Serotonin: another player in the complex pathogenesis of no-reflow phenomenon

"No-reflow" fenomeninin karmaşık patogenezinde başka bir oyuncu: Serotonin

Myocardial no-reflow after primary percutaneous coronary intervention (PCI) or thrombolysis may negate advantages of reperfusion therapy. Indeed, compromised microcirculation does not allow providing normal blood flow to the myocardium despite an epicardial vessel reopening. No-reflow has a prognostic role for both mortality and adverse left ventricular remodelling which is the cause of left ventricular failure (1). In humans, no-reflow is caused by the variable combination of four pathogenetic components: 1) distal atherothrombotic embolization; 2) ischemic injury; 3) reperfusion injury; and 4) susceptibility of coronary microcirculation to injury. For each of them, it is possible to detect different predictors thus allowing specific therapies to be used in order to prevent no-reflow phenomenon (2). Importantly, both distal embolization and ischemia-reperfusion injury are associated with release of potent vasoconstrictors, which further impair the microcirculation.

In the paper "Relationship between no-reflow phenomenon and serotonin levels in patients with acute ST-elevation myocardial ınfarction who underwent primary percutaneous ınterventi-on" (3) Topsakal et al. have tried to find a pathogenetic correlation between levels of serotonin (5-hydroxytryptamine) on no-reflow phenomenon following a primary PCI in patients with acute ST-elevation myocardial infarction (MI). Serotonin (5-hydroxytryptamine) that is synthesized from the essential amino aminoacid L-tryrophan is a vasoconstrictor and an effective stimulant for the smooth muscles (4) and it could play a role in no-reflow phenomenon.

In the study, they enrolled 40 patients presented at hospital within the first 12 hours of chest pain excluding those who were undergoing thrombolytic therapy or receiving selective serotonin reuptake inhibitors. Levels of serotonin were evaluated in blood samples collected from the coronary ostium by using catheter without side holes. Serotonin values were obtained from serum and thrombocytes.

No-reflow phenomenon was angiographically defined as a flow of TIMI 2 or less without the presence of dissection, mechanical obstruction, significant residual stenosis or other plausible causes (5, 6).

Their experiment showed that while mean level of serotonin in thrombocytes in patients with reflow was 476±208 ng/10^9 thrombocytes, it was 542±273 ng/10^9 thrombocytes in patients with no-reflow. Although the mean level of serotonin in thrombocytes was obser0ved to be higher in the no-reflow group, the difference was not statistically significant (p=0.39). Furthermore, whereas mean serum serotonin level in reflow group was 41.4±40.8 ng/ml, it was noted to be 66.7±45.7 ng/ml in no-reflow group. Again, although the mean level of serum serotonin was observed to be higher in the no-reflow group, the difference was not statistically significant (p=0.07).

However, they found, that the mean baseline serum high sensitivity- C-reactive protein (hs-CRP) level in the no-reflow group was significantly higher [5.4 (3.1-31.0) vs. 3.1(3.1-15.4), p=0.014] as in reflow group.

Due to the small sample size, the differences in serotonin levels did probably not reach the statistical significance. The findings of the study are however in line with those of previous studies, which have shown higher circulating levels of other potent vasoconstrictors such as endothelin-1 (ET-1) and thromboxane A2 (TX-A2) in patients with no-reflow (7, 8). Interestingly, both ET-1 and TX-A2 have pleiotropic effects above their role as vasoconstrictors. Indeed, ET-1 is an important modulator of neutrophil, leucocyte function, and a stimulator of surface expression of adhesion molecules, while TX-A2 is a potent stimulus for platelet aggregation. Similarly, a complex role of serotonin in ischemia-reperfusion injury has been demonstrated. Previous experimental studies have shown a release of serotonin following atherosclerotic plaque rupture in hypercholesterolemic rabbit model and decrease in distal microvascular resistance, removing microvascular obstruction after the administration of

