Longitudinal, circumferential and radial systolic left ventricular function in patients with heart failure and preserved ejection fraction

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Introduction. Heart failure with preserved left ventricular ejection fraction (HFPEF) is an epidemiologically serious disease. Noninvasive diagnosis of HFPEF remains challenging. The current diagnosis is based on evidence of diastolic dysfunction, albeit systolic dysfunction is also present but not included in the diagnostic algorithm. The aim of this study was to analyze the longitudinal (long), circumferential (circ) and radial (rad) component of systolic left ventricular (LV) function in patients with exertional dyspnea of unexplained etiology and normal left ventricular ejection fraction (LVEF).

Methods. One hundred and twenty-two patients with exertional dyspnea of unexplained etiology and normal LVEF and 21 healthy controls, underwent echocardiography examination at rest and at the end of symptom-limited exercise. We analysed the longitudinal, circumferential and radial deformation of myocardium using two dimensional speckle tracking echocardiography in all subjects.

Results. Patients with exertional dyspnea and preserved LVEF were divided into group A1 (46 patients meeting the criteria for the diagnosis HFPEF) and group A2 (76 patients without HFPEF). Group A1 had significantly worse longitudinal and circumferential systolic LV function than group A2. Subjects in group A1 compared to group A2 showed significantly different strain rates during atrial contraction (SR A), circ and ratio of peak early trans-mitral flow velocity (E) and strain rate E wave (E / SR E) circ. Multivariate logistic regression analysis showed that the SR parameter A circ is an independent predictor of HFPEF (odds ratio 0.550, 95% confidence interval: 0.370 – 0.817, *P* value 0.003).

Conclusion. Longitudinal and circumferential LV deformation was significantly more impaired in patients with HFPEF than in patients with exertional dyspnea without HFPEF. In patients with exertional dyspnea and normal LVEF, the value of SRA circ appears to be a significant and independent predictor of HFPEF. This parameter may, in the future complement the diagnostic algorithm for HFPEF.

Key words: Speckle tracking echocardiography, exertional dyspnea, longitudinal, radial and circumferential left ventricular systolic function, heart failure with preserved ejection fraction

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INTRODUCTION

Heart failure with preserved left ventricular ejection fraction (HFPEF) is a common disease with a morbidity and mortality not significantly different from heart failure with depressed left ventricular function (HFrEF) (ref.¹⁻³). Patients with HFPEF have diastolic and systolic heart failure despite normal left ventricular ejection fraction (LVEF) (ref.⁴⁻⁷). A noninvasive diagnosis of HFPEF is based on the evidence of diastolic dysfunction but the presence of systolic dysfunction is not currently included in the diagnostic algorithm⁴. Evaluation of deformation (strain, S) and strain rate (strain rate, SR) using 2D speckle tracking echocardiography quantifies the longitudinal, circumferential and radial component of LV systolic function. There is substantial evidence for impaired single deformation parameters in patients with HFPEF (ref.⁸⁻¹⁰). Some authors stress the longitudinal dysfunction⁹, others emphasise both longitudinal and circumferential¹¹ and some report impaired longitudinal, radial and circumfer-

ential left ventricular systolic function⁸. Discrepant results may be due to varying degrees of LV systolic dysfunction in patients with HFPEF in the populations studied. As shown by Paulus et al.² a noninvasive diagnosis of HFPEF remains challenging with the necessity to combine a number of parameters to build a definite diagnosis. The aim of this study was hence to assess the longitudinal, radial and circumferential LV function in patients with exertional dyspnea and normal LVEF and to determine new key diagnostic parameters for HFPEF.

METHODS

Study cohort

Patients with chronic exertional dyspnea and normal LVEF (> 50%) in sinus rhythm were included in the study. Subjects were selected from patients examined at I. Department of Internal Medicine/Cardioangiology of St. Anne's University Hospital. All patients underwent

elective invasive coronary angiography and those with significant coronary artery disease were excluded. In total, 122 patients (group A1 and group A2) and 21 healthy controls were involved in the study. Group A1 ($n = 46$) included patients meeting the criteria for the diagnosis HFPEF. Group A2 ($n = 76$) included patients without HFPEF. HFPEF was defined according to the criteria established by Paulus², which defines the value of other parameters used in the diagnosis HFPEF. Also patients with exercise-induced HFPEF were enrolled in group A1. The criteria were defined as increase in the ratio of peak early transmitral flow velocity (E) and peak early diastolic annular velocity (E') - $E / E' > 15$ or $E / E' > 13$ while measuring on septal annulus¹². The third group consisted of healthy controls (group B, $n = 21$). All subjects underwent complete laboratory blood testing, spirometry, coronary angiography, electrocardiogram, chest X-ray, echocardiography and bicycle ergometry.

Exclusion criteria were as follows: presence of significant stenosis of coronary artery (a value up to 40%), congenital heart disease, valvular heart disease, cardiomyopathy, pulmonary disease, liver and renal insufficiency and anemia. Healthy controls had no risk factors (hypertension, diabetes mellitus or hypolipoproteinemia) for developing HFPEF. Informed written consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the St Anne's University hospital institutional Review Board.

