Nicorandil effect on myocardial perfusion in patients with slow coronary flow phenomenon assessment by gated myocardial perfusion SPECT

Vahid Reza Dabbagh Kakhki[1], Ali Eshraghi[2], Narjes Ayati[1], Mohammad Vojdanparast[2], Ramin Sadeghi[1], Azadeh Rezvani Khorashad[1]

[1]Nuclear Medicine Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Cardiovascular Department, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Introduction: Patients with the coronary slow flow phenomenon (SCF) frequently experience angina episodes. The purpose of this study was to determine efficacy of nicorandil in myocardial perfusion in patients with SCF.

Methods: Twenty patients (50.85 ± 12.96 y) with SCF were studied. We evaluate coronary slow flow according to protracted thrombolysis in myocardial infarction (TIMI) frame count. After diagnosis of SCF, all patients underwent dipyridamole stress/rest gated ^{99m}Tc-sestamibi SPECT. Subsequently, the patients received 10 mg nicorandil BD (20 mg per day). After starting nicorandil for one month, patients underwent dipyridamole stress/rest gated ^{99m}Tc-sestamibi SPECT again. Gated SPECT images were analyzed based on 17-segment scoring system, and QPS (quantitative perfusion SPECT) and QGS (quantitative gated SPECT) softwares were used.

Results: In patients with SCF subtle perfusion abnormality was noticed. With nicorandil consumption, EDV and ESV were decreased and LVEF was increased in both stress and rest gated SPECT phases ($P>0.05$). After nicorandil consumption, decreased in most semi-quantitative perfusion indices (Severity score; $P=0.03$, Extension score; $P=0.06$, RAW reversibility; $P=0.002$, severity reversibility; $P=0.03$ and Extension reversibility; $P=0.001$) except for RAW score were observed demonstrating significant difference with pre-nicorandil consumption quantities. In multi-vessels involvement with SCF, there was a trend to see more abnormality with more remarkable post-nicorandil change as compared to the patients with one vessel involvement.

Conclusion: The main finding of this study was better myocardial coronary flow after nicorandil consumption in patients with SCF specially those with multi-vessel involvement.

Key words: Angina; Nicorandil; Gated SPECT; Myocardial perfusion

Corresponding author: Azadeh Rezvani Khorashad, MD; Nuclear Medicine Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: Rezvania911@mums.ac.ir

INTRODUCTION

Slow coronary flow (SCF) is a phenomenon recognized as coronary microvascular disorder in the absence of obstructive epicardial coronary artery disease characterized with delayed passage of contrast medium in coronary angiography [1-3]. Different factors for the development of SCF phenomenon were described as: myocardial edema compressing the capillary lumen, microvascular spasm, leucocyte intravascular plugging, distal microembolization by fibrin or platelets, and reperfusion injury with loss of microvascular integrity [4-5]. nicorandil ,N-(2-hydroxyethyl)-nicotinamide nitrate, a hybrid adenosine triphosphate (ATP)-sensitive potassium channel opener and nitrate, is a substance with both nitrate-like and K-ATP channel-activating properties [6].

It is reported that nicorandil has preconditioning effects in the ischemic myocardium [7]. Some investigators showed intravenous or intracoronary administration of nicorandil could decrease the incidence of acute coronary syndrome in patients with SCF [8-10].

A randomized control trial about the nicorandil effect in angina showed decrease in cardiac events in patients with stable angina and acute myocardial infarction [8, 9, 11].

Regarding the uptake of ^{99m}Tc-trcers used in myocardial perfusion imaging such as ^{99m}Tc-Sestamibi into myocardial cells depends on myocardial blood flow, myocardial perfusion imaging is a well-established method to assess myocardial perfusion, diagnosis of coronary artery disease (CAD) and prognostication [12-14]. Thus, we assessed the effect of administration of nicorandil on SCF phenomenon by ^{99m}Tc-Sestamibi gated myocardial perfusion SPECT.

METHODS

Study participants

Between January 2015 and January 2016, we included 20 consecutive patients (age: 50.85±12.93; 35-75 years old) with history of stable angina and diagnosis of SCF. They referred for scheduled coronary angiography to Cardiology Department.

