# Novel Technique to Prevent No/Slow Flow During PCI by Sodium Nitroprusside Injection Time, Point and Method

**Sarbesh Kumar Jha[1], Chunguang Qiu[2], Zhangying Han[3], Atul Dwivedi[4], Guoju Sun[5], Xiaofei Qin[6], Guanghui Liu[7], Wenjie Lu[8], Xi Wang[9]**

**ABSTRACT**

**Introduction:** The no-reflow incidence appears to be highest in acute myocardial infarction patients who undergoes primary percutaneous coronary intervention (PCI) or during PCI of saphenous vein grafts. The intracoronary administration of medications that causes vasodilatation in small distal coronary vasculature forms the base of management of no-reflow. Sodium nitroprusside (NTP) does not require intracellular metabolism to induce vasodilatation in microcirculation. In view of above present study was undertaken to evaluate efficacy and usefulness of sodium nitroprusside in prevention of no/ slow reflow at the time of fixing stents and balloons simultaneously and complications associated with it.

**Material and Methods:** The current study comprised of 93 patients who were done percutaneous coronary interventions and were randomly divided into two groups namely: Drug (Nitroprusside) given group (n=47) and placebo group (n=46). A stent or a balloon on specific lesion was passed and then loading dose of sodium nitroprusside (50-100 micro gram) or normal saline (2-3ml) was prepared and injected through guiding catheter into coronary artery. Maximum Duration of decreased BP and TIMI Grade were noted. A Pearson correlation analysis was conducted to examine whether there is a relationship between Nitroprusside and Coronary Slow/No Reflow. A statistical analysis of numerical variables expressed as mean±SD was done using ANOVA.

**Results:** 5 cases of coronary slow/ no reflow in placebo group and no cases in nitroprusside group was reported. A significant and negative relationship between 2 parameters (r = .24, N = 93, p = .02). The Lowest SBP was 56 mmHg (Mean = 101.34, SD = 20.663), maximum SBP difference with in 2-3 minute each time drug was given was 100 mmHg (Mean = 29.38, SD = 18.431) and maximum duration of falling blood pressure was 180 seconds (Mean = 91.21, SD = 24.655).

**Conclusion:** Intracoronary Nitroprusside is useful for the prevention of the slow Reflow or No-Reflow Phenomenon Following PCI in Acute Myocardial Infarction. This knowledge can be utilized to prevent the coronary vaso-spasm during PCI which would be beneficial to reduce complications during and after PCI.

**Keywords:** Nitroprusside, Percutaneous coronary intervention

## INTRODUCTION

Primary percutaneous coronary intervention (PCI) improves the survival ST-segment elevation myocardial infarction (STEMI) patients. However, despite the presence of normal epicardial flow, post-procedural microvascular obstruction which substantially reduces the beneficial effects of PCI, remains an important limitation of the procedure.[1]

The phenomenon of no-reflow is characterized by an insufficient myocardial tissue perfusion in the presence of a patent epicardial coronary artery. The no-reflow incidence appears to be highest in acute myocardial infarction patients who undergoes primary percutaneous coronary intervention (PCI) or during PCI of saphenous vein grafts.[2]

Several key pathophysiological processes, usually in combination, including thrombus formation, distal embolization of athero- thrombotic debris, and endothelial dysfunction of the distal arteriolar and capillary bed, including microcirculatory vasospasm and endothelial desquamation are believed to be responsible for this complication.[3]

Various management methods have undergone evaluation trials with variable success rates, and continued understanding of this phenomenon suggests that prevention might be better than the cure in most settings (table-1).[4]

Slow flow and no-reflow with impaired myocardial perfusion can be diagnosed by angiography or by using adjunctive imaging modalities such as myocardial contrast echocardiography that can quantify myocardial perfusion.

The TIMI study group in 1985 introduced TIMI coronary flow grade which is a simple, qualitative tool to evaluate angiographic coronary flow rates to monitor the efficiency of thrombolytic therapy.[5] Improved TIMI grades have been shown to be correlated with improved outcomes.[6,7] Traditionally, in this scheme no-reflow is defined as TIMI grade 0 or 1, and slow flow is defined as TIMI grade 2.[5] The TFC method, first described by Gibson et al[8] provided a semi-quantitative method of assessing coronary flow.[9] The angiographic frames number

[1]Doctorate Student, Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, School of International Education (SIE), Zhengzhou University, Zhengzhou, Henan, P.R. China, 450052, [2]Professor and Director, Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, [3]Professor, Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, [4]PhD Student, Department of Orthopaedics, The First Affiliated hospital of Zhengzhou university, School of International Education (SIE), [5]Professor, Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China, 450052, [6]Professor, Department of Cardiology, [7]Doctor, Department of Cardiology [8]Doctor, Department of Cardiology [9]Doctor, Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China, 450052