Laboratory testing

The following serum parameters were measured: renal parameters (urea, creatinine, clearance of creatinine), ions, liver function parameters (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin), blood count and N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) in serum as a marker of heart failure.

Coronary angiography and spirometry

An assessment of coronary artery disease was performed by CT angiography or invasive coronary angiography.

Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) and their ratio were measured by standard spirometry. A value below 70% for any of the three parameters was considered pathological, and these patients were excluded from the study.

Echocardiography

Echocardiography was performed by the ultrasound systems Vivid 7 and 9 (GE, Milwaukee, WI, USA with M3S and M5S probes). All subjects were examined at rest and after physical exercise. In resting conditions, four-chamber (4-CH), two-chamber (2-CH) apical projection, short parasternal projection (PSAX) at the level of the mitral valve, papillary muscles and the apex and long parasternal (PLAX) projection were recorded. From the apical 4CH view, the Doppler assessment of flow velocities on the mitral and aortic valves, and also in the pul-

monary vein was obtained. LVEF was determined using Simpson's method from the 4-CH and 2-CH projection. Tissue Doppler of mitral annular motion was recorded in the septal and lateral position. Left ventricular dimensions were measured as recommended by the European Association of Echocardiography¹³. The moment of aortic valve closure (AVC) was set at the end-systole on the aortic valve Doppler flow for the calculation of endsystolic strains by speckle tracking assessment. Exercise echocardiography was performed immediately after physical exercise in the same body position as the rest examination. Measurements were always performed within 90 seconds following exercise. All data were saved and digitally analyzed using the system EchoPAC PC versions 6.1.0 and 108.1.5. (GE Medical Systems, Horten, Norway).

Bicycle ergometry

Bicycle ergometry was performed for quantification of exertional dyspnea and assessment of LV diastolic function. A bicycle ergometer (Kettler X7S, Siemens, Germany) was used for the examination. The examination was performed in sitting position. The initial workload was set at 25 W and was increased every two minutes by 25 W up to subject tolerance. The examination was discontinued when shortness of breath or fatigue of the lower limbs occurred. Maximal exercise tolerance was measured in Metabolic Equivalents units (METs) as recommended by the American College of Sports Medicine¹⁴.

2D strain and strain rate assessment

The offline evaluation was performed in two basic acquired projections. Circumferential and radial deformations were evaluated in PSAX projection at the level of papillary muscles while the longitudinal deformation was assessed in the apical 4-CH projection. Four to five cardiac cycles were recorded in each projection during echocardiographic examination. Two to three cycles of myocardial contraction were assessed from each record, the first and last cycle were not analyzed. The evaluation was done manually by placing tracing lines of endocardium in endsystole. The software detected automatically the area of evaluation and myocardium was divided into 6 segments, which were analyzed using speckle tracking. Global longitudinal peak systolic (syst strain) and endsystolic strain (endsys strain) and also the value of longitudinal strain rate were assessed from the 4-CH projection. Peak systolic strain was determined as the maximum value of strain in systole, endsystolic strain was determined on the deformation curve at the moment of AVC. Circumferential endsystolic and systolic strain and strain rate (SR) and endsys radial strain (strain endsys rad) were determined from PSAX projection at the level of papillary muscles. SR rad values and peak systolic strain rad were not determined because the radial evaluation software did not create global curve. The curves were not evaluated, in case of poor image quality in given projections.

Statistical analysis

Basic clinical characteristics and parameters of conventional and speckle tracking echocardiography were

analyzed and compared between the groups. To describe the basic data standard statistical measurements were used: absolute and relative frequencies for categorical variables, the median with the lower (25%) and upper (75%) quartile for continuous variables. Most variables did not present a normal distribution (Shapiro-Wilk test), and therefore non-parametric tests were used. For comparison of all three groups (A1, A2 and B) in continuous parameters, the Kruskal-Wallis test was conducted. For a detailed comparison between the groups, Mann Whitney test with Bonferroni correction for multiple comparisons was performed. A chi-square test was applied to compare the groups of categorical data. Correlation of parameters SR circ A and E / E' was evaluated by calculating Spearman's correlation coefficients. Univariate and multivariate regression analysis were performed to determine the predictors of HFPEF and relation of predictors. Predictors were searched for group A1 (patients with HFPEF) towards the group A2 (patients without HFPEF) as a reference. Various multivariate models were used for parameters with potential predictive power (providing at least $P < 0.1$ in univariate logistic regression). Logistic regression coefficients and standard errors (SE) and P -values are presented together with the Odds Ratios (OR) and their 95% confidence intervals. Receiver operating characteristic curves (ROC) were constructed to

identify the sensitivity, specificity and the area under the curve (AUC) and optimal cutoff values of independent predictors of the presence HFPEF. Results with P -values < 0.05 were considered statistically significant.

RESULTS

Basic demographic characteristics of the study population are summarized in Table 1. Patients in group A were significantly older, used more diuretics and beta-blockers than patients in group A2, however there were no significant differences in ACE inhibitor usage between the groups (Table 1). Serum creatinine levels were generally lower in the control group compared to group A1 and A2.

Systolic blood pressure was significantly higher in patients (groups A1,2) versus controls.

