International Journal of Advanced Biomedicine
An International Journal

http://dx.doi.org/10.18576/ab/010204

Immediate Effect of Sublingual Isosorbide Dinitrate in Patients with Coronary Slow Flow Phenomenon (CSFP)

Hassam Mansour[1,*], *Ramadan Ghaleb*[2] *and Hassan Ellaban* [1]

[1] October 6th University, Faculty of Medicine, Egypt.
[2] Aswan University, Faculty of Medicine, Egypt.

Received: 21 Feb. 2016, Revised: 22 Mar. 2016, Accepted: 24 Mar. 2016.
Published online: 1 Sep. 2016.

The coronary slow flow phenomenon (CSFP) is defined angiographically by delayed opacification of the distal vasculature in the absence of obstructive coronary artery disease. Recently, literatures are in favor of the coronary microvascular disorder hypothesis. In spite of its clinical impact and the explicit clinical equipoise in its management, only few studies are held to set clear guidelines.

Aim: We aimed to investigate the immediate effect of sublingual Isosorbide Dinitrate (ISDN) on Thrombolysis in Myocardial Infarction (TIMI) flow through assessment of total frame counts (TFCs) during coronary angiography.

Methods: A non-randomized interventional trial, the first eligible Thirty two CSFP patients presented to cathlab department at October 6th University were enrolled, a baseline angiographic picture assessment to check for eligibility and confirm safety parameters then sublingual 5mg of isosorbide dinitrate was administered followed by a follow up angiographic pictures one minute after isosorbide dinitrate administration for each participant, then coronary flow was compared before and one minute after isosorbide dinitrate administration . Heart rate, systolic and diastolic blood pressures, and TFCs in all 3 coronaries were recorded and the correction was done for LAD at a baseline assessment after study drug assignment.

Study population characteristics were respectively male to female 19 to 13, DM versus non DM were 13 versus 19, HTN versus non HTN were 19 versus 13, smoking versus nonsmoking 22 versus 10, Dyslipidemic versus normo lipidemics were 12 versus 20; the mean age was 54 ± 11 years.

Results: Significant cTFC changes among observations were detected by simple t-test comparisons, then a descriptive statistical analysis were carried out for percentage change between baseline and the post-treatment TFCs. In addition to covariance analysis (ANCOVA) with baseline score as a covariate for all variables.

Comparative TFCs angiography showed that TFCs were significantly lower in overall, (mean decrease of 95% CI- 35.2 %) showing a statistically significant TFCs reduction in all coronaries

Conclusion: Comparative angiographic TFCs and hemodynamic effects showed that TFCs were significantly lower after isosorbide dinitrate sublingual administration; this was associated with significant angiographic and clinical improvement without substantial hemodynamic changes.

Keywords: Coronary slow flow phenomenon (CSFP), isosorbide dinitrates (ISDN), total frame counts TFCs), Thrombolysis in Myocardial Infarction (TIMI), high-speed rotational atherectomy (HSRA), coronary artery disease (CAD), left anterior descending (LAD).

1 Background

The coronary slow flow phenomenon (CSFP) is an angiographic finding consists of a delay in the progression of the contrast injected into the coronary arteries during coronary angiography. This condition, which may affect one or all coronaries, was originally described by Tambe et al. in 1972. (1). The coronary slow flow phenomenon is either primary CSFP, also called syndrome Y (2) or secondary which may happen due to different etiologies like coronary ectasia, spasm, embolism, heart failure, connective tissue disorders and during intervention in acute myocardial infarction (3)

Isosorbide dinitrate is one of the most widely used drugs in the treatment of angina, it is a potent vascular arterio/venous dilator including coronary arteries through smooth muscles relaxation, so arteriolar relaxation reduces systemic vascular resistance consequently improving the coronary blood Flow.

