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TENECTEPLASE AS A NEW MEDICATION IN MANAGING NO-REFLOW

Milan Živković, Svetlana Apostolović, Milan Pavlović, Sonja Šalinger Martinović, Tomislav Kostić, Nenad Božinović and Emina Dimitrijević

No-reflow has been defined as "inadequate myocardial perfusion through a given segment of coronary circulation without angiographic evidence of a mechanical obstruction". Important components of the process are thought to include endothelial ischemic injury producing "blebs" of tissue that directly obstruct the microvasculature, leukocyte plugging of capillaries, and the vascular effects of reactive oxygen species. No-reflow can complicate any percutaneous intervention (PCI), though it is more common following acute myocardial infarctions (MI), particularly with prolonged occlusion times.

A 59-year-old woman presented to the hospital after two hours of continuous chest pain. Because of acute myocardial infarction of the inferior and lateral wall, she underwent direct stenting to an occlusion in the right coronary artery. Despite successful implantation of stents revascularization failed. In absence of aspiration devices and other pharmacological agent we decide to apply 30 mg (6000 IU) tenecteplase intracoronary. Three min after administration TIMI flow grade improved from TIMI 0 to TIMI 3.

Managing no-reflow can be approached in a number of different ways and needs to be tailored to the type of intervention being performed. As confirmed in practice, prevention is better than cure and both mechanical and pharmacological approaches can be employed in high risk cases. In the setting of acute myocardial infarction the most effective preventative measure is the rapid opening of the vessel and as such the development of a robust and efficient primary PCI service is integral to the avoidance of this complication.

Managing no-reflow will become increasingly important with the wider development of primary PCI. Within the setting of acute myocardial infarctions with no reflow as primary percutaneous intervention complication, there are potential important future pharmacological regimens that may become established and one of them can be tenecteplase. *Acta Medica Medianae 2012; 51(1):42-45.*

Key words: *no-reflow, acute myocardial infarction, primary PCI, tenecteplase*

Clinical Center Niš, Clinic for Cardiovascular Diseases

Contact: Milan Živković
Clinical Center Niš
Clinic for Cardiovascular Diseases
Bul. Dr Zorana Djindjića 48
18000 Niš, Serbia
E-mail: milanserbia@hotmail.com

Introduction

No-reflow has been defined as "inadequate myocardial perfusion through a given segment of coronary circulation without angiographic evidence of a mechanical obstruction" (Eeckhout). Although first suggested for the cerebral circulation, its importance in cardiac tissue was shown in canine experiments, where the removal of a vessel clamp after 90 minutes failed to restore normal coronary flow (Kloner). No-reflow can complicate any percutaneous intervention (PCI), though it is more common following acute myocardial infarctions (MI), particularly with prolonged occlusion times.

The pathophysiology of the process is complex and not fully understood and is likely to include more than one process in each individual and may differ in different lesions. Important components of the process are thought to include endothelial ischemic injury producing "blebs" of tissue that directly obstruct the microvasculature, leukocyte plugging of capillaries, and the vascular effects of reactive oxygen species. Microembolisation of atheroma and thrombus and intravascular activation of the extrinsic coagulation pathway has also been suggested (ref to Reffelmann and Kloner review).

Clinically, no-reflow is important as it predicts a poorer outcome and is associated with ongoing symptoms and persistent ECG changes. In comparison to patients attaining TIMI 3 flow patients with no-reflow have an increased incidence of ventricular arrhythmias, early congestive cardiac failure, cardiac rupture and cardiac death. As such, it is important in this article to consider which strategies have data to support their use in the prevention or treatment of no-reflow.

Case report

A 59-year-old woman presented to the hospital after two hours of continuous chest pain. ECG on admition showed ST elevation in D2, D3, aVF and V5-V6 neg T (Figure 1). Echocardiography showed that inferior and posterior walls were discinetic and lateral wall in basal and medial segment was hypocontractile. She was a havy smoker, hypertensive.

Because of acute myocardial infarction of the inferior and lateral wall, she underwent direct stenting to an occlusion in the right coronary artery, primary PCI (Figure 2). She received standard premedication: heparin 5000 IU, clopidogrel loading dose 600 mg, acetylsalicylic acid 300 mg and pantoprazole 40 mg i.v.

During intervention, she developed a transitory complete AV block. Temporary pacemaker is positioned but suboptimal coronary flow was achieved, and she subsequently developed no reflow (Figure 3).

Despite succesful implantation of stents, revascularization failed. In the absence of aspiration devices and other pharmacological agents, we decide to apply 30 mg (6000 IU) tenecteplase intracoronary. Three minutes after administration, TIMI flow grade improved from TIMI 0 to TIMI 3 (Figure 4).