**Corresponding author:** Prof Chunguang Qiu, Department of Cardiology, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China 450052

**How to cite this article:** Sarbesh Kumar Jha, Chunguang Qiu, Zhangying Han, Atul Dwivedi, Guoju Sun, Xiaofei Qin, Guanghui Liu, Wenjie Lu, Xi Wang. Novel technique to prevent no/slow flow during PCI by sodium nitroprusside injection time, point and method . International Journal of Contemporary Medical Research 2017;4(4):874-878.

for contrast to reach a particular distal segment in the coronary artery with cine-angiography performed at 30 frames per second through a 6-F catheter was designated the TIMI frame count. The table 2 summarises distal landmarks and normal reference ranges.

The intracoronary administration of medications that causes vasodilatation in small distal coronary vasculature forms the base of management of no-reflow. Sodium nitroprusside (NTP) does not require intracellular metabolism to induce vasodilatation in microcirculation as it is a direct nitric oxide donor.[2]

In view of above present study was undertaken to evaluate efficacy and usefulness of sodium nitroprusside in prevention of no/ slow reflow and complications associated with it.

## MATERIAL AND METHODS

The present prospective study was a randomized, double blind, placebo-controlled clinical trial comprised of 93 patients who were done percutaneous coronary interventions (PCI) in our catheter laboratory (Cath. Lab.) from October 2012 to February 2013 and were divided into two groups namely: Drug (Nitroprusside) given group (n=47) and placebo group (n=46). About 1000 of patients were done percutaneous coronary interventions (PCI) in our catheter laboratory (Cath. Lab.) during this period and patients fulfilling the inclusion criteria were enrolled in the present study. Ethical clearance was obtained from the institute before initiation of the study. Informed consent was obtained from the patients. Patients aged≥18 years, with NSTEMI (Non–ST-segment elevation myocardial infarction) and STEMI (ST-segment elevation myocardial infarction), TIMI (Thrombolysis In Myocardial Infarction) 3 before Percutaneous coronary intervention were included in the study. Patients contraindicated for PCI (SBP≤9ommHg, cardiogenic shock, ISR, LM, CKD (eGFR<mL), pregnancy, culprit lesion located in bypass graft) were excluded from the study.

Coronary angiography was performed from radial approach using Judkins technique in conventional projections. During each injection, 6–8 ml contrast agent was manually delivered. Cine rate was 15 frames per second. For each patient, CAG was done at first and TIMI grade was noted for each coronary artery. Then all the patients were confirmed with TIMI Frame Count (TFC). Length of the lesion was measured by DICOM software. Patients were randomly divided into Nitroprusside (NSP) group (N=47) or placebo group (N=46) (figure 1). Before giving NSP or placebo, we passed a stent or a balloon on specific lesion and then loading dose of sodium nitroprusside (50-100 micro gram) or normal saline (2-3ml) was prepared and injected through guiding catheter into coronary artery. After this, we fixed stent or balloon for each lesion simultaneously. Blood pressure and heart rate were recorded before and after each drug. Maximum Duration of decreased BP and TIMI Grade were also checked and noted after each drug or placebo.

Patient's data were collected from our hospital data base. Routine clinical and laboratory parameters were done before the procedure. Blood samples are collected from the antecubital vein were sent to the laboratory for analysis collected within an hour. Clinical parameters (age, sex, past and social history and statin dose, troponin T, CKMB, total cholesterol, triglyceride, HDL, LDL, hsCRP, MPV. Uric Acid, Fibrinogen, Hemoglobin and HCT) were selected and noted for each patient.

## STATISTICAL ANALYSIS

SPSS, version 20.0 Inc., Chicago,IL,USA, was used for statistical analysis. ANOVA and Pearson correlation analysis was conducted to examine whether Intracoronary Nitroprusside has on excellent effect on prevent of Coronary Slow/No Reflow. Pearson correlation, Logistic regression was done multivariable

| PCI Type | Incidence of No-Reflow |
|---|---|
| All PCI | 0.6%- 2% (7,104) |
| Primary PCI | 8.8%- 11.5% (1,7) |
| SVG PCI | 8% - 15%(68,105) |
| Rotational artherectomy | ≤ 16% (75,76) |