*Corresponding author e-mail: mansour.hossam@gmail.com

Previous few interventional trials with regard to its effect in CSFP had been done in specific study populations to compare its effect with other vasodilators in no-reflow/slow flow during high-speed rotational atherectomy (HSRA) in patients with complex coronary artery disease (CAD). (22).

This trial was followed by another trial in known microvascular dysfunction (23) then in heart failure patients. (24)

However, validity and transitional controversy could not resolve clinical equipoise for management of CSFP necessitating more focus to set evidence based guidelines.

The reported incidence of CSFP is 1%-7% in patients undergoing diagnostic angiography because of clinical suspicion of cardiovascular diseases (4) occurs most commonly in young men and smokers, and in patients admitted with acute coronary syndrome (5).

Metabolic syndrome was also proved to be more frequent in CSFP in the presence of higher total cholesterol, low-density lipoprotein-cholesterol, fasting glucose and body mass index levels (6)

The evaluation of CSFP was initially described subjectively by visual judgment (1). A semi-quantitative

Assessment of coronary blood flow is the thrombolysis in myocardial infarction (TIMI) flow grade classification, which. Reflects the speed and completeness of the passage of the injected contrast through the coronary tree, however its variability may limit its application widely (7).

Coronary flow is graded on a scale of 0 through 3 depending on flow characteristics, No-reflow is traditionally defined as TIMI grade 0 or 1, and slow flow is defined as TIMI grade 2 in this scheme. (18) . Improved TIMI grades have been shown to be correlated with improved outcomes. (19, 20)

The TFC method, first described by Gibson et al, provided a semi quantitative method of assessing coronary flow. (8). The number of angiographic frames for contrast to reach a specified distal segment in the coronary artery with cineangiography performed at 30 frames per second through a 6-F catheter was designated the TFC. A further correction is made in the TFC for the left anterior descending artery (LAD), given its longer length relative to the other coronary arteries, by dividing the TFC in the LAD by a factor of 1.7, which yields the corrected TFC (cTFC). Normal coronary and microvascular function usually yield a cTFC of <20, a slow flow of cTFC of 20 through 40, and a no-reflow cTFC of >40. (20)

The prognostic significance of the cTFC was studied in an analysis of patients enrolled in the TIMI studies, in which it was shown to be an independent predictor of mortality. (8)

Of course, the accuracy of these methods depends on several factors, such as amount of contrast injected, length of injection, and fluoroscopic time, as well as systemic blood pressure. For example, a contrast injection rate increase of more than 1 mL/s by hand injection can decrease the cTFC by two frames. (21)

Due to the important role of endothelium in the regulation of vascular tone, platelet activity, leukocyte adhesion, vascular smooth muscle proliferation and is intimately involved in the development of atherosclerosis, so, endothelial dysfunction is considered as one of the cardinal mechanisms responsible for CSFP especially after the recent finding demonstrating that baseline and peak exercise endothelin-1 plasma concentrations were higher and nitric oxide plasma concentrations were lower in slow coronary flow Patients (9, 10).

Another important responsible factor is the coronary vessels themselves whether at the level of the epicardial vessels which are also referred to as “conductance vessels”, because they do not pose any resistance to blood flow or , the small vessels less 400 μm (“resistive vessels”), which primarily regulate myocardial blood flow in the absence of any significant obstructive epicardial stenosis (11,12)

At the level of the epicardial coronary arteries, the blood flow patterns depend on the geometry and motion of these vessels (13). Disturbed laminar blood flow occurs in arterial segments with geometric irregularities such as curvatures, branches, and bifurcations (14) where in these complex regions the low blood velocity rates tend to occur. However, small vessels dysfunction has been typically involved in the pathogenesis of CSFP since its first description (1). Confirming this hypothesis, investigators reported fibro-muscular hyperplasia, medial hypertrophy, myo-intimal proliferation, as well as endothelial edema, thickening and degeneration in the coronary micro-vessels (15).

Inflammation also is a contributing factor to several cardiovascular conditions and inflammatory mechanisms have also been observed in the context of CSFP. Li *et al*. (16) showed that the plasma concentration of high-sensitivity C-reactive protein and interleukin-6 was increased in CSFP patients.

