Left Ventricular Diastolic Function: Comparison of Slow Coronary Flow Phenomenon and Left Ventricular Hypertrophy in the Absence of Obstructive Coronary Disease

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Abstract

Background

An interplay of myocardial structural abnormalities and coronary arterial dysfunction underlies the worsening left ventricular compliance. The conventionally used angina drugs have demonstrated a beneficial effect on both angina and coronary flow in cases with microvascular dysfunction and non-obstructive coronary disease. Despite that, vasoactive therapy only partially affects diastolic function in this patient population.

Purpose

This retrospective study was planned to evaluate the association of myocardial mass, delayed epicardial coronary flow, and vasoactive drugs with parameters of diastolic function in two cohorts with preserved left ventricular function and non-obstructive coronary disease in patients with slow coronary flow phenomenon (SCFP) and patients with the hypertensive disease and left ventricular hypertrophy.

Material and methods

The epicardial coronary flow was evaluated in 48 patients with unstable angina in the absence of coronary stenosis >50%, by applying the methods of corrected thrombolysis in myocardial infraction frame count (cTFC). The abnormalities in the left ventricular function were assessed by echocardiography using PW-Doppler of the diastolic mitral inflow and tissue Doppler imaging. Twenty-one (43.8%) patients were diagnosed with SCFP, and twelve patients (25%) had slow epicardial coronary flow, hypertensive disease, and ventricular hypertrophy (SF_{LVH}). The remaining 15 (31.3%) were patients with ventricular hypertrophy, hypertension, and non-delayed epicardial coronary flow (NF_{LVH}).

Results

The patients with SF_{LVH} showed reduced peak early diastolic lateral mitral annular velocity (e'_L) when compared to SCFP (7.1±1.9cm/s vs 8.6±2.1 cm/s, p=0.045) and NF_{LVH} (7.1±1.9 cm/s vs 8.7±1.8 cm/s, p=0.018). A borderline significant difference was observed for the peak early diastolic septal mitral annular velocity ($e'S$) between the patients with SF_{LVH} and SCFP (7.0±1.3 cm/s vs 8.3±2.1 cm/s, p=0.057). The ratio of mitral diastolic inflow velocity to early diastolic velocity of the mitral annulus (E/e') in the SF_{LVH} group was a tendency higher than E/e' of the patients with SCFP (9.8±3.1 vs. 8.2±2.1, p=0.084) and NF_{LVH} (9.8±3.1 vs. 7.8±1.5, p=0.051) .In the group with left ventricular hypertrophy, E/e' >10 was more frequently observed in patients with a marked delay in the epicardial flow (33.1 ± 13.1 frames vs. 25.4 ± 11.8 frames, p=0.011) and higher left ventricular mass (146.9 ± 17.7 g/m2 vs. 126.1 ± 121.5 g/m2, p=0.027).

Conclusions

Patients with microvascular angina represent a diverse population. The echocardiographic parameters of left ventricular relaxation (e') and end-diastolic pressure (E/e') are abnormally altered in the population with left ventricular hypertrophy compared to SCFP. The delayed epicardial flow further impairs diastolic function in hypertensive patients with hypertrophy and non-obstructive coronary disease.

Introduction

Studies in cohorts with heart failure with preserved ejection fraction (HFpEF) in the absence of coronary atherosclerosis have observed a stiffer left ventricle and reduced longitudinal systolic function in patients with pronounced epicardial coronary flow abnormalities [1,2]. In addition, the results of prior experimental and animal models have indicated that an interplay of myocardial structural abnormalities and coronary arterial dysfunction underlied the worsening left ventricular compliance [3].

Major classes of conventionally used angina drugs have demonstrated beneficial effects on ischemia and coronary flow in cases with microvascular dysfunction and non-obstructive coronary disease. Nevertheless, the medications only partially affect diastolic function in this patient population [4-7].

Thus, this retrospective study was designed to evaluate the association of myocardial mass, delayed epicardial coronary flow, and vasoactive drugs with parameters of diastolic function in two cohorts with preserved left ventricular function and non-obstructive coronary disease. Specifically, the two cohorts included patients with slow coronary flow phenomenon (SCFP) and patients with hypertensive disease and left ventricular hypertrophy.

