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Resolution of Refractory No-Reflow With Intracoronary Epinephrine

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Refractory no-reflow is associated with adverse outcomes in patients undergoing percutaneous coronary intervention. Charts were reviewed to identify 29 consecutive patients in whom intracoronary epinephrine was administered for refractory no-reflow. The effects of intracoronary epinephrine on coronary flow (TIMI grade), cardiac rhythm, and systolic blood pressure in the cardiac catheterization laboratory were assessed. Administration of intracoronary epinephrine (mean dose, 139 ± 189 μg) resulted in significant improvement in coronary flow. After administration, TIMI 3 flow was established in 69% of patients. Overall, TIMI flow significantly increased (mean TIMI flow form 1.0 ± 1.0 to 2.66 ± 0.55; $P = 0.0001$). Intracoronary epinephrine resulted in significant but tolerable increase in heart rate (72 ± 19 to 86 ± 26 beats/min; $P = 0.009$), but no cases of acute dysrhythmia. These findings indicate that intracoronary epinephrine may exert salutary effects in patients suffering refractory no-reflow following elective or acute coronary interventions. *Cathet Cardiovasc Intervent 2002;57:305–309.*

Key words: angioplasty; percutaneous coronary intervention; complications; saphenous vein graft

INTRODUCTION

Coronary no-reflow, the failure to achieve sustained myocardial perfusion despite patent epicardial coronary vessels following otherwise successful coronary interventions, complicates 0.6%–10% of percutaneous coronary interventions and is associated with adverse outcomes, including myocardial infarction and death [1,2]. No-reflow is observed more frequently in patient undergoing percutaneous coronary interventions for acute coronary syndromes or interventions on degenerated saphenous vein bypass grafts [1–4].

The pathophysiology of no-reflow has not been fully delineated, but is complex and likely multifactorial. Postulated mechanisms include microvascular embolization of thrombus and plaque components, myocardial edema attributable to ischemia and reperfusion injury, microvascular spasm, endothelial dysfunction, and chemical and neural reflexes [2,3,5–8]. Various pharmacologic therapeutic interventions have been employed to reverse no-reflow. Intracoronary administrations of nitroglycerine, calcium channel blockers, adenosine, papaverine, and abciximab have been reported as efficacious [6,9–16]. However, success rates are variable and in some cases no-reflow is refractory to multiple agents.

Strategies to prevent no-reflow appear promising. In patients undergoing mechanical rotational atherectomy, intraprocedural infusion of an anti–no-reflow cocktail of saline, calcium channel blocker, and nitroglycerine appears to reduce the incidence of no-reflow [17]. Preliminary observations with filter-type protective devices also suggest preventative strategies may limit no-reflow [18,19]. However, at present, no-reflow continues to pose an often unpredictable and refractory challenge to the interventionalist.

Observations from selected cases in our institution suggested that intracoronary epinephrine could reverse refractory no-reflow. In addition to its chronotropic and inotropic effects on the heart, epinephrine exerts potent coronary vasodilatory effects via B2 receptor activation [19–21]. Accordingly, we performed a retrospective analysis of the angiographic, hemodynamic, and clinical effects of intracoronary epinephrine administered in patients developing refractory no-reflow following percutaneous intervention.

MATERIALS AND METHODS

We analyzed the William Beaumont Hospital cardiac catheterization laboratory database to identify 29 consec-

