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Variable Response of Coronary Flow to Vasodilators and Risk of Ischemia in Slow Coronary Flow

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Abstract: ***Our purpose was to compare the incidence of positive stress electrocardiographic tests (EST) in patients with slow coronary flow phenomenon (SCFP) and in patients with non-obstructive coronary disease (NCAD) with slow flow associated with left ventricular hypertrophy (LVH) secondary to hypertension (SCFLVH). Our second objective was to study the response of epicardial coronary flow to the intracoronary glyceryl trinitrate (GTN) given concomitantly with conventional anti-ischemic medication. The coronary flow was assessed using the corrected thrombolysis in myocardial infarction (TIMI) frame count method (cTFC) in 86 consecutive patients, with cTFC >25 frames and unstable angina treated with β-blocker (BB) alone, with BB and oral nitrate (BB+N) and with β-blocker (BB), calcium channel blocker (CCB), with or without oral nitrate, BB+CCB±N before and after the intracoronary injection of glyceryl trinitrate, GTN (200 µg). A subgroup of 57 (65.5%) patients underwent EST conducted. Results: The incidence of positive EST was significantly positively associated with the smaller indices of the end-diastolic, systolic volumes and the intake of BB as monotherapy. Least positive EST was observed on combined therapy that included CCB. The intracoronary nitrate administration lead to as tendency improved coronary flow at rest in the subgroup with SCFLVH (cTFCn - 33.9±10 frames vs 39.7±14.8 frames, p= 0.091). This response was most pronounced in patients with SCFLVH receiving combined therapy with BB+CCB±N (SCFLVH vs. SCFP - cTFCn 29.2±4.6 frames vs. 41.6±12.1 frames, p-NS). In conclusion, in absence of obstructive coronary disease, partial reversibility of the increased coronary vascular resistance after intracoronary GTN is observed at rest only with therapy that included CCB. This relationship is pronounced in NCAD and slow flow secondary to hypertensive disease in contrast to SCFP. Greater cardiac volumes may partially contribute to lower risk of stress-induced ischemia.***

Keywords: slow coronary flow phenomenon, left ventricular hypertrophy, TIMI frame count, nitrates, calcium channel blockers, exercise stress electrocardiography

1. Introduction

In patients with slow coronary flow phenomenon (SCFP) and those with ventricular hypertrophy related to hypertension in the absence of obstructive coronary disease impairment in epicardial coronary flow could be detected and characterized in severity at angiography [1, 2]. The usage of different class of vasoactive drugs (even for antihypertensive treatment as only indication) has been shown to alter to various degee the coronary flow reserve [3, 4]. Previous studies have suggested that the compromised coronary flow in the absence of obstructive coronary atherosclerosis was an indicator of worsening ischemia despite the use of antianginal therapy [1, 5]. In particular, the effect of nitrates – a conventional anti-ischemic drug class on angina in patients with minimal coronary disease has been described in studies as variable [6].

2. Purpose

The purpose of this retrospective single-centre cohort study was to compare the incidence of positive stress electrocardiographic tests (EST) in two types of patients with non-obstructive coronary disease (NCAD) – patients with slow coronary flow phenomenon (SCFP) and those with slow flow associated with left ventricular hypertrophy (LVH) secondary to hypertension (SCF_{LVH}). Our second objective was to study the response of epicardial coronary flow to the intracoronary glyceryl trinitrate (GTN) given concomitantly with conventional anti-ischemic medication.

3. Material, methods and results

3.1 Study group

A study cohort consisting of 86 consecutive patients with coronary stenoses <50% and delayed coronary contrast progression (cTFC > 25 frames) in at least one coronary artery, admitted with unstable angina to the University Hospital 'Alexandrovska' was retrospectively analyzed.

