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Treatment of No-Reflow in Degenerated Saphenous Vein Graft Interventions: Comparison of Intracoronary Verapamil and Nitroglycerin

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No-reflow has been reported after 10–15% of percutaneous interventions on degenerated saphenous vein grafts. In this prospective study of 36 degenerated saphenous vein graft lesions (32 patients), no-reflow (TIMI flow <3 in the absence of a significant lesion or dissection) occurred in 15/36 (42%) lesions. A total of 32 episodes of no-reflow occurred after angioscopy (n = 14), extraction atherectomy (n = 10), balloon angioplasty (n = 2) or stent implantation (n = 6). Intragraft nitroglycerin (100–300 μg) alone resulted in no improvement in TIMI flow in the setting of no-reflow (TIMI flow 1.2 ± 0.6 to 1.4 ± 0.8, P = NS). Intragraft verapamil (100–500 μg) resulted in improvement in flow in all 32 episodes (TIMI flow 1.4 ± 0.8 before, to 2.8 ± 0.5 after verapamil, $P < 0.001$). Although verapamil increased TIMI flow after all episodes of no-reflow, two (6.3%) had persistent no-reflow (TIMI 1) despite verapamil, associated with non-Q wave myocardial infarction. In conclusion, treatment of no-reflow with verapamil during degenerated vein graft interventions was associated with reestablishment of TIMI 3 flow in 88% of cases. In contrast, intragraft nitroglycerin alone was ineffective for reversing no-reflow. © 1996 Wiley-Liss, Inc.

Key words: no-reflow, verapamil, vein graft

INTRODUCTION

The no-reflow phenomenon was originally described in experimental models of acute myocardial infarction and has been defined as a failure to reperfuse myocardial tissue in the absence of epicardial coronary obstruction [1]. No-reflow complicates between 2 and 10% of all percutaneous interventional procedures [2–4]. Higher rates of no-reflow occur in the setting of acute myocardial infarction, vein graft interventions, and with the use of atherectomy devices [5,6]. The increased incidence of no-reflow in these situations suggests that intracoronary thrombus and distal embolization of atherosclerotic debris may play a major role. Experimental studies suggest that distal microvascular spasm triggered by the release of vasoactive substances is the primary cause of no-reflow [1,7–9]. Treatment of no-reflow with nitrates, heparin, and thrombolytics has been ineffective [2,3,5]. In contrast, the value of intracoronary calcium channel blockers is well reported, and both intracoronary verapamil [2,3,5] and diltiazem [4] have been reported to be useful in treating no-reflow, but prospective data are limited. The mechanism of action of calcium channel blockers is poorly understood, but microvascular and macrovascular spasm may be calcium mediated [10].

The purpose of this study was to prospectively examine the use of intracoronary verapamil and nitroglycerin to treat no-reflow in a series of interventions on high risk vein graft lesions.

MATERIALS AND METHODS

Study Population

Between September 1994 and March 1995, 32 consecutive patients undergoing interventions on 36 degenerated saphenous vein grafts were studied prospectively. No-reflow occurred in 15/36 (42%) of degenerated vein graft interventions. During these 15 interventions, there were 32 separate episodes of no-reflow which required drug treatment. The baseline demographics of the patient population are shown in Table I. The mean patient age was 68 ± 8 years and the mean age of the vein grafts was 8.4 ± 3.1 years. The study protocol was performed in

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TABLE I. Baseline Patient Demographics

Age (yr)	68 ± 8
Age of vein graft (yr)	8.4 ± 3.1
Previous myocardial infarction	53%
Anginal class 3 or 4	100%
Hypertention	63%
Hypercholesterolemia	44%
Diabetes mellitus	28%
Smoking (within 6 mo)	25%

accordance with an investigational protocol approved by the Human Investigation Committee of William Beaumont Hospital (Fig. 1).

Procedure

The interventional device utilized to treat the degenerated vein graft was chosen by the attending cardiologist based on clinical and angiographic criteria. Combined extraction atherectomy and stent implantation was utilized in 47%; PTCA and stent implantation in 37%; extraction atherectomy and PTCA in 9%; and PTCA alone in 7%. Coronary angioscopy (Baxter) was performed prior to intervention in 78%, to assess the intraluminal contents of the degenerated vein graft, as previously described [11].

