Episcleral Venous Tortuosity Indicates Increased Ventricular Filling Pressure in Heart Failure with Reduced Ejection Fraction

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Abstract

Objectives: In chronic venous hypertension (HT), the adaptation of smooth muscle-poor veins typically occurs with corkscrew-like morphology. The observation of episcleral venous tortuosity (EVT) seems to be a simple and important method for the detection of chronic venous HT using the eye. Whether EVT can provide knowledge about left ventricular (LV) end diastolic pressure via the surrogate marker of lateral ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E') in heart failure (HF) with reduced ejection fraction (HFrEF) is unknown.

Materials and Methods: The study included 200 cases of HFrEF and 200 control subjects with normal ejection fractions and similar ages (59.3±7.6 and 58.6±6.8 years, respectively) and sex distribution. EVT was determined using a simple visual light source. Echocardiographic parameters were measured using accepted methods.

Results: EVT was found in 43 (21.5%) cases in the HFrEF group and 15 (7.5%) subjects in the control group. In the control group, areas under receiver operating characteristic curves for the LV lateral E/E' (>10.5), right ventricular (RV) lateral E/E' (>5.5), and LV mass index (>115 g/m^2) distinguished subjects with and without EVT (p<0.05). The detection of tortuosity in episcleral veins in the HFrEF group was correlated with the LV lateral E/E' (>15.25), RV E/E' (>12.2), tricuspid annular plane systolic excursion (TAPSE); <1.45, LV mass index (>106 g/m^2), atrial fibrillation, and presence of long-term HF.

Conclusion: Tortuosity in episcleral veins in patients with HFrEF can predict the LV lateral E/E' (>15.25), RV E/E' (>12.2), TAPSE (<1.45), and LV mass index (>106 g/m^2) with sensitivity (65.1%, 30.2%, 74.4%, and 53.5%, respectively) and specificity (96.8%, 97.4%, 62.4%, and 77.1%, respectively).

Keywords: Episcleral venous tortuosity, heart failure with reduced ejection fraction, ventricular filling pressure, E/E', TAPSE

Introduction

Approximately 75% of the total blood volume is in the venous system, comprised mainly of the small veins and venules[1]. Most of the vascular venous system is far from areas that can be observed directly. However, the episcleral veins are visible because of the clarity and transparency of the conjunctiva.

The main venous drainage of the limbus occurs through episcleral veins, and then combines with the discharge from the ophthalmic veins. These veins are then drained into the superior and inferior orbital veins and cross into the jugular venous system[2,3]. As direct observation of the vortex veins, which account for the largest portion of venous drainage of the eyes, is difficult, the identification of tortuosity in the episcleral veins seems to be a simply made and important finding.

Systolic and diastolic dysfunctions increase the filling pressure. When the stroke volume is no longer maintained by compensatory mechanisms, such as the Frank-Starling law, the ventricle dilates to maintain end-diastolic pressure and stoke volume. A reduction of cardiac output leads to decreases in systemic and pulmonary vascular function and renal function. Venous pooling increases the venous blood volume and pressure[4], which may affect the episcleral veins visible in the eye.

The contraction and relaxation of smooth muscle cells cause temporary changes in blood flow or pressure, whereas chronic increases in transmural pressure, such as venous hypertension (HT), create vascular re-modelling to normalize the wall stress[5].

In arteries, re-modelling occurs in the form of arterial wall thickening. Adaptation in veins with thin walls and weak smooth muscle typically occurs with corkscrew-like morphology[6,7].

In heart failure (HF) with reduced ejection fraction (EF) (HFrEF), increased venous pressure may result in dilatation and folding of all body veins at various ratios over the long term[8] The right ventricular (RV) and left ventricular (LV) ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E') ratio is correlated with ventricular filling pressure and is simple to measure. LV lateral E/E' ratios >14 correlate well with LV end diastolic pressure or pulmonary capillary wedge pressure[9]. Among all echo parameters, a lateral E/E' ratio >10 was defined as the best marker of diastolic dysfunction, with a detection rate of 86%, superior to the rate of 70% for transmitral Doppler measures[10].

What clues might episcleral venous tortuosity (EVT), which can be detected on the front segment of the eye with a simple light source by opening the eyelid, give us about E/E', a surrogate parameter for ventricular filling pressure, in patients with HFrEF?

