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EDITORIAL

"Goldilocks" Approach to Deferred Stenting in ST-Segment–Elevation Myocardial Infarction

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For many years, interventional cardiologists have subscribed to the dogma "time is muscle" recognizing the urgency of reopening an occluded artery in ST-segment–elevation myocardial infarction (STEMI). With the advent of primary angioplasty/stenting[1] and the implementation of systems of care for STEMI,[2] outcomes have substantially improved.[3] Despite the marked improvement in treatment times and outcomes in STEMI, myocardial no-reflow remains an important limitation to the current approach to primary percutaneous coronary intervention. This phenomenon, characterized by slow flow to the distal myocardium, is noted in 5% to 30% of patients with STEMI[4] and is associated with a significantly worse mortality.[5] Myocardial no-reflow is thought to be a result of various inciting factors including ischemic-related injury leading to myocardial edema, reperfusion injury leading to further cellular edema, as well as intravascular hemorrhage, endothelial dysfunction, and distal embolization, all resulting in microvascular obstruction[4] (Figure).

Over decades, a variety of adjunctive approaches have been studied to reduce this injury, including angioplasty-assisted thrombolysis,[6] thrombus aspiration,[7] intracoronary IIb/IIIa inhibitors,[8] and intracoronary vasodilators[9] but none of these strategies have proven to be definitively successful.

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As an alternative approach to reduce the no-reflow phenomenon in STEMI, delayed stenting has also been evaluated in a small number of randomized studies. In a study of 101 patients in the DEFER-STEMI (Deferred Stenting versus Immediate Stenting to Prevent No- or Slow-Reflow in Acute ST-Segment Elevation Myocardial Infarction) trial,[11] patients received deferred stent placement after a median time of 9 hours from initial reperfusion, with evidence of greater myocardial salvage (final infarct size by cardiac magnetic resonance imaging indexed to the initial area at risk) at 6 months. Following this promising study, the DANAMI 3-DEFER (Deferred versus Conventional Stent Implantation in Patients with ST-Segment Elevation Myocardial Infarction) multicenter, open label, randomized controlled study of 1215 patients in Denmark took a more ambitious approach to questioning the value of deferred stenting—in this case, stenting occurred 3 days after initial reperfusion.[12] However, at 3.5 years of follow-up, they found no difference in their combined clinical end point and only a minimally higher left ventricular ejection fraction in the deferred stenting group at 1 year. Further limiting this approach, 2% of the deferred group could

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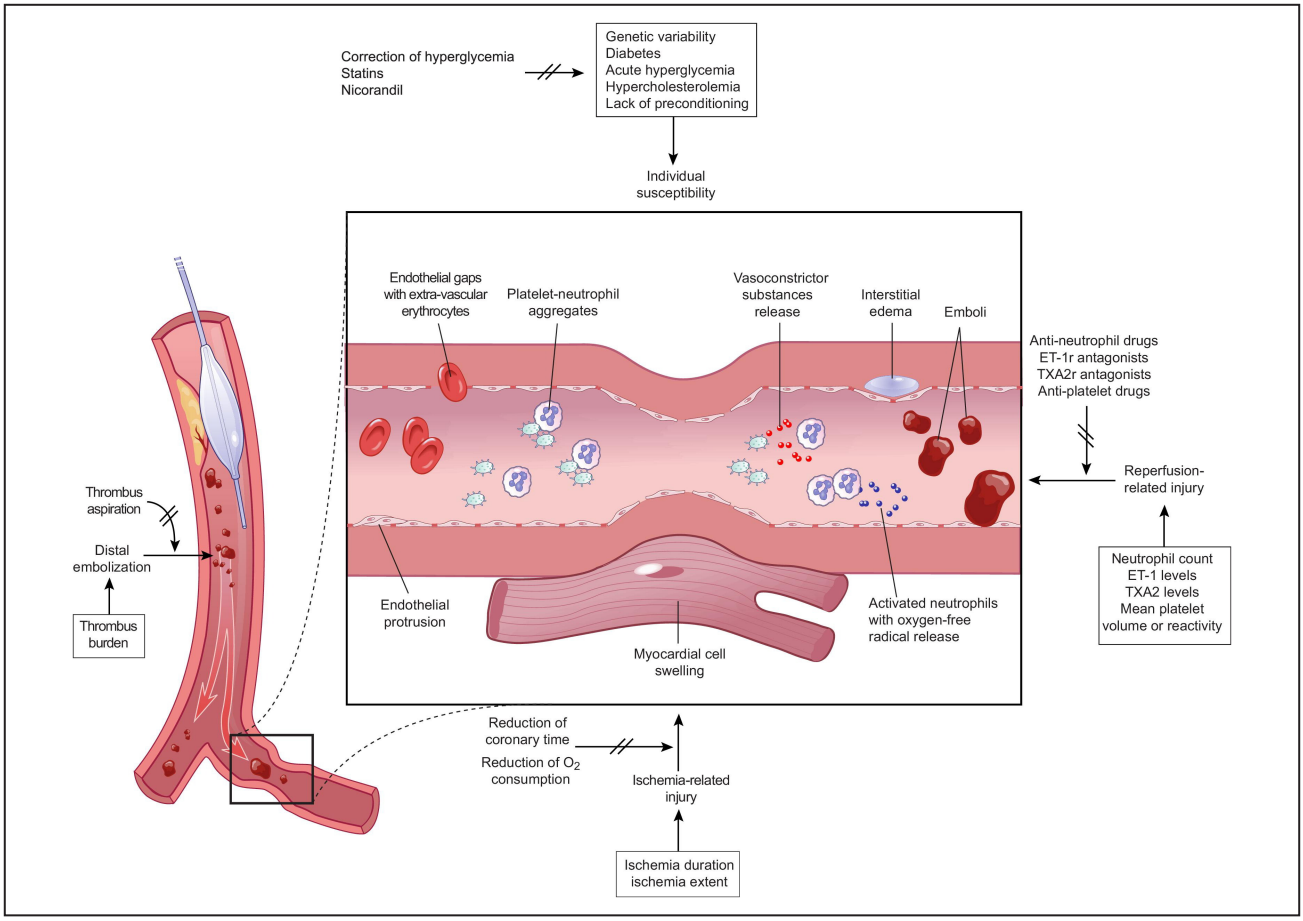