Exclusion criteria were previous coronary revascularization procedures, thrombolytic therapy for myocardial infarction, left ventricular systolic dysfunction, wall motion abnormalities at rest, cardiomyopathy, coronary aneurysm, ectasia and fistula, valve disease, acute or chronic inflammatory disease, recent fracture/wound/surgical procedure, any type of shock, neoplastic disease, suboptimal angiographic imaging, the usage of first generation dihydropyridine (e.g. nifedipine) as non-slow-release preparation, the usage of non-selective β-blocker (e.g. propranolol) and third generation of β-blocker (nebivolol). The SCFP was a subgroup of patients with coronary stenoses no greater than 40%, without LVH on echocardiography.
All patients have signed written informed consent forms for all diagnostic tests. This retrospective study was approved by the Ethics Committee of University Hospital 'Alexandrovska', and complied with the Declaration of Helsinki.

3.2 Methods

The indications for coronary angiography included symptoms of angina unresponsive to medical treatment, electrocardiographic (ECG) signs of ischemia at rest or inducible at stress test. Angiography was performed using the femoral approach, with nonionic contrast medium (Iopamidol 370), 6Fr coronary catheters, and without discontinuing therapy. At least two orthogonal views for the right coronary artery, with at least 5 views (including 2 coronal views) for the left coronary artery, were evaluated. In all patients, coronary artery flow was assessed by applying the thrombolysis in myocardial infarction (TIMI) frame count method, at baseline and after the intracoronary application of 200 µg glyceryl trinitrate (GTN) [7]. The angiograms were recorded at a speed of 12.5 frames/s. TIMI frame count (TFC) was corrected for the length of the left anterior descending coronary artery (LAD) by dividing the TFC measured in the LAD by 1.7.

The diagnoses of unstable angina, hypertension, dyslipidemia, and diabetes mellitus were consistent with accepted guidelines [8-11]. Current smoking status was considered a risk factor. Information regarding medication usage (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker - ACE-I/ARB; β-blocker – BB; calcium channel blocker – CCB; oral nitrate – N; antithrombotic agent - aspirin or clopidogrel; statin) was collected.

Fifty seven patients (65.5%) underwent symptom-limited exercise stress electrocardiographic test (EST) on the modified Bruce protocol at the time of this hospital admission [12]. Few patients have been referred after abnormal stress ECG tests, performed at other hospitals. For data analysis, provocation of angina, angina-like symptoms, ST depression $\geq$ 2 mm in two electrocardiographically associated precordial leads and/or $\geq$ 1 mm in leads from extremities were criteria for positive ESTs. The patients with equivocal tests were excluded from further analysis.

The left ventricular systolic indices and function were assessed using 2D-mode echocardiography and standard criteria [13]. LVH was defined as a thickness of the interventricular septum (IVS) or the posterior wall (LVPW) of the left ventricle $\geq$ 12 mm on echocardiography.

The analysis of data was performed by applying the Statistical Package for Social Sciences (SPSS) version 19.0 (IBM Corp., Armonk, NY, USA). The categorical variables were presented as counts and percentages, the continuous variables were presented as mean and standard deviation (SD). The Chi-square test or Fisher's exact test was applied in the comparison of the categorical variables. The normality of continuous variables was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Depending on the result of Levene's test, the variables with normal distribution were compared by means of Student's t-test or Welch test. For defining the difference between two repeated measurements of a continuous variable (for example cTFC before and after intracoronary GTN), a paired sample t-test was applied. The variables without normal distribution were tested using the Mann-Whitney U test. The Kaplan-Meier method was applied in the analysis of the clinical outcome. P-values lower than 0.05 were considered statistically significant.

3.3 Results

In the present study, the patients with SCF_{LVH} demonstrated greater ventricular wall thickness, tended to have larger epicardial coronary lumen diameters and higher incidence of non-stenotic coronary disease. A marginally lower incidence of positive stress ECGs was also observed in this group (Table 1 and 2).

Table 1: Clinical, echocardiographic and angiographic features of SCFP and SCF_{LVH}