Materials and Methods

Study Inclusion Criteria

The study included 200 HFrEF cases (EF≤45%) and 200 control subjects not diagnosed as HF, with normal EFs (≥50%), of similar ages (59.3±7.6 and 58.6±6.8 years, respectively) and sex distribution.

Study Exclusion Criteria

Cases with ocular surface disease; those with infectious and inflammatory diseases, such as conjunctivitis, episcleritis, scleritis, uveitis, keratitis, and pterygium; those who had undergone eye operations; and those who had glaucoma, acne rosacea, keratoconjunctivitis sicca, exophthalmos, or lagophthalmos were not included in the study.

Biomicroscopic Examination to Distinguish Conjunctival and Episcleral Veins

After visual eye inspection using a simple light source, biomicroscopic examination was performed for each patient. The conjunctiva and tenon veins may be moved manually over the sclera, but the episcleral veins do not move. After the patient's blood pressure was confirmed to be below 140/100 mmHg, 2.5% phenylephrine was administered as drops to ensure differentiation of the conjunctival and episcleral veins. Cases with

biomicroscopically detected reduced vein size after 20-30 min were included in the conjunctival vein group, and those with no detected reduction were included in the episcleral vein group.

Biomicroscopy was used to check whether the vein could be moved manually, whether blood flow was in the centrifugal flow direction, and whether the flow was pulsatile. Veins that could not be moved manually, those that displayed centrifugal flow, and those without pulsatile flow were accepted as episcleral[11,12]. Additionally, the location of an outlet blood flow point about 1-3 mm from the limbus was considered to favor classification into the episcleral vein group. Veins in which pulsatile flow was observed visually and those in which blood flow was not distinguishable biomicroscopically were considered to belong to the episcleral artery group[13]. EVT was recorded as present or absent, regardless of whether it was in one or both eyes or whether it occurred together with conjunctival venous tortuosity. Digital photographs of tortuous episcleral veins taken in the best imaging position are provided in Figure 1.

Echocardiographic Data Acquisition

Echocardiography was performed with a Philips Epic 7 ultrasound system equipped with tissue Doppler technology and a 3.5-MHz transducer, using the QLAB software system. The images were taken after short expiration from apical four-chamber views. Pulse Tissue Doppler Image (TDI) volume samples were recorded from the mitral annulus (lateral side) and tricuspid annulus (free wall side) in parallel with each wall. End-systolic and end-diastolic LV area and volume images were taken from the apical four chambers. The left ventricular ejection fraction (LVEF) was calculated from these data. Mitral and tricuspid inflow patterns were also assessed from apical four-chamber views, and early wave maximal velocities were measured. The RV tricuspid annular plane systolic excursion (TAPSE), (cm) was measured using the M-mode as described previously. The systolic pulmonary
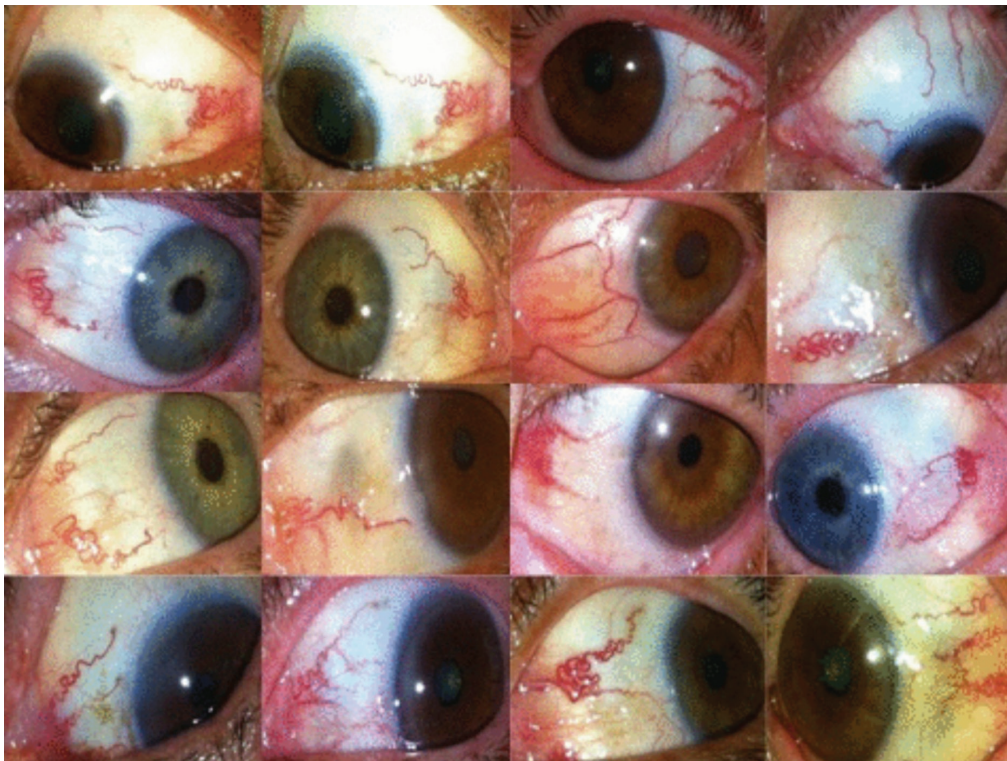

