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RESISTANT TO VASOACTIVE DRUGS EPICARDIAL FLOW IN SLOW CORONARY FLOW PHENOMENON

Cardiology

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ABSTRACT

Our purpose was to compare the effect of three different conventional anti-ischemic therapies and of intracoronary glyceryl trinitrate (GTN) on coronary flow and the clinical outcome 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 (SCFLVH). Study design - a retrospective single-center cohort study. The coronary flow was assessed using the corrected thrombolysis in myocardial infarction (TIMI) frame count method (cTFC) in 87 consecutive patients, with cTFC >25 frames and unstable angina treated with β-blocker (BB), 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). Compared with SCFP, the intracoronary nitrate administration improved the coronary flow as tendency 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 the group with SCFP, an insignificantly higher incidence of ischemic-driven hospital readmissions was observed during follow-up. In the whole study population, the period free of adverse events was least in duration in the patients that recieved BB+N, intermediate with the intake of BB alone and longest in the patients treated with BB+CCB±N (38.6±10.3 days vs. 51.7±6.5 days vs. 73±6 days, p-NS). In conclusion, in the absence of obstructive coronary disease, partial reversibility of the increased coronary vascular resistance after intracoronary GTN is observed only with CCB therapy in patients with slow flow secondary to hypertensive disease, but not in SCFP.

KEYWORDS

slow coronary flow phenomenon, left ventricular hypertrophy, TIMI frame count, nitrates, calcium channel blockers

INTRODUCTION

The slow coronary flow phenomenon (SCFP) was first described by Tambe as delayed opacification of the epicardial coronary segments in the absence of significant coronary and myocardial disease, associated with resting angina refractory to therapy [1]. In patients with ventricular hypertrophy related to hypertension, impairment in the epicardial coronary flow observed at angiography has been reported [2]. 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, 3]. Particularly, the effect of nitrates on angina symptoms in patients with minimal coronary atherosclerosis has been inconsistent [4].

PURPOSE

The purpose of this single-center retrospective cohort study was to describe and compare the effect of conventional anti-ischemic medications and intracoronary glyceryl trinitrate (GTN) on coronary flow and the clinical outcome in two types of patients with non-obstructive coronary disease (NCAD) and slow flow – patients presenting with SCFP and those with slow coronary flow associated with left ventricular hypertrophy (LVH) secondary to hypertension (SCFLVH).

METHODS

A study cohort consisting of 87 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 and 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.

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) [5]. 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 [6-9]. 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 three patients (60.9%) underwent symptom-limited exercise stress electrocardiographic test (EST) on the modified Bruce protocol at the clinic [10]. 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 > 2 mm in two electrocardiographically associated precordial leads and/or > 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 [11]. LVH was defined as a thickness of the interventricular septum (IVS) or the posterior wall (LVPW) of the left ventricle > 12 mm on echocardiography.

A history of subsequent hospital admissions with diagnosis unstable

angina and acute myocardial infarction (major adverse cardiac events, MACE), for a period of 28.7±29.2 months (1 – 89 months), was obtained during follow-up visits, telephone interviews, and using data from medical records.

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 Chi-square test or Fisher's exact test was applied in the comparison of the categorical variables. The continuous variables were presented as mean and standard deviation (SD). 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.

RESULTS

In the present study, the patients with SCFLVH 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).

Table 1. Clinical, echocardiographic and angiographic features of SCFP and SCFLVH

Variable	N	SCFP1 N (%)	SCFLVH 2 N (%)	P
Age, years	52/34	56.9 ± 8.1	59.5 ± 8.3	NS
BSA3, 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
DM4		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
GFR5, ml/min/1.73 m2	12/16	107.7±35	88.4±30.2	NS
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)	
Dves6, mm	52/34	3.6±0.8	3.9±0.7	0.092
cTFC7, frames	52/27	38±8.9	39.7±12.7	NS
SBP8, mmHg	33/29	129.4±14.7	132.9±19.9	NS
DBP9, mmHg	9/27	77.2±6.2	79.7±12.1	NS
HR10, bpm	39/31	69.1±8.1	69.7±8.5	NS
IVS11, mm	43/31	10.4±0.8	12.6±0.2	<0.0001
LVPW12, mm	44/31	10.4±0.8	12.6±1.0	<0.0001
LVH13		0 (0%)	34 (100%)	NS
EDVI14, ml/m2	50/30	114.3±21.1	116.5±19.4	NS
ESVI15, ml/m2	50/30	37.9±9.3	36.2±10.5	NS
EF16, %	50/30	67.3±5	68.5±6.1	NS
Positive exercise stress ECGs17		22 (78.6)	9 (50)	0.058
No BB CCB N		8 (15.7)	1 (3)	NS
BB18		25 (49)	16 (48.5)	NS
BB+CCB±N19		2 (3.9)	7 (21.3)	NS
BB+N20		8 (15.7)	7 (21.3)	NS
ACE-I/ARB21		32 (62.7)	26 (78.8)	NS
Statin		36 (69.2)	26 (78.8)	NS
Aspirin/Clopidogrel		45 (90)	27 (84.4)	NS