Parameters of conventional and speckle tracking echocardiography are shown in Table 2. Patients in group A1 differed from group A2 in echocardiographic parameters important for diagnosing HFPEF, such as left atrial volume index (Lavi), deceleration time of the E wave (DT), E', E / E'. Furthermore, patients in group A1 had significantly lower absolute values of long peak systolic and end-systolic strain and SR A circ in comparison to group A2. On the other hand ratio E / SR E circ was significantly

Table 1. Baseline clinical parameters.

	Group A1	Group A2	Group B	<i>P</i>
Demographics				
Age (years)	68.5 (7.95) ^a	63.3 (7.90) ^b	63.1 (7.17) ^b	0.001
Males	14 (30.4 %)	20 (26.3 %)	8 (38.1 %)	0.566
Hypertension (n)	40 (87.0 %)	68 (89.5 %)	NA	0.381
Diabetes (n)	15 (32.6 %)	19 (25.0 %)	NA	0.413
Hyperlipidaemia (n)	29 (63.0 %)	35 (46.1 %)	NA	0.093
Obesity (n)	23 (50.0 %)	27 (35.5 %)	5 (23.8 %)	0.092
BMI (kg/m ²)	29.5 (4.51)	28.9 (4.91)	27.4 (3.83)	0.186
Medication				
Diuretics (n)	27 (58.7 %) ^a	32 (42.1 %) ^b	NA	0.010
Beta-blockers (n)	34 (73.9 %) ^a	36 (47.4 %) ^b	NA	0.006
Hypolipidaemics (n)	30 (65.2 %)	40 (52.6 %)	NA	0.228
ACEi/AT II (n)	33 (71.7 %)	50 (65.8 %)	NA	0.630
Aspirin (n)	14 (30.4 %)	35 (46.1 %)	NA	0.068
Laboratory				
Creatinine in serum (μmol/L)	83.7 (16.58) ^a	80.8 (16.59) ^a	72.6 (10.40) ^b	0.035
NT-proBNP (ng/L)	446.3 (422.12) ^a	122.5 (88.86) ^b	99.4 (83.94) ^b	< 0.001
Vital signs				
Systolic BP (mmHg)	135.9 (19.67) ^a	131.3 (15.09) ^a	122.9 (11.02) ^b	0.036
Diastolic BP (mmHg)	84.7 (9.91)	83.8 (8.45)	81.0 (5.15)	0.214
Heart rate (bpm)	71.5 (12.59) ^a	74.0 (12.00) ^{a,b}	79.5 (10.60) ^b	0.028
NYHA	2.5 (0.50) ^a	2.1 (0.33) ^b	NA	< 0.001

P: statistical test comparing groups A1, A2, B

^{a,b,c}: marks of mutual statistically significant differences between the compared variants A1, A2, B

(i.e.: ^a for group A1, ^b for group A2 and ^c for group B in a specific row signifies there is a difference between groups A1 and A2, and A1 and B, but no difference between A2 and B.)

NA: not available, BP: blood pressure, BMI: body mass index, ACEi: angiotensin-converting enzyme inhibitor, AT II: angiotensin II receptor blocker, NT-proBNP: N-terminal pro B-type natriuretic peptide

higher in group A2. Additionally, there was a significant difference between the A1 and A2 group in long and circ SR, circ endsystolic parameters, peak systolic strain and in ratio E / E' SR long. Due to a poor echocardiography image quality, long S and SR were not evaluated in 6 patients (4.9%) and circ S and SR S in 17 patients (13.9%).

Importantly, the multivariate analysis revealed that SR A circ, E' parameters and N-terminal B-type natriuretic peptide (NT-proBNP) were independent predictors of HFPEF (Table 3 and 4). An increase in the E' parameter of 1 reduced the chance of inclusion of the patient in group A1 (patients with HFPEF) by approximately 63% (0.37x) against inclusion in group A2. NT-proBNP and E' are already used in the diagnosis of HFPEF. Thus we were interested in the outcome of SR A circ. An increase of the parameter SR A circ in 0.1 decreased the chance to

include patients in group A1 (patients with HFPEF) by about half (0.55x) against inclusion in group A2.

In the ROC analysis, SR A circ the cut-off value was set at 0.7 with a specificity of 70.9% and sensitivity of 64%. Correlation of SR A circ and E / E' ratio, the value of rs was - 0.252 at $P = 0.024$.

DISCUSSION

In this study, we assessed the longitudinal, circumferential and radial components of LV systolic deformation by 2D speckle tracking echocardiography. The main aim of the study was to determine the potential predictor value of systolic deformation parameters in the diagnosis of HFPEF. We showed that the longitudinal and circumfer-

Table 2. Echocardiographic conventional and speckle tracking parameters.