Figure. The mechanisms leading to the pathogenesis of coronary microvascular obstruction leading to myocardial no-reflow: (1) ischemia-related injury, (2) reperfusion-related injury, (3) distal embolization, and (4) individual susceptibility to microvascular obstruction.
ET-1 indicates entothelin-1; and TXA2, thromboxane A2. Adapted from Niccoli et al with permission.[10] Copyright ©2009 Elsevier.

not wait the full predefined deferral period, requiring urgent stent implantation.

Indeed, the concept of a "MIMO" or minimally invasive mechanical intervention[13] to limit reperfusion injury is not new; but if this conceptual approach has merit, we have yet to get it right.[14] Perhaps the prior studies waited too long to stent, and the hypothesis should be retested with a much shorter time interval. If the delay to stenting is too long, we risk prolonged ischemic injury; but if the wait is too short, we risk overly aggressive reperfusion that will lead to reperfusion injury. This "Goldilocks" approach to determining the optimal time to stenting (not *too* long and not *too* short) may in fact be needed to get it "just right."

In this issue of the *Journal of the American Heart Association (JAHA)*, Sezer et al. set out to test this concept in a nuanced way.[15] They hypothesized that pressure-controlled, gradual reopening of an acutely occluded coronary artery facilitates some reperfusion to the distal myocardium (thus limiting ischemic injury), while avoiding the reperfusion injury resulting from abrupt pressure changes. The goal is to identify the right balance between the two so as to safely limit the myocardial edema and intramyocardial hemorrhage that lead to extravascular compression of the microcirculation. Essentially, gradual reperfusion may allow time for stunned arterioles to restore their vasoconstrictor response. In contrast to prior studies, the authors chose to measure their outcomes in the form of coronary hemodynamics with direct pressure and flow monitoring in the vessel and selected a deferred stenting period of only 30 minutes in light of animal models suggesting that this short period is enough to allow recovery of coronary autoregulation.[16,17]

Among 20 patients in the final analysis, half were treated with an immediate stenting approach and half with a pressure controlled reperfusion with delayed stenting approach (PCRDS). For the PCRDS group, a 1.5 mm balloon was used to restore thrombolysis in myocardial infarction 3 flow, after which stenting was

delayed for 30 minutes to allow recovery of autoregulatory tone of the arterioles. The primary end point was zero-flow pressure at the end of a 60-minute marking period. The secondary end point was the hyperemic microvascular resistance at the same time point. Zero-flow pressure, defined as the calculated pressure at which coronary flow would cease, was chosen on the basis of earlier reports supporting this hemodynamic marker to be the best predictor of myocardial infarct size.[17] Continuous pressure and flow signals were measured every 10 minutes, as well as with hyperemia every 20 minutes over the following hour and a half. Indeed, they found that during the first 30 minutes, there were differences in mean resting and hyperemic distal pressures—those who had not yet been stented demonstrated lower distal pressures. After delayed stenting, distal pressures became comparable between the 2 groups. Zero-flow pressure and hyperemic microvascular resistance were significantly lower with PCRDS when compared with immediate stenting. The differences in zero-flow pressure, hyperemic microvascular resistance, and arteriolar resistance index persisted through the end of the monitoring period, suggesting better coronary microcirculatory protection. Additionally, peak biomarkers including troponin and creatine kinase were significantly lower in the PCRDS group.