Non obstructive atheromatous plaques, diffuse calcification along the coronary vessel wall with intimal thickening are demonstrated in patients with CSFP by using IVUS technique and flow rate measurements (17)

2 Methods

A non-randomized interventional trial, the first eligible Twenty seven CSFP patients presented to cathlab department at October 6th University were enrolled, a baseline angiographic picture assessment to check for eligibility and confirm safety parameters then sublingual 5mg of isosorbide dinitrate was administered followed by a follow up angiographic pictures one minute after isosorbide dinitrate administration, for each participant we compared before and one minute after isosorbide dinitrate administration . Heart rate, systolic and diastolic blood pressures, and TFCs in all 3 coronaries were recorded and

the correction was done for LAD at a baseline assessment after study drug assignment

Study population characteristics as shown in (Table 1), were respectively male to female 19 to 13 DM versus non DM were 13 versus 19, HTN versus non HTN were 19 versus 13

Table 1 Participant Characteristics and results (n = 32).

Patient	Age	Sex	DM	HTN	Smoking	Lipidemic	TFC before ISDN	TFC after (ISDN)	TFC Difference
1	48	F	None	HIN	SM	Normo	33	20	13
2	40	F	None	None	SM	Normo	31	22	9
3	41	F	DM	HIN	SM	Normo	34	19	15
4	56	M	None	HIN	SM	Hyper	32	20	12
5	45	M	DM	HIN	None	Hyper	32	18	14
6	50	M	None	None	SM	Normo	30	22	8
7	50	M	None	None	SM	Normo	35	19	16
8	58	F	DM	HIN	None	Normo	33	30	3
9	57	M	DM	HIN	None	Hyper	29	15	14
10	48	M	DM	None	SM	Hyper	29	29	0
11	44	F	None	HIN	SM	Normo	28	26	2
12	45	F	None	None	SM	Hyper	27	25	2
13	45	M	DM	None	None	Normo	33	23	10
14	50	M	None	None	SM	Normo	34	15	19
15	59	M	None	HIN	SM	Normo	29	20	9
16	58	M	DM	HIN	SM	Hyper	34	27	7
17	52	M	DM	HIN	SM	Hyper	30	21	19
18	56	F	DM	HIN	None	Normo	34	15	19
19	32	M	None	HIN	SM	Normo	28	14	14
20	38	M	None	HIN	SM	Normo	27	15	12
21	31	M	None	None	SM	Hyper	27	12	15
22	50	M	None	None	SM	Normo	30	22	18
23	56	M	None	HIN	SM	Normo	34	17	17
24	55	F	DM	None	None	Normo	36	21	15
25	63	M	None	None	SM	Hyper	29	19	10
26	44	F	None	HIN	None	Normo	30	12	18
27	48	M	None	HIN	None	Normo	32	12	20
28	30	F	DM	None	SM	Hyper	30	22	8
29	60	F	DM	HIN	None	Hyper	26	26	0
30	52	F	None	None	SM	Normo	29	27	2
31	47	F	None	HIN	SM	Hyper	35	30	5
32	41	M	DM	HIN	None	Normo	27	24	3

(Table1: Characteristics of the study population and results, DM = Diabetes Mellitus; HTN = Hypertension; SM = Smoking; NORMO = Normolipidemic, Hyper = Hyperlipidemic)

Table 2: Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
TFC before ISDN	32	26	36	31.47	2.830
TFC after ISDN	32	12	30	20.59	5.242
TFC Difference	32	0	20	10.88	6.236
Valid N (listwise)	32				

Table 3: One-Sample Test

	Mean Difference	95% Confidence Interval of the Difference
TFC before ISDN	30.844	29.82
TFC after ISDN	20.594	18.70
TFC Difference	10.875	8.63

Table 4: Paired Samples Test

	Paired Differences			
	Mean	Std. Deviation	Std. Error Mean	95% COI of the Difference
				Lower

Pair 1	TFC before ISDN - TFC after ISDN	10.250	5.924	1.047	8.114

smoking versus nonsmoking 22 versus 10, Dyslipidemic versus normo lipidemics were 12 versus 20; the mean age was 54 ± 11 years. Heart rate, systolic and diastolic blood pressures, and TFCs in all 3 coronaries were recorded and the correction was done for LAD at a baseline assessment after administering nitroglycerine.

