No-Reflow Phenomenon

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Primary percutaneous angioplasty (pPCI), represents the reperfusion strategy of choice for patients with STEMI according to current international guidelines of the European Society of Cardiology. Coronary no-reflow is characterized by angiographic evidence of slow or no anterograde epicardial flow, resulting in inadequate myocardial perfusion in the absence of evidence of mechanical vessel obstruction. No reflow (NR) is related to a functional and structural alteration of the coronary microcirculation.

myocardial infarction no-reflow percutaneous coronary intervention acute coronary syndrome

1. Introduction

Cardiovascular diseases and, in particular, acute myocardial infarction with ST-segment elevation (STEMI) represent a major cause of mortality in industrialized countries. Primary percutaneous angioplasty (pPCI) represents the reperfusion strategy of choice for patients with STEMI according to current international guidelines of the European Society of Cardiology (ESC) [1]. However, even after the restoration of culprit vessel patency, suboptimal coronary reperfusion, less than three according to the Thrombolysis in Myocardial Infarction (TIMI) score, may occur, with slow, incomplete, or absent coronary flow in the affected coronary artery [2]. This phenomenon, which can regress spontaneously in about half of the cases, is called “no-reflow” (NR) or microvascular obstruction (MVO), and can complicate up to 60% of STEMI cases [1][3]. NR can occur in both the setting of acute coronary syndrome and in the stable patient and is due to a structural and functional alteration of the coronary microcirculation. In addition, it is associated with an increased incidence of rehospitalization, negative ventricular remodeling, malignant arrhythmias, and heart failure and is an independent predictor of myocardial infarction and death [4][5][6]. Among the risk factors, the researchers can list cardiovascular risk factors such as: an age over 65 years, hypertension, smoking, dyslipidemia, diabetes, renal failure, inflammatory processes, and a history of atrial fibrillation, and procedure-related factors such as: the presence of an increased thrombotic load, delayed presentation, high-pressure inflations, and the use of debulking devices [7][8].

2. Pathophysiological Mechanisms

NR is related to a functional and structural alteration of the coronary microcirculation and the researchers can list four main pathophysiological mechanisms: distal atherothrombotic embolization, ischemic damage, reperfusion injury, and individual susceptibility to microvascular damage [9] (**Figure 1**). A complex atherosclerotic plaque can lead to distal embolization phenomena both during the acute and procedural phases, leading to increased distal vascular resistance and additional microinfarcts that promote the release of pro-inflammatory and vasoconstrictive

substances [10][11]. The severity of ischemic injury is directly proportional to the duration of ischemia time. Ischemic damage results in the death of cardiomyocytes, endothelial cells, and formation of interstitial edema with impaired nitric oxide production and subsequent microcirculation obstruction favored by vascular endothelial growth factors (VEGF) release that increase vascular permeability [12][13]. Reperfusion injury, on the other hand, is caused by the abrupt restoration of blood flow at the level of the damaged microcirculation, causes direct cardiomyocyte damage with an influx of inflammatory neutrophils during reperfusion that promotes the production of inflammatory cytokines, free oxygen radicals, vasoactive substances, and proteolytic enzymes [14][15]. The presence of preexisting endothelial dysfunction or genetic mutations, such as the 1976TC polymorphism of the gene for adenosine receptors and various ion channels, increases the susceptibility to microvascular dysfunction and no-reflow [16][17].