Variable	*N*	*SCFP*[1] *N (%)*	*SCF_{LVH}*[2] *N (%)*	*P*
Age, years	52/34	56.9 ± 8.1	59.5 ± 8.3	NS
BSA[3], m	46/32	1.92±0.22	1.96±0.19	NS
Men		23 (44.2)	14 (41.2)	NS
Women		29 (55.8)	20 (58.8)	NS
Hypertension		39 (75)	34(100)	NS
Dyslipidemia		27 (67.5)	22 (73.3)	NS
DM[4]		10 (19.2)	7 (20.6)	NS
Obesity		15 (28.8)	7 (20.6)	NS
Smoking		5 (9.6)	2 (5.9)	NS
Anemia		5 (22.7)	2 (33.3)	NS
GFR[5], ml/min/1.73 m^2	12/16	107.7±35	88.4±30.2	NS
Positive exercise stress ECGs[6]		22 (78.6)	9 (50)	0.058
No vasoactive drugs		7 (12.7)	3 (5.5)	NS
BB[7]		27 (49.1)	24 (43.6)	NS
BB+CCB±N[8]		8 (14.5)	20 (36.3)	NS
BB+N[9]		13 (23.6)	8 (14.5)	NS
ACE-I/ARB[10]		32 (62.7)	26 (78.8)	NS
Statin		36 (69.2)	26 (78.8)	NS
Aspirin/Clopidogrel		45 (90)	27 (84.4)	NS

Legend: [1]SCFP - slow coronary flow phenomenon; [2]SCF_{LVH} – slow coronary flow associated with left ventricular hypertrophy secondary to hypertension; [3]BSA – body surface area; [4]DM – diabetes mellitus; [5]GFR – glomerular filtration rate; [6]ECG - electrocardiography; [7]BB - therapy with β-blocker; [8]BB+CCB±N – therapy with β-blocker, calcium channel antagonist and oral nitrate; [9]BB+N - intake of β-blocker and oral nitrate; [10]ACE-I/ARB – usage of angiotensin converting enzyme inhibitor or angiotensin receptor blocker

Table 2: Echocardiographic and angiographic data

Variable	*N*	*SCFP N (%)*	*SCF_{LVH} N (%)*	*P*
Coronary stenosis		7 (13.5)	12 (35.3)	0.082
30% stenosis		3 (5.8)	4 (11.8)	
40% stenosis		1 (1.9)	3 (8.8)	NS
50% stenosis		1 (1.9)	0 (0)	
Dves[1], mm	52/34	3.6±0.8	3.9±0.7	0.092
cTFC[2], frames	52/27	38±8.9	39.7±12.7	NS
SBP[3], mmHg	33/29	129.4±14.7	132.9±19.9	NS
DBP[4], mmHg	9/27	77.2±6.2	79.7±12.1	NS

HR[5], bpm	39/31	69.1±8.1	69.7±8.5	NS
IVS[6], mm	43/31	10.4±0.8	12.6±0.2	<0.0001
LVPW[7], mm	44/31	10.4±0.8	12.6±1.0	<0.0001
LVH[8]		0 (0%)	34 (100%)	NS
EDVI[9], ml/m^2	50/30	114.3±21.1	116.5±19.4	NS
ESVI[10], ml/m^2	50/30	37.9±9.3	36.2±10.5	NS
EF[11], %	50/30	67.3±5	68.5±6.1	NS

Legend: [1]Dves - epicardial coronary lumen diameter; [2]cTFC - corrected TIMI frame count; [3]SBP, [4]DBP - systolic and diastolic blood pressures; [5]HR - heart rate; [6] IVS/[7]LVPW – interventricular septum/left ventricular posterior wall; [8]LVH - left ventricular hypertrophy; [9]EDVI, [10]ESVI – indices of end-diastolic and end-systolic volume; [11]EF – ejection fraction ; the rest abbreviations are the same as those in table 1

In all patients, the administration of intracoronary GTN resulted in marked vasodilation (Table 3).

Table 3: Coronary flow and hemodynamic parameters at baseline and after intracoronary GTN