Figure 1. Examples of tortuous episcleral veins. The two photographs in the first line show no change in the episcleral vein as a result of phenylephrine collyre instillation

artery pressure (mmHg) was calculated using the maximal tricuspid regurgitant (TR) jet.

Early diastole (E') velocities with mitral and tricuspid annuli peak velocities were measured from the lateral wall base. LV E/E', peak TR velocity, differences in the RV E/E' ratio, LV diastolic diameter (cm), right ventricle diastolic diameter mid (cm), left atrial volume index (LAVI), (mL/m^2), left atrial minor (cm), right atrial minor (cm), mitral insufficiency (stage), tricuspid insufficiency (in meters per second), inferior vena cava (IVC) diameter (cm), and IVC collapse (+/–) were also measured. LV Hypertrophy was assessed using the echocardiographically determined LV mass index (LVMI) (g/m^2). The LV mass was calculated using the cubed formula and converted to the LVMI. All measurements were performed as described in relevant guidelines[14,15]. All values were the means of three measurements. The intra-class correlation coefficient was 0.90 (0.88-0.92) for all measurements.

Informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was received for this study from Ankara Keçiören Training and Research Hospital (decision no: 1101, date: 09.03.2016).

Statistical Analysis

Data were analyzed using SPSS (ver. 11.5 for Windows; SPSS Inc., Chicago, IL, USA). The normality of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Data were presented as mean ± standard deviation or median (ranges). Mean differences between groups were assessed using the Student's t test, and medians were compared using the Mann-Whitney U test. Nominal data were analyzed using the Pearson's chi-squared or Fisher's exact test. The optimal cut-off point for each clinical measurement for the discrimination of cases with and without ocular findings was determined by receiver operating characteristic (ROC) analyses. Areas under the curves were calculated to determine the maximum sum of sensitivity and specificity for significant findings. Sensitivity, specificity, positive predictive values (PPVs),

and negative predictive values (NPVs) were also calculated to determine the best cut-off point for each clinical measurement. The best predictor(s) for the discrimination of cases with and without ocular findings was determined by multiple logistic regression analyses using the backward likelihood ratio procedure. Adjusted Odds ratios (ORs), 95% confidence intervals (CIs), and Wald statistics were also calculated. All variables with p<0.25 in univariable analysis were entered into the multivariable model, along with all variables of known clinical importance. P values <0.05 were considered to be significant.

Results

The average ages in the two groups were 59.3±7.6 and 58.6±6.8 years (p=0.628). No difference was observed between the groups in the presence of HT, diabetes mellitus (DM), or smoking or in the glucose or hemoglobin concentration. The creatinine and low-density lipoprotein cholesterol levels, echocardiographic values, and presence of atrial fibrillation (AF) and pretibial edema differed between the groups. The mean duration of HF in the HFrEF group was 4 years (range, 1-8 years). The mean stage, according to the New York Heart Association (NYHA) classification, was 2 (range, 1-4). The main characteristics and echocardiographic data for the HFrEF and control groups are summarized in Table 1.

EVT was observed in 43 (21.5%) persons in the HFrEF group [right eye, n=23 patients; left eye, n=20 (both eyes, n=8)] and 15 (7.5%) persons in the control group [right eye, n=7; left eye, n=8 (both eyes, n=4); p<0.001]. Twenty-three (39%) female and 35 (60%) male subjects had EVT (p=0.817). No difference was observed in systolic or diastolic blood pressure between the groups with (n=58) and without (n=342) EVT (p=0.419 and p=0.728, respectively).