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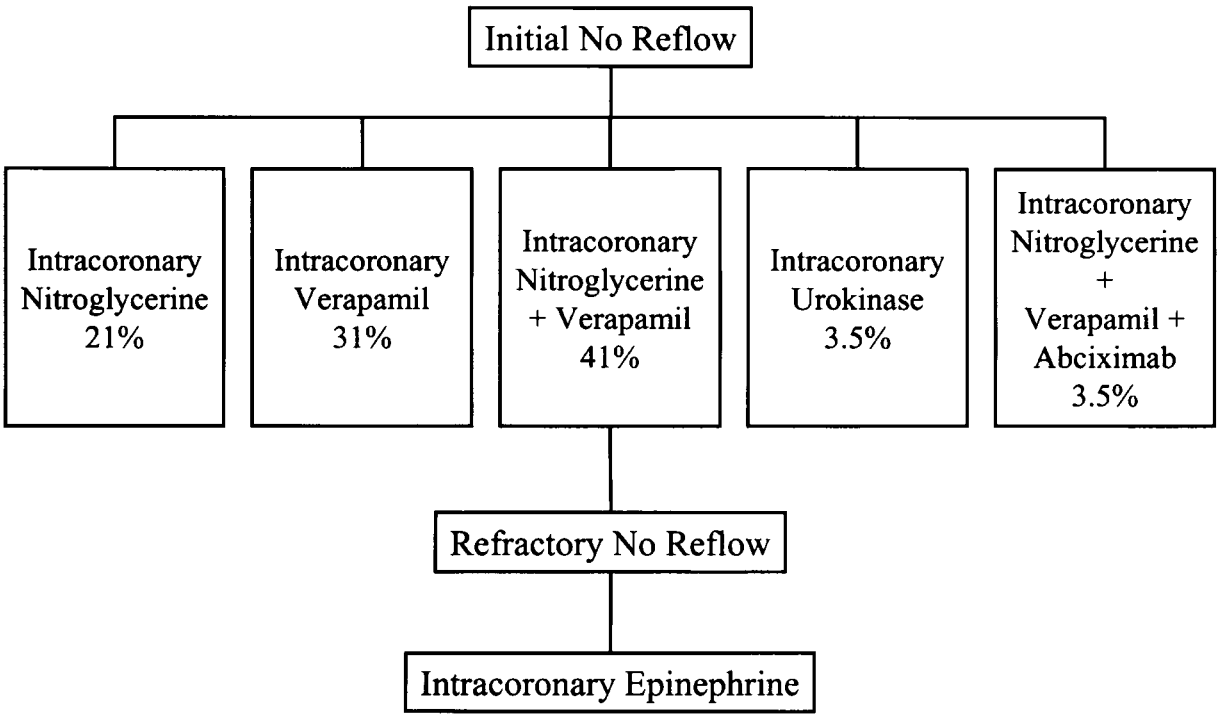

Fig. 1. Distribution of drug therapy.

utive patients receiving intracoronary epinephrine for refractory no-reflow from 1 January 1997 to 31 December 1998. No-reflow was defined as TIMI 0–1 flow in the absence of abrupt closure, high-grade stenosis ($\leq$ 50%), flow-limiting dissection, intraluminal thrombosis, or coronary spasm. To be considered refractory, TIMI flow $\leq$ 2 had to persist despite intracoronary administration of at least one other pharmacologic intervention.

Angiography and percutaneous intervention were performed employing standard techniques. All patients received 325 mg of aspirin, intravenous heparin, and beta blockers as tolerated. Percutaneous interventions and treatments for no-reflow were chosen at the discretion of the operator. The dosages of intracoronary epinephrine (range, 50–200 μg) were adjusted based on the presence and severity of systemic hypotension, with larger and repeated doses for profound hypotension given accordingly. A subgroup of patients with hypotension occurring as a consequence of refractory no-reflow was also analyzed for their hemodynamic responses to intracoronary epinephrine.

Clinical variables collected for all patients included hemodynamics, cardiac rhythm, and the timing and dosages of intracoronary epinephrine as well as other pharmacologic therapies for no-reflow. Catheterization data included procedure indication, procedural details, and angiographic analysis including TIMI flow throughout the procedure. Outcome data included procedural success defined as $\leq$ 50% stenosis, final flow grade TIMI 3, and recovery of hemodynamics. Data regarding transvenous pacer and intraaortic balloon pump usage as well as in-hospital mortality were collected.

RESULTS

Of the 29 patients receiving intracoronary epinephrine for refractory no-reflow, 7 (24%) underwent elective percutaneous intervention, and in 22 others (76%) refractory no-reflow developed following percutaneous coronary intervention in the setting of acute coronary syndromes. Refractory no-reflow developed after balloon angioplasty alone in 35% of patients, after stent implantation in 59%, and following angiojet in 7% of cases. No-reflow occurred more often in the setting of multivessel disease as compared to single-vessel disease (83% vs 17%).

No-reflow was initially treated with intracoronary nitroglycerine in 21% of patients (mean dose, 188 $\pm$ 38 μg), verapamil in 31% (mean dose, 348 $\pm$ 132 μg), nitroglycerine + verapamil in 41% of patients, urokinase in 3.5% of patients, and verapamil, + nitroglycerine + abciximab in 3.5% of patients (Fig. 1).

