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Cardiology

Does chronic venous insufficiency affect cardiac functions? A speckle tracking echocardiography study

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ABSTRACT

Objectives: The aim of this study was to investigate whether there is subtle cardiac dysfunction in patients with chronic venous insufficiency.

Methods: Age and sex matched 56 patients with a score of C3 and above in the Clinical, Etiological, Anatomical, Pathophysiological classification and 56 healthy volunteers were included in the study. All subjects were evaluated by detailed echocardiographic examination, including two-dimensional strain echocardiographic analysis by speckle tracking method.

Results: Mitral E wave deceleration time (EDT), E and A wave velocity, E/e' ratio for left ventricle, tricuspid EDT, E/e' ratio for right ventricle and systolic pulmonary artery pressure were found high as significant statistically in patients groups ($p < 0.05$). But no any statistically significant difference was observed in other parameters between two groups.

Conclusions: There may be an increase in diastolic filling pressures in patients with chronic venous insufficiency due to the increased preload in the supine position. This condition seems to be clinically important in patients at high risk for heart failure due to the presumption of the early treatment of chronic venous insufficiency may reduce the risk of heart failure evolvement.

Keywords: Chronic venous insufficiency, echocardiography, strain, heart failure, speckle tracking

Chronic venous insufficiency (CVI) is a disease characterized by persistent venous hypertension that affects the venous system of the lower extremities, which can lead to pain, edema, skin changes and wounds [1]. The prevalence of patients with varicose veins has been reported up to 60 % in the adult population [2]. The peripheral venous system is a continuation of the arterial system and, thus, of the heart, acting as a reservoir to store blood and as a conduit for its return to the heart. Effective functioning of the peripheral venous system requires patency of the venous system with one-way functioning venous valves and muscle pump efficiency [3, 4]. Venous pathology develops when the return of blood to the heart is impaired due to impaired valvular function of the veins, increased venous pressure due to venous congestion and ineffective muscle pump function. This leads to venous hypertension, increases especially when stand-

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ing or moving [5]. In addition to venous valves, venous return is closely related to the pressure gradient between the heart and systemic capillaries and the right ventricle [6-8].

Several studies show differences in cardiac Doppler findings between patients with CVI and healthy volunteers, especially those with the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) class 3 and above [9-11]. No study has examined subclinical left and right ventricular dysfunctions in patients with dysfunctional peripheral venous system. In this study, we aimed to investigate if any subclinical cardiac dysfunction in patients with CVI by assessing the ventricular function of the heart with two-dimensional (2D) myocardial strain analysis and other cardiac function parameters.

METHODS

The local ethics committee approved the study (University of Health Scinence, Bursa Yuksek Ihtisas Research and Training Hospital, Clinical Research Ethics Committee, REC number: 2011-KAEK-25 2022/04-02). Our study is cross-sectional in design. The CEAP classification system categorizes patients with CVI in ascending order according to the severity of their clinical condition, guides their diagnosis and treatment, and is used in research purposes. The CEAP classification divides patients with CVI into 7 classes (C0-C6) [12].

All patients who applied to cardiovascular surgery outpatient clinic between April 2022 and February 2023 were screened. Applied inclusion criteria were as follows: being over 18 years old and C3 and above according to CEAP classification. Exclusion criteria were as follows (1) Diseases that may have impact on cardiac function such as coronary artery disease, valvular heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, pericardial constriction; (2) The patient is taking any medication; (3) Anemia and thyroid dysfunction, (4) History of deep venous thrombosis and deep vein insufficiency; (5) Liver diseases; (6) Glomerular filtration rate < 60 ml/min; (7) Previously unknown structural cardiac disease detected during echocardiographic evaluation for the current study; and (8) No giving informed consent for the study. The control group was selected from healthy volunteers who did not have any disease and did not take any medication. 56 patients (min-max age: 23-68 years) and 56 healthy volunteers (min-max age: 25-68 years) with equivalent age, gender and Body Mass Index (BMI) who met the inclusion and exclusion criteria were included in the study. Written informed consent was obtained from all participants.

Ultrasonographic Evaluation

Duplex ultrasound evaluation of lower extremity veins was performed using a 7.5 MHz linear transducer (Toshiba, USDI-790A) while the subjects standing. Evaluation of the iliocaval system was performed in the supine position. The compression/release method was used for venous insufficiency assessment. Venous reflux time was measured after abrupt cessation of manual compression at the saphenofemoral junction and distally along the great saphenous vein tracing. If reflux lasting more than 0.5 seconds was detected, saphenofemoral vein junction/significant saphenous vein insufficiency was diagnosed [6].