Our study inclusion criteria were as follow; (1) on coronary angiographic studies, arterial narrowing did not exceed 50% in any of the three main coronary arteries and (2) delayed opacification in at least one of the main coronary arteries was documented. We evaluate coronary slow flow according to protracted TIMI frame count. The TIMI frame count was determined quantitatively by incorporating the method described by Gibson et al. [15]. In brief, using a standard cine viewer, the number of cine

frames between the first and last frames were calculated. The first frame was identified as the time when contrast media first appeared at the origin of an epicardial artery, touched both borders of its wall, and advanced in an anterograde manner [15]. The frame in which the dye opacified, a distal landmark branch was designated as the final frame. Due to its greater length, if left anterior descending artery (LAD) was used for frame count determination, the resultant count was divided by 1.7, thus producing a final corrected TIMI frame count [15]. Patients with diabetes mellitus, hypertension cardiomyopathy, congenital heart or vulvar disease were excluded from this study. All patients underwent dipyridamole stress/rest gated ^{99m}Tc-sestamibi myocardial perfusion SPECT (Gated SPECT) in two times. After diagnosis of SCF, all patients underwent dipyridamole stress/rest gated ^{99m}Tc-sestamibi SPECT. After that, the patients received 10 mg nicorandil BD (20 mg per day). Following starting nicorandil for one month, patients underwent dipyridamole stress/rest gated ^{99m}Tc-sestamibi SPECT again. This study protocol was approved by the local Ethics Committee of Mashhad University of Medical Sciences.

Stress/rest gated myocardial perfusion SPECT

Stress/rest gated myocardial perfusion imaging was performed using single-day stress/rest protocol. Test orders were randomized to ensure that 50% of participants underwent the stress first, while the remainder underwent the rest test at the beginning.

All patients underwent dipyridamole stress / rest Gated SPECT in two times: when patients didn't use nicorandil and when patients were on nicorandil consumption. The acquisition was performed using a dual-headed gamma camera, (Siemens, dual head variable angle). For stress imaging, 4 minutes after dipyridamole infusion, 600 MBq of ^{99m}Tcsestamibi was injected, while SPECT data were acquired 90 min later. For rest imaging, SPECT data were acquired 90 min after injecting 600 MBq of ^{99m}Tcsestamibi. In both studies, 32 projection images were obtained in 6° increments over an orbit of 180° at a rate of 8 frames per cardiac cycle using electrocardiogram-gated acquisition. The image matrix size was 128×128, and low energy high resolution collimator was used. Collected data were reconstructed into short axial, horizontal long axial, and vertical long axial SPECT images with ordered-subsets expectation maximization and without attenuation correction.

Tomographic images were analyzed visually as well as quantitatively. 17-segemnt 5 scale scoring system was used for determination of summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS) [16-19]. Non-gated data were

analyzed using QPS (quantitative perfusion SPECT) automated program (Cedars-Sinai, Los Angeles, CA, USA), which facilitated the automatic measurement of the SSS, SRS, SDS and TPD (Total Perfusion Deficit).

Subsequently, each reconstructed short-axis ECG-gated SPECT image was processed using the QGS (quantitative gated SPECT) program developed by Germano et al, to automatically calculate the left ventricular (LV) end-diastolic volume (EDV), LV end-systolic volume (ESV) and LV ejection fraction (LVEF) [20].

Coronary angiography

For all patients, multidirectional coronary angiography using the Judkins' method was performed. According to the American Heart Association criteria [21], the proximal and mid locations of 3 major coronary arteries were defined. We evaluate SCF according to protracted Thrombolysis in Myocardial Infarction (TIMI) frame count. The TIMI frame count was determined quantitatively by incorporating the method described by Gibson et al. [15]. As mentioned above patients with SCF were diagnosed. According to report of angiography, patients were divided into two groups: patients with SCF in one vessel and patients with SCF in more than one vessel (2- or 3-vessels involvement with SCF: defined as multi-vessels).

Statistical analysis

The data were analyzed using SPSS for Windows, version 16 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± SD and normality of data was checked Kolmogorov–Smirnov test. Differences in proportions were judged by $\chi2$ test. Paired T test was performed for asses the comparison between before and after consumption of nicorandil or between rest and stress Gated SPECT variables including EDV, ESV and LVEF. Furthermore Independent sample T test was performed for comparison the relation of scintigraphic findings between one vessel involvement and more than one vessel involvements. P value less than 0.05 considered as significant level.

