6] Wang L, Yan F, Yang Y, et al. Quantitative Assessment of Skin Stiffness in Localized Scleroderma Using Ultrasound Shear-Wave Elastography. *Ultrasound Med Biol* 2017; 43: 1339-47.
- [7] İçen YK, Demirtaş AO, Koç AS, et al. Liver stiffness value obtained with ElastPQ ultrasound increases with NYHA class in chronic heart failure patients and reduced ejection fraction. *Turk Kardiyol Dern Ars* 2019; 47: 281-93.
- [8] Sumbul HE, Koc AS, Gülümsek E. Renal cortical stiffness is markedly increased in pre-diabetes mellitus and associated with albuminuria. *Singapore Med J* 2019. doi: 10.11622/smedj.2019052.
- [9] Demirtas AO, Koc AS, Sumbul HE, et al. Liver stiffness obtained by ElastPQ ultrasound shear wave elastography independently determines mean right atrial pressure. *Abdom Radiol (NY)* 2019; 44:3030-39.
- [10] Sumbul HE, Koc AS, Demirtas D, et al. Increased renal cortical stiffness obtained by share-wave elastography imaging significantly predicts the contrast-induced nephropathy in patients with preserved renal function. *J Ultrasound* 2019; 22: 185-91.
- [11] Koc AS, Sumbul HE, Gülümsek E. Increased renal cortical stiffness in patients with advanced diabetic kidney disease. *Saudi J Kidney Dis Transpl* 2019; 30: 138-50.
- [12] Koc AS, Pekoz BC, Donmez Y, et al. Usability of Achilles tendon strain elastography for the diagnosis of coronary artery disease. *J Med Ultrason* 2019; 46: 343-51.
- [13] Koc AS, Sumbul HE. Prediabetes Is Associated with Increased Liver Stiffness Identified by Noninvasive Liver Fibrosis Assessment: ElastPQ Ultrasound Shear Wave Elastography Study. *Ultrasound Q* 2019. doi: 10.1097/RUQ.0000000000000419.
- [14] Koc AS, Sumbul HE. Renal cortical stiffness obtained by shear wave elastography imaging is increased in patients with type 2 diabetes mellitus without diabetic nephropathy. *J Ultrasound* 2018; 21: 279-85.
- [15] Adriaenssens N, Belsack D, Buyl R, et al. Ultrasound elastography as an objective diagnostic measurement tool for lymphoedema of the treated breast in breast cancer patients following breast conserving surgery and radiotherapy. *Radiol Oncol* 2012; 46: 284-95.
- [16] Berry GP, Bamber JC, Mortimer PS, et al. The spatio-temporal strain response of oedematous and nonoedematous tissue to sustained compression in vivo. *Ultrasound Med Biol* 2008; 34: 617-29.
- [17] Righetti R, Garra BS, Mobbs LM, et al. The feasibility of using poroelastographic techniques for distinguishing between normal and lymphedematous tissues in vivo. *Phys Med Biol* 2007; 52: 6525-41.
- [18] Suehiro K, Morikage N, Yamashita O, et al. Differentiation of functional venous insufficiency and leg lymphedema complicated by functional venous insufficiency using subcutaneous tissue ultrasonography. *J Vasc Surg Venous Lymphat Disord* 2017; 5: 96-104.
- [19] Suehiro K, Nakamura K, Morikage N, et al. Real-time tissue elastography assessment of skin and subcutaneous tissue strains in legs with lymphedema. *J Med Ultrason* 2014; 41: 359-64.
- [20] Lang RM, Bierig M, Devereux RB, et al. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-63.
- [21] Bankir M, Sumbul HE, Koc AS, et al. Elastography detected solid organ stiffness increased in patients with acromegaly. *Medicine (Baltimore)* 2019; 98: e14212.