	Group A1	Group A2	Group B	<i>P</i>
Conventional echocardiography				
EDVi (mL/m ²)	46.8 (11.54)	45.0 (8.75)	44.3 (8.39)	0.528
ESVi (mL/m ²)	16.8 (5.89)	15.1 (4.29)	13.8 (3.94)	0.154
LV EF (%)	64.7 (6.35) ^a	66.6 (5.96) ^{a,b}	69.5 (3.91) ^b	0.008
LV mass index (g/m ²)	103.5 (26.65) ^a	83.5 (17.15) ^b	84.2 (17.70) ^b	< 0.001
LAVi (mL/m ²)	35.4 (9.36) ^a	28.0 (6.48) ^b	28.2 (5.33) ^b	< 0.001
Ard-Ad (ms)	-12.0 (20.17)	-15.1 (17.30)	-9.5 (17.87)	0.534
E (cm/s)	79.6 (18.08) ^a	72.2 (15.47) ^b	70.8 (11.64) ^b	0.026
A (cm/s)	89.1 (16.98) ^a	77.7 (13.07) ^b	72.6 (10.64) ^b	< 0.001
DT (ms)	191.8 (40.38) ^a	179.9 (28.55) ^{a,b}	166.6 (21.18) ^b	0.013
E/A	0.9 (0.26)	0.9 (0.22)	1.0 (0.13)	0.235
E' (cm/s)	7.6 (2.13) ^a	9.1 (1.93) ^b	9.6 (1.29) ^b	< 0.001
E/E'	10.9 (2.64) ^a	8.2 (1.93) ^b	7.5 (1.65) ^b	< 0.001
A' (cm/s)	9.5 (1.95) ^a	10.8 (2.15) ^b	11.0 (1.63) ^b	0.005
E'/A'	0.8 (0.24)	0.9 (0.25)	0.9 (0.20)	0.055
S' (cm/s)	7.3 (1.09) ^a	8.8 (1.48) ^b	8.7 (1.11) ^b	< 0.001
Speckle tracking				
SR S long (L/s)	-0.9 (0.21) ^a	-1.0 (0.22) ^a	-1.2 (0.24) ^b	0.002
SR E long (L/s)	1.1 (0.47) ^a	1.2 (0.39) ^a	1.4 (0.30) ^b	0.013
SR A long (L/s)	0.8 (0.33) ^a	0.9 (0.25) ^{a,b}	1.0 (0.26) ^b	0.048
Syst. Strain long (%)	-16.1 (5.56) ^a	-18.5 (3.71) ^b	-20.7 (3.26) ^c	0.001
Endsys. Strain long (%)	-15.9 (5.63) ^a	-18.3 (3.72) ^b	-20.7 (3.26) ^c	0.001
SR S circ (L/s)	-1.0 (0.32) ^a	-1.2 (0.31) ^b	-1.2 (0.28) ^b	0.021
SR E circ (L/s)	1.2 (0.36) ^a	1.4 (0.50) ^b	1.5 (0.41) ^b	0.020
SR A circ (L/s)	0.7 (0.28) ^a	1.0 (0.33) ^b	0.9 (0.25) ^b	0.001
Syst strain circ (%)	-17.8 (5.57) ^a	-20.8 (4.37) ^b	-20.5 (4.65) ^{a,b}	0.034
Endsys strain circ (%)	-17.7 (5.65) ^a	-20.5 (4.46) ^b	-20.1 (4.38) ^b	0.049
E/SR E long	84.2 (43.72) ^a	71.0 (27.21) ^a	55.6 (12.42) ^b	0.018
E/SR E circ	76.3 (26.15) ^a	57.0 (22.67) ^b	52.5 (17.00) ^b	0.001
Endsys. Strain rad (%)	38.6 (14.14)	42.0 (16.52)	36.3 (18.89)	0.398

^{a,b,c}: marks of mutual statistically significant differences between the compared variants A1, A2, B

(i.e.: ^a for group A1, ^b for group A2 and ^c for group B in a specific row signifies there is a difference between groups A1 and A2, and A1 and B, but no difference between A2 and B.)

iA: peak late transmitral flow velocity, A': peak late diastolic annular velocity, DT: deceleration time of E wave, E: peak early transmitral flow velocity, E': peak early diastolic annular velocity, S': peak systolic annular velocity

EDVi: end-diastolic volume index, ESVi: end-systolic volume index, EF: ejection fraction, LAVi: left atrial volume index, LV: left ventricular, Ad: duration of late transmitral filling wave, Ard: duration of atrial reversal flow

SR: strain rate, long: longitudinal, circ: circumferential, rad: radial, syst: systolic, endsyst: endsystolic

ential systolic left ventricular function was significantly reduced in patients with HFPEF. HFPEF patients had significantly lower values of longitudinal peak systolic, end-systolic strain and SR A circ in comparison to group A2 (patients with exertional dyspnoea). On the other hand ratio E / SR E circ was significantly higher in HFPEF patients than in the patients without HFPEF.

Previous research is not consistent in terms of impairment in single deformation parameters in patients with HFPEF (ref.¹⁵). Animal model have shown that decrease in the longitudinal strain is a sensitive marker of HFPEF progression¹⁶. Moreover, patients with peak global longitudinal strain ≤ 15 have greater morbidity and mortality in both HFPEF and HFREF (ref.¹⁵). Speckle tracking echocardiography can be used as an indicator of treat-

ment outcomes in patients with heart failure¹⁵. The longitudinal component of systolic myocardial function is often affected before development of circumferential or radial impairment⁸. Other work indicates deterioration of circumferential and longitudinal deformation at the end of systole in patients with HFPEF compared to healthy subjects^{10,17}.