**Table-1:** Incidence of angiographic No- reflow in various PCI settings[4]

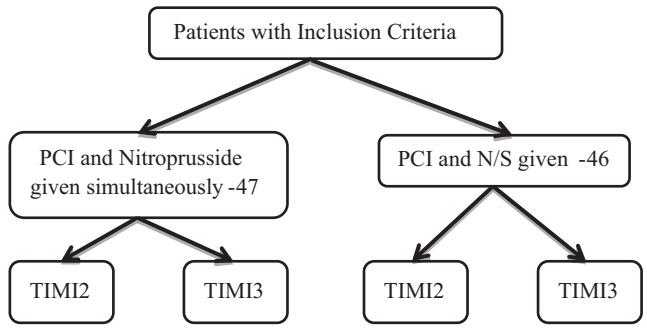


**Figure-1:** Shows distribution of cases for present study

| TIMI Flow Grades [5] | | |
|---|---|---|
| TIMI 0 | | No contrast flow beyond the site of occlusion (no perfusion) |
| TIMI 1 | | Contrast flow beyond the site of occlusion but failing to opacify entire artery (penetration with minimal perfusion) |
| TIMI 2 | | Contrast flow beyond the site of occlusion ond opacification of the entire artery but at rate slower than normal(partial perfusion) |
| TIMI 3 | | Normal flow, with opacification of the entire artery at a normal rate. |
| Normal flow: cTFC <20-22<br>Distal landmark: LAD, LCx, distal bifurcation of the branch segments with the longest total distance; RCA, first branch of the posterolateral artery. | | |
| cTFC (19) | | MBG (18) |
| LAD : Normal | 36±3 | Blush 0: No appearance of blush or contrast density (also persistent staining of myocardium) |
| Normal cTFC | 21±2 | Blush 1: Minimal myocardial blush or contrast density. |
| LCx Normal | 22±4 | Blush 2: Moderate myocardial blush or contrast density. |
| RCA Normal | 20±3 | Blush 3: Normal |

**Table-2:** Schemes to describe coronary and myocardial blood flow during coronary angiography

to see association between investigation and no reflow was done to see the association between other test parameters. A Pearson correlation analysis was conducted to examine whether there is a relationship between Nitroprusside and Coronary Slow/No Reflow.

## RESULTS

Among 93 patients, 5 cases of coronary slow/ no reflow in placebo group and no case in nitroprusside group was reported. The results revealed a significant and negative relationship (r = .24, N = 93, p = .02). The correlation was weak in strength. Nitroprusside was inversely significantly correlated with coronary slow/no reflow meaning that Nitroprusside can significantly prevent coronary slow/no reflow by this new method. Regarding complication of Nitroprusside we monitored the Blood Pressure carefully during the whole procedure. The Lowest SBP was 56 mmHg (Mean = 101.34, SD = 20.663), maximum SBP difference between before and after each time

| | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Lowest SBP | 47 | 56 | 153 | 101.34 | 20.663 |
| Max SBP Difference | 47 | 5 | 100 | 29.38 | 18.431 |
| Max Duration of Falling BP | 47 | 66 | 180 | 91.21 | 24.655 |
| Valid N (list wise) | 47 | - | - | - | - |

**Table-3:** Descriptive study of complication of Nitroprusside

| Variable | OR | 95% confidence interval (CI) | | *P* value |
|---|---|---|---|---|
| | | Lower Bound | Upper Bound | |
| Patient BMI | 5.409 | .594 | 49.242 | .834 |
| Smoking Status | 7.000 | .750 | 65.356 | .242 |
| Drinking Status | .460 | .049 | 4.294 | .545 |
| Hypertension | .944 | .150 | 5.946 | 1.000 |
| Diabetes | .707 | .075 | 6.652 | .347 |
| Troponin T | .753 | .053 | 10.771 | .068 |
| CKMB | 1.016 | .941 | 1.096 | .798 |
| Total Cholesterol | .992 | .429 | 2.293 | .944 |
| Triglyceride | .951 | .410 | 2.205 | .261 |
| HDL | 3.224 | .035 | 293.999 | .412 |
| LDL | .894 | .349 | 2.293 | .964 |
| hsCRP | 1.069 | .782 | 1.461 | .673 |
| Mean Platelet Volume | 5.008 | .914 | 27.423 | .280 |
| Uric Acid | .991 | .979 | 1.003 | .354 |
| Fibrinogen | .295 | .092 | .946 | .059 |
| Haemoglobin | .993 | .823 | 1.058 | .309 |
| HCT | 4.390E-016 | 1.543E-040 | 1249189093 | .210 |
| Statin Dose | .994 | .903 | 1.094 | .545 |