All data are presented as the mean +1SEM. So that statistical significance was assumed if the null hypothesis could be rejected at the .05/n probability level.

Significant cTFC changes among observations were detected by both simple (Table3), and Paired t-test comparisons (Table4), followed by descriptive statistics(Table2), for percentage change between baseline and post-treatment and analysis of covariance (ANCOVA) with baseline score as a covariate was done via SPSS to estimate means through the univariate utility, allowing stratified analysis for each study characteristics stratum to control for potential confounding variables.

3 Results

Comparison of systolic and diastolic blood pressures and TFCs before and one minute after isosorbide dinitrate. Showed systolic and diastolic blood pressures (Mean decrease of 10 % and 4%, respectively) in contrast with pre administration. Heart rates increased with Mean difference 5%, and TFCs angiography demonstrated a significant reduction in all coronaries (Mean decrease of 35.2 %,) as shown in (Figures 1,2,3) demonstrated a significant ($p = 0.05$), After isosorbide dinitrate, Showing statistically significant improvement in the TFCs in CSFP after Sublingual isosorbide dinitrate administration.

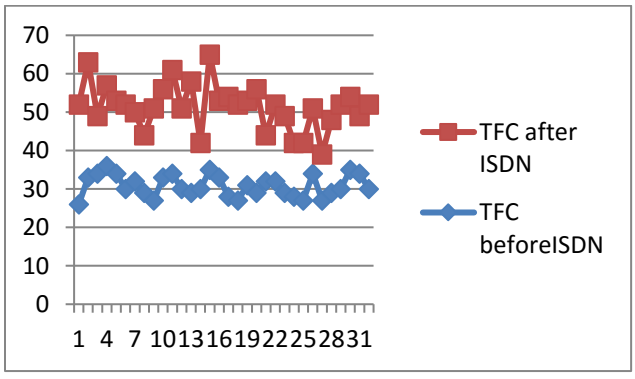

Figure1: Line graph comparative TFC Before and after ISDN.

Covariance analysis showed no influential age difference between responders and non-responder participants. However, the Males (Table6-Figure5), nonlipidemic participant (Table5-Figure4), has the higher statistical significance variability among the stratified groups. The nonsmoker (Table7-Figure6), nondiabetic (Figure7), and hypertensive(Table8-Figure8), stratified groups showed a slight higher responses and mild statistical variability with mean differences less than 10% rather than their opposite groups.

Table 5 ANCOVA-Comparative Covariance analysis for Normal and hyperlipidemia participants.

Lipidemic		TFC before ISDN	TFC after ISDN	TFC Difference
Hyper	Mean	30.00	22.00	8.83
	N	12	12	12
	Std. Deviation	2.796	5.576	6.235
Normo	Mean	31.35	19.75	12.10
	N	20	20	20
	Std. Deviation	2.796	4.983	6.060
Total	Mean	30.84	20.59	10.88
	N	32	32	32
	Std. Deviation	2.830	5.242	6.236

Table 6 ANCOVA-Comparative Covariance analysis for Gender differences.