As shown by Cioffi et al.¹⁸ circumferential and longitudinal dysfunction and its combination are present in up to one quarter of patients with HFPEF while radial systolic LV function remains preserved^{11,19}. This is consistent with our results as we found no significant difference in radial function between patients with HFPEF and healthy controls. This may be explained by the frequent occurrence of left ventricular hypertrophy in patients with hyper-

Table 3. Echocardiographic conventional and speckle tracking parameters, selected demographic parameters, median and quartile in addition.

Parameter	Group A1 Median (25% percentile-75% percentile)	Group A2 Median (25% percentile-75% percentile)	Group B Median (25% percentile-75% percentile)
A (cm/s)	88.00 (76.00 - 105.00)	76.00 (68.00 - 89.00)	73.00 (67.00 - 79.00)
A' (cm/s)	9.60 (8.00 - 11.00)	10.60 (9.30 - 11.75)	11.20 (9.70 - 12.50)
Ard-Ad (ms)	-10.00 (-28.00; -1.00)	-14.00 (-25.00; -3.00)	-11.00 (-20.00 - 5.00)
BMI (kg/m ²)	29.50 (26.00 - 33.00)	28.00 (26.00 - 31.00)	28.00 (25.00 - 29.00)
DT (ms)	188.00 (166.50 - 209.50)	176.00 (158.00 - 198.00)	161.00 (151.00 - 188.00)
E (cm/s)	78.00 (67.00 - 91.00)	71.00 (62.00 - 81.50)	70.00 (62.00 - 79.00)
E/A	0.82 (0.68 - 1.10)	0.92 (0.81 - 1.08)	0.99 (0.92 - 1.03)
E/E'	10.45 (9.20 - 12.40)	7.85 (6.85 - 9.25)	7.20 (6.30 - 8.80)
E/SR E circ	70.00 (56.92 - 87.27)	53.13 (43.57 - 64.00)	46.92 (40.50 - 62.31)
E/SR E long	65.08 (55.79 - 107.50)	65.00 (51.67 - 82.73)	53.85 (47.65 - 58.18)
E' (cm/s)	7.15 (6.30 - 8.70)	9.05 (7.85 - 10.55)	9.30 (8.80 - 10.30)
E'/A'	0.74 (0.59 - 0.89)	0.86 (0.67 - 1.03)	0.86 (0.78 - 0.99)
EDVi (mL/m ²)	45.00 (39.00 - 55.00)	43.50 (38.00 - 51.50)	45.00 (41.00 - 49.00)
Endsys strain circ (%)	-18.00 (-21.70 -14.20)	-20.50 (-23.20; -17.50)	-21.20 (-23.20; -17.30)
Endsys. Strain long (%)	-16.50 (-20.10; -12.00)	-18.25 (-21.40; -15.35)	-20.90 (-23.60; -19.00)
Endsys. Strain rad (%)	36.50 (30.60 - 45.20)	41.50 (30.80 - 52.40)	33.50 (22.90 - 46.80)
ESVi (mL/m ²)	16.00 (12.00 - 21.00)	15.00 (12.00 - 18.00)	14.00 (11.00 - 16.00)
Creatinine in serum (μ mol/L)	83.50 (71.00 - 98.00)	83.00 (67.00 - 93.00)	74.00 (67.50 - 79.50)
LAVi (mL/m ²)	36.50 (31.00 - 41.00)	28.00 (24.00 - 33.50)	28.00 (24.00 - 32.00)
LV EF (%)	64.00 (60.00 - 69.00)	66.00 (63.00 - 71.00)	70.00 (67.00 - 73.00)
LV mass index (g/m ²)	99.50 (85.00 - 118.00)	82.00 (70.00 - 97.50)	91.00 (72.00 - 94.00)
NT-proBNP (ng/L)	268.00 (178.00 - 681.00)	96.65 (67.00 - 150.75)	84.70 (41.00 - 120.00)
NYHA	2.00 (2.00 - 3.00)	2.00 (2.00 - 2.00)	NA
S' (cm/s)	7.45 (6.70 - 7.90)	8.55 (7.60 - 9.70)	8.70 (7.70 - 9.20)
SR A circ (L/s)	0.60 (0.50 - 0.90)	0.90 (0.70 - 1.20)	0.90 (0.80 - 1.10)
SR A long (L/s)	0.70 (0.50 - 1.00)	0.90 (0.70 - 1.10)	1.00 (0.80 - 1.20)
SR E circ (L/s)	1.10 (0.90 - 1.30)	1.40 (1.10 - 1.70)	1.30 (1.20 - 1.90)
SR E long (L/s)	1.00 (0.60 - 1.30)	1.20 (0.80 - 1.35)	1.40 (1.10 - 1.60)
SR S circ (L/s)	-1.00 (-1.30; -0.80)	-1.20 (-1.40; -1.00)	-1.30 (-1.40; -1.00)
SR S long (L/s)	-0.90 (-1.10; -0.80)	-1.05 (-1.20; -0.80)	-1.20 (-1.30; -1.10)
Syst strain circ (%)	-18.00 (-21.70; -14.20)	-20.80 (-23.20; -17.90)	-21.30 (-23.50; -17.40)
Syst. Strain long (%)	-16.80 (-20.20; -12.00)	-18.25 (-21.65; -15.75)	-20.90 (-23.80; -19.10)
Heart rate (bpm)	70.50 (62.00 - 79.00)	73.50 (65.00 - 83.50)	81.00 (72.00 - 84.00)
Diastolic BP (mmHg)	82.50 (80.00 - 90.00)	80.00 (80.00 - 90.00)	80.00 (80.00 - 85.00)
Systolic BP (mmHg)	130.00 (120.00 - 150.00)	130.00 (120.00 - 140.00)	120.00 (120.00 - 130.00)
Age (years)	69.50 (62.00 - 73.00)	64.00 (58.50 - 69.00)	64.00 (59.00 - 66.00)