Therapy	*Before GTN*	*After GTN*	*Δ*	*P*
Dves	3.6±0.8	4±0.8	-0.3±0.3	<0.0001
cTFC	36.1±0.9	34.9±14.7	1.2±14	NS
SBP	128.3±18.8	121±17.4	7.3±22.5	0.010
DBP	76.1±5.5	80.4±5.3	-4.3±5.5	0.046
HR	70.7±8.8	74.3±9	-3.6±7.4	0.010
SCFLVH				
Dves	3.9±0.6	4.2±0.6	- 0.3±0.3	<0.0001
cTFC	38.3±9.3	33.9±10	5.5±9.2	0.050
SBP	134.2±20.8	120.9±16	-13.4±24	0.036
DBP	80±14.1	75±0.0	5±14.1	NS
HR	70.1±8.5	77.7±9.5	- 7.6±6	<0.0001
SCFP				
Dves	3.5±0.8	3.9±0.8	- 0.4±0.4	<0.0001
cTFC	37.8±8.9	39.7±14.8	- 1.8±13.2	NS
SBP	128.4±18.9	120±18.1	- 8.4±19.2	0.026
DBP	76.7±2.9	78.3±7.6	- 1.7±7.6	NS
HR	70.7±8.3	74.9±9.6	- 4.2±7.2	0.001

Legend: [1]Dvesn - post-nitrate epicardial coronary lumen diameter; [2]cTFCn - corrected TIMI frame count after GTN; [3]EDP_{LVn} - end-diastolic pressure in left ventricle after GTN; [4]SBPn, [5]DBPn - systolic and diastolic blood pressure after GTN; [6]HRn - heart rate after GTN

The administration of GTN was associated with a tendency for improved blood flow in the SCF_{LVH} group when compared with the SCFP group (Table 4). Following GTN, considerably lower values of end-diastolic pressure (EDP) were measured in the left ventricle (EDP_{LVn}) in the SCFP group (Table 4).

Table 4: Difference in flow and hemodynamic parameters after GTN between SCF_{LVH} and SCFP

Variables	*SCF_{LVH}*	*SCFP*	*P*
Dvesn[1]	4.2±0.6	3.9±0.8	NS
cTFCn[2]	33.9±10	39.7±14.8	0.091
EDP_{LVn} [3]	10.9±2.5	8.5±2.9	0.049
SBPn[4]	124.5±17.2	124.4±19.1	NS
DBPn[5]	81.1±7.4	81.1±11.6	NS
HRn[6]	77.7±9.5	74.5±9.5	NS

Although not significant, the improved epicardial flow in SCF_{LVH} after the intracoronary application of 200 µg GTN was pronounced with for the patients on therapy with BB+CCB±N (SCF_{LVH} vs SCF - 29.2±4.6 frames (n=6) vs. 41.6±12.1 frames (n=5), p-NS) (Table 5).

Table 5: Coronary flow and hemodynamic parameters association with the anti-ischemic therapy in SCF_{LVH} and SCFP

Therapy	*N*	*SCFP*	*SCF_{LVH}*	*P*
No vasoactive drugs				
Dves	8/2	3.6±0.4	4.2±0.9	NS
Dvesn	7/2	3.9±0.4	4±0.0	NS
cTFC	8/2	35.9±8.6	59.5±34.7	NS
cTFCn	7/2	44.6±19.4	38.5±7.9	NS
EDP_{LVn}	2/2	5±1.4	7±1.4	NS
BB		**SCFP**	**SCF_{LVH}**	
Dves	25/16	3.6±0.7	3.8±0.8	NS
Dvesn	24/10	3.7±0.7	4.1±0.9	NS
cTFC	25/16	37.6±8.5	34.2±9.3	NS
cTFCn	25/10	35.7±11.1	35.4±9.6	NS
EDP_{LVn}	7/10	8.3±3.6	9.4±2	NS
BB+N		**SCFP**	**SCF_{LVH}**	
Dves	8/7	3.5±0.3	4.2±0.3	NS
Dvesn	7/6	3.8±0.3	4.4±0.3	NS
cTFC	8/7	38±7.9	40.6±13.4	NS
cTFCn	7/6	43.1±22.4	38±14.3	NS
EDP_{LVn}	1/0	8.4±2.9	-	NS
BB+CCB±N		**SCFP**	**SCF_{LVH}**	
Dves	6/8	3.7±1.2	3.6±0.6	NS
Dvesn	5/6	4.1±1.4	4.2±0.6	NS
cTFC	6/8	43.8±11.8	37.3±7.3	NS
cTFCn	5/6	41.6±12.1	29.2±4.6	NS
EDP_{LVn}	4/1	12.5±5.2	16	NS

Legend: abbreviations are the same as in table 1 and table 4

In $SCF_{LVH,}$ the smaller epicardial coronary lumen at baseline and following GTN, also the smaller end-diastolic/systolic volumes correlated positively with the risk of ischemia at stress ECG test (table 6).