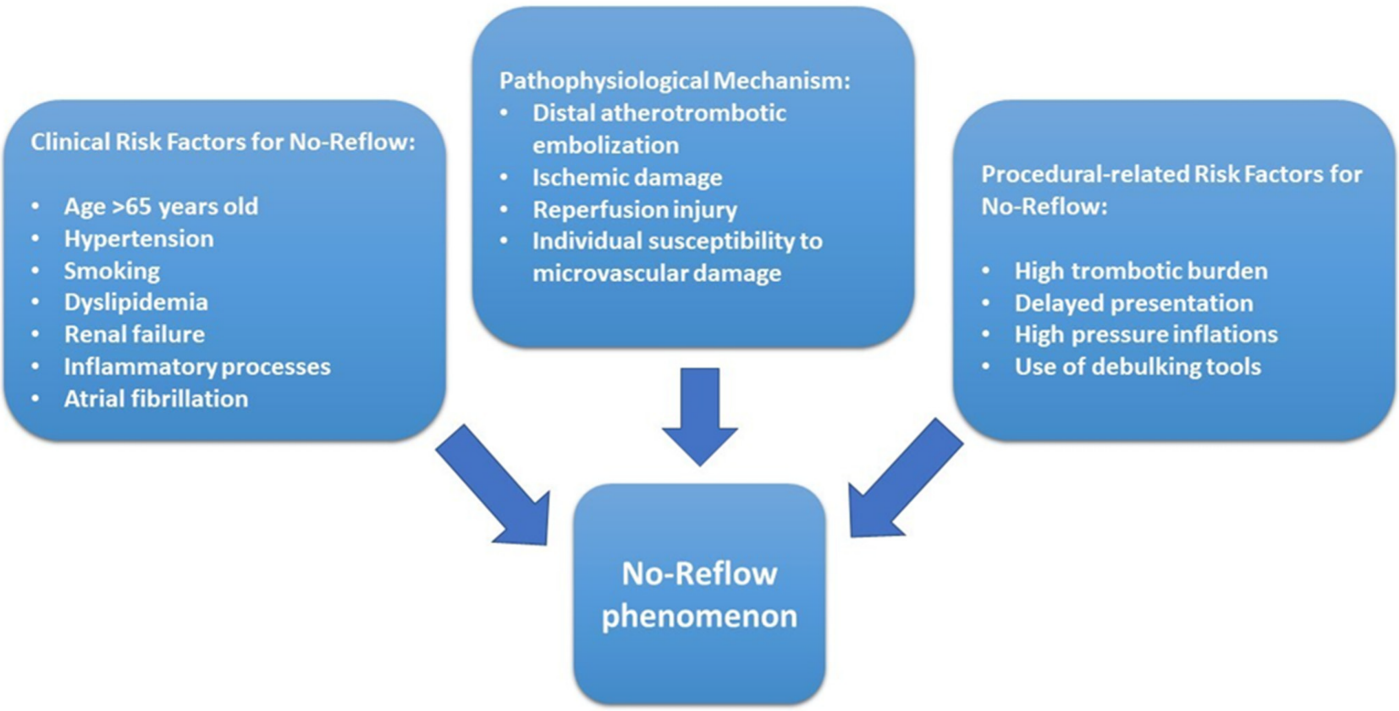

Figure 1. Summary of all the different factors involved in the genesis of the NR phenomenon.

3. Diagnosis of No-Reflow

Coronary angiography during pPCI is the most frequently used diagnostic method for the diagnosis of NR that, thanks to the use of TIMI flow classification, allows to classify coronary flow on a scale from 0, absence of flow, to 3, presence of normal flow [2]. Next to this, we also have the TIMI frame count that evaluates the number of frames required for the contrast agent to fill the distality of the coronary arteries. An increased number of frames constitutes an indirect index of NR [18]. However, because of the poor sensitivity and specificity of this, another angiographic assessment was subsequently introduced by evaluating the degree of myocardial “blush” (MBG). Blush, in fact, assesses the intensity of myocardial tissue radiopacity obtained by injection of contrast medium into

the epicardial coronary arteries and the rapidity with which this impregnation decreases [19] (**Table 1**). MBG also ranges from 0 to 3 and is diagnostic of NR for values of 0–1 [1].

Instead, a more accurate invasive assessment is possible through flow parameters or resistance parameters. Coronary flow reserve (CFR), in fact, through the ratio of coronary flow during maximal hyperemia to coronary flow at rest, provides information about the microcirculation in the absence of epicardial stenosis. A value < 2.0 was associated with the presence of MVO with a sensitivity of 79%. In addition, the measurement of coronary blood flow velocity using intracoronary Doppler guidance allows for the detection of the typical flow pattern associated with NR, characterized by early retrograde systolic flow and rapid deceleration of diastolic flow [20][21]. The microvascular resistance index (IMR), based on the principle of thermodilution, is defined as the product of distal coronary pressure and the mean transit time of a bolus during maximum hyperemia using a dual pressure and temperature guide, and provides an assessment of microcirculation independent of hemodynamic parameters. IMR values > 25 correlate with the presence of MVO, and a post-procedure IMR > 40 units has been associated with a higher rate of in-hospital adverse events, mortality, and readmission for heart failure at 1-year follow-ups [22][23]. Alternatively, IMR under conditions of maximal hyperemia incorporates Doppler flow velocity to estimate flow, and values > 2.5 mmHg/cm/s are predictive of MVO [21][24]. Recently, angiography-derived IMR (IMR_{angio}) has been studied, with good diagnostic accuracy in predicting both IMR > 40 units and the presence of large MVOs on cardiac MRI being documented [25]. Another new technology is CorFlow Therapy™ (CoFl™), which combines real-time microvascular assessment with the ability to administer intracoronary drugs [26]. This device determines transient coronary occlusion by balloon inflation, incremental infusions of crystalloid at a predefined flow rate, and simultaneous measurement of distal pressure beyond balloon occlusion. The flow and pressure quotient can be used to derive dynamic microvascular resistance and have real-time diagnosis of microvascular dysfunction. Initially validated in a porcine model, early results from the MOCA I trial are encouraging in terms of safety, applicability, and the ability to detect MVO immediately after pPCI [27].