This study presented a novel approach to assessing the microcirculatory response to reperfusion in STEMI using detailed measurements and calculations to report the distal coronary pressure, microvascular resistance, and zero-flow pressure. Not only does this study demonstrate a potential advantage of stepwise reopening of the coronary artery over traditional immediate stenting, it demonstrated—for the first time in humans—the natural history of microvascular hemodynamic changes that are seen after immediate reperfusion of a totally occluded artery. The gradual deterioration in microvascular perfusion over time after abrupt restoration of coronary flow supports animal findings demonstrating reperfusion injury leading to microvascular dysfunction, edema, and intramyocardial hemorrhage.

There remain important considerations related to this study. First, the study protocol mandated a 30-minute time delay from initial reperfusion to stenting in the PCRDS arm. This time delay was chosen based on earlier work suggesting recovery of coronary autoregulation within 30 minutes of reperfusion.[16] Yet, the ideal delay remains uncertain, and it is possible that different time intervals to reperfusion might influence the findings reported in this study. Second, the authors used a standard 1.5 mm balloon size to achieve distal pressure in all arteries. It is unknown whether this 1.5 mm balloon would respond differently across various vessel sizes and the myocardial territories portended by these vessels. Third, this small study was unable to address the potential impact of PCRDS among women, with only 1 female patient enrolled in the trial. Given evidence of sex differences in coronary microvascular function (particularly coronary flow reserve) and potential association with long term outcomes in deferred lesions,[18] any future study must include a representative proportion of female patients. Finally, prior studies aimed to reduce myocardial no-reflow have shown encouraging results when using surrogate end points[19] but when these methods were tested in larger clinical trials, the results were disappointing.[7,8] Although future studies of PCRDS might focus on other more traditional markers of tissue-level reperfusion including myocardial blush grade or cardiac magnetic resonance imaging measurements of infarct size, ultimately, clinical outcomes will be the true test of impact.

This balloon-delayed stenting approach to limit reperfusion injury must also be considered in the context of competing strategies that use alternate mechanisms to reduce infarct size with delayed reperfusion. Early studies of left ventricular unloading in animal models have shown marked reduction of infarct size through the reduction of left ventricular pressure and volume to reduce myocardial oxygen demand.[20] The feasibility of using the Impella CP to achieve this in humans has recently been demonstrated.[21] The ongoing Door-to-UnLoad Pivotal Trial[22] aims to randomize ≈685 patients with anterior STEMI to Impella support and delayed reperfusion versus immediate reperfusion. Perhaps the ultimate answer will lie in finding the right permutation of approaches to achieve delayed reperfusion, using more than one mechanism of action.