A single dose of 1 cc epinephrine was given in 22 (76%) patients; a second dose of intracoronary epinephrine was required in 6 (21%) and multiple doses administered in 1 (3%) patient. Administration of intracoronary epinephrine (mean dose, 139 $\pm$ 189 μg) resulted in significant overall improvement in coronary flow (mean

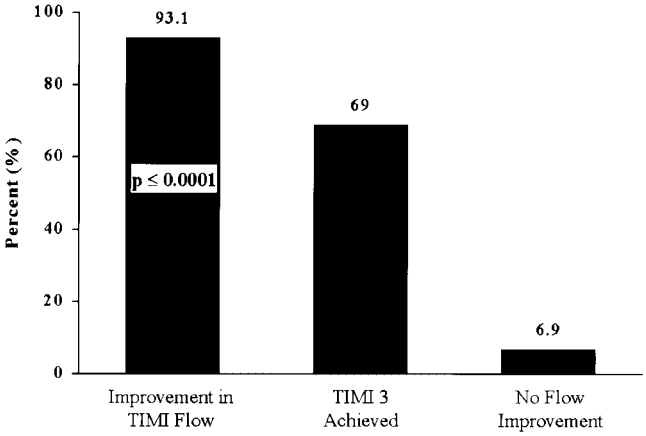

Fig. 2. Initial treatment of no-reflow.

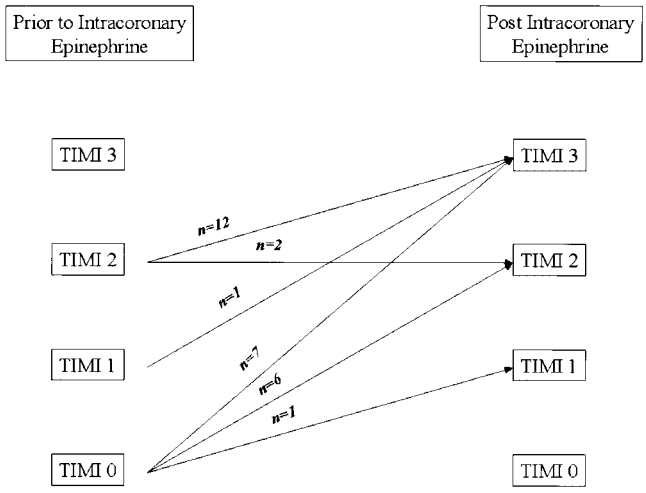

Fig. 3. TIMI flow prior to and after administration of intracoronary epinephrine.

TIMI flow from 1.0 ± 1.0 to 2.66 ± 0.55; $P = 0.0001$) (Fig. 2). There was improvement in coronary flow of at least one TIMI flow grade in 27 (93%) patients, two flow grades in 14 (48%) cases, and three flow grades in 7 (24%) others (Fig. 3). Not surprisingly, intracoronary epinephrine resulted in significant increases in heart rate (72 ± 19 to 86 ± 26; $P = 0.0009$), but fortunately no cases of acute dysrhythmia. Hypotension associated with no-reflow developed in 14 (48%) patients. However, following administration of intracoronary epinephrine, all but three patients (10%) were normotensive at the end of the procedure. For the group overall, systolic blood pressure at the end of the procedure was restored to preprocedural levels (124 ± 39 to 125 ± 29 mm Hg; $P =$ NS).

During the procedure, intra-aortic balloon pump counterpulsation was required in five (17%) patients, transvenous pacing in five (17%) cases, and both intra-aortic balloon counterpulsation and transvenous pacing in three (10%) patients. Two patients (7%) required cardiopulmonary resuscitation during their episodes of no-reflow and one patient (3.4%) died despite therapeutic measures.

DISCUSSION

The present observations demonstrate that intracoronary epinephrine exerts salutary effects in patients suffering refractory no-reflow developing following elective or acute percutaneous coronary interventions. Despite no-reflow refractory to traditional pharmacologic interventions, administration of intracoronary epinephrine resulted in significant improvement in TIMI flow in almost all patients and restored normal flow in the majority of cases.