Materials And Methods

This research consisted of a single-center, cohort, retrospective study. The study group consisted of 48 patients. Only patients diagnosed with non-obstructive coronary disease (defined as the absence of coronary stenosis of >50% at the time of quantitative coronary angiography) were included in the study. The patients were admitted with unstable angina to the University Hospital 'Alexandrovska' in Sofia between 2006 and 2008. Thirty-nine patients (70%) underwent symptom-limited exercise stress electrocardiographic tests on the modified Bruce protocol in this clinic prior to angiography [8]. For the remainder of the group, the angiographic study was performed because of angina refractory to optimal anti-ischemic treatment. Twenty-one (43.8%) patients were diagnosed with SCFP, and twelve patients (25%) had slow epicardial coronary flow and ventricular hypertrophy associated with hypertension. Furthermore, fifteen patients (31.3%) had ventricular hypertrophy subsequent to hypertension and normal epicardial coronary flow. The patients with coronary stenoses no greater than 40% and without LVH comprised the SCFP group. Hypertension was defined as clinically measured systolic blood pressure (BP) values ≥140 mmHg and/or diastolic BP values ≥90 mmHg [9]. The diagnosis of hypertension was based on the results of prior multiple BP measurements, which were taken on separate occasions over a period of time and included at least three visits and at least two BP measurements per visit [10]. The diagnosis was made after BP assessment over a maximal period of several months for patients with only slightly elevated BP with large spontaneous variations in BP [10]. Both patients with only clinically measured hypertension and only home-based BP elevation were also diagnosed as hypertensive patients. The diagnostic procedures also included medical history for systemic hypertension controlled by the intake of BP-lowering drugs and instrumental investigations (continuous 24-hour ambulatory BP monitoring).

Epicardial coronary flow was evaluated by using the corrected thrombolysis in myocardial infarction (TIMI) frame count (cTFC) method [11]. This method represented a quantitative measurement of epicardial coronary flow velocity. Specifically, it was defined by the number of cineframes required for contrast to first obtain standardized distal coronary landmarks [11]. The following distal landmark branches were used for the analysis: the distal bifurcation of the left anterior descending branch (LAD); in the circumflex system, the distal bifurcation of the segment with the longest total distance; and in the right coronary artery (RCA), the first branch of the posterolateral artery [11]. This discrepancy in the length of the LAD and the other coronary arteries was corrected or adjusted by dividing the TIMI frame count of the LAD by a factor of 1.7 [11].

All of the patients underwent standard echocardiography (including 2D, M-mode, spectral, color Doppler techniques, and tissue Doppler imaging [TDI]). The echocardiography was performed in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [12,13]. The LV ejection fraction (EF) was measured using the Simpson method. Values of LVEF lower than 50% were the sole criterion for defining left ventricular systolic dysfunction.

The following diastolic function indices were determined: early (E-wave) and late (A-wave) maximal rates of the left ventricular diastolic filling (diastolic mitral valve inflow); the time of attenuation of the E-wave (deceleration time [DT]); and peak early diastolic mitral annular septal (e's) and lateral (e'L) velocities. Left ventricular hypertrophy (LVH) was defined as a thickness of the ventricular septum (IVS) or the posterior wall (LVPW) of the left ventricle ≥12 mm on echocardiography, as well as myocardial mass greater than 95 g/m2 for the female patients and greater than 115 g/m2 for the male patients. The myocardial mass was calculated by using the linear method:

0.8x1.04 x [(EDD-IVS-LVPW)3 - EDD3]+0.6 grams;

EDD was the dimension of the left ventricle at end-diastole. The myocardial mass of each patient was divided by the body surface area.

In our study report, we used the phrases 'left ventricular hypertrophy subsequent to systemic hypertension' or 'left ventricular hypertrophy related to systemic hypertension' to address this specific alteration in heart structure as part of the complex pathologies that are induced by systemic hypertension and included the term 'hypertensive heart disease.'

The exclusion criteria for the study included previous coronary revascularization procedures, thrombolytic therapy for myocardial infarction, left ventricular systolic dysfunction (LVEF <50%), wall motion abnormalities at rest, cardiomyopathy, coronary aneurysm, ectasia and fistula, valve disease, acute or chronic inflammatory disease, recent fracture or surgical procedures, and any type of shock and neoplastic disease. In addition, cases with suboptimal angiographic or echocardiographic imaging study results were also excluded from the study.

All of the patients signed written informed consent forms for all diagnostic tests. This retrospective study was approved by the Ethics Committee of University Hospital 'Alexandrovska' (incoming No of approval: 298/Oct 31, 2018) and complied with the Declaration of Helsinki.

The analysis of the data was performed by using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as counts and percentages, and continuous variables were presented as the mean and SD. Categorical variables were analyzed via the chi-squared test or Fisher's exact test. The normality of the continuous variables was tested by using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Depending on the results of Levene's test, the variables with a normal distribution were compared with the Student's t-test or the Welch test. The nonparametric variables were analyzed with the Mann-Whitney test. One-way ANOVA was applied to evaluate the difference between three continuous variables. Associations with α <0.05 were considered to be statistically significant.

Results

The three groups did not significantly differ with respect to cardiovascular risk profile, systolic function parameters, or the type of vasoactive therapy that was used. The patients with SF_{LVH} and NF_{LVH} more frequently used (although insignificantly) diuretics and less frequently used antiplatelet therapy than those with SCFP (Table 1).