Angiographic Analysis

No-reflow was defined as any Thrombolysis in Myocardial Infarction (TIMI) flow <3 in the absence of spasm, dissection, high-grade residual stenosis or occlusive thrombus at the original target lesion. No-reflow was initially treated according to attending physician preference with either intracoronary nitroglycerin (WWO) (200 μg) in 16 cases or intracoronary verapamil (RDS) (100–250 μg) in 16 cases. If there was no response to initial treatment, intracoronary verapamil (100–250 μg) was administered. The total dose of verapamil per patient ranged from 250 to 1250 μg. Verapamil and nitroglycerin were administered via the guiding catheter if TIMI flow = 2 or injected into the distal vessel through the central lumen of a balloon catheter if TIMI flow was ≤1. Patients who did not fully respond to either nitroglycerin or verapamil were treated with intraaortic balloon counterpulsation at the conclusion of the procedure.

In-Hospital Outcome

In-hospital events included recurrent ischemia necessitating repeat catheterization or percutaneous intervention, non-Q and Q wave myocardial infarction, coronary artery bypass graft surgery and death. Three sets of CPK enzymes and MB fraction were drawn every 8 hours after the procedure in all patients. The association between final TIMI flow and in-hospital complications was assessed.

Statistical Analysis

Statistical analysis was performed using a Student's *t* test for continuous variables or the Fisher exact test for categorical variables. A P value of <0.05 was considered statistically significant.

RESULTS

Incidence of No-Reflow

No-reflow occurred in 15 (42%) of 36 degenerated vein graft interventions; there were 32 separate episodes of no-reflow including TIMI flow = 2 in 17 and TIMI flow ≤1 in 15. The cause of no-reflow was angioscopy in 14 (44%), extraction atherectomy in 10 (31%), stent implantation in 6 (19%) and balloon angioplasty in 2 (6%). All patients with no-reflow after stent implantation had prior episodes of reversible no-reflow after angioscopy, extraction atherectomy, or PTCA. Of the 32 episodes of no-reflow, 5 (15.6%) were TIMI 0 flow, 10 (31.2%) were TIMI 1 flow, and 17 (51.2%) were TIMI 2 flow. Of the 14 episodes of no-reflow associated with angioscopy, TIMI ≤1 flow was seen in 4 cases. Only 1 of the 10 episodes of extraction atherectomy induced no-reflow involved TIMI flow ≤1. The remaining 10 episodes of severe no-reflow (TIMI flow ≤1) were associated with stent implantation or high pressure balloon inflation.

Treatment of No-Reflow

Intracoronary NTG resulted in no significant change in TIMI score: TIMI flow was 1.2 ± 0.5 before NTG and 1.4 ± 0.7 after NTG (P = NS; Fig. 2). Only 3/16 (19%) no-reflow episodes showed an improvement after nitroglycerin. In contrast, in the verapamil treated episodes, TIMI flow increased from 1.4 ± 0.8 verapamil to 2.8 ± 0.5 after verapamil ($P < 0.001$; Fig. 3). All 32 episodes improved by at least 1 TIMI grade and 28/32 (88%) improved to TIMI 3 after the first dose of verapamil; the response was similar in the 16 episodes treated with initial intracoronary verapamil as well as the 16 episodes which failed to reverse after NTG. Four patients had TIMI flow ≤2 despite verapamil; all were treated with intraaortic balloon counterpulsation. In addition, six patients who had transient no-reflow which reversed with verapamil also had balloon pumps placed after the procedure because of operator preference.

There were no differences in the incidence or reversibility of no -reflow based on the device used, although the absolute numbers were small. No-reflow after angioscopy and/or extraction atherectomy was always reversible after intracoronary verapamil; irreversible no-