In conclusion, we commend the authors for their bold efforts to answer these critical questions among a tenuous group of patients in the heat of an acute myocardial infarction, and not giving up on the concept of deferred stenting despite earlier negative studies. Their findings reinsert a question mark into the currently accepted treatment approach to primary percutaneous coronary intervention. In the end, Goldilocks got it right, but we suspect the story on delayed stenting in STEMI is just beginning.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361:13–20. doi: 10.1016/S0140-6736(03)12113-7
2. Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. *Circulation*. 2007;116:217–230. doi: 10.1161/CIRCULATIONAHA.107.184043
3. Gandhi S, Garratt KN, Li S, Wang TY, Bhatt DL, Davis LL, Zeitouni M, Kontos MC. Ten-year trends in patient characteristics, treatments, and outcomes in myocardial infarction from National Cardiovascular Data Registry Chest Pain-MI Registry. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008112. doi: 10.1161/CIRCOUTCOMES.121.008112
4. Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J*. 2016;37:1024–1033. doi: 10.1093/eurheartj/ehv484
5. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GFH, Fokkema ML, de Smet BJGL, van den Heuvel AFM, Anthonio RL, Jessurun GA, Tan E-S, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet*. 2008;371:1915–1920. doi: 10.1016/S0140-6736(08)60833-8
6. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet*. 2006;367:569–578. doi: 10.1016/S0140-6736(06)68147-6
7. Jolly SS, James S, Džavík V, Cairns JA, Mahmoud KD, Zijlstra F, Yusuf S, Olivecrona GK, Renlund H, Gao P, et al. Thrombus aspiration in ST-segment-elevation myocardial infarction: an individual patient meta-analysis: Thrombectomy Trialists Collaboration. *Circulation*. 2017;135:143–152. doi: 10.1161/CIRCULATIONAHA.116.025371
8. Thiele H, Wöhrle J, Hambrecht R, Rittger H, Birkemeyer R, Lauer B, Neuhaus P, Brosteanu O, Sick P, Wiemer M, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet*. 2012;379:923–931. doi: 10.1016/S0140-6736(11)61872-2
9. Su Q, Nyi TS, Li L. Adenosine and verapamil for no-reflow during primary percutaneous coronary intervention in people with acute myocardial infarction. *Cochrane Database Syst Rev*. 2015; CD009503. doi: 10.1002/14651858.cd009503.pub3
10. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. *J Am Coll Cardiol* 2009;54:281–292. doi: 10.1016/j.jacc.2009.03.054
11. Carrick D, Oldroyd KG, McEntegart M, Haig C, Petrie MC, Eteiba H, Hood S, Owens C, Watkins S, Layland J, et al. A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). *J Am Coll Cardiol*. 2014;63:2088–2098. doi: 10.1016/j.jacc.2014.02.530
12. Kelbæk H, Høfsten DE, Køber L, Helqvist S, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, De Backer O, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. *Lancet*. 2016;387:2199–2206. doi: 10.1016/S0140-6736(16)30072-1
13. Isaaz K, Robin C, Cerisier A, Lamaud M, Richard L, Da Costa A, Sabry MH, Gerenton C, Blanc JL. A new approach of primary angioplasty for ST-elevation acute myocardial infarction based on minimalist immediate mechanical intervention. *Coron Artery Dis*. 2006;17:261–269. doi: 10.1097/00019501-200605000-00010
14. Mahmoud AN, Saad M, Elgendy AY, Mentias A, Elgendy IY. Deferred or immediate stent implantation for primary percutaneous coronary intervention: a meta-analysis of randomized trials. *Catheter Cardiovasc Interv*. 2018;91:260–264. doi: 10.1002/ccd.27240
15. Sezer M, Escaned J, Broyd CJ, Umman B, Bugra Z, Ozcan I, Sonsoz MR, Ozcan A, Atici A, Aslanger E, et al. Gradual versus abrupt reperfusion during primary percutaneous coronary interventions in ST-segment elevation myocardial infarction (GUARD). *J Am Heart Assoc*. 2022;11:e024172. doi: 10.1161/JAHA.121.024172
16. Ambrosio G, Weisman HF, Mannisi JA, Becker LC. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. *Circulation*. 1989;80:1846–1861. doi: 10.1161/01.CIR.80.6.1846
17. Patel N, Petraco R, Dall'Armellina E, Kassimis G, Maria GLD, Dawkins S, Lee R, Prendergast BD, Choudhury RP, Forfar JC, et al. Zero-flow pressure measured immediately after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction provides the best invasive index for predicting the extent of myocardial infarction at 6 months. *JACC Cardiovasc Interv*. 2015;8:1410–1421. doi: 10.1016/j.jcin.2015.04.029
18. Chung J-H, Lee KE, Lee JM, Her A-Y, Kim CH, Choi KH, Song YB, Hahn J-Y, Kim HY, Choi J-H, et al. Effect of sex difference of coronary microvascular dysfunction on long-term outcomes in deferred lesions. *JACC Cardiovasc Interv*. 2020;13:1669–1679. doi: 10.1016/j.jcin.2020.04.002
19. Svilaas T, Vlaar PJ, van der Horst IC, Diercks GFH, de Smet BJGL, van den Heuvel AFM, Anthonio RL, Jessurun GA, Tan E-S, Suurmeijer AJH, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med*. 2008;358:557–567. doi: 10.1056/NEJMoa0706416
20. Saku K, Kakino T, Arimura T, Sunagawa G, Nishikawa T, Sakamoto T, Kishi T, Tsutsui H, Sunagawa K. Left ventricular mechanical unloading by total support of impella in myocardial infarction reduces infarct size, preserves left ventricular function, and prevents subsequent heart failure in dogs. *Circ Heart Fail*. 2018;11:e004397. doi: 10.1161/CIRCHEARTFAILURE.117.004397
21. Kapur NK, Alkhouli MA, DeMartini TJ, Faraz H, George ZH, Goodwin MJ, Hernandez-Montfort JA, Iyer VS, Josephy N, Kalra S, et al. Unloading the left ventricle before reperfusion in patients with anterior ST-segment elevation myocardial infarction. *Circulation*. 2019;139:337–346. doi: 10.1161/CIRCULATIONAHA.118.038269
22. Parikh MJ, Schuleri KH, Chakrabarti AK, O'Neill WW, Kapur NK, Wohns DH. Door-to-unload: left ventricular unloading before reperfusion in ST-elevation myocardial infarction. *Future Cardiol*. 2021;17:549–559. doi: 10.2217/fca-2021-0006