Patients	SCFP n, %	SF$_{LVH}$ n,%	NF$_{LVH}$ n,%	P-value
Age	56.3±8.9	59.1±8.5	57.5±9	0.704
Men	10 (47.6%)	4 (33.3%)	1 (6.7%)	NS
Women	11 (52.4%)	8 (66.7%)	14 (93.3%)	NS
Hypertension	17 (81%)	12 (100%)	15 (100%)	NS
Dyslipidemia	17 (81%)	12 (100%)	10 (80%)	NS
Diabetes mellitus	3 (14.3%)	6 (50%)	3 (20%)	NS
Smoking	3 (14.3%)	1 (8.3%)	4 (26.4%)	NS
BMI, kg/m^2	28.5±3.7	29.5±3.7	28.7±3.2	0.752
EDVI, ml/m^2	62±14	62±15	72±20	0.144
ESVI, ml/m^2	19±4	20±7	23±7	0.110
EF, %	68±4	71±7	68±7	0.352
IVS, mm	10.4±0.8	12.4±1.1	12.4±1.8	<0.0001
LVPW, mm	10.3±0.9	12±1	12.2±1.4	<0.0001
Positive exercise ECG	9 (56.3%)	5 (50%)	8 (61.5%)	NS
β-blocker	11 (55%)	4 (33.3%)	6 (40%)	
β-blocker+CCB±nitrate	5 (25%)	5 (41.7%)	7 (46.7%)	NS
β-blocker+nitrate	4 (20%)	3 (25%)	2 (13.3%)	
ACE-I/ARB	11 (52.4%)	11 (91.7%)	14 (93.3%)	NS
Statin	14 (66.7%)	6 (50%)	8 (53.3%)	NS
Aspirin/Clopidogrel	20 (95%)	12 (100%)	11 (73.3%)	0.042
Diuretics	4 (19%)	7 (58.3%)	10 (66.7%)	NS

TABLE 1: Clinical profile and echocardiographic, angiographic data.

SCFP: Slow coronary flow phenomenon; SF$_{LVH}$: Left ventricular hypertrophy and slow coronary flow secondary to hypertension; NF$_{LVH}$: Left ventricular hypertrophy and non-delayed coronary flow; DM: Diabetes mellitus; EDVI, ESVI: Indices of end-diastolic and end-systolic volume; EF: Ejection fraction; IVS: Thickness of ventricular septum; LVPW: Thickness of left ventricular posterior wall; ACE-I/ARB: Angiotensin-converting enzyme inhibitor/Receptor antagonist.

The patients with LV hypertrophy and delayed epicardial flow showed reduced lateral early diastolic mitral annular velocity (e'L) when compared to SCFP and NF$_{LVH}$. A borderline significant difference was observed for the septal early diastolic mitral annular velocity (e's) of SF$_{LVH}$ and SCFP. Moreover, the filling pressures (E/e') in the SF$_{LVH}$ tended to be higher than the E/e' of the patients with SCFP and NF $_{LVH}$ (Figure 1, Tables 2-3).

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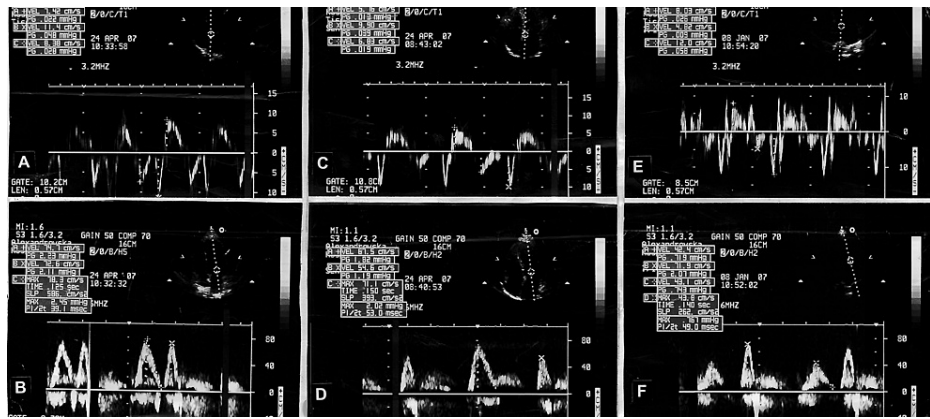
4 of 12

FIGURE 1: Peak early septal diastolic velocity of mitral annulus: e's and ratio of the peak early diastolic mitral valve inflow velocity to peak early septal diastolic velocity of mitral annulus: E/e's.

A-B: Patient with SCFP: e'_s: 7.4 cm/s; E: 75 cm/s; E/e'_s: 10.6;

C-D: Patient with NF_{LVH}: e'_s: 5.8 cm/s; E: 67 cm/s; E/e'_s: 10.1;

E-F: Patient with SF_{LVH}: e'_s: 4.6 cm/s; E: 72 cm/s; E/e'_s: 15.7.