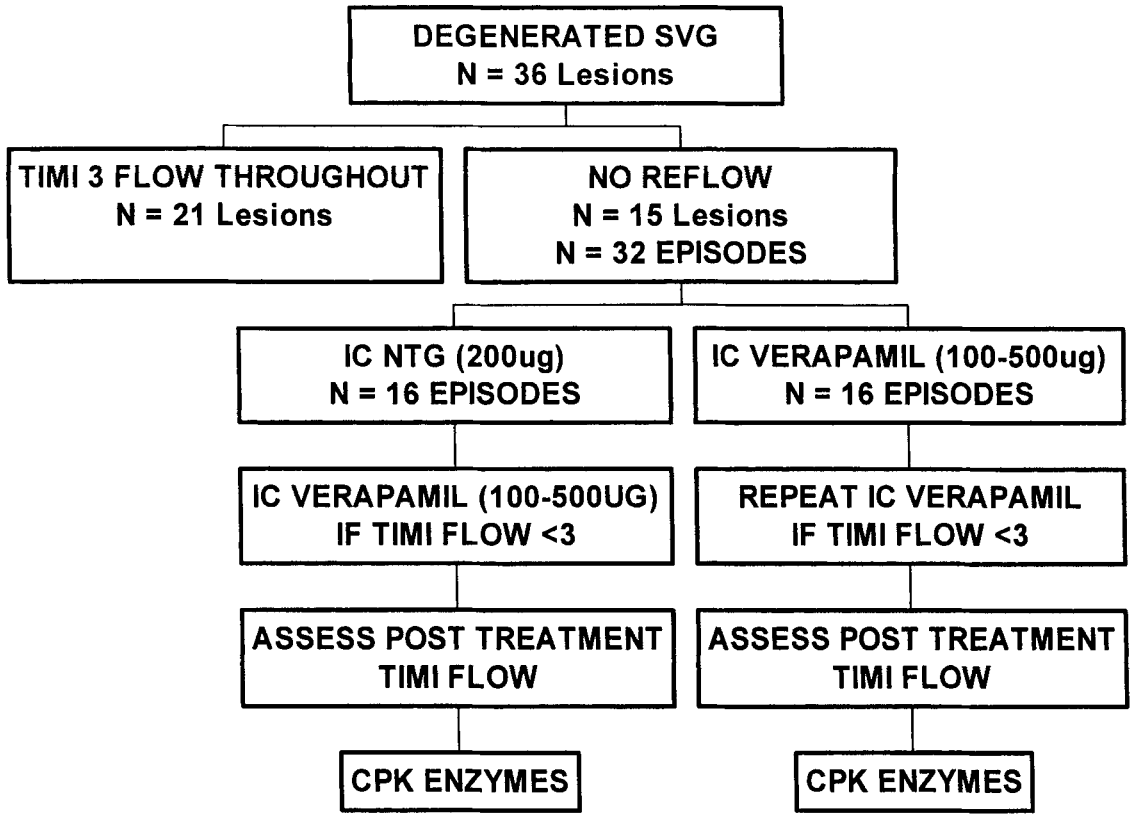

Fig. 1. Treatment alogrithm for no-reflow in 36 vein graft lesions.

reflow (final TIMI flow ≤ 1) occurred after stent implantation, but was preceded by earlier episodes of no-reflow after angioscopy and/or extraction atherectomy.

Other Procedural Complications

Procedural complications other than the no-reflow phenomenon were rare. Angiographically visible macroembolization of vein graft debris occurred in only 1 of the 15 cases which was also complicated by no-reflow. Other angiographic complications aside from no-reflow included distal embolization (3.1%), and dissection (12.5%). Flow limiting dissections were successfully treated with stent implantation. There were no episodes of symptomatic bradycardia, atrioventricular block, or hypotension associated with verapamil use.

In-Hospital Complications

No patients had stent thrombosis, Q wave myocardial infarction, emergency revascularization by coronary artery bypass graft surgery or PTCA, or died. Two patients (6.3%) had a non Q wave myocardial infarction (CPK-MB > 25 IU/liter); both had TIMI flow ≤ 1 at the conclusion of the procedure. The remaining 13 patients did not suffer in-hospital events or elevation of CPK isoenzymes (Fig. 4).

DISCUSSION

The most important finding of this study is the effectiveness and safety of intracoronary verapamil for the treatment of no-reflow. In contrast, intracoronary nitroglycerin alone is not useful for reversal of no-reflow. In addition, the no-reflow phenomenon is extremely common in complex vein graft interventions and the rate of at least a transient decrease in flow approaches 50%.