tension or HFPEF (ref.¹¹). Our results indicate, that the study population was in the middle stage of the disease as circumferential and longitudinal systolic function was already impaired, whereas the radial function remained preserved. The lack of consistency in studies on HFPEF may be explained by various phases of HFPEF captured in different studies. According to Petersen et al.¹⁹, the value of longitudinal, radial and circumferential strain correlates with the patient's exercise tolerance.

Two-dimensional speckle tracking echocardiography is an imaging method for measuring myocardial deformation parameters "strain (S) and strain rate (SR)." These parameters describe systolic and diastolic myocardial function in three mutually perpendicular planes^{21,22}. Speckle tracking echocardiography imaging may be used for early detection of regional systolic and diastolic LV dysfunction^{8,23,24} in patients with preserved LVEF and cardiovascular risk factors. It also may be used for detection of a variety of heart pathologies reflected in myocardial function such as ischemia, valvular disease or abnormal substances for example proteins deposition.

The endocardium is sensitive to ischemia and is preferentially affected by fibrosis, which increases with age even in clinically asymptomatic individuals^{25,26}. The endocardium consists mainly of longitudinal fibers. Therefore it is not surprising that the longitudinal strain gradually decreases with age²¹. Longitudinal strain also decreases with diminished myocardial perfusion²⁷, with isolated LV non-compaction cardiomyopathy²⁸ and cardiac amyloidosis²⁹. Impaired longitudinal systolic strain is associated with an increased risk of serious cardiovascular disease and atrial fibrillation³⁰.

In the present study we focused on the assessment of LV systolic function using 2D speckle tracking echocardiography. Diagnosis of early phase of HFPEF is often difficult. Sometimes even the combination of non-invasive tests is not sufficient to detect all patients with HFPEF (ref.³¹) and exercise testing is necessary to diagnose the disease^{32,33}. In patients with HFPEF a deterioration of longitudinal systolic function detected by 2D speckle tracking echocardiography is a far more accurate indicator of abnormal LV systolic function than reduced systolic mitral annular velocity evaluated by the Doppler echocardiography⁴. A new predictive factor is needed to help in the diagnosis of early HFPEF stages; according to our research SR A circ parameter seems to be a good example. The lower the value of the SR A circ parameter, the higher was the probability of HFPEF diagnosis. The negative correlation of SR A circ and E / E' shown in our study demonstrated a relationship between SR A circ and LV filling pressures. The independent predictive value of SR A circ in diagnosis of HFPEF needs to be confirmed by other studies. Whether a positive SR A circ parameter can complement the existing Doppler parameters for a diagnosis HFPEF needs to be determined.

SRA circ parameter reflects the function of the left atrium. It is well established that left atrial dysfunction is associated with the development of HFPEF. An abnormal strain of the left atrium in patients with sinus rhythm may be associated with clinical manifestations of HFPEF.

Table 4. Asociation of potencial predictive factors with heart failure with preserved ejection fraction, Univariate logistic regression.

Parameters included in model	Unit	Odds Ratio (95% CI)	P
A (cm/s)	5	1.05 (1.02 - 1.08)	<0.001
A'(cm/s)	1	0.74 (0.60 - 0.92)	0.005
E (cm/s)	5	1.03 (1.00 - 1.05)	0.021
E/E'	1	1.72 (1.38 - 2.15)	<0.001
E/SR E circ	1	1.03 (1.01 - 1.05)	0.004
E' (cm/s)	1	0.68 (0.55 - 0.84)	<0.001
E'/A'	0.1	0.16 (0.03 - 0.90)	0.037
Endsys strain circ (%)	0.1	1.13 (1.02 - 1.25)	0.023
Endsys strain long (%)	0.1	1.13 (1.02 - 1.24)	0.014
LAVi (mL/m ²)	5	1.13 (1.07 - 1.20)	<0.001
LVmass index (g/m ²)	5	1.05 (1.02 - 1.07)	<0.001
NT-proBNP (ng/L)	20	1.01 (1.00 - 1.01)	<0.001
NYHA	1	6.07 (2.45 - 15.03)	<0.001
S' (cm/s)	1	0.39 (0.26 - 0.59)	<0.001
SR A circ (L/s)	0.1	0.03 (0.00 - 0.24)	<0.001
SR E circ (L/s)	0.1	0.23 (0.07 - 0.80)	0.02
SR S circ (L/s)	0.1	8.71 (1.48 - 51.26)	0.017
SR S long (L/s)	0.1	18.12 (2.29 - 143.35)	0.006
Syst strain circ (%)	0.1	1.14 (1.02 - 1.27)	0.016
Syst strain long (%)	0.1	1.13 (1.02 - 1.24)	0.017
Age (years)	5	1.09 (1.03 - 1.15)	0.001

Table 5. Asociation of potencial predictive factors with heart failure with preserved ejection fraction, Multivariate logistic regression.