Patients	SCFP	SF_{LVH}	P-value
Depic mm	3.7±1.0	4.1±0.8	0.137
cTFC frames	36.2±13.4	37.9±11.9	0.447
E cm/s	75.7±30.0	64.3±12.8	0.267
A cm/s	54.1±20.5	54.5±21.4	0.835
DT msec	190.1±41	182.7±30	0.815
E/A	1.2±0.8	1.8±1.6	0.358
e'_L cm/s	8.6±2.1	7.1±1.9	0.045
e's cm/s	8.3±2.1	7.0±1.3	0.057
E/e'	8.2±2.1	9.8±3.1	0.084
Myocardial mass, gr/m^2	89.5±13.2	127.2±21.3	<0.0001

TABLE 2: Indices of diastolic function and coronary flow: difference of SCFP and SFLVH.

Depic: Epicardial coronary diameter; cTFC: Corrected TIMI frame count; E- and A-wave: Peak early and late rates of diastolic left ventricular filling; DT: Time of decrease in early diastolic left ventricular filling; e'_L and e'_S: Peak early diastolic lateral and septal mitral annular velocities; E/e': Ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity.

Patients	SF$_{LVH}$	NF$_{LVH}$	P-value
Depic, mm	4.1±0.8	3.3±0.7	0.057
cTFC, frames	37.9±11.7	20±4.1	<0.0001
E, cm/s	64.3±12.8	59.1±12.6	0.274
A, cm/s	54.5±21.4	56.4±20	0.814
DT, msec	182.7±30.4	180.7±36.5	0.884
E/A	1.8±1.6	1.3±1.0	0.695
e'$_L$, cm/s	7.1±1.9	8.7±1.8	0.018
e's, cm/s	7.0±1.3	7.7±1.8	0.148
E/e'	9.8±3.1	7.8±1.5	0.051
Myocardial mass, gr/m^2	127.2±21.3	133.2±24.4	0.506

TABLE 3: Indices of diastolic function in patients with hypertrophy with and without delayed coronary flow.

SF$_{LVH}$: Slow coronary flow associated with left ventricular hypertrophy secondary to hypertension; NF$_{LVH}$: Patients with left ventricular hypertrophy and non-delayed coronary flow; Depic: Epicardial coronary diameter; cTFC: Corrected TIMI frame count; E-wave and A-wave: Peak early and late rates of diastolic left ventricular filling; DT: Time of decrease in early diastolic left ventricular filling; e'$_L$ and e'$_S$: Peak early diastolic lateral and septal velocities of the mitral annulus; E/e': Ratio of early diastolic mitral inflow velocity to early diastolic velocity of the mitral annulus.

Increased early mitral inflow velocity and reduced longitudinal septal function (e's) corresponded to the presence of left ventricular hypertrophy in the entire non-obstructive disease cohort (Table 4).

Patients	SCFP (n=21)	LVH (n=27)	P-value
Depic, mm	3.7±1.0	3.7±0.8	0.906
cTFC, frames	36.2±12.3	28±12.3	0.025
E, cm/s	74.7±30	61.4±12.2	0.042
A, cm/s	56.1±20.5	55.5±20.2	0.926
DT, msec	190.1±41	181.6±33.3	0.444
E/A	1.3±0.8	1.5±1.3	0.714
e'$_L$, cm/s	8.6±2.1	8.0±2.0	0.284
e's, cm/s	8.3±2.1	7.4±1.6	0.079
E/e'	8.2±2.1	8.7±2.6	0.501
Myocardial mass, gr/m^2	89.5±13.2	130.6±22.9	<0.0001

TABLE 4: Mitral inflow and tissue Doppler echocardiography in diastole patients with SCFP compared to patients with left ventricular hypertrophy.

Depic: Epicardial coronary diameter; cTFC: Corrected TIMI frame count; E- and A-wave: Peak early and late rates of diastolic left ventricular filling; DT: Time of decrease in early diastolic left ventricular filling; e'L and e'S: Peak early diastolic lateral and septal mitral annular velocities; E/e': Ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity.

Diastolic function parameters were similar in the slow coronary flow patients and those with left ventricular hypertrophy with the normal flow (Table 5).

Patients	SCFP+SF$_{LVH}$ (n=27)	NF$_{LVH}$ (n=15)	P-value
Depic, mm	3.8±1.0	3.4±0.7	0.090
cTFC, frames	36.8±12	20±4.1	<0.0001
E, cm/s	70.9±25.4	59.1±11.6	0.092
A, cm/s	55.5±20.5	56.4±20	0.887
DT, msec	187.5±87.3	180.7±36.5	0.569
E/A	1.5±1.2	1.3±1.0	0.688
e'$_L$, cm/s	8.1±2.1	8.7±1.8	0.331
e's, cm/s	7.9±1.9	7.7±1.8	0.456
E/e'	8.8±2.6	7.8±1.5	0..153
Myocardial mass, gr/m^2	103.2±24.6	133.2±24.4	<0.0001

TABLE 5: Diastolic function parameters in patients with delayed epicardial coronary flow with and without hypertrophy: a comparison with left ventricular hypertrophy and normal flow.

