

# Does the Inhibition of the Final Common Pathway of Platelet Aggregation Reduce the No-Reflow Phenomenon During Primary Percutaneous Coronary Intervention? Tirofiban no Infarto Agudo do miocárdio e a não Reperusão (TIARA)

Igor Matos Lago<sup>1</sup>, J. Antonio Marin-Neto<sup>1</sup>, Moysés de Oliveira Lima-Filho<sup>1</sup>, Antonio Pazin Filho<sup>2</sup>, Geraldo Luiz Figueiredo<sup>1</sup>, Jorge Luis Haddad<sup>1</sup>, Roberto Botelho<sup>3</sup>, Ricardo Barbosa<sup>4</sup>, Ulisses Marques Gianechini<sup>4</sup>, Breno de Siqueira<sup>4</sup>

## ABSTRACT

**Background:** Primary percutaneous coronary intervention is currently the preferred method to treat patients with ST-segment elevation acute myocardial infarction. The no-reflow phenomenon, which is the inability to reperfuse a region of the myocardium after restoration of patency of a previously occluded epicardial coronary artery, is observed in a considerable proportion of these patients. The benefit of IIb/IIIa glycoprotein inhibitors, blocking the final common pathway of platelet aggregation, has been suggested in studies of acute coronary syndromes, but their actual efficacy in the context of no-reflow in patients treated with primary percutaneous coronary intervention remains unclear. **Methods:** The aim of this multicenter, double-blinded, placebo controlled study is to assess the impact of the early administration of the low molecular weight glycoprotein IIb/ IIIa inhibitor tirofiban on the incidence of no-reflow using angiographic and electrocardiographic methods to determine: (1) the epicardial coronary flow, using the TIMI score, and the microcirculatory flow, using the MBG score of opacification and myocardial flow; (2) the resolution of the ST segment elevation, as the final index of the success of reperfusion. **Conclusions:** If the decrease in no-reflow incidence at 90 minutes and 24 hours after primary percutaneous coronary intervention is confirmed, this pilot study should guide the implementation of a larger study to investigate the possible impact of the systematic inhibition of the final common pathway of platelet

## RESUMO

**A Inibição da Via Final Comum da Agregação Plaquetária Reduz o Fenômeno de Não Reperusão Durante a Intervenção Coronária Percutânea Primária? Tirofiban no Infarto Agudo do miocárdio e a não Reperusão (TIARA)**

**Introdução:** A intervenção coronária percutânea primária é hoje o método preferencial de reperusão na abordagem de pacientes com infarto agudo do miocárdio com supradesnívelamento do segmento ST. Em boa parte desses casos, ocorre o fenômeno de não reperusão, que é a incapacidade de se reperfundir uma região do miocárdio após o restabelecimento da patência de uma artéria coronária epicárdica previamente ocluída. O benefício de inibidores da glicoproteína IIb/IIIa, bloqueando a via final comum da agregação plaquetária, tem sido sugerido em estudos de síndromes coronárias agudas, mas persistem pontos obscuros quanto à sua real eficácia, no contexto da não reperusão, em pacientes tratados com intervenção coronária percutânea primária. **Métodos:** Investigação multicêntrica que avaliou o impacto da administração precoce do inibidor da glicoproteína IIb/IIIa de baixo peso molecular tirofiban, em forma duplo-mascarada, controlada por placebo, sobre a ocorrência de não reperusão, empregando métodos angiográficos e eletrocardiográfico para documentar (1) os fluxos coronário epicárdico, pelo escore TIMI, e microcirculatório, pelo escore MBG de opacificação e escoamento miocárdicos; (2) a resolução

<sup>1</sup> Laboratories of Hemodynamics and Interventional Cardiology, Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil.

<sup>2</sup> Emergency Units, Department of Internal Medicine, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil.

<sup>3</sup> Instituto do Coração do Triângulo Mineiro, Uberlândia, MG, Brazil.

<sup>4</sup> Fundação Santa Casa de Misericórdia de Franca, Hospital do Coração, Franca, SP, Brazil.

**Correspondence to:** Igor Matos Lago. Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo. Campus Universitário, s/n – Monte Alegre – CEP: 14048-900 – Ribeirão Preto, SP, Brazil.

E-mail: igormatoslago@gmail.com

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aggregation on the mortality of ST-segment elevation acute myocardial infarction patients.

**DESCRIPTORS:** Myocardial infarction. Percutaneous coronary intervention. Myocardial reperfusion. Thrombolytic therapy. Treatment outcome.