Address for Correspondence/Yazışma Adresi: Giampaolo Niccoli, MD, Istituto di Cardiologia Università Cattolica del Sacro Cuore L.go A. Gemelli, 8 Roma, Italia
Phone: 39-6-3051166 Fax: 39-6-3055535 E-mail: gniccoli73@hotmail.it

doi:10.5152/akd.2010.067

ritanserin, a 5-hydroxytryptamine-2 receptor antagonist (9). Therefore, those animal studies established that serotonin increased the damage in cardiac tissue occurring as a result of ischemia by means of 5-hydroxytryptamine-2 receptor and that 5-hydroxytryptamine-2 receptor antagonists could be beneficial in decreasing the damage (10). Accordingly, selective antagonists of both ET-1 and TX-A2 have been shown to have beneficial effects at the microvascular level after coronary ligation and reperfusion in the animal model of experimental MI (11, 12).

As a result of the same study, the mean baseline serum hs-CRP level in the no-reflow group was established to be significantly higher in patients with no-reflow. Hs-CRP is an inflammation marker with a half-life of 19 hours and it is released six hours after a coronary event, on average. Chronic low-grade inflammation is known to affect epicardial tone, microvascular tone and neutrophil function (13). Recent studies have demonstrated that high baseline CRP levels in patients treated by primary PCI predict a worse short-term prognosis (14). Results of a recent study conduct by our group do not support the hypothesis that the worse outcome associated with high CRP levels may be mediated by a higher risk of no-reflow (15).

The reasons for these discrepant results are not clear, but different selection criteria likely play a role. In particular, the time from chest pain onset to balloon and CRP assessment may be of major relevance in this context. Indeed, high CRP levels assessed late from chest pain onset (e.g. after 6 h) might largely reflect an inflammatory reaction to ongoing necrosis, thus limiting the assessment of the potential pathophysiological link between basal inflammatory state and post-PCI coronary no-reflow. An earlier detection of increased CRP levels (e.g., within 6 h of chest pain onset, as in our study), on the other hand, would more likely suggest the presence of a basal inflammatory condition, preceding the acute event, and thus more probably reflect a potential pathogenetic relevance of inflammation in the mechanisms of no-reflow.

Although, potent vasoconstrictors including serotonin may be target of additional therapies against no-reflow, it is worth nothing that no-reflow has a multifactorial pathogenesis with a variable prevalence of different pathogenetic mechanisms in different patients. Thus, assessing predictors of each mechanism is important in the evaluation of the patients. Furthermore, in the setting of no-reflow prevention is definitely more effective that treatment. In particular, reducing ischemic time is crucial for reducing the rate of final no-reflow (16). Finally, preserving innate cardioprotective mechanisms, such ischemic preconditioning is also of importance and drugs or beverages able to block this form of innate protection should be avoided in the patient at risk of MI (17).

A limitation of the study by Topsakal et al. (3) is also the lack of use of IIb-IIa inhibitors and manual thrombus aspiration (MTA) which are recommended by the last published ESC guidelines on the treatment of patients with acute ST elevation MI. In particular, abciximab has a class of recommendation IIA, with MTA having a class IIA. They have a preventive role at different time points as IIb-IIa antagonist may be administered before hospital arrival or in the catheterization laboratory before vessel reopening, while MTA is usually performed after the wire has crossed the occlusion. Finally, in the catheterization laboratory high dose of adenosine may help in the prevention of no-reflow (18). Antagonist of serotonin may be also used in the prevention of no-reflow but adequate dosing should be used taking in mind that in the acute phase levels of serotonin may be particularly high.

Another potential explanation of the borderline differences on serotonin levels observed in the present study may be found in the definition of no-reflow, indeed TIMI flow 3 may be also no-reflow if the Myocardial Blush Grade is 0-1. Furthermore, more sensitive imaging modalities as magnetic resonance imaging are emerging as potent instrument for the diagnosis and the follow-up of no-reflow phenomenon (19).

Future studies assessing the role of new drugs against no-reflow should keep in mind these considerations about the complex pathogenesis of the phenomenon, which may increase the rate of non responders. Furthermore, the choice of the diagnostic modalities is essential for a correct evaluation of response to therapy. Finally, appropriate dosage of drugs should be tested as the acute phase of MI exponentially increase levels of substances involved in the pathogenesis of no-reflow.