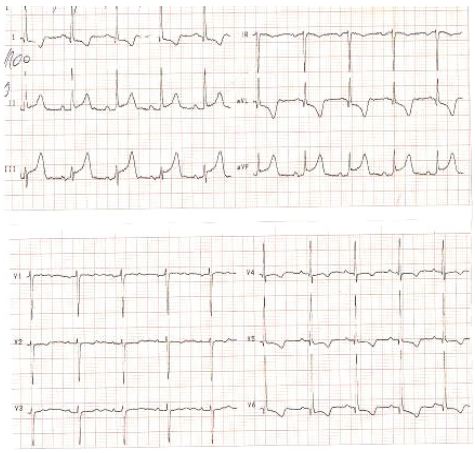

Figure 1. ECG on admittion

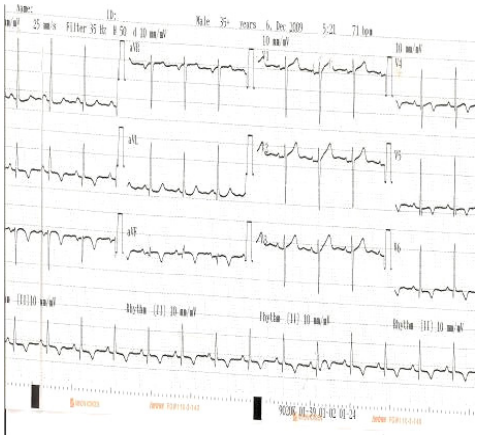

Figure 5. ECG on discharge from hospital

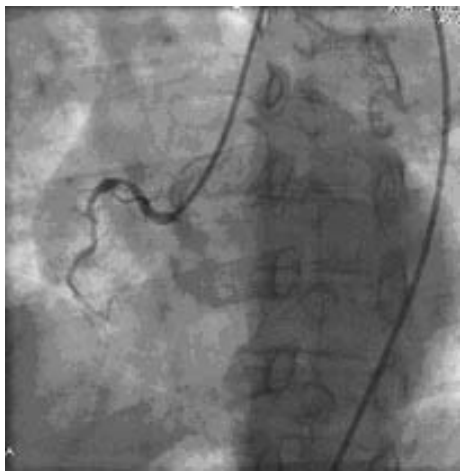

Figure 2. Native RCA

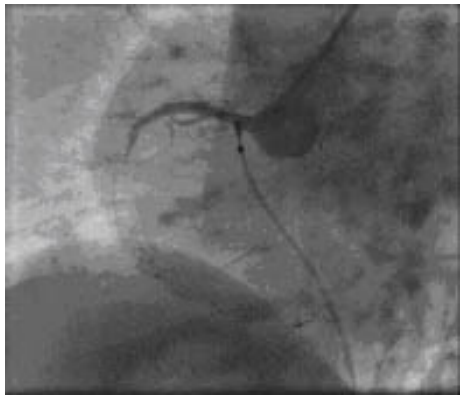

Figure 3. Post stenting no-reflow at RCA

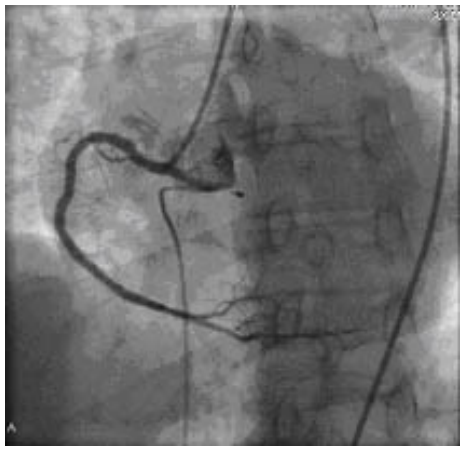

Figure 4. TIMI flow 3 after intracoronary administration of tenecteplase

The patient was transfered to coronary care unit for further monitoring and medical treatment. She was dependent on temporary pacemaker for 6 hours, after that it was removed and the patient was hemodynamic and rhithmically stable. Further treatment include: beta blocker, clopidogrel, aspirin, ACE inhibitor, statin and gastroprotection. Her ECG on discharge from hospital on the 5th day was with negative T waves in inferior leads and biphase T waves in lateral leads (Figure 5).

Discussion

Managing no-reflow can be approached in a number of different ways and needs to be tailored to the type of intervention being performed. As in all practice prevention is better than cure and both mechanical and pharmacological approaches can be employed in high risk cases (2). It is important to remember that the diagnosis first has to be established by the exclusion of other causes of reduced flow – in particular the presence of a dissection must be discounted by imaging the vessel in multiple planes (1).