Incidence of No-Reflow

The no-reflow phenomenon occurs at a high rate after degenerated saphenous vein graft interventions [5]. This is particularly true if the lesions are associated with angiographic haziness, filling defects, or ulcerations. Often, these vein grafts are not intervened upon secondary to the high risk of periprocedural complications including the no-reflow phenomenon. Sustained no-reflow was seen in 6.3% of cases in this study which is similar to reported rates of no-reflow after interventions in these grafts. However, the standard definition of no-reflow does not include transient no-reflow; thus, the rate of transient no-reflow is likely under-reported and may approach 50% in high risk, thrombotic, degenerated vein grafts. Although the strict definition of no-reflow in this study (TIMI flow <3) may have overestimated the inci-

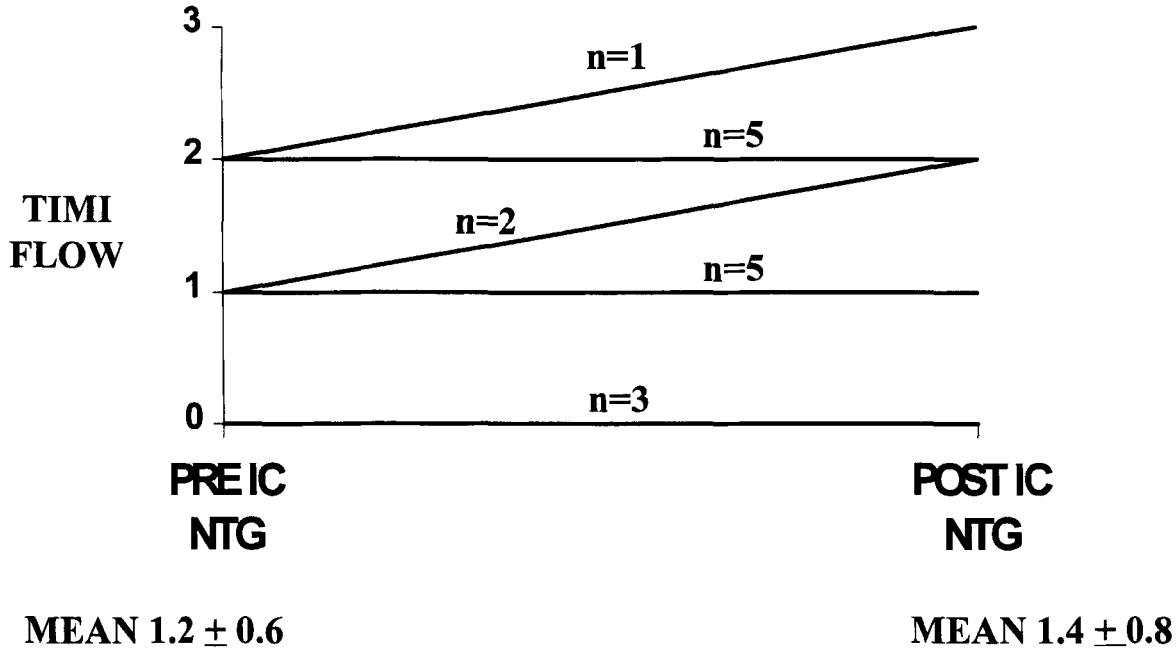

Fig. 2. TIMI flow before and after intracoronary nitroglycerin (n = 16).