In the HFrEF group, the frequency of HT and median TAPSE level were significantly lower and the median HF duration, median RV E/E', LV E/E', LVMI and AF frequency were significantly higher in those with EVT than in those without EVT (all p<0.05). The characteristics

Table 1. Main characteristics and ecocardiographic measurements of heart failure and control groups

Main characteristics	HFrEF patients (n=200)	Control patients (n=200)	p value
Age (year) (n)	59.3±7.6	58.6±6.8	0.628
Gender (male/female) (n)	85/115	90/110	0.615
Systolic BP (mmHg)	128±19	124±16	0.084
Diastolic BP (mmHg)	75±14	70±12	0.349
Heart rate (bpm)	69 (40-130)	68 (45-130)	0.01
Body mass index (kg/m²)	26.6 (18-34)	27.03 (18-34)	0.24
Hypertension presence(n)	92 (52%)	85 (48%)	0.481
Tobacco use (n)	79 (48.5%)	84 (51.5%)	0.611
Diabetes (n)	49 (47.6%)	54 (52.4%)	0.567
LDL Cholesterol (mg/dL)	111 (56-243)	89 (64-216)	<0.001
Glucose (mg/dL)	91 (64-254)	87 (62-229)	0.568
Hemoglobin (gr/dL)	12 (6.5-15)	12.4 (6.9-19)	0.704
Creatinine (mg/dL)	1.0 (0.5-1.8)	0.79 (0.4-1.8)	<0.001
Echocardiography parameters			
Ejection fraction (%)	35 (20-45)	63 (50-66)	<0.001
LVDD (cm)	6.2 (4.8-7.2)	5.6 (4.5-6.4)	<0.001
RVDD (mid) (cm)	4.4 (3.4-5.4)	3.5 (2.8-4.1)	<0.001
LV mass index (g/m²)	91 (56-118)	102 (78-132)	0.001
LA minor diameter(cm)	4.1 (3.0-5.1)	3.4 (2.8-4.0)	<0.001
LAVI (mL/m²)	32 (27-47)	21 (15-36)	<0.001
RA minor diameter (cm)	4.6 (3.4-5.8)	3.3 (2.8-4.0)	<0.001
RV E/E'	10.1 (5.4-22)	5.2 (3-9.2)	<0.001
LV E/E'	11.3 (5.3-21.4)	8.2 (5.3-14.2)	<0.001
Pulmonary artery diameter (cm)	2.1 (1.7-2.6)	1.8 (1.3-2.5)	<0.001
SPAB (mmHg)	50 (30-74)	25 (22-35)	<0.001
IVC diameter (cm)	2 (1.7-2.4)	1.8(1.5-2.4)	<0.001
IVC collapse ≤%50 (+/-)	70/130	25/175	<0.001
TAPSE (cm/s)	1.5 (1-2.4)	1.9 (1.5-2.5)	<0.001
Tricuspid insufficiency (m/s)	3.2 (2.9-4.2)	2.6 (2-3.2)	<0.001
Mitral insufficiency (≥2) (+/-)	171/29	14/186	<0.001
Characteristics			
QRS duration (ms)	140 (110-170)	100 (70-120)	<0.001
AF presence (+/-)	34/166	-/200	<0.001
Coronary AD presence(n)	93 (49.2%)	96 (50.8%)	0.764
PTE presence (+/-)	26/174	11/189	0.007
ACEI usage (+/-)	138/62	135/65	0.83
Betablocker usage (+/-)	151/49	42/158	<0.001
Coumadin or NOAC usage (+/-)	28/172	-/200	<0.001
Antilipidemic usage (+/-)	20/180	30/170	0.173
Diuretic usage (+/-)	134/66	3/197	<0.001
Acetylsalicylic usage (+/-)	117/83	143/57	0.009

HFrEF: Heart failure reduced ejection fraction, Bpm: Beat per minute, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LH: Left ventricle hypertrophy, LA: Left atrium, RA: Right atrium, RV: Right ventricle, SPAB: Systolic pulmonary artery pressure, LAVI: Left atrium volume index, IVC: Inferior vena cava, AF: Atrial fibrillation, Coronary AD: Coronary artery disease, PTE: Pretibial edema, ACEI: Angiotensin-converting enzyme inhibitor, NOAC: New oral anticoagulant, LDL: Low density lipoprotein, n: Number, BP: Blood pressure, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity, TAPSE: Tricuspid annular plane systolic excursion