In the setting of acute myocardial infarction the most effective preventative measure is the rapid opening of the vessel and as such the development of a robust and efficient primary PCI service is integral to the avoidance of this complication. One study also suggests that direct stenting, as opposed to balloon predilatation, may help to prevent no-reflow in acute myocardial infarction, if this is technically possible (JACC 2002).

An additional strategy is the use of extraction catheter devices in the setting of a large thrombus burden and poor distal coronary flow as an adjunct or alternative to balloon angioplasty (6). Finally, but certainly not the last in established no-reflow, there is a number of pharmacological options.

Over the years, attention has been focused on a large number of different agents (Verapamil, Adenosine, Nitroglycerine, Nicorandil). The use of glycoprotein inhibitors (GP IIbIIIa) is largely established in the setting of no reflow such as Tirofiban or Abciximab. Usage of thrombolytic agents in this phenomenon is a rare case, but as our case shows it can be very efficient (4,5).

An important issue on the mode of delivery of agents, particularly in the setting of established no-reflow, needs to be considered. The pathology of the process is at the level of the microvascular bed – as such, it is entirely illogical to attempt to treat the condition with agents given through the catheter to the proximal portion of the vessel when flow is poor. As such, agents should be delivered to the distal bed with either a multi-function probing catheter or an over-the-wire balloon (7).

Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Conclusion

Managing no-reflow will become increasingly important with the wider development of primary PCI. Interventional cardiologists are increasingly performing these procedures and this will also necessitate robust strategies to avoid no-reflow.

It is clear that pharmacological agents and distal protection devices are important in the treatment of high risk cases, and further studies may establish the adjuvant use of tenecteplase. Within the setting of acute myocardial infarctions with no reflow as primary percutaneous intervention complication, there are potential important future pharmacological regimens that may become established and one of them can be tenecteplase. Further clinical trials will be required to study the routine application of tenecteplase as pharmacological solution in acute MI**.**

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TENEKTEPLAZA KAO NOVI LEK U REŠAVANJU NO-REFLOW FENOMENA

Milan Živković, Svetlana Apostolović, Milan Pavlović, Sonja Šalinger Martinović, Tomislav Kostić, Nenad Božinović i Emina Dimitrijević

No-reflow se definiše kao "neadekvatna perfuzija miokarda kroz odgovarajući segment koronarne cirkulacije bez angiografskog dokaza o mehaničkoj opstrukciji". Smatra se da je značajna komponenta ovog procesa ishemijska povreda endotela koja dovodi do stvaranja "mehurića" tkiva, što direktno opstruiše mikrovaskulaturu, dovodi do nakupljanja leukocita u kapilarima i ispoljavanja vaskularnih efekata slobodnih kiseoničnih radikala. No-reflow može komplikovati bilo koju perkutanu koronarnu intervenciju (PCI), ali je, ipak, češći nakon akutnog infarkta miokarda (AIM), naročito sa prolongiranim vremenom okluzije.

Rešavanje no-reflow fenomena može se postići na više različitih načina i treba biti prilagođeno intervenciji koja se izvodi. Kao i uvek u praksi, prevencija je bolja od lečenja i oba, farmakološki i mehanički pristup rešavanja, mogu se primeniti kod visokorizičnih bolesnika. Kod akutnog infarkta miokarda najefikasnija preventivna mera je brzo otvaranje krvnog suda i upravo je zbog toga neophodno uspostavljanje primarne PCI kao efikasne mere da bi se izbegla ovakva komplikacija.

Žena 59 godina starosti primljena je u bolnicu nakon 2 sata konstantnih bolova u grudima. Radi se o akutnom infarktu miokarda inferiornog i lateralnog zida. Bolesnica je podvrgnuta direktnom stentiranju okludirane desne koronarne arterije. Uprkos uspešnoj implantaciji stenta, revaskularizacija izostaje. Zbog nedostatka uređaja za aspiraciju tromba i ostalih farmakoloških agenasa odlučujemo da aplikujemo 30 mg (6000 IU) tenekteplaze intrakoronarno. Stepen se popravlja sa TIMI 0 na TIMI 3 3min nakon davanja leka TIMI flow.

Rešavanje no-reflow fenomena postaje sve značajnije sa daljim razvojem primarne PCI. Kod akutnog infarkta miokarda sa no-reflow fenomenom kao komplikacijom primarne perkutane koronarne intervencije, postoje značajni budući farmakološki načini rešavanja koji mogu biti primenjeni i jedan od njih može biti tenekteplaza. *Acta Medica Medianae 2012;51(1):42-45.*

***Ključne reči**: no-reflow, akutni infarkt miokarda, primarna PCI, tenekteplaza*