Echocardiographic Evaluation

Two-dimensional transthoracic echocardiography was performed in all patients and the control group. Morning fasting blood samples were taken before the procedure. Echocardiography was performed by an experienced echocardiographer blinded to the patient's data. A Vivid E95 platform with a 3.5 MHz transducer was used for the procedure. (GE Vingmed Ultrasound AS, Horten, Norway). Echocardiographic parameters were evaluated according to the recommendations of the American Society of Echocardiography guidelines [13]. Standard 2D, colour, pulse and continuous Doppler data were measured and recorded while the patient was lying supine in the left decubitus position with the patient in end-expiration. Modified Simpson's method was used for volumetric chamber evaluation. Right ventricular end-diastolic and end-systolic area, right ventricular fractional area change (FAC) were measured. Tricuspid valve annular plane systolic excursion (TAPSE), tricuspid valve and mitral valve inflow velocities (E and A waves) and E wave deceleration time (EDT) were measured accordingly. Tricuspid and mitral annular tissue Doppler velocities (s, e' and a' waves) were obtained as recommended by the guidelines [13-15]. Using colour Doppler, systolic pulmonary artery pressure (sPAP) was obtained from the tricuspid regurgitation jet through different windows using Bernoulli's equation and right atrial pressure was estimated by measuring vena cava inferior diameters and collapsibility index [16, 17]. Left ventricle (LV) and right ventricle (RV) myocardial performance index was calculated as the sum of isovolumetric contraction and relaxation time divided by left ventricular ejection time.

For right ventricular strain analysis (RVS), the Automated Function Imaging (AFI) technique with speckle tracking method was used (Automated Function Imaging, Version 112, GE Healthcare, Horten, Norway) [13]. RV-focused apical four-cavity image was preferred for analysis[18]. Electrocardiography gated loop recording was obtained from the acquired image. Loop recordings' frame rate was > 60-110 frames per second. In particular, “3-click” methods were used to reduce variability. With the 3-click method, a U-shaped region of interest (ROI) was created by automatically determining the endocardial borders by the software after placing a point at the tricuspid annulus lateral, medial and RV apex. ROI was manually corrected if necessary. Once the optimal ROI was obtained and confirmed, right ventricular free wall longitudinal strain (RVFWLS) and RV global longitudinal strain (GLS) were obtained [19, 20].

The same software was used for left ventricular strain analysis (LVS). Similarly, loop recordings were obtained from standard apical four-space, apical two-space and apical three-space windows. At the end-systole of each loop, points were manually placed on both edges of the mitral valve and the apex of the left ventricle using the 3-click method, and the software automatically drew the endocardial borders to create the ROI. Automated endocardial and epicardial borders of the ROI were manually corrected when necessary. Left ventricular global longitudinal strain value (LVGLS) was obtained from the optimal ROI registration of all three loops (Fig. 1a and b) [21].

Doppler and strain measurements were done 3 times consecutively while the subjects were in end-expiration, and the arithmetic mean of the measurements was recorded. Intraclass correlation coefficient test was performed in 10 randomized patients to assess intraobserver reliability in the measurement of each RVGLS and LVGLS. The intra-class correlation coefficient was 0.92 (0.81-0.98) for RVGLS, and was 0.88 (CI: 0.71-0.96) for LVGLS.

Statistical Analysis

All statistical analyses were performed using SPSS version-26. According to the Kolmogorov-Smirnov test, continuous variables showing normal distribution were expressed as mean ± standard variable (SD), continuous variables not showing normal distribution were expressed as median (25th - 75th per-