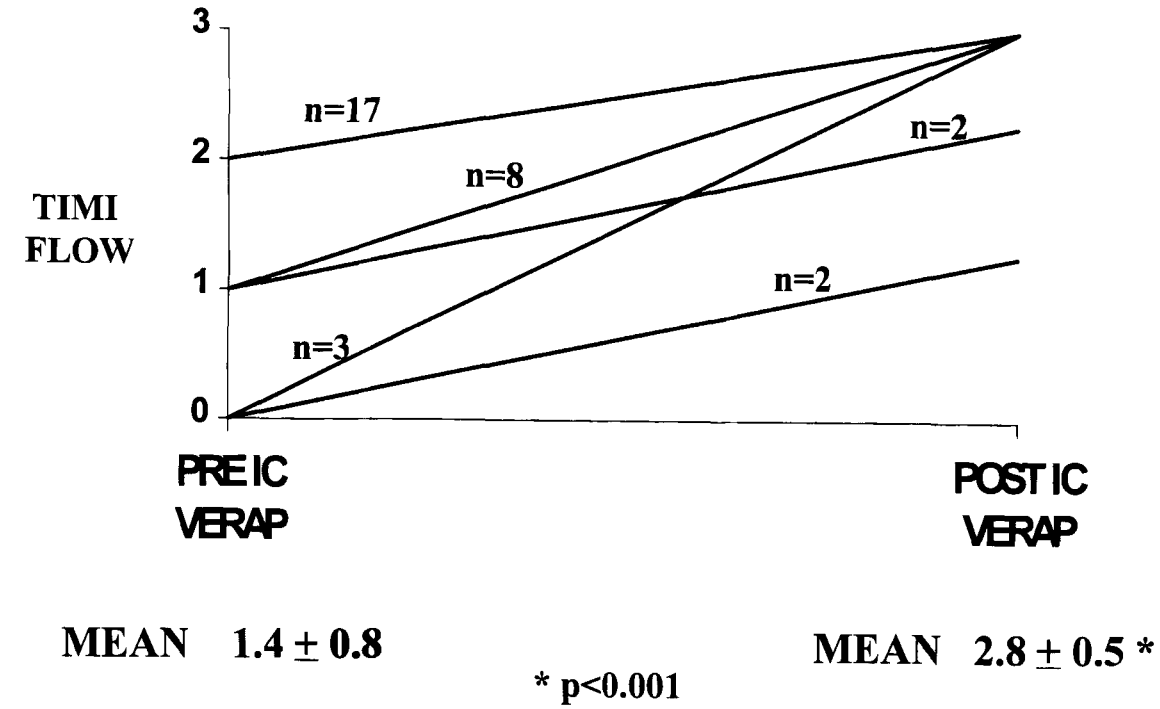

Fig. 3. TIMI flow before and after intracoronary verapamil (n = 32).

dence of no-reflow, the importance of treating "slow flow" (TIMI 2 flow) situations is emphasized. Verapamil effectively converted all episodes of "slow flow" (17/17) to TIMI 3 flow. None of the patients with transient mild no-reflow (TIMI 2 flow) which was reversed by verapamil suffered post procedure CPK elevations.

Etiology of No-Reflow

While this study was not designed to examine mechanisms of no-reflow, there were several characteristics which may shed some insight into the potential etiologic factors. The low incidence of angiographic distal mac-

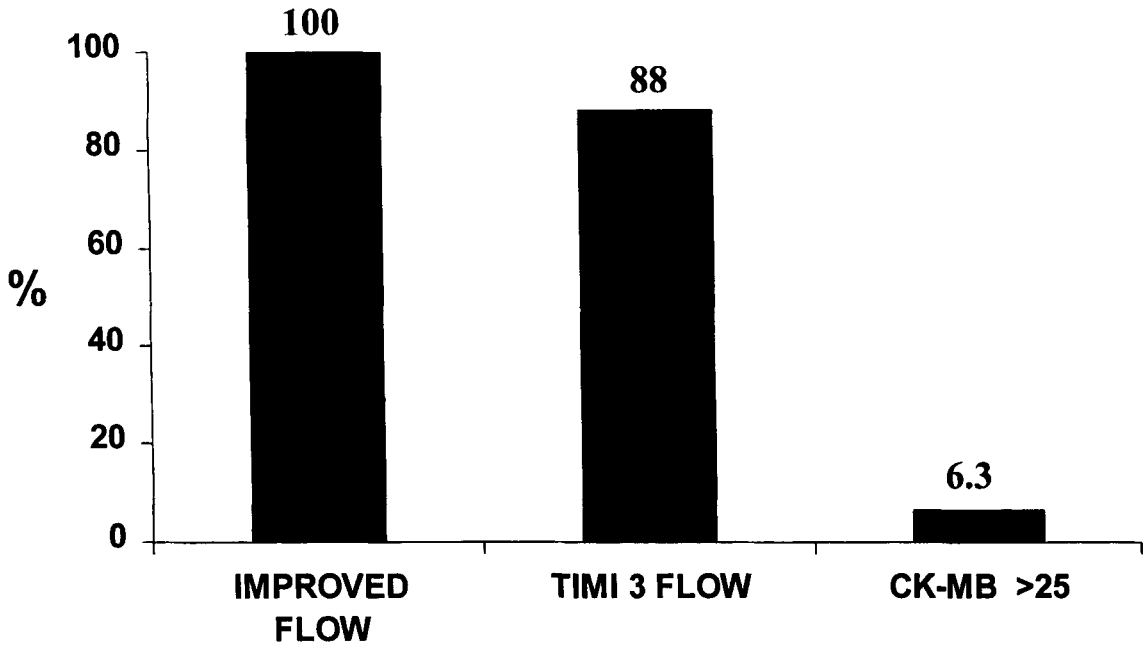

Fig. 4. In-hospital outcome after treatment for no-reflow.