No-reflow develops in 0.6%–10% of patients, undergoing percutaneous intervention [1,2] and is associated with adverse in-hospital outcomes including myocardial infarction and death [1,2,4,5]. No-reflow also appears to be an independent predictor of long-term cardiac death and myocardial infarction [1,22]. No-reflow has been reported in up to 50% of patients undergoing primary angioplasty for acute myocardial infarction and up to 71% undergoing percutaneous coronary intervention on degenerated saphenous vein grafts [1–4]. The increased incidence of no-reflow in this patient group may contribute to the high mortality (up to 15%) in these patients at highest risk for no-reflow. No-reflow often results in abrupt and profound hemodynamic deterioration, with resultant hemodynamic improvement following no-reflow resolution [6,7].

Although the precise mechanisms underlying no-reflow have not been fully delineated, it undoubtedly reflects a complex and multifactorial pathophysiologic process. Furthermore, the specific mechanisms and pathophysiology likely vary in individual cases. For example, patients undergoing elective intervention on a degenerated vein graft or mechanical rotational atherectomy of a native vessel may develop no-reflow predominantly attributable to microvascular embolization of particulate debris, resulting in no-reflow due to microvascular clogging [23] (what we term "microvascular no-reflow"). In contrast, patients with extensive anterior myocardial infarction reperfused late typically manifest substantial myocardial necrosis and the effects of reperfusion injury together resulting in interstitial and myocyte edema, which may be accompanied by hemorrhage. No-reflow in such cases is likely predominantly myocardial, with inability to perfuse the regional microvasculature attributable in great part to extrinsic resistance exerted on the collapsible capillary bed by increased intramyocardial pressure resulting from interstitial and myocyte edema with or without hemorrhage. Clearly, such patients may also suffer microvascular no-reflow due to distal embo-

lization of thrombotic and plaque materials, as well as from ischemic reperfusion injury that primarily damages the endothelium. Undoubtedly, the anatomic and pathophysiologic mechanisms underlying no-reflow in an individual case will influence responses to therapeutic intervention.

Advances in interventional techniques have reduced the incidence of no-reflow. Utilization of pharmacologic cocktails during rotablator atherectomy and use of distal filtration protection devices in saphenous vein graft interventions appear to reduce the incidence of no-reflow [24,25]. Nevertheless, no-reflow persists as an important clinical problem. Various pharmacologic strategies have been employed for the treatment of no-reflow. Intracoronary verapamil (100–500 μg), diltiazem (2.5–3.5 mg), adenosine (12.1 ± 3.4 mg), papaverine (10 mg/10 sec), and abciximab have also been reported as efficacious. However, despite administration of these agents singularly and in combination, no-reflow may persist.

Our study in patients with refractory no-reflow is the first to demonstrate the beneficial effects of intracoronary epinephrine. Although epinephrine has not previously been reported for the treatment of no-reflow, epinephrine exerts potent coronary vasodilatory effects via B2 receptor activation, in addition to its chronotropic and inotropic effects on the heart [8,20–22,26,27]. In our study, despite no-reflow refractory to one or more traditional agents, and regardless of the degree of hemodynamic deterioration, intracoronary epinephrine consistently improved coronary flow and frequently completely reversed no-reflow. Improvement in coronary flow was established with salutary effects on blood pressure in those patients exhibiting hypotension with no-reflow. Previous studies employing dosages similar to those used in our study have shown that intracoronary epinephrine can restore blood pressure in cases of refractory hypotension [28].

It is important to consider limitations pertinent to the methods of this study. This analysis is retrospective and therefore subject to selection bias. Angiographic analysis of coronary flow is qualitative, and although TIMI flow grade is the standard for measurement, it does not precisely quantitate flow changes or distinguish microvascular versus myocardial mechanisms of no-reflow. No-reflow is typically treated rapidly and cineangiographic documentation of flow responses was not always obtained after each medication administration. Therefore, it is possible that delayed and/or synergistic actions of one or more of the medications administered contributed to the resolution of refractory no-reflow. This retrospective nature of this analysis limits conclusions regarding the optimal sequence of pharmacologic strategies that should be employed for no-reflow. Retrospective review also limits data regarding the precise quantitative temporal responses of coronary flow and systemic hemodynamics to pharmacological interventions.

In summary, the present observations document that intracoronary epinephrine may exert salutary effects in patients developing refractory no-reflow following percutaneous coronary interventions. Intracoronary epinephrine was well tolerated and resulted in prompt and dramatic recovery of flow in the majority of patients. Further studies will be necessary to determine whether intracoronary epinephrine should be used primarily or in combination with other agents for the treatment of no-reflow.

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