**Table-4:** Multivariable logistic regression of the test parameter.

| Characterics | Nitroprusside Group (No. of patients) | Placebo Group (No. of patients) |
|---|---|---|
| Patient Age | 61.47± 11.455(47) | 60.83 ± 9.64 (46) |
| Patient BMI | 25.47±3.445(47) | 25.30±9.641(46) |
| Smoking Status | .32±.471(47) | .46±.504(46) |
| Drinking Status | .32±.471(47) | .37±.488(46) |
| Hypertension | .66±.479(47) | .57±.501(46) |
| Diabetes | .26±.441(47) | .26±.444(46) |
| Troponin T | .15630±.431101(37) | .14797±.303132(39) |
| CKMB | 19.91±28.022(34) | 24.10±23.217 (39) |
| Total Cholesterol | 4.1570±1.27329 (44) | 4.1821±1.13559 (42) |
| Triglyceride | 1.7184±1.27681(44) | 1.6431±.92062 (42) |
| HDL | .90707±.23374 (44) | 1.0200±.2844 (42) |
| LDL | 2.6339±1.10714 (44) | 2.5952±.97173 (42) |
| hsCRP | 6.1957±10.59592 (37) | 9.5597±27.55959(33) |
| Mean Platelet Volume | 9.257±1.8053 (44) | 8.722±1.4394 (41) |
| Uric Acid | 318.26±87.631 (45) | 307.79±67.843 (42) |
| Fibrinogen | 3.0368±.67357 (41) | 3.0961±.88891 (41) |
| Statin Dose | 13.62±10.719(47) | 13.48±4.815(46) |
| Max Stent Size | 28.87±5.507(47) | 28.46±6.098(46) |
| Max Pressure Applied | 17.49±4.096(47) | 16.70±3.632(46) |

**Table-5:** Demographic characteristics and baseline laboratory data among two groups

drug was given was 100 mmHg (Mean = 29.38, SD = 18.431) and maximum duration of falling blood pressure was 180 seconds (Mean = 91.21, SD = 24.655) (table 3). From all the parameters (biological and biochemical) investigated as shown in tables 4 and 5, no any significance nor any significant correlation was found with Coronary Slow/No reflow. Slow Coronary Flow was defined as TIMI flow grade 2 or more than upper limit of each TFC (i.e. greater than two standard deviations). No-reflow was defined as TIMI flow grade 0-1. After 3 year follow up of slow flow cases among 5 cases 2 of them Died, 3 alive.

## DISCUSSION

A number of treatment methods may be employed for prevention of slow or no-reflow during primary PCI. First, given the central role of duration of ischemia in the pathogenesis of impaired flow, primary PCI should be performed as soon as possible to limit ischemia reperfusion injury. In the catheterization laboratory, adjunctive pharmacotherapy with glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa) and mechanical devices to prevent distal embolization have emerged as potentially beneficial in improving epicardial and myocardial perfusion. The most studied agent in this class in the treatment of AMI is Abciximab.[10] Various studies have demonstrated specifically the beneficial role of using GPIIb/IIIa inhibitors during primary angioplasty on coronary microvascular flow using the coronary flow wire measurements,[11] and myocardial contrast echocardiography.[12]

SNP breaks down in circulation to release nitric oxide (NO) which leads to activation of guanylate cyclase in vascular smooth muscle and increases production of cGMP intracellularly which further activates Protein Kinase G which activates phosphatases which inactivate Myosin light chains which are involved in muscle contraction. The final outcome is relaxation of vascular smooth muscle, which further dilate vessels. In the human heart, both total peripheral resistance as well as venous return is reduced by nitric oxide, consequently decreases both preload and afterload. Hence, can be used in severe cardiogenic heart failure.[13]

Initial studies of nitroprusside encompassing angioplasty, stent deployment or rotational atherectomy on either SVGs or native vessels demonstrated highly significant, rapid and safe improvement of no-reflow by a variety of criteria.[14] No significant hypotension or other adverse clinical events were reported.

This study aimed to demonstrate the efficacy and usefulness of sodium nitroprusside in prevention of no/ slow reflow and complications associated with it. At the end of study we had 5/46 (10.64%) cases of coronary slow/ no reflow in placebo group and no case in Nitroprusside group. The correlation was weak in strength by analysis not by comparison to any literature. Nitroprusside was inversely significantly correlated with coronary slow/no reflow meaning that Nitroprusside can significantly prevent coronary slow/no reflow by this new method.

From all the parameters (biological and biochemical) investigated, no any significance nor any significant correlation was found with Coronary Slow/No reflow; which supported our belief of the mechanism of coronary slow/no reflow is due to coronary vasospasm.