Legend: 1SCFP - slow coronary flow phenomenon; 2SCFLVH – slow coronary flow associated with left ventricular hypertrophy secondary to hypertension; 3BSA – body surface area; 4DM – diabetes mellitus; 5GRF – glomerular filtration rate; 6Dves - epicardial coronary lumen diameter; 7cTFC - corrected TIMI frame count; 8SBP, 9DBP - systolic and diastolic blood pressures; 10HR - heart rate; 11 IVS/12LVPW – interventricular septum/left ventricular posterior wall; 13LVH - left ventricular hypertrophy; 14EDVI, 15ESVI – indices of end-diastolic and end-systolic volume; 16EF – ejection fraction 17ECG - electrocardiography; 18BB - therapy with β-blocker; 19BB+CCB±N – therapy with β-blocker, calcium channel antagonist and oral nitrate; 20BB+N - intake of β-blocker and oral nitrate; 21ACE-I/ARB – usage of angiotensin converting enzyme inhibitor or angiotensin receptor blocker Effect of intracoronary GTN and anti-ischemic therapy In all patients, the administration of intracoronary GTN resulted in marked vasodilation (Table 2).

Table 2. Coronary flow and hemodynamic parameters at baseline and after intracoronary GTN

Therapy	Before GTN	After GTN	Δ1	P
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: 1Δ – difference between the baseline and the repeated measurement; the other abbreviations are the same as in table 1

The administration of GTN was associated with a tendency for improved blood flow in the SCFLVH group when compared with the SCFP group (Table 3). Following GTN, considerably lower values of end-diastolic pressure (EDP) were measured in the left ventricle (EDPLVn) in the SCFP group (Table 3).

Table 3. Difference in flow and hemodynamic parameters after GTN between SCFLVH and SCFP

Variables	SCFLVH	SCFP	P
Dvesn1	4.2±0.6	3.9±0.8	NS
cTFCn2	33.9±10	39.7±14.8	0.091
EDPLVn 3	10.9±2.5	8.5±2.9	0.049
SBPn4	124.5±17.2	124.4±19.1	NS
DBPn5	81.1±7.4	81.1±11.6	NS
HRn6	77.7±9.5	74.5±9.5	NS

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

Although not significant, the improved epicardial flow in SCFLVH after the intracoronary application of 200 µg GTN was pronounced with for the patients on therapy with BB+CCB±N (SCFLVH vs SCF - 29.2±4.6 frames (n=6) vs. 41.6±12.1 frames (n=5), p-NS) (Table 4).

Table 4. Coronary flow and hemodynamic parameters association with the anti-ischemic therapy in SCFLVH and SCFP