Table 2. Demographic and clinical characteristics of subjects in the groups with and without episcleral venous tortuosity in the heart failure group

Variables	Episcleral venous tortuosity		p value
	No (n=157)	Yes (n=43)	
Age (years)	59.4±8.0	59.2±7.3	0.859
Female, n (%)	52 (33.1%)	14 (32.6%)	0.945
HT, n (%)	78 (49.7%)	14 (32.6%)	**0.046**
Smoking, n (%)	60 (38.2%)	19 (44.2%)	0.478
DM, n (%)	43 (27.4%)	6 (14.0%)	0.070
EF % (min-max)	35 (20-45)	35 (20-45)	0.676
NYHA (stage)	2 (1-4)	2 (2-4)	0.173
HFrEF duration (years)	3 (1-8)	5 (2-8)	**<0.001**
QRS ms	140 (120-170)	135 (110-160)	0.594
Ischemia, n (%)	73 (46.5%)	20 (46.5%)	0.999
E/E' (RV) ratio	10 (5-17.8)	10.1 (5-22)	**0.003**
E/E' (LV) ratio	11.2 (5-18)	16 (7-22)	**<0.001**
TAPSE (cm)	1.5 (1-2.4)	1.3 (1.0-1.9)	**<0.001**
LV mass index (g/m²)	93 (74-110)	106 (96-118)	**<0.001**
LA minor (cm)	3.9 (3-4.9)	4.08 (3.2-5.1)	**0.015**
LAVI (mL/m²)	32.5 (24-42)	33.4 (25-48)	**0.038**
LVDD (cm)	6.2 (4.8-7.2)	6.2 (4.8-7.2)	0.818
RVD mid (cm)	4.4 (3.4-5.4)	4.4 (3.4-5.4)	0.712
LA minor (cm)	5.2 (2.8-6.5)	5.2 (3.2-6.5)	0.767
MI (stage)	2 (0-4)	2 (0-4)	0.280
TI (m/s)	3.2 (2.6-4.0)	3.2 (2.6-4.0)	0.542
SPAB (mmHg)	50 (30-74)	50 (30-74)	0.561
P_{art} diameter (cm)	2.1 (1.7-2.6)	2.1 (1.7-2.6)	0.433
RA_{min} diameter (cm)	3.9 (3.4-4.8)	4.09 (3.6-4.8)	0.025
IVC diameter (cm)	2.0 (1.7-2.4)	2.0 (1.7-2.4)	0.770
IVC collapse, n (%)	89 (56.7%)	22 (51.2%)	0.518
AF (+/-)	5 (3.2%)	29 (67.4%)	**<0.001**
PTE (+/-)	19 (12.1%)	8 (18.6%)	0.269

EF: Ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LV: Left ventricle, RV: Right ventricle, LA: Left atrium, LAVI: Left atrium volume index, MI: Mitral insufficiency, TI: Tricuspit insufficiency, SPAB: Systolic pulmonary artery pressure, Part: Pulmonary artery, RA_{min}: Right atrium minor, IVC: Inferior vena cava, AF: Atrial fibrillation, PTE: Pretibial edema, DM: Diabetes mellitus, NYHA: New York Heart Association, min: Minimum, max: Maximum, n: Number, HT: Hypertension, HFrEF: Heart failure reduced ejection fraction, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
Significant changes are shown as bold

of subjects in the HFrEF group with and without EVT are shown in Table 2.

The factors best distinguishing subjects with and without EVT in the HFrEF group were the LV lat E/E', presence of AF, and HF duration (p<0.01). After adjustment according to other possible risk factors, LV E/E' >15.25 increased the probability of EVT 25 times (95% CI, 6.677-97,145; p<0.001), the presence of AF increased the probability of EVT 23 times (95% CI, 6.320-89.352; p<0.001), and lengthy HF duration significantly increased the probability of EVT (OR=1.503; 95% CI, 1.118-2.020; p=0.007).