Table 6: SF_{LVH} – correlates of positive stress test

SCF_{LVH}	*N*	*Negative EST %*	*Positive EST %*	*P*
Age, years	6/20	56.2±8.5	57.3±8.9	NS
Male sex	2/6	33.3	28.6	NS
Female sex	4/15	66.7	71.4	NS
Hypertension	3/16	50	46.2	NS
DM	0/5	0	23.8	NS
Obesity	2/6	33.3	28.6	NS
Smoking	1/1	16.7	4.8	NS
Stenoses	1/4	16.7	19	NS
EDVI, ml/m2	6/19	68.9±12.9	55.6±11.2	0.022
ESVI, ml/m2	6/19	24±7.7	16.9±3.8	0.006

EF, %	6/19	64.3±4.5	69.1±5.3	NS
Dves, mm	6/20	4.3±1.1	3.4±0.6	0.009
cTFC, frames	6/21	33.8±5.9	40.8±11.5	NS
Dvesn, mm	6/21	4.7±1.2	3.8±0.6	0.017
cTFCn,frames	6/21	42.3±16	40.3±19.5	NS

Table 7: SCFP – variables associated with ischemic stress ECG

SCFP	*N*	*Negative EST %*	*Positive EST %*	*P*
Age, years	18/13	58.3±7.5	61.3±7.9	NS
Male sex	4/5	22.2	35.7	NS
Female sex	14/9	77.8	64.3	NS
Hypertension	18/14	100	100	NS
DM	3/3	16.7	21.4	NS
Obesity	4/5	22.2	35.7	NS
Smoking	6/0	33.3	0	NS
Stenoses	3/8	16.7	57.1	NS
EDVI, ml/m2	14/10	66.1±16.8	62.1±14	NS
ESVI, ml/m2	14/10	21.3±7.6	18.8±4.1	NS
EF, %	18/12	67.1±9	67.8±5.7	NS
Dves, mm	18/14	3.6±0.9	3.7±0.6	NS
cTFC, frames	18/14	30.9±17.9	31.6±10.7	NS
Dvesn, mm	17/13	3.9±0.9	4.1±0.5	NS
cTFCn, frames	17/13	26.8±13.1	32.4±8.6	NS

In the whole study population, the incidence of positive EST was significantly positively associated with the smaller indices of the end-diastolic, systolic volumes and the intake of BB as monotherapy. Least positive EST were observed on combined therapy that included CCB in small subset of patients.

Table 8: Patients with NCAD and slow coronary flow – indicators of the incidence of positive EST

NCAD	*N*	*Negative EST %*	*Positive EST %*	*P*
Age, years	24/33	57.8±7.6	58.9±8.6	NS
Male sex	6/11	25	31.4	NS
Female sex	18/24	75	68.6	NS
Hypertension	21/30	87.5	85.7	NS
DM	3/8	12.5	22.9	NS
Obesity	2/6	33.3	28.6	NS
Smoking	1/1	16.7	4.8	NS
Stenoses	1/4	16.7	19	NS
EDVI, ml/m2	6/19	68.9±12.9	55.6±11.2	0.022
ESVI, ml/m2	6/19	24±7.7	16.9±3.8	0.006
EF, %	6/19	64.3±4.5	69.1±5.3	NS
Dves, mm	6/20	4.3±1.1	3.4±0.6	0.009
cTFC, frames	6/21	33.8±5.9	40.8±11.5	NS
Dvesn, mm	6/21	4.7±1.2	3.8±0.6	0.017
cTFCn, frames	6/21	42.3±16	40.3±19.5	NS
CCB intake	11/4	47.8	11.8	NS
BBmono therapy	6/23	26.1	67.7	0.003

4. Discussion

We observed a distinct effect of conventional anti-ischemic drugs (calcium channel blockers, intracoronary GTN) in two subsets of slow flow patients, and non-obstructive coronary disease. In contrast to the patients SCFP, the patients with slow flow secondary to ventricular hypertrophy associated with hypertension (SCF_{LVH}) demonstrated improved coronary flow after the intracoronary application of nitrates. This effect to GTN appears only with concomitant intake of CCB. The incidence of ischemic stress ECG tests was also least with the intake of CCB. Smaller cardiac volumes in the whole group and also the smaller epicardial lumen diameters in the group with SCF_{LVH} were also related with higher incidence of positive EST.