Depic: Epicardial coronary diameter; cTFC: Corrected TIMI frame count; E- and A-wave: Peak early and late rates of diastolic left ventricular filling; DT: Time of decrease in early diastolic left ventricular filling; e'L and e'S: Peak early diastolic lateral and septal mitral annular velocities; E/e': Ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity.

In the group with SCFP and the entire study group, E/e' in the highest tertile (E/e'>10) was not dependent on either coronary flow velocity or myocardial mass. In the presence of left ventricular hypertrophy, E/e'>10 was more frequently observed in patients with a marked delay in epicardial flow and higher left ventricular mass. In the group with delayed epicardial flow (including SCFP and patients with slow flow in the presence of LVH), E/e' was significantly related only to the elevated myocardial mass (Table 6).

SCFP	E/e'<10 (n=14)	E/e'>10 (n=7)	P-value
Depic, mm	3.7±1.2	3.5±0.6	0.574
cTFC, frames	36.7±11.9	35±14.4	0.787
Myocardial mass, gr/m^2	86.1±19.4	97.8±14.9	0.064
LVH (SF$_{LVH}$+NF$_{LVH}$)	**E/e'<10 (n=19)**	**E/e'>10 (n=8)**	**P-value**
Depic, mm	3.6±0.8	3.8±0.9	0.640
cTFC, frames	25.4±11.8	33.1±13.1	0.011
Myocardial mass, gr/m^2	126.1±21.5	146.9±17.7	0.027
SCFP + SF$_{LVH}$	**E/e'<10 (n=21)**	**E/e'>10 (n=12)**	**P-value**
Depic, mm	3.9±1.1	3.8±0.8	0.800
cTFC, frames	37.1±11.9	36.4±12.5	0.887
Myocardial mass, gr/m^2	95.3±18.4	116.9±28.6	0.031
All patients	**E/e'<10 (n=33)**	**E/e'>10 (n=15)**	**P-value**
Depic, mm	3.7±1.0	3.7±0.8	0.983
cTFC, frames	30.3±12.7	35±13	0.262
Myocardial mass, gr/m^2	109.7±27.3	120.2 ± 29.8	0.257

TABLE 6: E/e' relation with the myocardial mass and coronary flow.

SCFP: Slow coronary flow phenomenon; SF$_{LVH}$: Slow coronary flow associated with left ventricular hypertrophy secondary to hypertension; NF$_{LVH}$: Patients with left ventricular hypertrophy and non-delayed coronary flow; Depic: Epicardial coronary diameter; cTFC: Corrected TIMI frame count.

The majority of patients were using bisoprolol or metoprolol (92.9%) as monotherapy or combined with one of the following calcium channel blockers: amlodipine, felodipine, or lercanidipine (97.6%). None of the patients used first-generation dihydropyridines (e.g., nifedipine). One patient was on therapy with oral verapamil hydrochloride; the other two patients were on therapy with a first-generation β-blocker (atenolol). The β-blocker of the third generation (nebivolol) was included in the treatment regimen along with the CCB of one participant. The intake of diuretics was not associated with a lower preload (E/e' no diuretics vs. E/e' diuretics 8.7±2.5 [n=27] vs. 8.2±2.2 [n=21], p=0.557). The difference in diastolic function parameters in relation to the vasoactive therapy used in the groups with SCFP and patients with LVH could not be discussed due to the small sample size. However, the early-diastolic septal and lateral mitral annular velocities seemed to be substantially reduced. E/e' was higher in the patients with LVH on therapy with β-blocker with nitrate compared to these variables in the LVH subgroup taking β-blocker alone or combined with a calcium blocker (Tables 7-8).

SCFP	β-blocker (n=11)	β-blocker+CCB±nitrate (n=5)	β-blocker+nitrate (n=5)	P-value
Depic, mm	3.4±0.8	4.0±1.1	4.2±1.5	NS
cTFC, frames	33.7±13.4	45.2±12.3	30.8±3.3	NS
E, cm/s	73.6±8.0	67.4±22	85.3±63.3	NS
A, cm/s	52.6±17.5	67.8±28.9	53±23.6	NS
DT, sec	191±52.2	206±23	177.5±14.4	NS
E/A	1.3±0.9	0.88±0.16	1.3±1.1	NS
e'_L , cm/s	8.8±2.3	7.8±0.8	9.1±2.8	NS
e's, cm/s	8.7±2.2	7±1.9	8.8±2.1	NS
E/e'	8.2±2.4	8.8±1.7	7.3±2.5	NS
Myocardial mass, gr/m^2	90.7±14.9	95±10	82±10.4	NS
SBP, mmHg	132.1±18.7	133.8±13.8	126.7±9.8	NS
DBP, mmHg	82±10.8	72.5±12.6	76.2±23.6	NS
HR, beat/min	70.2±6.3	65.8±7.8	76.2±23.6	NS

TABLE 7: Vasoactive therapy and indices of diastolic function in the group with SCFP.