Areas below ROC curves were significant for the RV E/E', LV E/E', TAPSE, and LVMI in distinguishing subjects with and without EVT in the HFrEF group (p<0.05). The best cut-off points were: >12.2, >15.25, <1.45, and >106

Table 3. Area below the ROC curve and 95% confidence intervals for clinical measurements in distinguishing between the groups with and without episcleral venous tortuosity in the HFrEF group

Variables	AUC	%95 Confidence intervals	p value
E/E' (LV) ratio	0.845	0.765 – 0.925	**<0.001**
E/E' (RV) ratio	0.657	0.542 – 0.752	**0.003**
TAPSE (cm)	0.720	0.638 – 0.802	**<0.001**
LV mass index (g/m²)	0.675	0.578 - 0.771	**<0.001**
LA minor (cm)	0.575	0.420 - 0.609	0.067
LAVI (mL/m²)	0.545	0.415- 0.685	0.071
LVDD (cm)	0.511	0.412 - 0.611	0.820
$RVDD_{mid}$ (cm)	0.518	0.420 - 0.617	0.712
TI (m/s)	0.530	0.434 - 0.625	0.550
SPAB (mmHg)	0.529	0.432 - 0.625	0.566
P_{art} diameter (cm)	0.539	0.441 - 0.636	0.439
RA_{min} (cm)	0.512	0.414 - 0.610	0.808
IVC diameter (cm)	0.514	0.420 - 0.608	0.774

AUC: Area under the curve, TAPSE: Tricuspid annular plane systolic excursion, LV: Left ventricle, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LA: Left atrium, LAVI: Left atrium volume index, TI: Tricuspid insufficiency, SPAB: Systolic pulmonary artery pressure, P_{art}: Pulmonary artery diameter RA: Right atrium, IVC: Inferior vena cava, HFrEF: Heart failure with reduced ejection fraction, ROC: Receiver operating characteristic, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
Significant changes are shown as bold

g/m^2, respectively (sensitivity, 30.2%, 65.1%, 74.4%, and 53.5%; specificity, 97.4%, 96.8%, 62.4%, and 77.1%; PPV, 76.5%, 84.8%, 35.2%, and 39.0%; and NPV, 83.5%, 91.0%, 89.9%, and 85.8%, respectively). Data for the other characteristics are provided in Table 3.

In the control group, the tobacco usage frequency, DM frequency, median RV E/E', LV E/E', LVMI, and IVC collapse frequency were significantly higher in those with EVT than in those without EVT (p<0.05). The characteristics of subjects with and without EVT in the control group are shown in Table 4.

The factors best distinguishing subjects with and without EVT in the control group were the LV E/E', LVMI >115 g/m^2, and IVC collapse. ORs were determined for these factors. After adjustment according to other possible risk factors, the probability of EVT was increased significantly with an increased LV E/E' (OR=3.2; 95% CI, 1.522-6.789; Wald=9.369; p=0.002) LVMI >115 g/m^2 (OR=45.542; 95% CI, 3.631-571.161; Wald=8.758; p=0.003), and presence of IVC collapse (OR=11.323; 95% CI, 1.220-105.062; Wald=4.559; p=0.033).

Areas below ROC curves were significant for the RV E/E' (0.831; 95% CI, 0.672-0.989; p<0.001), LV E/E (0.864; 95% CI, 0.730-0.998; p<0.001), and LVMI >115 g/m^2 (0.910; 95% CI, 0.817 to >1.000; p<0.001). The best cut-off points for these indicators were >5.5, >10.5, and >115 g/m^2, respectively (sensitivity, all 73.3%; specificity, 94.6%, 100.0%, and 97.8%; PPV, 52.4%, 100.0%, and 73.3%; and NPV, 97.8%, 97.9%, and 97.8%, respectively).

Discussion

In this study, common findings in patients with EVT in both groups were increased LV E/E', RV E/E', and the LVMI. In the HFrEF group, EVT was associated with LV E/E' >15.25, RV E/E' >12.2, TAPSE <1.45 cm, and LVMI >106 g/m^2 (in order of decreasing sensitivity and specificity), presence of AF, and longer HF duration.