Giampaolo Niccoli, Cristina Spaziani
Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

Conflict of interest: None declared.

References

1. Bolognese L, Carrabba N, Parodi G, Santoro GM, Buonamici P, Cerisano G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004; 109: 1121-6.
2. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009; 54: 281-92.
3. Topsakal R, Kaya MG, Karakaya E, Günebakmaz Ö, Doğan A, İnanç MT, et al. No-reflow phenomenon and serotonin levels in patients with acute ST-elevation myocardial infarction who underwent primary percutaneous intervention. Anadolu Kardiyol Derg 2010: 10; 259-7.
4. Kawai C. Pathogenesis of acute myocardial infarction. Novel regulatory systems of bioactive substances in the vessel wall. Circulation 1994; 90: 1033-43.
5. Piana RN, Paik GY, Moscucci M, Cohen DJ, Gibson CM, Kugelmass AD, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. Circulation 1994; 89: 2514-8.
6. Morishima I, Sone T, Mokuno S, Taga S, Shimauchi A, Oki Y, et al. Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. Am Heart J 1995; 130: 239-43.
7. Niccoli G, Lanza GA, Shaw S, Romagnoli E, Gioia D, Burzotta F, et al. Endothelin-1 and acute myocardial infarction: a no-reflow mediator after successful percutaneous myocardial revascularization. Eur Heart J 2006; 27: 1793-8.
8. Niccoli G, Giubilato S, Russo E, Spaziani C, Leo A, Porto I, et al. Plasma levels of thromboxane A2 on admission are associated

with no-reflow after primary percutaneous coronary intervention. Eur Heart J 2008; 29: 1843-50.
9. Taylor AJ, Bobik A, Berndt MC, Ramsay D, Jennings G. Experimental rupture of atherosclerotic lesions increases distal vascular resistance: a limiting factor to the success of infarct angioplasty. Arterioscler Thromb Vasc Biol 2002; 22: 153-60.
10. Vitola JV, Forman MB, Holsinger JP, Kawana M, Atkinson JB, Quertermous T, et al. Role of endothelin in a rabbit model of acute myocardial infarction: effects of receptor antagonists. J Cardiovasc Pharmacol 1996; 28: 774-83.
11. Schumacher WA, Grover GJ. The thromboxane receptor antagonist SQ 30,741 reduces myocardial infarct size in monkeys when given during reperfusion at a threshold dose for improving reflow during thrombolysis.J Am Coll Cardiol 1990; 15: 883-9.
12. Libby P. Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 2006;83 Suppl: 456S-460S.
13. Yip HK, Hang CL, Fang CY, Hsieh YK, Yang CH, Hung WC, et al. Level of high-sensitivity C-reactive protein is predictive of 30-day outcomes in patients with acute myocardial infarction undergoing primary coronary intervention. Chest 2005; 127: 803-8.
14. Brasil D, Temsah RM, Kumar K, Kumamoto H, Takeda N, Dhalla NS. Blockade of 5-HT(2A) receptors by sarpogrelate protects the heart against myocardial infarction in rats. J Cardiovasc Pharmacol Ther 2002; 7: 53-9.
15. Niccoli G, Lanza GA, Spaziani C, Altamura L, Romagnoli E, Leone AM, et al. Baseline systemic inflammatory status and no-reflow phenomenon after percutaneous coronary angioplasty for acute myocardial infarction. Int J Cardiol 2007; 117: 306-11.
16. Nallamothu BK, Bradley EH, Krumholz HM. Time to treatment in primary percutaneous coronary intervention. N Engl J Med 2007; 357: 1631-8.
17. Tomai F, Crea F, Gaspardone A, Versaci F, De Paulis R, Penta de Peppo A, et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K channel blocker. Circulation 1994; 90: 700-5.
18. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. Circulation 2000; 101: 2154-9.
19. Albert TS, Kim RJ, Judd RM. Assessment of no-reflow regions using cardiac MRI. Basic Res Cardiol 2006; 101: 383-90.