Parameter	Unit	P	Odds Ratio (95% CI)
NT-proBNP (ng/L)	20	0.001	1.208 (1.078 - 1.355)
E'(cm/s)	1	0.003	0.368 (0.192 - 0.708)
SR A circ (L/s)	0.1	0.003	0.550 (0.370 - 0.817)

A decreased strain of the left atrium and left ventricle was recently described in patients with HFPEF (ref.³⁴⁻³⁶). The function of the left atrium (using strain rate) is highly predictive of a final diagnosis of heart failure. The dysfunction of the left atrium may be one mechanisms for the initial development of symptoms in patients with HFPEF (ref.³⁴). A deterioration of the left atrium strain and hence left atrium dysfunction is associated with increased left ventricle end-diastolic pressure and increased NT-proBNP levels³⁷.

Study limitations

Several limitations of the study need to be acknowledged. Firstly, global longitudinal, radial and circumferential S and SR were evaluated only in one echocardiographic projection, it would be more accurate to assess them using 3D echocardiography³⁸. The evaluation software limited us to assess the global peak systolic strain rad and rad SR. For this reason, we do not have the results to compare with the longitudinal and circumferential components. Further, the results may have been

influenced by the different stages of disease in the study population used.

CONCLUSION

The parameters quantifying circumferential and longitudinal deformation are significantly reduced in patients with HFPEF compared to patients with exertional dyspnea without HFPEF. In patients with exertional dyspnea having normal LVEF SR A circ value seems to be a significant and independent predictive factor of HFPEF. SR A circ may be in combination with other parameters used in the diagnosis of HFPEF.

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REFERENCES

- Borlaug BA, Walter JP. Heart Failure With Preserved Ejection Fraction: Pathophysiology, Diagnosis and Treatment. *Eur Heart J* 2011;32:670-9.
- Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How To Diagnose Diastolic Heart Failure: A Consensus Statement on the Diagnosis of Heart Failure and Echocardiography Associations of The European Society of Cardiology. *Eur Heart J* 2007;28:2539-50.
- MacIver DH, Townsend M. A novel mechanism of heart failure with normal ejection fraction. *Heart* 2008;94:446-9.
- McMurray J, Pfeffer MA. New Therapeutic Options in Congestive Heart Failure: Part II. *Circulation* 2002;105:2223-8.
- Mishiro Y, Oki T, Yamada H, Onose Y, Matsuoka M, Tabata T, Wakatsuki T, Ito S. Use of angiotensin II stress pulsed tissue Doppler imaging to evaluate regional left ventricular contractility in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2000;13:1065-73.
- Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? *Heart* 2002;87:121-5.
- Yu CM, Lin H, Yang H, Fung JW, Ho PY, Sanderson JE. Progression of systolic abnormalities in patient with "isolated" diastolic heart failure and diastolic dysfunction. *Circulation* 2002;105:1195-201.
- Mizuguchi Q, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Oki T. The functional role of longitudinal, circumferential and radial myocardial deformation for regulating the early impairment of left ventricular contraction and relaxation in patients with cardiovascular risk factors: A study with Two-dimensional strain imaging. *J Am Soc Echocardiogr* 2008;21(10):1138-44. doi:10.1016/j.echo.2008.07.016.
- Koshizuka R, Ishizu T, Kameda Y, Kawamura R, Seo Y, Aonuma K. Longitudinal Strain Impairment as a Marker of the Progression of Heart Failure with Preserved Ejection Fraction in a Rat Model. *J Am Soc Echocardiogr* 2013;26:316-23.
- Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD; PARAMOUNT Investigators. Impaired Systolic Function by Strain Imaging in Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol* 2014;63:447-56.
- Van Heerebeek L, Borbely A, Niessen HWM, Bronzwaer JG, van der Velden J, Stienen GJ, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006;113:1966-73.
- Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of left ventricular filling pressure with exercise. *J Am Coll Cardiol* 2006;47:1891-900.
- Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. Or filter your current search Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography 1989;2(5):358-67.
- Swain DP, Leutholtz BC. Exercise prescription. A case Study Approach to the ACSM Guidelines. 2nd edition. Human Kinetics 2007.
- Stamper MR, Mann DL, Nguyen JS, Cota F, Colmenares C, Dokainish H. Speckle Stain Echocardiography Predicts Outcome in Patients with Heart Failure with both Depressed and Preserved Left Ventricular Ejection Fraction. *Echocardiography* 2014;32(1):72-8. doi: 10.1111/echo.12613.
- Koshizuka R, Ishizu T, Kameda Y, Kawamura R, Seo Y, Aonuma K. Longitudinal strain impairment as a marker of the progression of heart failure with preserved ejection fraction in a rat model. *J Am Soc Echocardiogr* 2013;26:316-23.
- Yip GW-K, Zhang Q, Xie J-M, Liang YJ, Liu YM, Yan B, Lam YY, Yu CM. Resting global and regional left ventricular contractility in patients with heart failure and normal ejection fraction: insights from speckle-tracking echocardiography. *Heart* 2011;97:287-94.
- Cioffi G, Senni M, Tarantini L, Faggiano P, Rossi A, Stefanelli C, Russo TE, Alessandro S, Furlanello F, de Simone G. Analysis of Circumferential and Longitudinal Left Ventricular Systolic Function in Patients With Non-Ischemic Chronic Heart Failure and Preserved Ejection Fraction (from the CARRY-IN-HFpEF Study). *Am J Cardiol* 2012;109:383-9.
- Sengupta PP, Korinek J, Belohlavek M, Narula J, Vannan MA, Jahangir A, Khandheria BK. Left ventricular structure and function. Basic science for cardiac imaging. *J Am Coll Cardiol* 2006;48:1988-2001.
- Petersen JW, Nazir TF, Lee L, Garvan CS, Karimi A. Speckle tracking echocardiography-determined measures of global and regional left ventricular function correlate with functional capacity in patients with and without preserved ejection fraction. *Cardiovascular ultrasound* 2013;11:20(<http://cardiovascularultrasound.com/content/11/1/20>).
- Onose Y, Oki T, Mishiro Y, Yamada H, Abe M, Manabe K, Kageji Y, Tabata T, Wakatsuki T, Ito S. Influence of aging on systolic left ventricular wall motion velocities along the long and short axes in clinically normal patients determined by pulsed tissue Doppler imaging. *J Am Soc Echocardiogr* 1999;12:921-6.
- Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-9.
- Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: clinical applications. *Heart* 2010;96:2032-40.
- Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: basic principles. *Heart* 2010;96:716-22.
- Gerstenblith G, Frederiksen J, Yin FC, Fortuin NJ, Lakatta EG, Weisfeldt ML. Echocardiographic assessment of a normal adult aging population. *Circulation* 1977;56:273-8.
- Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1: myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;56:786-94.
- Moore CC, McVeigh ER, Zerhouni EA. Noninvasive measurement of three-dimensional myocardial deformation with tagged magnetic