Sex		TFC before ISDN	TFC after ISDN
F	Mean	31.23	22.69
	N	13	13
	Std. Deviation	3.193	5.407
M	Mean	30.58	19.16
	N	19	19
	Std. Deviation	2.610	4.741
Total	Mean	30.84	20.59
	N	32	32
	Std. Deviation	2.830	5.242

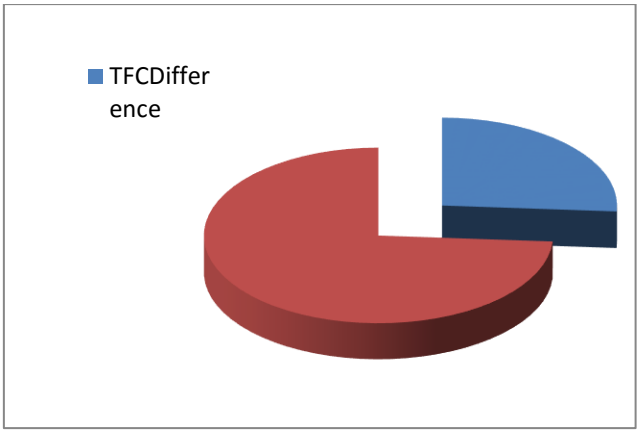

Figure2: Pie graph showing TFC difference Frequency percentage.

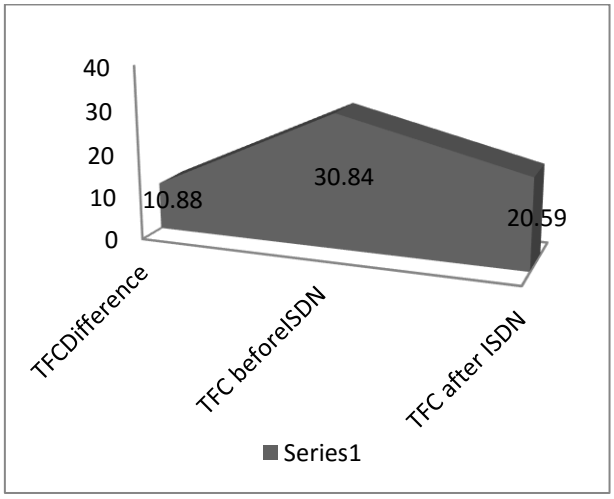

Figure3: Graph comparative TFC difference, before and After ISDN.

Table 7: ANCOVA-Comparative Covariance analysis for Smokers and non-smokers.

Smoking		TFC before ISDN	TFC after ISDN
None	Mean	31.20	19.60
	N	10	10
	Std. Deviation	3.155	6.168
SM	Mean	30.68	21.05
	N	22	22
	Std. Deviation	2.732	4.855
Total	Mean	30.84	20.59
	N	32	32
	Std. Deviation	2.830	5.242

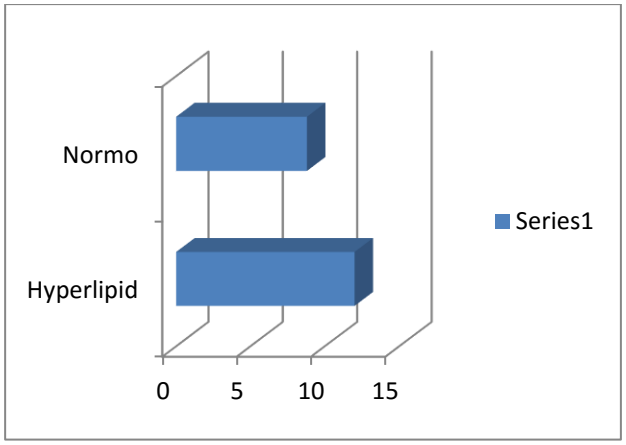

Figure4: Bar graph comparative analysis for Normal and hyperlipidemia participants.