Therapy				
No BB CCB N	N	SCFP	SCFLVH	P
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
EDPLVn	2/2	5±1.4	7±1.4	NS
SBP	6/2	120.8±14.3	130.5±33.2	NS
SBPn	7/2	113.6±15.7	120±14.1	NS
DBPn	4/0	78.8±6.3	90	NS
HR	8/1	67.4±10.4	90	NS
HRn	7/1	73.9±10.9	100	NS
BB		SCFP	SCFLVH	
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
EDPLVn	7/10	8.3±3.6	9.4±2	NS
SBP	16/13	130.8±14.8	126.9±15.2	NS
SBPn	15/13	121.6±21.6	119.1±13.6	NS
DBP	5/4	77±8.4	70±8.2	NS
DBPn	6/6	77.5±8.4	70±8.2	NS
BB+N		SCFP	SCFLVH	
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
EDPLVn	1/0	8.4±2.9	-	NS
SBP	5/7	130.6±18.5	124±9.6	NS
SBPn	7/6	109.4±18.6	124±9.6	NS
DBPn	3/1	66±5	75	NS
HR	7/7	66.4±8.5	66.1±7.3	NS
HRn	7/2	71.9±8.7	79±15.6	NS
BB+CCB±N		SCFP	SCFLVH	
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
EDPLVn	4/1	12.5±5.2	16	NS
SBP	4/7	137.5±12.6	135.3±26.4	NS
SBPn	5/6	127±13	124.2±22.5	NS
DBPn	2/2	90	75±7.1	NS
HR	4/7	70.8±6.1	69.2±7.6	NS
HRn	4/5	76.5±6.6	69.2±8.6	NS

Legend: abbreviations are the same as in table 1 and table 3
Additionally, the therapy with ACE-I/ARB, statin (as tendency), and antithrombotic agent (aspirin/clopidogrel) was associated with an improved coronary flow after intracoronary GTN (Table 5).

Table 5. Intake of ACE-I/ARB, statin and aspirin or clopidogrel – association with epicardial flow

Therapy	N	SCFP	SCFLVH	P
ACE-I/ ARB				
Dves	32/26	3.4±0.6	3.9±0.6	0.001
Dvesn	26/21	3.8±0.6	4.1±0.6	NS
cTFC	32/26	39.2±9.7	38.9±13	NS
cTFCn	26/21	41.4±14.3	33.8±10.3	0.046
EDPLVn	15/6	9.2±4	9.3±2.5	NS
SBP	21/23	132.1±15.9	131.7±21.1	NS
SBPn	23/22	119.4±18.8	119.7±15.6	NS
DBP	6/5	75±4.5	76±13.4	NS
DBPn	11/7	79.4±10.3	77.3±5.2	NS
HR	23/24	69±8.9	69.4±8.1	NS
HRn	22/17	75.4±9	73.8±10.2	NS
CCB 1		5 (16.7%)	6 (24%)	NS
Statin	N	SCFP	SCFLVH	
Dves	36/26	3.7±0.7	3.9±0.7	NS
Dvesn	30/19	4.1±0.7	4.1±0.5	NS
cTFC	36/26	38.8±4.5	38.5±10.4	NS
cTFCn	31/19	40.9±17.8	33±9.42	0.054
EDPLVn	16/8	9.2±2.9	10.4±3.2	NS
CCB		23 (63.9%)	20 (76.9%)	NS
ACE-I/ARB		4 (11.4%)	5 (20%)	NS
Aspirin/ Clopidogrel	N	SCFP	SCFLVH	
Dves	45/27	3.6±0.8	3.8±0.7	NS
Dvesn	36/22	4.0±0.9	4.2±0.7	NS
cTFC	45/27	37.8±9	37.4±10.5	NS
cTFCn	39/22	38.9±13.9	31.6±7.7	0.029
EDPLVn	22/7	9.3±3.8	10.3±3.4	NS
CCB		28 (62.2%)	20 (74.1%)	NS
ACE-I/ARB		6 (14.3%)	8 (29.6%)	NS

Legend: 1 CCB – usage of calcium channel blocker; the other abbreviations are the same as in table 1 and table [3]

Incidence of positive stress ECG tests In the study population evaluated, a marginally higher incidence of positive stress ECG tests was observed with the long-term use of BB alone when compared with other therapies (BB+N, BB+CCB±N, and no vasoactive therapy as a combined variable) – 5 (31.3) vs. 20 (57.1), p= 0.056.

In patients with SCFP, criteria for reversible myocardial ischemia were more frequently detected on stress ECG testing with borderline clinical significance (Table 1).

Follow-up
In total, 46 patients (52.9%) were re-evaluated during the follow-up. The incidence of hospital readmissions during this period was 54.3% (n=25). Myocardial infarction was documented as an adverse event in one patient, and the remaining patients were readmitted with a diagnosis of unstable angina.