**P**rimarily percutaneous coronary intervention (PPCI), usually with stent implant, is considered the preferred reperfusion strategy, due to its association with high rates of recanalization of the occluded artery, reduction in ischemic myocardial damage progression and, more importantly, mortality reduction in ST-segment elevation myocardial infarction (STEMI).<sup>1</sup> However, patency restoration of a previously occluded epicardial artery is not always accompanied by adequate reperfusion of the myocardium that depends on it.<sup>2</sup> This no-reflow phenomenon (NRP) occurs in a variable proportion of patients (5% to 50%) and has negative impact on the known benefits of PPCI, namely: (a) early complications after myocardial infarction (arrhythmias, pericardial effusion, cardiac tamponade, and heart failure); (b) adverse left ventricular remodeling; (c) late readmissions for heart failure; (d) increased mortality rate.<sup>2,3</sup> No-reflow is a complex and dynamic process that involves several physiopathological components such as distal atherothrombotic embolization, ischemic lesion, reperfusion lesion, and intrinsic susceptibility to coronary microcirculation combined with the effects of ischemia and reperfusion lesion.<sup>3,4</sup> This phenomenon may or may not be reversible, depending on the net result of the functional and/or anatomical abnormalities of coronary microcirculation, as well as the therapeutic approach used for its prevention and treatment.

It can be diagnosed at different stages by various methods, among which are coronary angiography, electrocardiography, and noninvasive imaging methods, such as myocardial echocardiography with contrast and magnetic resonance.<sup>5,6</sup>

Coronary angiography with contrast is usually used to evaluate non-reperfusion during PPCI by gradation of the epicardial flow using the Thrombolysis In Myocardial Infarction (TIMI) score: TIMI 0 indicates no perfusion (without flow after coronary lesion); TIMI 1 represents minimum perfusion (contrast surpasses the lesion, but shows no opacification of the vessel downstream); TIMI 2 indicates partial perfusion (contrast surpasses the lesion and there is opacification in the distal vessel, but with slower speed than in the adjacent vessels); TIMI 3

do supradesnívelamento do segmento ST, como índice final do sucesso da reperfusão. **Conclusões:** Se comprovada redução da incidência de não reperfusão tanto 90 minutos como 24 horas após a intervenção coronária percutânea primária, este estudo-piloto, deve nortear a implementação de estudo mais abrangente, para investigar o possível impacto do bloqueio.

**DESCRITORES:** Infarto do miocárdio. Intervenção coronária per cutânea. Reperfusion miocárdica. Terapia trombolítica. Resultado do tratamento.

occurs in cases of complete perfusion (contrast surpasses the lesion at the same speed as in adjacent vessels). Gradation of the opacification aspect and myocardial outflow is indicated by the Myocardial Blush Grade (MBG) score: MBG 0 indicates no myocardial opacification and no myocardial outflow; MBG 1 indicates mild opacification and slow myocardial outflow; MBG 2 corresponds to moderate opacification and somewhat increased myocardial outflow, but still lower than that observed in other arteries without lesions; MBG 3 indicates normal opacification and myocardial outflow comparable to that observed in other arteries without lesions.<sup>7,8</sup>

Through the electrocardiogram (ECG), non-reperfusion is inferred by analyzing the ratio of the ST-segment elevation before and after treatment and its complete resolution (> 70%), which rules out the occurrence of NRP. Lower degrees of ST-segment resolution characterize the occurrence of NRP, and moderate (30% to 70%) to severe (< 30%) degrees of reperfusion are commonly observed.<sup>9,10</sup>

These integrated data stratify these patients in varying degrees of no-reflow. Angiographically, non-reperfusion is characterized if epicardial TIMI  $\leq 2$ , or when, even in cases of epicardial TIMI = 3, the degree of opacification and myocardial outflow by MBG is not  $\geq 2$ . These aspects as well as diagnostic factors have prognostic consequences, as several studies have shown that patients with TIMI 3, MBG 2-3, and resolution of ST > 70% have a better outcome compared to those with TIMI < 3, MBG 0-1, and ST resolution < 70%.<sup>10-12</sup>

Numerous therapeutic strategies have been used in the NRP approach in primary PCI, among which are the use of drugs such as inhibitors of the final common pathway of platelet aggregation (abciximab, tirofiban, and eptifibatide), vasodilators (dinitrates and trinitrates, adenosine, verapamil, and sodium nitroprusside), anti-inflammatory drugs (statins), antithrombotic agents (heparin and bivalirudin), metabolic inhibitors (nicorandil), and mechanical devices, such as distal filter protection catheters and thrombus aspirators. These investigations

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