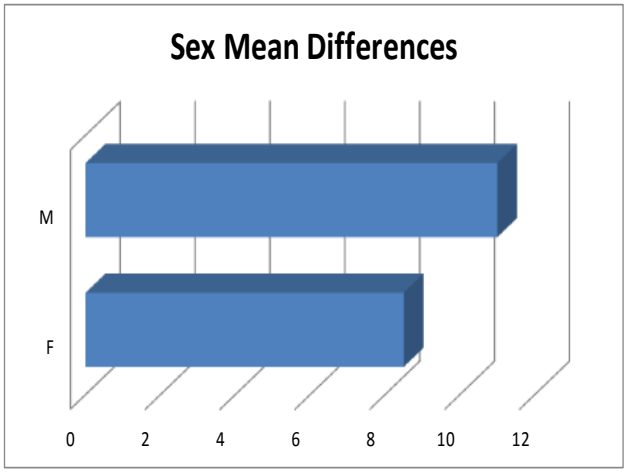

Figure 5: Bar Graph Comparative analysis for Gender differences.

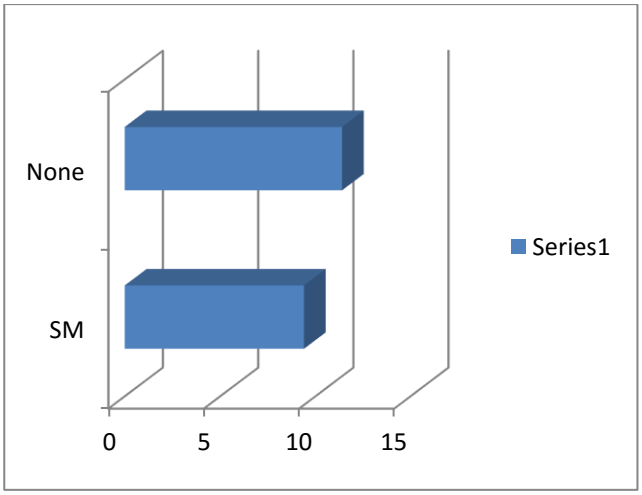

Figure 6: Bar graph comparative analysis for Smokers and non-smokers participants.

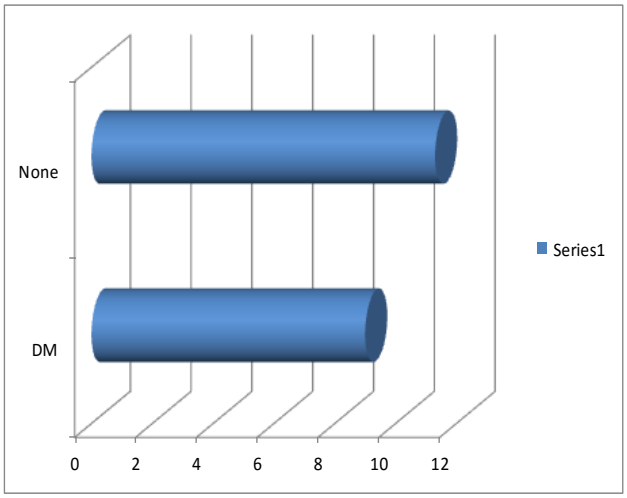

Figure 7: Bar Graph Comparative analysis for Diabetic and non-Diabetic participants.

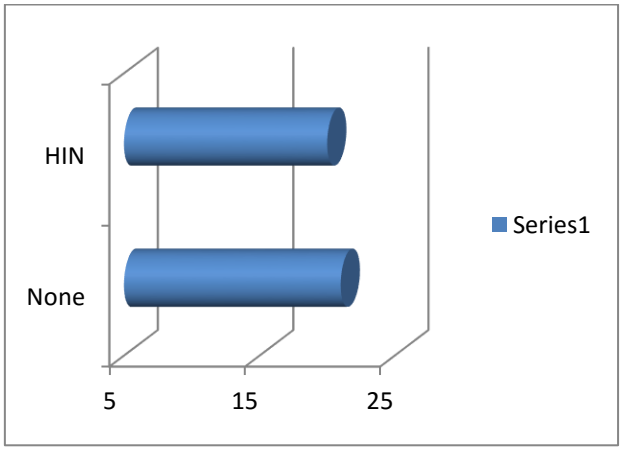

Figure 8: Bar Graph comparative analysis for Hypertensive and non-Hypertensive.