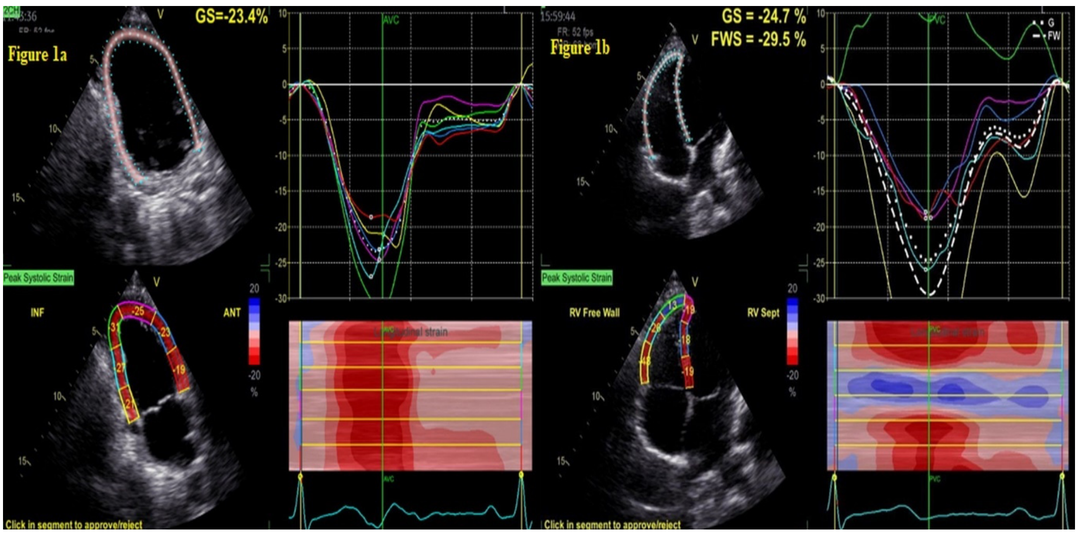

Fig. 1. **(a) showing the region of interest of apical two chamber view and left ventricular global longitudinal strain, (b) showing the region of interest of right ventricle focused apical four chamber view and right ventricular free wall and global longitudinal strain**

centile), and categorical variables were expressed as a percentage (%). Descriptive statistics of demographic, clinical characteristics and laboratory parameters of the patient and control groups were performed. The patient and control groups' demographic, clinical, laboratory and echocardiographic variables were compared using Independent Samples t-test (for normally distributed variables) or Mann-Whitney U Test (for non-normally distributed variables). A p - value less than 0.05 was considered statistically significant.

RESULTS

The mean age was 46.07 ± 12.29 years in the patient group and 46.39 ± 11.92 years in the control group (p = 0.824). The gender distribution of both groups was comparable (71.4% male). According to CEAP classification, 25 (44.6%), 24 (42.9%) and 7 (12.5%) patients were categorized in C3, C4 and C5 classes, respectively, while no patient was in C6. In the study group 6 (10.7%) patients had vena saphena parva failure in addition to vena saphena magna and also 2 (3.5 %) patients had perforating vein insufficiency. Demographic, clinical and laboratory parameters of the patients and control group are shown in Table 1.

When left ventricular echocardiographic variables of the patient and control groups were compared, mitral EDT, mitral E and A wave velocities and E/e' ratio were significantly higher in the patient group than in the control group (p = 0.04, p = 0.004, p = 0.029 and p = 0.002 respectively). In comparing right ventricular parameters, statistically significant increases in tricuspid EDT, tricuspid E/e' and sPAP values were found in the patient group. Tables 2 and 3 show LV and RV echocardiographic parameters of the patient and control groups.

DISCUSSION

In the present study, patient and control groups were compared in terms of many echocardiographic cardiac

Table 1. Demographic and laboratory findings of the patient and control groups

Parameters	Patients (n = 56)	Controls (n = 56)	*p* value
Age (years)	46.07 ± 12.29	46.39 ± 11.92	0.824
Male, n (%)	40 (71.4)	40 (71.4)	1
Current smoking, n (%)	26 (46.4)	22 (39.3)	0.636
BMI (kg/m^2)	29.65 (26.38-32.68)	28.98 (26.58-32.63)	0.92
GSV diameter (mm)	7.20 (6.35-7.57)	4.05 (3.8-4.30)	**< 0.001**
CrCl* (mL/min)	99.17 (91.93-112.419	106.78 (96.19-11.85)	0.16
Sodium (mEq/L)	139 (137.25-140)	138 (137.25-140.75)	0.63
Potassium (mmol/L)	4.4 (4.1-4.57)	4.4 (4.2-4.5)	0.45
ALT (IU/L)	19.50 (16.00-32.50)	21 (16-32)	0.99
AST (IU/L)	19.32 ± 4.44	18.91 ± 5.58	0.14
Total cholesterol (mg/dL)	204.29 ± 50.15	205.82 ± 39.69	0.07
Triglyceride (mg/dL)	136 (96-256)	155 (118.25-198)	0.99
Hemoglobin (g/dL)	14.95 (13.72-16.22)	14.55 (13.75-15.60)	0.13
White blood cell, (× 10^3/mL)	8.27 ± 1.84	7.74 ± 1.83	0.99
TSH (mIU/L)	1.48 (0.80-2.46)	1.32 (0.75-2.1)	0.43

Data are shown as median ± standard deviation or median (25th-75th) or n (%). ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, BMI = Body mass index, CAD = Coronary artery disease, CrCl = Creatinine Clearance, GSV = Great saphenous vein, TSH = Thyroid-stimulating hormone,
*Calculated according to the Cockcroft-Gault equation

function parameters, including 2D strain analysis. Except for some Doppler parameters, no significant differences were detected between the study groups. To the best of our knowledge, our study is the first to analyze subclinical right and left ventricular functions with 2D strain analysis in patients with CVI.

The present study found a statistically significant elevation in the left ventricular echocardiographic parameters including mitral EDT, E and A wave velocity and E/e' ratio in the patient group. No difference was found in left ventricular strain and other functional parameters between patient and control groups. Among RV echocardiographic parameters, tricuspid EDT, tricuspid E/e' ratio and sPAP were significantly higher in patients in whose sPAP's could be measured. No significant difference were found in RV FWLS, GLS and other functional parameters.