- resonance imaging during graded local ischemia. *J Cardiovasc Magn Reson* 1999;1:207-22.
28. Bellavia D, Michelena HI, Martinez M, Pellikka PA, Bruce CJ, Connolly HM, Villarraga HR, Veress G, Oh JK, Miller FA. Speckle myocardial imaging modalities for early detection of myocardial impairment in isolated left ventricular non-compaction. *Heart* 2010;96:440-7.
29. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography in both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;98:1442-8.
30. Su H-M, Lin T-H, Hsu P-Ch, Lee WH, Chu CY, Lee CS, Voon WC, Lai WT, Sheu SH. Global left ventricular longitudinal systolic strain as a major predictor of cardiovascular events in patients with atrial fibrillation. *Heart* 2013;99:1588-96.
31. Patel H, Hayward C, di Mario C. Heart Failure with Preserved Ejection Fraction: Are the Current Definitions Too Strict? *Heart* 2014;doi:10.1136/heartjnl-2014-306118.64.
32. Meluzin J, Sitar J, Kristek J, Prosecky R, Pesl M, Podrouzková H, Soska V, Panovsky R, Dusek L. The role of exercise echocardiography in the diagnostics of heart failure with normal left ventricular ejection fraction. *European Journal of Echocardiography* 2011;12:591-602.
34. Donal E, Thebault CH, Lund LH, Kervio G, Reynaud A, Simon T, Drouet E, Nonotte E, Linde C, Daubert JC. Heart failure with a preserved ejection fraction additive value of an exercise stress echocardiography. *European Heart Journal Cardiovascular Imaging* 2012;13:656-65.
35. Sanchis L, Gabrielli L, Andrea R, Falces C, Duchateau N, Perez-Villa F, Bijns B, Sitges M. Left atrial dysfunction relates to symptom onset in patients with heart failure and preserved left ventricular ejection fraction. *Eur Heart Jour - Cardiovascular Imaging* 2015;16:62-7.
36. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009;2:10-5.
37. Morris DA, Gailani M, Vaz Porez A, Blaschke F, Dietz R, Haverkamp W, Ozcelik C. Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. *J Am Soc Echocardiogr* 2011;24:651-62.
38. Kurt M, Tanboga IH, Aksakal E, Kaya A, Isik T, Ekinci M, Bilen E. Relation of left ventricular end-diastolic pressure and N-terminal pro-brain natriuretic peptide level with left atrial deformation parameters. *Eur Heart Jour* 2012;13:524-30.
39. Luo X-X, Fang F, Lee AP-W, Sun JP, Li S, Zhang ZH, Sanderson JE, Kwong JS, Zhang Q, Wang J, Yu CM. What can three-dimensional speckle-tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? *International Journal of Cardiology* 2014;172:132-7.