In our study, an additional post-nitrate improvement in coronary flow was observed only in the subgroup with SCF_{LVH} receiving CCBs. All of the three anti-ischemic medical therapies were ineffective regarding the impairment in the coronary flow in the group with SCFP. Patients without coronary atherosclerotic lesions but with dysfunctional epicardial coronary arteries have demonstrated variable flow responses to intracoronary nitrate, with a post-nitrate increase in coronary flow that produced myocardial ischemia in some patients [14]. It has been shown in earlier angiographic studies investigating the coronary slow flow phenomenon, that the myocardial flow improved with intracoronary nitrates but to a lesser degree when compared with CCBs [15]. Several reports in microvascular angina cohorts have documented improved flow, reduced frequency of ischemia, and in particular improved symptom control during stress with the intake of CCB [3, 16, 17]. The results can be explained by their effects on coronary mico- and macrovascular vasodilation. Correspondingly, in cohorts demonstrating left ventricular remodeling secondary to hypertension, the therapy with nitrates reportedly contributes to greater coronary flow reserves despite the lack of effect on myocardial mass, fibrosis and microcirculation [18] and CCBs increase the coronary flow reserve [19].

Additional explanation for the baseline and post-nitrate difference in coronary flow in our study could be the intake of BBs as sole anti-antianginal drug by greater number of patients with SCFP. Microvascular spasms and precipitation of ischemia are potential complications with first- and second-generation selective BBs as monotherapy in NCAD owing to unopposed α2-adrenergic constriction [20]. This observation is supported by the higher incidence of positive exercise ECGs and more severely impaired coronary flow in the subgroup of SCFP and SCF_{LVH} patients using BB as sole anti-ischaemic medication.

In summary, a delayed baseline coronary flow is a characteristic angiographic sign of coronary microvascular dysfunction [21], and also of coronary macro- and microvascular spasm [22]. The intracoronary nitrate administration has led to reversal of coronary microvascular spasm in studies [23, 24] but remained ineffective in contrast to CCB in cases of microvascular dysfunction [25]. Our results are in agreement with these facts. Therefore, we can speculate that only the coronary flow abnormalities related to ventricular hypertrophy secondary to hypertension respond to therapy in somewhat similar to microvascular spasm pattern – they are easily reversible by the intracoronary application of nitrates given as addition to a background therapy with CCB.

Also of note is that we found a considerably higher end-diastolic pressure in left ventricle following the intracoronary application of NTG (EDP_{LVn}) in SF_{LVH} when

compared to SCFP. End-diastolic pressure in left ventricle when it is abnormally high interferes with coronary flow and contributes to ischemia in sub-endocardium. However, a certain increase in EDP_{LV} within the reference range could be beneficial as hypothesis provided the fact that there is a pressure gradient of flow in the arteriolar region in non-obstructed but dysfunctional coronary arterioles [26, 27]. Moreover, myocardial flow improvement along with the increase in the aortic diastolic pressure has been previously demonstrated [28].

Enlargement in the epicardial coronary lumen and greater EDV were typically found in the patient subgroup with hypertension and LVH (SF_{LVH}). Similar pathologic alterations in hypertensive disease have been demonstrated in previous studies [29, 30] and predicted lower frequency of stress-induced ischemia [29]. On the contrary the coronary diameters and the cardiac volumes did not vary substantially in relation with the incidence of positive EST in the SCFP group.

5. Conclusion

In the absence of obstructive coronary disease, partial reversibility of the increased coronary vascular resistance after intracoronary GTN is observed at rest and during exercise only with therapy that includes CCB. This relationship is pronounced in NCAD and slow flow secondary to hypertensive disease in contrast to SCFP. Greater cardiac volumes and epicardial lumen diameters also may partially contribute to lower risk of stress-induced ischemia in patients with impaired coronary flow at rest.

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