SCFP: Slow coronary flow phenomenon; Depic: Epicardial coronary diameter; cTFC: Corrected TIMI frame count; E-wave and A-wave: Peak early and late rates of diastolic left ventricular filling; DT: Time of decrease in early diastolic left ventricular filling; e'_L and e'_S: Peak early diastolic lateral and septal velocities of mitral annulus; E/e': Ratio of early diastolic mitral inflow to early diastolic mitral annular velocity; IVS: Thickness of ventricular septum; LVPW: Thickness of left ventricular posterior wall; SBP: Systolic blood pressure; DBP: Diastolic pressure; HR: Heart rate.

SCFP	β-blocker (n=11)	β-blocker+CCB±nitrate (n=5)	β-blocker+nitrate (n=5)	P-value

LVH	β-blocker (n=10)	β-blocker+CCB±nitrate (n=12)	β-blocker+nitrate (n=5)	P-value
Depic, mm	3.8±0.9	3.6±0.9	3.6±0.6	NS
cTFC, frames	24.2±6.7	30.1±16.3	30.4±9.3	NS
E, cm/s	63.7±12.1	59.1±11.3	62.4±16.2	NS
A, cm/s	54.9±16.2	55.3±23.7	57.4±22.0	NS
DT, sec	177.2±33	183.2±37.3	186±30.3	NS
E/A	1.3±0.8	1.7±1.6	1.4±1.2	NS
e'_L, cm/s	8.6±2.0	8.2±1.8	6.3±1.8	NS
e's, cm/s	7.5±1.5	7.9±1.5	6±1.4	NS
E/e'	9.0±2.5	7.7±1.6	10.4±3.7	NS
Myocardial mass, gr/m^2	124.7±23	127.3±18.8	150±25.3	NS
SBP, mmHg	132±16.4	130.2±3.9	147.4±17.1	NS
DBP, mmHg	85±4.1	82.5 ± 5.0	88.2 ± 28.9	NS
HR, beat/min	74.2±8.7	69.4±4.7	68±5.0	NS

TABLE 8: Vasoactive therapy and indices of diastolic function in patients with left ventricular hypertrophy: delayed and normal epicardial coronary flow.

LVH: Patients with left ventricular hypertrophy; Depic: Epicardial coronary diameter; cTFC: Corrected TIMI frame count; E-wave and A-wave: Peak early and late rates of diastolic left ventricular filling; DT: Time of decrease in early diastolic left ventricular filling; e'_L and e'_S: Early diastolic velocities of left ventricular wall and septum; E/e': Index of left ventricular preload; IVS: Thickness of ventricular septum; LVPW: Thickness of left ventricular posterior wall; SBP: Systolic blood pressure; DBP: Diastolic pressure; HR: Heart rate.

Discussion

Our results add to the current knowledge-specific data concerning the difference in diastolic function and the correlates of E/e' between two patient groups without obstructive coronary disease: SCFP and patients with hypertension, ventricular hypertrophy, and variably delayed epicardial coronary flow.

The two major determinants of left ventricular filling are ventricular relaxation and effective chamber compliance. Ventricular relaxation is a complex energy-dependent process during which the contractile elements are deactivated and return to their precontraction length [14]. The relaxation in the heart is dependent on the left ventricular load and the uniformity of myocyte inactivation. The chamber compliance describes the passive properties of the left ventricle during the diastolic flow of blood across the mitral valve [14]. A decrease in chamber compliance can be caused by increased myocardial stiffness (viscoelastic properties of the myocardium) or an increase in LV volume. A decrease in chamber compliance will increase left ventricular filling pressure [14]. For patients with preserved systolic function, the ratio of early mitral inflow velocity to early diastolic velocity of the mitral annulus (E/e') evaluated at echocardiography correlates better with the mean LV diastolic pressures than any other Doppler variable [15]. Moreover, E/e' <8 accurately predicts normal mean LV diastolic pressure, and E/e'>15 identifies increased mean LV diastolic pressure. Wide variability in diastolic pressure has been reported in subjects with an E/e' of 8 to 15 [16].

The mitral annular velocity (e′) was found to be weakly correlated in studies with invasive indices of relaxation (e.g., the constant of relaxation) [15]. However, e' could be used as a reliable index of diastolic function in patients with established heart disease because the effect of preload on e' decreases with worsening relaxation [16]. In disease states, relaxation abnormalities occur early and often precede significant contractile dysfunction [13]. The slow coronary flow phenomenon is a well-recognized pathology characterized by impaired epicardial coronary flow in the absence of any myocardial abnormality or coronary stenosis of >30% [17]. It has been previously found that despite a reduction in the longitudinal function in SCFP during speckle tracking echocardiography, the conventional echocardiographic tissue Doppler parameters of biventricular diastolic function did not differ between SCFP and normal subjects [18].