In a study by Rusinovich and Rusinovich [22], mitral and tricuspid E wave velocities, which indicate atrioventricular pressure gradient, were significantly lower, while A wave velocities representing atrial contraction were significantly higher in patients with CVI than the control group. Furthermore, mitral and tricuspid s' velocities representing ventricular systole were significantly increased [13, 22-24]. Mitral and tricuspid e' waves, that indicate myocardial relaxation, were comparable between the study groups [22, 24, 25]. Mitral septal and lateral and tricuspid E/e ratios were significantly lower in patient group compared to control group. These results differ from our study except for a similar increase in mitral A wave and no difference in mitral-tricuspid e' values. However, that study was a retrospective study in which patients from the CEAP 2 class were also included, and the control group was composed of subjects with normal Doppler findings from other studies. Differences in the study population, in particular the fact that all patients in our study were classified as C3 and above, may explain the difference in our results. Rusinovich and Rusinovich [22] explained that the increase in A velocity, a' velocity and s' velocity while no change of tricuspid E and e' velocity in severe venous insufficiency may be attributed to the more increased venous return in the supine position due to the high venous pressure in venous insufficiency.

In another study by Zhang *et al*. [9], a significant increase in tricuspid A-wave velocity, in mitral septal and lateral e' velocities and in septal a', s', lateral s' velocities were observed where as a significant decrease in tricuspid E wave velocity and E/A ratio were recorded in the patients with CVI compared to the control healthy group. No significant differences were found in mitral and tricuspid E/e ratios between the study groups [9]. The mean age of the patient group in this study was 55.2 ± 11.4 years, which is considerably higher than our study. In that study, 51 (40%) of the patients were in C2, 28 (22%) in C3, 50 (38%) in the C4 group and very few in CAEP 5 and 6, consisted mainly C4 patients. 57% of the patients were women. The results of th our study might have differed from the results of this study due to the fact that our study recruited a different study population including lower mean age, higher CEAP class and higher male ratio [11].

The high mitral and tricuspid E/e' ratios, indicators of ventricular filling pressures used to predict diastolic functions, suggest that ventricular filling pressures are high in patients with CVI. E/e' ratio can signify diastolic functions more accurately than other Doppler parameters and has prognostic importance [26, 27]. Mitral E velocity is primarily determined by the early transmitral pressure gradient and may also be elevated in the presence of high left ventricular filling pressures and increased preload [28, 29]. Again, in our study, mitral and tricuspid EDTs, which were not evaluated in previous studies, were found to be significantly higher in the patient group. EDT is a prognostically valid parameter of diastolic dysfunction that rises in stage 1 diastolic dysfunction, reflecting the time required to equalize the pressure difference between the atria and ventricles [30]. In addition, the fact that sPAP was found to be higher if it can be measured, in the patient group also suggests that there may be an increased preload in these patients [31]. These significant differences in diastolic Doppler parameters may suggest a relationship between CVI and diastolic dysfunction or an increased preload in such patients.

In our study, unlike the other studies [9, 22], all echocardiographic examinations were performed by a single echocardiographer between 2 groups whose age, gender, BMI and other clinical features were matched except for CVI. Detailed echocardiographic evaluation of the patients was performed by measuring not only Doppler parameters but also 2D strain analysis, dimensional, volumetric and various other functional parameters. The examination of each subject took approximately 30 minutes after lying supine for 5 minutes. The decongestion and venous hypertension in the lower extremities during supine position may have caused an increase mitral E-A wave velocity, mitral and tricuspid EDT, E/e ratios and sPAP values due to increased venous return. Detailed preoperative and postoperative echocardiographic evaluation of patients with CVI with a study to be conducted in an adequate patient group may illuminate the underlying mechanism.

Limitations

The study was single-centred and conducted with limited number of subjects.

CONCLUSION

There may be an increase in diastolic filling pressures in patients with CVI due to the increased preload in the supine position. This condition seems to be clinically important in patients at high risk for heart failure due to the presumption of the early treatment of chronic venous insufficiency may reduce the risk of heart failure evolvement.

Authors' Contribution

Study Conception: FK, FL, AKA, ABT; Study Design: FK, FL, FKÖ; Supervision: MD, ET, FV; Funding: FK, FL, FKÖ; Materials: N/A; Data Collection and/or Processing: FK, FL, ABT, AKA, FKÖ; Statistical Analysis and/or Data Interpretation: FL, ET, MD; Literature Review: FK, FL, FV; Manuscript Preparation: ET, FL, AKA, ABT, FK and Critical Review: ET, MD, FV, FK, FL.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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