roembolization suggests that microparticle embolization may cause distal microvascular spasm rather than actual vessel obstruction. However, the reason why balloon inflation or stent implantation causes more severe no-reflow than TEC or angioscopy is unknown. At least two possibilities exist to explain this phenomenon. First, balloon/stent inflation is more likely to induce breaking off of large, loose particles which are often seen by angioscopy in degenerated vein grafts [12]. Thus, aggressive attempts at extracting thrombus or debris prior to balloon inflation may help to decrease the incidence and severity of no-reflow. Second, in a situation where microvascular spasm already exists from previous episodes of no-reflow, a viscious cycle may be set up where balloon inflation can cause temporary vessel obstruction increasing stasis in the distal vascular bed and thrombosis or further spasm of the microvasculature. This phenomenon of stasis and thrombosis in the macrocirculation after spasm is well documented [13,14]. The distal spasm alone may be readily reversible with verapamil; however, if significant stasis and distal microvessel thrombosis occurs, verapamil alone may not fully reverse the no-reflow. Anecdotally, if verapamil administration through the guiding catheter fails to improve coronary flow, injection through the central lumen of the balloon catheter into the distal native vessel is often successful.

Treatment of No-Reflow

Although successful use of calcium channel blockers for no-reflow is previously well reported in the literature [2–5], this is the first prospective evaluation of nitroglycerin and verapamil in the treatment of this phenomenon. As was previously reported, intracoronary verapamil is extremely successful for reversal of no-reflow, whereas nitroglycerin is ineffective [2,3,5]. This is consistent with the hypothesis that calcium flux is intimately involved in the mechanism of no-reflow [15,16]. It also establishes that although nitroglycerin is an effective vasodilator, its effect on the microvasculature is limited. Given the frequency of no-reflow demonstrated in this degenerated vein graft study, the use of prophylactic intracoronary calcium channel blockers may demand consideration

More importantly, the risk of significant CPK enzyme elevation and postprocedure myocardial infarction seems to exist only if the no-reflow cannot be reversed by verapamil. Due to the high rate of success with treatment seen in this study, the clinical event rates are markedly lower than previously described after the no-reflow phenomenon. Previously no-reflow was associated with high myocardial infarction and in-hospital mortality rates [5]. The postprocedure infarction rate may be explained by the increased aggressive use of calcium channel blockers or an increased use of extraction atherectomy which may limit the severity of no-reflow seen. However, retrospective reports have shown that TEC can reduce the incidence of postprocedure CPK enzyme elevations after percutaneous saphenous vein graft interventions [17] and therefore, the high rates of TEC use in this study may also have contributed to the low myocardial infarction rates.

There were no complications associated with intracor-

onary verapamil administration, which is consistent with previous studies [2,3]. This is particularly significant given the higher doses of verapamil used in this study. Occasionally, hypotension and bradycardia are caused by no-reflow itself and many operators are hesitant to use intracoronary calcium antagonists. Based on our experience, hypotension or bradyarrhythmias in the setting of no-reflow should not be considered an absolute contraindication to calcium blocker administration. In extreme circumstances, the concurrent use of vasopressor agents to increase perfusion pressure may be necessary.

Recommendations

The data on the treatment of no-reflow are now reasonably clear. Intracoronary calcium channel blockers are effective in reversing no-reflow in a majority of cases. The liberal use of these agents has not been associated with any significant side effects. Therefore, the risk/benefit considerations should lead to a strong recommendation for the use of intracoronary verapamil for the treatment of no-reflow. Future studies may also demonstrate that other agents such as adenosine or papaverine may also be useful for the treatment of no-reflow. Although difficult to perform, randomized studies may also be necessary.

Limitations

This study has several limitations. First, although patients received nitroglycerin or verapamil initially in response to no-reflow, this decision was not randomized but rather the choice of the attending physician (WWO vs. RDS). This may have biased the data; however, there was no evidence that the no-reflow was different or more severe in the nitroglycerin cases and these cases served as a control population. Second, assessment of drug efficacy was based on angiographic TIMI flow. This can be subjective, and the interpreter of cine films was not blinded to treatment. Future studies on no-reflow could rely on more objective data such as that provided by the doppler flow wire.