According to earlier studies, the epicardial coronary flow in cases with left ventricular hypertrophy was frequently characterized as being delayed at angiography [19], which is similar to the epicardial flow of patients with SCFP. Our analysis showed an abnormal diversion in diastolic function parameters (e' and E/e')

in patients with hypertensive heart disease and weakly or moderately elevated LV mass compared to those diagnosed with SCFP. A few studies emphasized that the coronary flow in hypertension was substantially reduced when adjusted for LV mass [20] and was inversely correlated with the volume of myocardial mass and myocardial fibrosis [21]. The tendency toward abnormal perfusion at rest in the hypertrophied heart has been related to arterial remodeling that is out of proportion to the hypertrophied myocardium and the increased extravascular forces acting on intramural arteries [21,22]. Notably, the index of left ventricular mass in diastole could accurately predict the invasively measured left ventricular pressure and E/e' ratio in cohorts with hypertensive heart disease [23].

It has been recently reported that the epicardial coronary arterial lumen volume to LV mass ratio modified the coronary arterial resistance in the presence of only minimal coronary disease [24]. Our results replicate the findings on coronary flow in the setting of hypertensive heart disease and extend the knowledge in the non-obstructive coronary disease field by comparing it with SCFP. Furthermore, we demonstrated that delayed epicardial flow in left ventricular hypertrophy is related to more severely reduced left ventricular relaxation and elevated LV filling pressures compared to SCFP.

In agreement with previous findings [7,25,26], our results also suggested that the long-term usage of β-blockers and calcium antagonists could not normalize the elevated left ventricular filling pressures in patients with left ventricular hypertrophy, despite their beneficial effects on diastolic parameters and myocardial mass. Conversely, long-term therapy with oral nitrates may predispose patients to higher LV diastolic pressures via different mechanisms [27,28].

The cases of uncertain prognostic accuracy of E/e' (normal subjects, heavy mitral annular calcification, mitral valve disease, obstructive coronary disease, and regional ventricular dysfunction) [13] were excluded from the study; thus, an increased E/e' ratio is expected to reliably correlate with higher LV filling pressures in our cohort. The e' decreases with age [29]. On average, our study patients were younger (mean age: 57.3±8.7 years; two-thirds of patients being younger than 60 years); thus, the observed abnormalities in the diastolic parameters e' and E/e' should be discussed in relation to their cardiovascular morbidities.

Conclusions

Patients with microvascular angina represent a diverse population. The echocardiographic parameters of left ventricular relaxation (e') and end-diastolic pressure (E/e') are abnormally altered in the population with left ventricular hypertrophy compared to those in SCFP. The delayed epicardial flow further impairs diastolic function in hypertensive patients with hypertrophy and non-obstructive coronary disease.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Ethics Committe of th University Hospital 'Alexandrovska', Sofia, Bulgaria issued approval Incoming No:298/Oct 31,2018. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Sucato V, Evola S, Novo G, et al.: Angiographic evaluation of coronary microvascular dysfunction in patients with heart failure and preserved ejection fraction. Microcirculation. 2015, 22:528-533. 10.1111/micc.12223
2. Shah SJ, Lam CS, Svedlund S, et al.: Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J. 2018, 39:3439-3450. 10.1093/eurheartj/ehy531
3. Camici PG, Tschöpe C, Di Carli MF, Rimoldi O, Van Linthout S: Coronary microvascular dysfunction in hypertrophy and heart failure. Cardiovasc Res. 2020, 116:806-816. 10.1093/cvr/cvaa023
4. Li L, Gu Y, Liu T, et al.: A randomized, single-center double-blinded trial on the effects of diltiazem sustained-release capsules in patients with coronary slow flow phenomenon at 6-month follow-up. PLoS One. 2012, 7:e38851. 10.1371/journal.pone.0038851
5. Mehta HH, Morris M, Fischman DL, et al.: The spontaneous coronary slow-flow phenomenon: reversal by intracoronary nicardipine. J Invasive Cardiol. 2019, 31:42-45.
6. Gunes Y, Tuncer M, Guntekin U, Ceylan Y, Sahin M, Simsek H: Regional functions of the left ventricle in patients with coronary slow flow and the effects of nebivolol. Ther Adv Cardiovasc Dis. 2009, 3:441-446. 10.1177/1753944709345926
7. Barron AJ, Hughes AD, Sharp A, et al.: Long-term antihypertensive treatment fails to improve E/e' despite regression of left ventricular mass: an Anglo-Scandinavian cardiac outcomes trial substudy. Hypertension. 2014, 63:252-258. 10.1161/HYPERTENSIONAHA.113.01360
8. Mclnnis KJ, Balady GJ, Weiner DA, Ryan TJ: Comparison of ischemic and physiologic responses during

exercise tests in men using the standard and modified Bruce protocols. Am J Cardiol. 1992, 69:84-89. 10.1016/0002-9149(92)90680-W