RESULTS

Patient's characteristics

From 20 patients, 8 (40%) and 12 (60%) patients were male and female respectively. Table 1 shows frequency of coronary artery disease involving with SCF. According to angiography reports, we divided study patients with SCF into two groups; patients with one vessel involvement (10 patients) and patients with more than one vessel involvements (10

patients). Most of the patients in group with one vessel involvement had involvements in LCX, and then RCA or LAD. Most of the patients in group with more than one vessel involvement had involvement in three vessels.

Table 1: Frequency of coronary artery involvement with slow coronary flow.

Coronary artery	Frequency
LCX	5 (40%)
RCA	3 (15%)
LAD	2 (10%)
LAD+LCX	3 (15%)
LCX+RCA	3 (15%)
LCX+RCA+LAD	4 (20%)

LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery

Perfusion SPECT findings

Five (25%) patients had normal pattern, 8 (40%) had reversible defect, 3 (15%) patients had fixed defect and 4 (20%) patients had Fixed+reversible defect in their myocardial perfusion tomograms. The patient had minimal defects findings in their tomograms. Before administration of nicorandil, the SSS and SRS were 2.85±1.6 and 0.95±1.2 respectively (P<0.05).

After nicorandil administration, the SSS and SRS were 1.9±1.12 and 1.05±1.05 respectively (P<0.05). The summed stress score during nicorandil consumption was significantly less than pre-nicorandil administration (P=0.009), while no significant difference was noticed in SRS.

Table 2 represents the comparison of scintigraphic segments at rest and stress in pre- and post-nicorandil consumption. We analyzed polar maps for stress and rest findings using QPS software: Raw polar maps (RAW); severity polar maps, extension polar maps (EX) and reversibility polar maps. We calculated mean scores derived from 17 myocardial segments in these polar maps. This table shows that after nicorandil consumption, most of scintigraphic findings except RAW score had significant difference in two phases of the study. Polar map severity score (P=0.03), polar map extension score (P=0.06), RAW reversibility (P=0.002), severity reversibility (P=0.03) and Extension reversibility (P=0.001) were significantly decreased after consumption of nicorandil.

TPD was decreased after nicorandil loading but this difference was not significant (P=0.24).

Gated SPECT findings

Table 3 compares the left ventricular function indices before and following consumption of nicorandil.

Table 2: Perfusion and Polar map findings with and without nicorandil consumption in patients with slow coronary flow. (SSS: summed stress score; SRS: Summed rest sore; TPD: Total perfusion deficit).

Variable polar map scores	Stress (Mean± SD)			Rest (Mean± SD)		
	Without nicorandil	With nicorandil	p-value	Without nicorandil	With nicorandil	p-value
Mean Raw score	80.23±2.87	80.63±2.15	0.36	80.78±2.98	81.13±2.50	0.20
Mean Severity score	0.63±0.19	0.50±0.14	0.03	0.47±0.12	0.44±0.10	0.22
Mean Extension score	5.15±3.70	3.35±2.92	0.06	2.87±0.60	1.91±0.43	0.02
	Without nicorandil			**With nicorandil**		**p-value**
Mean Raw reversibility	1.53±1.27			0.43±1.51		0.002
Mean Severity reversibility	0.50±0.13			0.45±0.09		0.03
Mean Extension reversibility	2.29±1.73			1.16±0.85		0.001
TPD	0.045±0.007			0.036±0.004		0.24

Table 3: Gated left ventricular functional indices in patients with slow coronary flow: with and without consumption of nicorandil (EDV: End diastolic volume; ESV: End systolic volume; LVEF: Ejection fraction).

Variable	Stress Phase (Mean± SD)			Rest Phase (Mean± SD)		
	No nicorandil	With nicorandil	p-value	No nicorandil	With nicorandil	p-value
EDV	53.15±7.17	52.35±7.89	0.16	48.95±6.90	48.70±7.01	0.58
ESV	16.30±5.21	15.20±5.07	0.92	17.65±3.89	17.20±4.13	0.44
LVEF	69.75±9.90	69.85±8.79	0.10	67.10±8.42	67.30±7.12	0.79

Among studied parameters: EDV and ESV were decreased after nicorandil consumption in both stress and rest gated images, while LVEF was increased. However differences following and without consumption of nicorandil in both rest and stress phases were not significant.

We analyzed all perfusion and functional indices derived from gated myocardial perfusion SPECT; the difference between two phases of study was more significant in patients with multi-vessel evidence of SCF.