Table 8: ANCOVA-Comparative Covariance analysis for Hypertensive and nonhypertensive.

HTN		TFC before ISDN	TFC after ISDN
HIN	Mean	30.89	20.05
	N	19	19
	Std. Deviation	2.865	5.730
None	Mean	30.77	21.38
	N	13	13
	Std. Deviation	2.891	4.538
Total	Mean	30.84	20.59
	N	32	32
	Std. Deviation	2.830	5.242

4 Discussion

CSFP is not uncommon angiographic finding, many potential etiologies and several factors play a role in the pathogenesis of CSFP like endothelial dysfunction, epicardial vessel anatomy, small coronary vessels disease and inflammatory process. Until now, the therapeutic approach is not very clear; however, anti-atherosclerotic treatment and vasodilators may help.

In 2008, an early interventional trial based on nitroglycerin administration in patients with syndrome X who have microvessel dysfunction and congestive heart failure speculated that nitroglycerin may induce severely slow flow and transient ST-segment elevation due to functional stenosis and a delay in the dilatation of microvessels (24). However, the excluded population could not offer a robust generalizable valid data.

In 2009, a completed interventional trial to compare the effect of intracoronary adenosine and isosorbide dinitrate on no-reflow/slow flow during rotational atherectomy in patients with complex coronary artery disease was done with encouraging results as either drugs showed safety and effectiveness in decreasing the incidence of no-reflow/slow flow (22). However, the study design was based on success of the intervention, in hospital mortality and rate of unnecessary revascularization as endpoints, with no quantitative surrogate measures or covariate analysis.

In 2010, a similar trial to compare the effects of isosorbide dinitrate and nicorandil on the CSFP using a quantitative TIMI flow and TFCs as a surrogate marker advocating the microvascular dysfunction theory as the most likely mechanism of the coronary slow flow phenomenon (CSFP). (23)

Our Study design was based on TCFs in all the three coronaries as a quantitative surrogate endpoint in addition to hemodynamic heart rate, systolic and diastolic blood pressures as a hemodynamic exploratory markers, covariate analysis based on statistical multivariate analysis and regression assumed to avoid the confounding bias.

The Study has shown a statistical significance in TFCs reduction in all coronaries (mean decrease of 35.2 %) demonstrated a significant ($p = 0.05$), after isosorbide dinitrate sublingual administration.

Covariance analysis did not reveal a significant confounding variables between responders and non-responders participants, nevertheless nonsmoker, nonlipidemic ,nondiabetic and hypertensive stratified groups showed a slightly higher responses and mild statistical variability with mean differences less than 10% rather than the opposite groups.

In spite of the small sample size and the non-randomized design, the strong statistical significance and the anticipated subsequent clinical improvement of CSFP after isosorbide dinitrate administration, lighting up the endothelial

dysfunction, the low nitric oxide plasma concentrations during events and the microvascular causality hypothesis in the CSFP, encourages further large scale and ancillary randomized controlled trials.

5 Conclusion and Recommendations

Comparative angiographic TFCs and hemodynamic effects showed that TFCs were significantly lower in overall, (Mean decrease of 95% CI- 35.2 %) showing a statistically significant TFCs reduction in all coronaries demonstrated a significant result (p = 0.05), after isosorbide dinitrate sublingual administration. Associated with significant angiographic and clinical improvement without substantial hemodynamic changes.

This could give a chance for the oral nitrates to be included in the management of coronary slow flow in patients with objective ischemic evidence. Larger randomized trials are needed to confirm these results.

References

[1] Tambe AA, Demany MA, Zimmerman HA, et al. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding. Am Heart J 1972; 84:66-71.

[2] Leone MC, Gori T, Fineschi M. The coronary slow flow phenomenon: a new cardiac "Y" syndrome? Clin Hemorheol Microcirc 2008; 39:185-90.