9. Williams B, Mancia G, Spiering W, et al.: 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018, 39:3021-3104. 10.1093/eurheartj/ehy339

10. Mancia G, De Backer G, Dominiczak A, et al.: 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2007, 28:1462-1536. 10.1093/eurheartj/ehm236

11. Gibson CM, Murphy S, Menown IB, et al.: Determinants of coronary blood flow after thrombolytic administration. J Am Coll Cardiol. 1999, 34:1403-1412. 10.1016/S0735-1097(99)00397-6

12. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the Ameriacn Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016, 17:412. 10.1093/ehjci/jew041

13. Nagueh SF, Smiseth OA, Appleton CP, et al.: Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016, 29:277-314. 10.1016/j.echo.2016.01.011

14. Nishimura RA, Tajik AJ: Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol. 1997, 30:8-18. 10.1016/S0735-1097(97)00144-7

15. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ: Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation. 2000, 102:1788-1794. 10.1161/01.cir.102.15.1788

16. Firstenberg MS, Greenberg NL, Main ML, Drinko JK, Odabashian JA, Thomas JD, Garcia MJ: Determinants of diastolic myocardial tissue Doppler velocities: influences of relaxation and preload. J Appl Physiol. 2001, 90:299-307. 10.1152/jappl.2001.90.1.299

17. Beltrame JF: Defining the coronary slow flow phenomenon . Circ J. 2012, 76:818-820. 10.1253/circj.cj-12-0205

18. Xing Y, Shi J, Yan Y, et al.: Subclinical myocardial dysfunction in coronary slow flow phenomenon: Identification by speckle tracking echocardiography. Microcirculation. 2019, 26:e12509. 10.1111/micc.12509

19. Evola S, Cuttitta F, Evola G, et al.: Early detection of coronary artery flow and myocardial perfusion impairment in hypertensive patients evidenced by myocardial blush grade (MBG) and thrombolysis in myocardial infarction (TIMI) frame count (TFC). Intern Med. 2012, 51:1653-1660. 10.2169/internalmedicine.51.7385

20. Rabkin SW: Considerations in understanding the coronary blood flow- left ventricular mass relationship in patients with hypertension. Curr Cardiol Rev. 2017, 13:75-83. 10.2174/1573397112666160909093642

21. Tanaka M, Fujiwara H, Onodera T, Wu DJ, Matsuda M, Hamashima Y, Kawai C: Quantitative analysis of narrowings of intramyocardial small arteries in normal hearts, hypertensive hearts, and hearts with hypertrophic cardiomyopathy. Circulation. 1987, 75:1130-1139. 10.1161/01.cir.75.6.1130

22. Bache RJ: Effects of hypertrophy on the coronary circulation . Progr Cardiovasc Dis. 1988, 30:403-440. 10.1016/0033-0620(88)90005-9

23. Nakabachi M, Yamada S, Iwano H, et al.: Ventricular mass influences relationship between filling pressure and early-diastolic ratio of inflow velocity to mitral annular velocity (E/e′). Circ J. 2018, 82:732-738. 10.1253/circj.CJ-17-1019

24. Taylor CA, Gaur S, Leipsic J, et al.: Effect of the ratio of coronary arterial lumen volume to left ventricle myocardial mass derived from coronary CT angiography on fractional flow reserve. J Cardiovasc Comput Tomogr. 2017, 11:429-436. 10.1016/j.jcct.2017.08.001

25. Jurkevicius R, Sakalyte G, Kavoliŭniene A: Effects of beta blockers on left ventricular diastolic function: the importance of optimal heart rate reduction. Acta Cardiol. 2007, 62:269-274.

26. Zaliunas R, Jurkevicus R, Zabiela V, Brazdzionyte J: Effect of amlodipine and lacidipine on left ventricular diastolic and long axis functions in arterial hypertension and stable angina pectoris. Acta Cardiol. 2005, 60:239-246. 10.2143/AC.60.3.2004999

27. Sydow K, Daiber A, Oelze M, et al.: Central role of mitochondrial aldehyde dehydrogenase and reactive oxygen species in nitroglycerin tolerance and cross-tolerance. J Clin Invest. 2004, 113:482-489. 10.1172/JCI19267

28. Zamani P, Akers S, Soto-Calderon H, et al.: Isosorbide dinitrate, with or without hydralazine, does not reduce wave reflections, left ventricular hypertrophy, or myocardial fibrosis in patients with heart failure with preserved ejection fraction. J Am Heart Assoc. 2017, 6:e004262. 10.1161/JAHA.116.004262

29. Caballero L, Kou S, Dulgheru R, et al.: Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. Eur Heart J Cardiovasc Imaging. 2015, 16:1031-1041. 10.1093/ehjci/jev083

2022 Semerdzhieva et al. Cureus 14(5): e24789. DOI 10.7759/cureus.24789

12 of 12