DISCUSSION

In present study, we included twenty consecutive patients with clinical diagnosis of stable angina and SCF phenomenon. We investigated nicorandil effect on myocardial perfusion using gated myocardial perfusion SPECT. Recently there has been some clinical trials on nicorandil, a hybrid of mitochondrial adenosine triphosphate-sensitive K channel opener and nitrates, on its beneficial effect as an adjunctive therapy for patients with acute myocardial infarction (MI) [8, 9, 22, 23]. Nicorandil can increase the recovery of postischemic contractile dysfunction and decrease the infarct size, as well it is shown that nicorandil could decreased frequency and intensity of angina in patients with SCF [24]. Till now, there is few studies about the role of nicorandil medication in patients with SCF specially assessed by Gated SPECT.

In patients with SCF, we found higher decrement for EDV and ESV and higher increment for LVEF with consumption of nicorandil in both stress and rest gated myocardial perfusion phases though there was not statistically significant difference. Also previous study by Fukushima et al. [25] found that there were not any significant differences between nicorandil stress and rest of EDV, ESV and LVEF in acute ischemic heart failure patients. Hida et al. [26] found significant difference between ESV and LVEF between multivessel CAD and non mutivessel CAD involvement after adenosine triphosphate (ATP) loading.

Among patients with SCF, we concluded that all of scintigraphic findings including different QPS variable such as raw, extension, severity, and reversibility were improved after nicorandil consumption. Furthermore in SCF patients, improvement of EDV, ESV and LVEF after nicorandil consumption in both rest and stress myocardial perfusion imaging was expected. On the other hand, in multi-vessels involvement with SCF, there was a trend to see more difference after nicorandil consumption as compared to the patients with one vessel involvement. We concluded that in patients with SCF, use of nicorandil may provide better myocardial perfusion and relief of cardiovascular symptoms. Besides effect of nicorandil is more prominent in patients with multi-vessels disease. However, it should be mentioned that the perfusion changes in patients with SCF is very subtle.

Study limitation

One of shortcoming of our study was relatively small number of patients. A multicenter study with larger patient population, will more reliably demonstrate efficacy of nicorandil on increasing LVEF and decreasing EDV and ESV. The safety profile of nicorandil deserves more thorough investigation since long-term treatment with nicorandil might be beneficial for improvement of coronary blood flow in these patients.

CONCLUSION

The main finding of this study was significant difference between rest and stress status of perfusion scintigraphic findings. The principle findings was better myocardial coronary flow after nicorandil consumption in patients with SCF especially those with SCF multi-vessel involvement by improvement in different scores calculated by QPS software.

Acknowledgment

REFERENCES

1. Karagounis L, Sorensen SG, Menlove RL, Moreno F, Anderson JL. Does thrombolysis in myocardial infarction (TIMI) perfusion grade 2 represent a mostly patent artery or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the TEAM-2 study. Second Multicenter Thrombolysis Trial of Eminase in Acute Myocardial Infarction. J Am Coll Cardiol. 1992 Jan;19(1):1-10.

2. Ito H, Okamura A, Iwakura K, Masuyama T, Hori M, Takiuchi S, Negoro S, Nakatsuchi Y, Taniyama Y, Higashino Y, Fujii K, Minamino T. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. Circulation. 1996 Jun 1;93(11):1993-9.

3. Abbo KM, Dooris M, Glazier S, O'Neill WW, Byrd D, Grines CL, Safian RD. Features and outcome of no-reflow after percutaneous coronary intervention. Am J Cardiol. 1995 Apr 15;75(12):778-82.

4. Rezkalla SH, Kloner RA. No-reflow phenomenon. Circulation. 2002 Feb 5;105(5):656-62.

5. Kotani J, Nanto S, Mintz GS, Kitakaze M, Ohara T, Morozumi T, Nagata S, Hori M. Plaque gruel of atheromatous coronary lesion may contribute to the no-reflow phenomenon in patients with acute coronary syndrome. Circulation. 2002 Sep 24;106(13):1672-7.

6. Taira N. Nicorandil as a hybrid between nitrates and potassium channel activators. Am J Cardiol. 1989 Jun 20;63(21):18J-24J.

7. Miura T, Kawamura S, Tatsuno H, Ikeda Y, Mikami S, Iwamoto H, Okamura T, Iwatate M, Kimura M, Dairaku Y, Maekawa T, Matsuzaki M. Ischemic preconditioning attenuates cardiac sympathetic nerve injury via ATP-sensitive potassium channels during myocardial ischemia. Circulation. 2001 Aug 28;104(9):1053-8.