Conclusions

No-reflow occurred after 42% of percutaneous interventions in degenerated saphenous vein grafts. Treatment with intracoronary nitroglycerin alone is ineffective for reversing no-reflow. Treatment with intracoronary verapamil is successful in improving no-reflow in all cases with normalization of TIMI flow in 88% of cases. Additionally, patients with transient no-reflow reversed by intracoronary verapamil do not suffer postprocedure myocardial infarction. A prospective trial examining the use of prophylactic intracoronary verapamil prior to each stage of saphenous vein graft interventions has been initiated.

REFERENCES

1. Kloner RA, Ganote CE, Jennings RB: The "no reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 54:1496–1508, 1974.
2. Piana RN, Paik GY, Moscucci M, Cohen DJ, Gibson CM, Kugelmass AD, Carozza JP Jr, Kuntz RE, Baim DS: Incidence and treatment of no reflow after percutaneous coronary intervention. Circulation 89:2514–2518, 1994.
3. Pomerantz RM, Kuntz RE, Diver DJ, Safian RD, Baim DS: Intracoronary verapamil for the treatment of distal microvascular coronary artery spasm following PTCA. Cathet Cardiovasc Diagn 24:283–285, 1991.
4. Weyrens FJ, Mooney J, Lesser J, Mooney MR: Intracoronary diltiazem for "no reflow" following interventional therapy. Am J Cardiol (submitted for publication).
5. 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 75:778–782, 1995.
6. Safian RD, Niazi KA, Strzelecki M, Lichtenberg A, May MA, Juran N, Freed M, Ramos R, Gangadharan V, Grines CL, O'Neill WW: Detailed angiographic analysis of high speed mechanical rotational atherectomy in human coronary arteries. Circulation 88:961–968, 1993.
7. Punch J, Pees R, Cashmer B, Wilkins E, Dmith DJ, Till GO: Xanthine oxidase: Its role in the no reflow phenomenon. Surgery 11:169–176, 1992.
8. Seydoux C, Goy JJ, Davies G: Platelet and neutrophil imaging techniques in the investigation of the response to thrombolytic therapy and the no-reflow phenomenon. Am Heart J 125:1142–1147, 1993.
9. Ambrosio G, Weisman HF, Mannisi JA, Becker LC: Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. Circulation 80:1846–1861, 1989.
10. Villari B, Ambrosio G, Golino P, Ragni M, Focaccio A, Tritto I, Slavatore M, Chiarello M: The effects of calcium channel antagonist treatment and oxygen free radical scavenging on infarct size and the no-reflow phenomenon in reperfused hearts. Am Heart J 125:11–23, 1993.
11. Annex BH, Larkin TJ, O'Neill WW, Safian RD: Evaluation of thrombus removal by transluminal extraction atherectomy by percutaneous coronary angioscopy. Am J Cardiol 74:606–609, 1994.
12. Tilli F, Kaplan BM, Safian RD, Grines CI, O'Neill WW: Angioscopic plaque friability: A new risk factor for complications after saphenous vein graft interventions. J Am Coll Cardiol (abstract), 1996.
13. Bates ER, Krell MJ, Dean EN, O'Neill WW, Vogel RA: Demonstration of the "no-reflow" phenomenon by digital coronary angiography. Am J Cardiol 57:177–178, 1986.
14. Wilson RF, Lesser JR, Laxson DD, White SW: Intense microvascular constriction after angioplasty of acute thrombotic coronary artery lesions. Lancet 1:807–811, 1989.
15. Kawamure A, Fujiwara H, Uegaito T, Tanake M, Kawai C: Comparative effects of diltiazem, nifedipine, and verapamil on large and small coronary artery constriction induced by intracoronary acetylcholine in pigs. J Cardiovac Pharmacol 19:915–921, 1992.
16. Spessot M, Pedrinelli R: The interference by nicardipine and diltiazem on alpha-adrenergic receptor mediated vasoconstriction in isolated human subcutaneous arterioles. Clin Pharmacol Ther 54: 70–75, 1993.
17. Al-Shaibi KF, Goods CM, Jain SP, Negus BH, Babu R, Liu MW, Sutor CE, Dean LS, Parks JM: Does transluminal extraction atherectomy reduce distal embolization in saphenous vein grafts? Circulation 92:1–329, 1995.