PCI in the setting of AMI, due to the relatively high thrombus burden associated with plaque rupture and coronary occlusion is associated with high rates of distal embolization. In up to 16% of patients undergoing primary PCI, macroscopic distal embolization may be seen[15] and in 20% to 40% of patients suboptimal tissue perfusion may be seen despite restoration of TIMI 3 epicardial flow.[16,17] Normal micro vascular and coronary function generally yield a cTFC of <20, cTFC of 20 through 40 in case of a slow flow, and a no-reflow cTFC of >40.[18] The latter support our findings. Similarly, in an analysis of patients enrolled in the TIMI studies, the prognostic significance of the cTFC was studied which reported it to be an independent predictor of mortality.[9] IC bolus injection of nitroprusside as an adjunct to primary PCI improved angiographic TIMI flow by at least 1 grade in 9 of 11 patients (82%; $p = 0.007$).[19,20] Our use of NSP was significant in preventing slow flow. Treatment was uniformly safe. Myocardial microvascular perfusion, as assessed by an MBG score 0 to 3, independent of infarct artery patency, has been shown to be one of the major predictors of mortality after primary PCI.[21]

In this manner, slow flow would correspond with an MBG of 2 and true no-reflow would correlate with an MBG of 0 and 1. Certainly, the accuracy of these three methods depends on several factors, such as length of injection, amount of contrast injected, and fluoroscopic time, as well as systemic blood pressure.[22]

The limitation of the present study were firstly, we measured serum CK and CK-MB levels of AMI patients to evaluate during admission in hospital or before PCI. However, we could not assess enough about the impact of post PCI in both group patient using serum maximum CK and CK-MB levels. Second due to limitation of time we did not try with other drug to verify which the best so further study with longer is follow-up is required.

## CONCLUSION

Intracoronary administration of 100mcg of Nitroprusside immediately before PCI is a safe and simple procedure for preventing coronary slow flow phenomenon. From our study, we can conclude the intracoronary nitroprusside for the prevention of the slow/ No-Reflow Phenomenon during PCI in STEMI/ non-STEMI patients.

## REFERENCES


1. Zhao YJ, Fu XH, Ma XX et al. Intracoronary fixed dose of nitroprusside via thrombus aspiration catheter for the prevention of the no-reflow phenomenon following primary percutaneous coronary intervention in acute myocardial infarction. Experimental and Therapeutic Medicine. 2013;6:479-484.
2. Tesic MB, Stankovic G, Vukcevic V, Ostojic MC. The use of intracoronary sodium nitroprusside to treat no-reflow after primary percutaneous coronary intervention in acute myocardial infarction. Herz. 2010;35:114-8.
3. Rezkella SH, Kloner RA. No-reflow phenomenon. Circulation. 2002;105:656-662.
4. Klein LW, Kern MJ, Berger P, et al. Society of Cardiac Angiography and Interventions: Suggested management of the no-reflow phenomenon in the cardiac catheterization laboratory. Catheter CardiovascDiagn. 2003;60:194-201.
5. TIMI Study Group. The Thrombolysis in Myocardial

Infarction (TIMI) trial, phase I findings: TIMI Study Group. N Engl J Med. 1985;312:932-936.
6. 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.
7. 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.
8. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996;93:879-888.
9. Gibson CM, Murphy SA, Rizzo MJ, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Circulation. 1999;99:1945-1950.
10. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med. 2001;344:1895-1903.
11. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med. 2002;346:957-966.
12. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation. 1998;98:2695-2701.
13. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation. 1998;98:2695-2701.
14. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med. 2001;344:1895-1903.
15. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation. 1998;98:2695-2701.
16. van't Hof AW, Liem A, Suryapranata H, et al. Angiographic assessment of myocardial perfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation. 1998;97:2302-2306.
17. Henriques JP, Zijlstra F, Otteranger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart. J. 2002;23:1112-1117.
18. 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.
19. Ishii H, Ichimiya S, Kanashiro, et al. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment elevation myocardial infarction. Circulation. 2005;112:1284-1288.
20. Hang CL, Wang CP, Yip HK, et al. Early administration of intracoronary verapamil improves myocardial perfusion during percutaneous coronary interventions for acute myocardial infarction. Chest. 2005;128:2593-2598.
21. Stone GW, Peterson MA, Lansky AJ, et al. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. J Am CollCardiol. 2002;39:591-597.
22. 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.

**Source of Support:** Nil; **Conflict of Interest:** None

**Submitted:** 23-03-2017; **Accepted:** 26-04-2017; **Published:** 05-05-2017