DISCUSSION

To date, there is no evidence demonstrating that the conventional anti-ischemic therapy exerts a specific effect in a subpopulation with NCAD. In this study, we observed a distinct influence of different anti-ischemic drug combinations on coronary flow after the application of intracoronary GTN in two subsets of slow flow patients, with coronary stenoses quantitatively evaluated at angiography as no greater than 50%. In contrast to the patients SCFP, the patients with slow flow secondary to ventricular hypertrophy associated with hypertension (SCFLVH) demonstrated improved coronary flow after the intracoronary application of nitrates. This response to GTN appears to be associated with the intake of CCB.

Patients with angiographically normal but dysfunctional epicardial coronary arteries have demonstrated variable flow responses to intracoronary nitrate, with a post-nitrate increase in coronary flow producing signs and symptoms of myocardial ischemia in some patients [12]. 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 [14].

In cohorts demonstrating left ventricular remodeling secondary to hypertension, the therapy with nitrates reportedly contributes to greater coronary flow reserves but have no effect on ventricular mass and myocardial fibrosis [18].

BBs are another class of drugs with reported efficacy in the treatment of angina associated with significant coronary atherosclerosis. However, microvascular spasms and precipitation of ischemia are potential complications with first- and second-generation selective BBs as the sole antianginal medication in NCAD owing to unopposed α2-adrenergic constriction [15, 16]. This observation was supported by our results. In contrast, several reports in microvascular angina cohorts have documented improved flow and reduced ischemia, as well as improved symptom control during stress with the intake of CCB [3, 17, 18]. In our study, an additional post-nitrate improvement in coronary flow was observed in the patient subgroup receiving CCBs, emphasizing the considerable role of arteriolar vasodilation induced by CCBs in the reversal of flow impairment in both, patients with SCFP and slow coronary flow associated with hypertensive disease.

The long-term administration of optimal doses of CCBs and BBs leads to a reduction in hypertrophy and fibrosis, improving left ventricular diastolic function to some extent [19-21]. Additionally, CCBs increase the coronary flow reserve in patients with hypertensive heart disease [20].

Ischemia detected., ischemia detected by stress exercise ECG test was more common in the subgroup with SCFP. Accordingly, researchers have detected higher incidence of abnormal stress ECGs in patients diagnosed with SCFP when compared with patients presenting near-normal coronary arteries (< 40% stenosis) [22]. A delayed baseline coronary flow is a characteristic angiographic sign of coronary microvascular dysfunction [23], and of coronary macro- and microvascular spasm [24]. Previously, an inadequate effect of nitrates regarding the control of stress-induced angina has been reported in non-selected cohorts with NCAD [4]. The intracoronary nitrate

administration leads to reversal of coronary microvascular spasm but is less effective in the settings of microvascular dysfunction [25, 26]. The latter condition is generally accepted as being associated with distinct abnormalities in microcirculation. In agreement with these facts, we can speculate that of the coronary flow abnormalities in SCFP resemble microvascular dysfunction in respect to their susceptibility to positive modification. On the other hand, the abnormalities related to ventricular hypertrophy secondary to hypertension respond to therapy in similar to microvascular spasm pattern – they are easily reversible by the intracoronary application of nitrates.

Regarding ischemia worsening, we demonstrated a marginally lower rate of hospital readmissions in patients with LVH. This observation could be partially attributed to different medications – a more frequent administration of CCBs in the SCFLVH group, with BB utilized as vasoactive monotherapy in combination with nitrates in the SCFP group during follow-up. Oral nitrates have failed to improve the long-term prognosis in the absence of obstructive coronary atherosclerosis and have even increased the risk for cardiac events in large randomized studies [27, 28]. Additionally, the monotherapy with CCB improves exercise test tolerance, demonstrating a neutral effect on prognosis [2, 20] as was the effect also reported in our cohort. Given the small sample size of patients in our study, our findings suggest an association of oral nitrate therapy with substantially shorter event-free survival, without acceleration of ischemic symptoms. This impact is even more pronounced following the concomitant administration of β1-selective blockers without vasodilating activity. Notably, the events that hallmark the development of nitrate tolerance include increased oxidative stress, as well as the loss of platelet responsiveness to nitrogen oxide with potential for thrombosis, which might limit the positive effect observed following nitrate therapy [29, 30].

CONCLUSION

In the absence of obstructive coronary disease, partial reversibility of the increased coronary vascular resistance after intracoronary GTN is observed only with CCB therapy in patients with slow flow secondary to hypertensive disease, but not in SCFP.

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