Right Ventricular E/E' Ratio

The mean systemic filling pressure (PMSF) is the pressure in the vascular system during circulatory arrest. Venous return is determined by the pressure gradient

Table 4. Demographic and clinical characteristics of subjects in the groups with and without episcleral venous tortuosity in the control group

Variables	Episcleral venous tortuosity		p value
	No (n=185)	Yes (n=15)	
Age (years)	57.7±7.6	59.5±6.0	0.373
Female, n (%)	79 (42.7%)	10 (66.7%)	0.072
HT, n (%)	76 (41.1%)	9 (60.0%)	0.154
Tobacco use, n (%)	73 (39.5%)	11 (73.3%)	**0.011**
DM, n (%)	45 (24.3%)	9 (60.0%)	**0.005**
EF (min-max)	63 (50-66)	65 (60-65)	0.110
QRS (ms)	100 (70-120)	100 (80-120)	0.676
Ischemia, n (%)	87 (47.0%)	9 (60.0%)	0.333
E/E' (RV) ratio	5.2 (3-6)	7 (3-9)	**<0.001**
E/E' (LV) ratio	8.1 (5-10)	11.2 (6-14)	**<0.001**
TAPSE (cm) (min-max)	1.9 (1.5-2.5)	1.9 (1.7-2.4)	0.993
LV mass index (g/m²)	102 (78-132)	115 (96-132)	**<0.001**
LVDD (cm) (min-max)	5.6 (4.5-6.4)	5.6 (4.8-6.4)	0.998
RVD$_{mid}$ diameter (cm)	3.5 (2.8-4.2)	3.5 (2.9-4.1)	0.680
LA minor (cm)	3.6 (2.8-4.1)	3.4 (2.8-4.1)	0.197
LAVI (mL/m²)	21.8 (14-29)	22.1 (12-32)	0.154
MI (grade)	0 (0-1)	0 (0-1)	0.319
TI (m/s) (min-max)	2.6 (2.3-2.6)	2.5 (2.3-2.6)	0.568
SPAB (mmHg)	25 (22-35)	25 (22-35)	0.106
P$_{art}$ diameter (cm)	1.8 (1.5-2.5)	1.8 (1.3-1.8)	0.079
RA minor diameter (cm)	3.3 (2.8-4.0)	3.3 (2.8-3.7)	0.968
IVC diameter (cm)	1.8 (1.5-2.4)	1.8 (1.5-2.2)	0.586
IVC collapse (+/-)	21 (11.4%)	7 (46.7%)	**<0.001**
AF (+/-)	-	-	-
PTE (+/-)	10 (%5.4)	1 (%6.7)	0.586

HT: Hypertension, DM: Diabetes mellitus, EF: Ejection fraction, LV: Left ventricle, LVDD: Left ventricle diastolic diameter, RVDD: Right ventricle diastolic diameter, LA: Left atrium, LAVI: Left atrium volume index, RA: Right atrium, MI: Mitral insufficiency, TI: Tricuspid insufficiency, SPAB: Systolic pulmonary artery pressure, P$_{art}$: Pulmonary artery, IVC: Inferior vena cava, AF: Atrial fibrillation, PTE: Pretibial edema, RV: Right ventricle, E/E': Ratio between early mitral inflow velocity and mitral annular early diastolic velocity, TAPSE: Tricuspid annular plane systolic excursion
Significant changes are shown as bold

between the PMSF and right atrial pressure. The RV E/E' ratio is related closely to the RV filling pressures. Irrespective of RV systolic function, RV E/E' ratios >6 have been found to have a sensitivity of 79% and a specificity of 73% for the mean right atrial pressure ≥10 mm Hg[16]. Right atrial pressure is approximately 0 mmHg, and an increase of 1 mmHg reduces venous return by 14%[17].

Left Ventricular E/E′ Ratio

LV E/E' ratio >10 reflects decreased ventricular filling (elevated LV filling pressure corresponding to a mean post capillary wedge pressure >15 mm Hg), with a sensitivity of 97% and a specificity of 78%[18]. In the case of LV E/E' >12, dilated cardiomyopathies with similar systolic function were found to be more symptomatic[19]. In our study, the NYHA stage and pretibial edema did not differ between patients with and without EVT in the HFrEF group. The frequency of AF was significantly higher in patients with EVT. Increased LV end diastolic pressure increases AF formation[20]. LV E/E' >15 has independent predictive value for cardiac mortality and HF[21]. It has also been reported to be a predictor of LV dilatation after infarction[22].