8. Ishii H, Ichimiya S, Kanashiro M, Amano T, Imai K, Murohara T, Matsubara T. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. Circulation. 2005 Aug 30;112(9):1284-8.

9. Ito H, Taniyama Y, Iwakura K, Nishikawa N, Masuyama T, Kuzuya T, Hori M, Higashino Y, Fujii K, Minamino T. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. J Am Coll Cardiol. 1999 Mar;33(3):654-60.

10. Sakata Y, Kodama K, Komamura K, Lim YJ, Ishikura F, Hirayama A, Kitakaze M, Masuyama T, Hori M. Salutary effect of adjunctive intracoronary nicorandil administration on restoration of myocardial blood flow and functional improvement in patients with acute myocardial infarction. Am Heart J. 1997 Jun;133(6):616-21.

11. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. Lancet. 2002 Apr 13;359(9314):1269-75.

12. Glover DK, Ruiz M, Koplan BA, Watson DD, Beller GA. 99mTc-tetrofosmin assessment of myocardial perfusion and viability in canine models of coronary occlusion and reperfusion. J Nucl Med. 1999 Jan;40(1):142-9.

13. Kaul S, Villanueva FS. Is the determination of myocardial perfusion necessary to evaluate the success of reperfusion when the infarct-related artery is open? Circulation. 1992 May;85(5):1942-4.

14. Kaul S. Assessing the myocardium after attempted reperfusion: should we bother? Circulation. 1998 Aug 18;98(7):625-7.

15. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996 Mar 1;93(5):879-88.

16. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation. 1996 Mar 1;93(5):905-14.

17. Dabbagh Kakhki VR, Jabari H. Dipyridamole stress and rest gated 99mTc-sestamibi myocardial perfusion SPECT: left ventricular function indices and myocardial perfusion findings. Iran J Nucl Med. 2007;15(1):1-7.

18. Kakhki VR, Zakavi SR, Sadeghi R. Comparison of two software in gated myocardial perfusion single photon emission tomography, for the measurement of left ventricular volumes and ejection fraction, in patients with and without perfusion defects. Hell J Nucl Med. 2007 Jan-Apr;10(1):19-23.

19. Zakavi SR, Zonoozi A, Kakhki VD, Hajizadeh M, Momennezhad M, Ariana K. Image reconstruction using filtered backprojection and iterative method: effect on motion artifacts in myocardial perfusion SPECT. J Nucl Med Technol. 2006 Dec;34(4):220-3.

20. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, Van Train KF, Berman DS. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med. 1995 Nov;36(11):2138-47.

21. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975 Apr;51(4 Suppl):5-40.

22. Sugimoto K, Ito H, Iwakura K, Ikushima M, Kato A, Kimura R, Tanaka K, Masuyama T, Ogihara T, Kawano S, Fujii K. Intravenous nicorandil in conjunction with coronary reperfusion therapy is associated with better clinical and functional outcomes in patients with acute myocardial infarction. Circ J. 2003 Apr;67(4):295-300.

23. Ono H, Osanai T, Ishizaka H, Hanada H, Kamada T, Onodera H, Fujita N, Sasaki S, Matsunaga T, Okumura K. Nicorandil improves cardiac function and clinical outcome in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: role of inhibitory effect on reactive oxygen species formation. Am Heart J. 2004 Oct;148(4):E15.

24. Sani HD, Eshraghi A, Nezafati MH, Vojdanparast M, Shahri B, Nezafati P. Nicorandil versus nitroglycerin for symptomatic relief of angina in patients with slow coronary flow phenomenon: A randomized clinical trial. J Cardiovasc Pharmacol Ther. 2015 Jul;20(4):401-6.

25. Fukushima Y, Kumita S, Tokita Y, Sato N. Prognostic value of myocardial perfusion SPECT after intravenous bolus administration of nicorandil in patients with acute ischemic heart failure. J Nucl Med. 2016 Mar;57(3):385-91.

26. Hida S, Chikamori T, Tanaka H, Igarashi Y, Shiba C, Hatano T, Usui Y, Yamashina A. Postischemic myocardial stunning is superior to transient ischemic dilation for detecting multivessel coronary artery disease. Circ J. 2012;76(2):430-8.