[3] Gori T, Fineschi M. Two Coronary "Orphan" Diseases in Search of Clinical Consideration: Coronary Syndromes X and Y.Cardiovasc Ther 2011.

[4] Mangieri E, Macchiarelli G, Ciavolella M, et al. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn 1996; 37:375-81.

[5] Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon--a new coronary microvascular disorder. Cardiology 2002; 97:197-202.

[6] Yilmaz H, Demir I, Uyar Z. Clinical and coronary angiographic characteristics of patients with coronary slow flow. Acta Cardiol 2008; 63:579-84.

[7] Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987; 76:142-54.

[8] Gibson CM, Murphy SA, Rizzo MJ, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Circulation. 1999; 99:1945-1950.

[9] Camsarl A, Pekdemir H, Cicek D, et al. Endothelin-1 and nitric oxide concentrations and their response to exercise in patients with slow coronary flow. Circ J 2003; 67:1022-8.

[10] Sezgin N, Barutcu I, Sezgin AT, et al. Plasma nitric oxide level and its role in slow coronary flow phenomenon. Int Heart J 2005; 46:373-82.

[11] De Bruyne B, Hersbach F, Pijls NH, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. Circulation 2001; 104:2401-6.

[12] Maseri A, Crea F, Kaski JC, et al. Mechanisms of angina pectoris in syndrome X. J Am Coll Cardio 1991;17:499-506.

[13] Ramaswamy SD, Vigmostad SC, Wahle A, et al. Fluid dynamic analysis in a human left anterior descending coronary artery with arterial motion. Ann Biomed Eng 2004;32:1628-41.

[14] Chatzizisis YS, Coskun AU, Jonas M, et al. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol

[15] Mosseri M, Yarom R, Gotsman MS, et al. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation 1986; 74:964-72.

[16] Li JJ, Qin XW, Li ZC, et al. Increased plasma C-reactive protein and interleukin-6 concentrations in patients with slow coronary flow. Clin Chim Acta 2007;385:43-7.

[17] Cin VG, Pekdemir H, Camsar A, et al. Diffuse intimal thickening of coronary arteries in slow coronary flow. Jpn Heart J 2003; 44:907-19.

[18] The Thrombolysis in Myocardial Infarction (TIMI) trial, phase I findings: TIMI Study Group. N Engl J Med. 1985; 312:932-936.

[19] Simes RJ, Topol EJ, Holmes DR Jr, et al. Link between angiographic substudy and mortality outcomes in a large randomized trial of myocardial infarction. Importance of early and complete infarct artery reperfusion. GUSTO-I investigators. Circulation. 1995; 91:1923-1928.

[20] Cannon CP, Sharis PJ, Schweiger MJ, et al. Prospective validation of a composite end point in thrombolytic trials of acute myocardial infarction (TIMI 4 and 5). Thrombosis in Myocardial Infarction. Am J Cardiol. 1997;80:696-699.

[21] Dodge JT Jr, Rizzo M, Nykiel M, et al. Impact of injection rate on the Thrombolysis in Myocardial Infarction (TIMI) trial frame count. Am J Cardiol. 1998; 81:1268-1270.

[22] Tsao TP[1], Cheng SM, Cheng CC, Yang SP. Comparison of intracoronary adenosine and isosorbide dinitrate on no-reflow/slow flow during rotational atherectomy. Acta Cardiol. 2009 Apr; 64(2):225-30.

[23] Sadamatsu K[1], Tashiro H, Yoshida K, Shikada T, Iwamoto K, Morishige K, Yoshidomi Y, Tokunou T, Tanaka H. Acute effects of isosorbide dinitrate and nicorandil on the coronary slow flow phenomenon. Am J Cardiovasc Drugs. 2010;10(3):203-8.

[24] Yamashita K[1], Tasaki H. Intracoronary administration of isosorbide dinitrate induced severely slow flow and transient ST-segment elevation. Angiology. 2008 Jun-Jul;59(3):379-81.