TAPSE

The prevalence of RV systolic dysfunction increases with decreasing LVEF. In hypertensive HF, 53% RV systolic dysfunction was found with TAPSE[23,24]. Decreased TAPSE was found to be an independent predictor of cardiovascular death in the general population[25]. In HFrEF and HFpEF, cardiac risk increases by two to three times in patients with decreased TAPSE[26]. In one study, the sensitivity and specificity of TAPSE ≤1.9 cm and E/E' ≥10.7 were found to be 66% and 77%, and 66% and 62%, respectively, for the prediction of weak 6-m walking test performance[27]. In our study, the sensitivity of TAPSE <1.45 cm in the detection of EVT in patients with HFrEF was 74%.

Left Ventricular Wall Thickness

In the HFrEF group, EVT was detected in cases in which LV wall thickness was lesser, and the LV and RV filling parameter (E/E') values were greater than in the control group (cut-offs, LV E/E' >10.5, RV E/E' >5.5, and LVMI >115 g/m²). These findings suggest that in addition to the relatively low filling pressures, a greater LVMI increase was associated with the emergence of EVT in the control group.

Left Ventricular Mass Index

In the HFrEF group, EVT was detected in cases in which LV wall thickness was lesser, and the LV and RV filling parameter (E/E') values were greater than in the control group (cut-offs, LV E/E' >10.5, RV E/E' >5.5, and LVMI >115 g/m²). These findings suggest that in addition to the relatively low filling pressures, a greater LVMI increase was associated with the emergence of EVT in the control group. According to LaPlace's law, wall thickness increases in response to pressure overload in HT. The detection of EVT in patients with lower in the HFrEF group compared to those in the control group (LV mass, 106 vs 115 g/m²) may be due to the decrease in time after the increase in wall thickness as a result of chronic pressure increase[28].

Left Atrial Volume Index

An increase in left atrial diameter and LAVI suggest chronic severe LV filling characteristics. An increase in LV mass may be related to myocardial fibrosis and myocardial structural changes leading to HF. Among subjects in the HFrEF group with EVT (n=43), AF was present in 29 (67.4%) patients, whereas it was present in five (3.2%) patients without EVT (p<0.001)[29]. This finding reinforces the idea that an increase in LV end diastolic pressure may be an additive factor in the pathogenesis of EVT.

Whereas cigarette smoking and DM seemed to be effective predictors of the presence of tortuosity in the control group, HT was a more frequent indicator in the HFrEF group. HT-dependent wall stiffness can increase LAVI by increasing LV end-diastolic pressures[30]. Negative effects of tobacco and DM on the endothelium may contribute to tortuosity[31].

Vessel Wall Stress and Extracellular Matrix

As the volume is returned to the systemic circulation by the heart, the returning volume is equal to the stroke volume[32]. The volume stretching the vessel wall is called the stress volume. It accounts for 25-30% of the total blood volume in circulation with minimal sympathetic tone[33]. Vessel wall stress is the ratio of the transmural pressure difference and the inner wall diameter multiplied by the wall thickness. As the diameter increases and the thickness decreases during vasodilatation, circular tension stress is greater than vasoconstriction status[34].

A chronic increase in venous pressure was determined to be sufficient for venous re-modelling by experimental venous ligation. Hydrostatic pressure and wall stress were increased proximal to the ligation, and wide tortuous vein development was observed after 2 days[35]. In varicose vein re-modelling, changes in the extracellular matrix are the main factor and ensure increased essential rigidity to resist the chronic increase in wall stress[36]. Adaptation in smooth muscle cells and activities of matrix metalloproteinase (MMP) also change according to the duration and level of tension in the veins. MMP also plays a leading role in cardiac re-modelling[37]. MMP-9 upregulation is the common finding of terminal HF[38]. Similarly, MMP-9 activity was increased in human varicose veins and in rat veins with excess transmural pressure[39].

Study Limitations

As the differentiation of episcleral and arterial veins was performed using a method based on commonly known observations, precision may not have been attained in some patients. If the interrogation angle is >20° on TDIs, the velocity may be less measured than exact values. The fact that episcleral vessel diameters could not be measured is also a limitation.

Conclusion

The presence of tortuosity in episcleral veins in patients with HFrEF seems to be correlated with RV lateral E/E' (>12.2), LV lateral E/E' (>15.25), TAPSE (<1.45 cm), LVMI (>106 g/m²), AF, and the duration of long-term HF.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was received for this study from Ankara Keçiören Training and Research Hospital (decision no: 1101, date: 09.03.2016).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

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