Gadolinium-enhanced cardiovascular magnetic resonance imaging (MRI) is certainly the “gold standard” for NR diagnosis [1]. A 1% increase in the extent of MVO is associated with a 1.14-fold increased risk of 1-year mortality [6]. Coronary microvasculature becomes occluded due to the presence of erythrocytes, neutrophils, and cellular debris resulting in a lack of gadolinium enhancement in the endocardial nucleus [28]. The cardiac magnetic resonance (CMR) allows the visualization of myocardial damage through the use of different techniques including delayed gadolinium contrast enhancement (DGE) and T2-weighted images [29]. In addition, new parametric mapping techniques allow for the accurate quantification of myocardial damage based on changes in T1, T2, T2* release times and the assessment of extracellular volume [29]. T2 sequences, in addition to being critical for discriminating between acute and chronic myocardial infarction (generally, edema dissolves in approximately 4–6 weeks after infarction), allow for the identification of areas of intramyocardial hemorrhage (IMH) [30][31]. IMH is a strong predictor of left ventricular remodeling independent of infarct area, and it is closely associated with adverse outcomes. On T2-weighted images, areas of IMH appear of attenuated signal within high-signal edematous areas because of the presence of hemoglobin degradation products. The identification of areas of MVO requires the use of the contrastographic technique [32].

Gadolinium has an extravascular and extracellular distribution, so its wash-out is delayed in areas of increased extracellular/interstitial volume, such as areas of necrosis (in the acute phase) and fibrosis (in the chronic phase) [33]. DGE is assessed in T1-weighted images 10–15 min after gadolinium administration and is used to visualize the MVO, which appears as a dark, hypointense area surrounded by the hyperintensity of necrotic myocardium [32]. Alternatively, early contrastographic impregnation is a contrast-dependent technique in which T1-weighted acquisitions are performed just after contrast medium administration (after 1–3 min). Low-signal areas represent areas of MVO or thrombus. Finally, the first-pass perfusion (FPP) method is another contrast-dependent technique that allows the detection of even small areas of MVO [34]. FPP is a dynamic study and is based on the visualization of the time distribution of the bolus of the paramagnetic contrast agent during the first pass at the level of the myocardial microcirculation [33]. A perfusion defect is thus manifested as a region of contrastographic failure to impregnate myocardial tissue due to altered capillary microcirculation. However, the prognostic value of FPP is not as strong as for DGE, presumably in view of the fact that it also detects small areas of MVO [34].

ECG may also allow for a diagnosis of NR to be made. A resolution of ST-segment elevation <50% or <70%, depending on the cut-off used, after 60 to 90 min after reperfusion is indicative of NR [35][36].

Other diagnostic techniques used to assess NR are contrast-enhanced echocardiography and nuclear imaging with positron emission tomography and single-photon emission computed tomography [37][38][39]. Contrast-enhanced echocardiography is an examination that can be performed at the patient's bedside in which microbubbles of inert gas are typically administered intravenously, and NR is identified by areas of hypoperfusion [39][40]. However, the lack of sensitivity and/or the complexity of implementation make these techniques less attractive for the evaluation routine assessment of NR [1][41].

Table 1. Summarizes the main diagnostic methods available and their limitations.

Diagnostic Methods	Study Design	Results	Limitations
Coronary Angiography (MBG) [42]	777 prospectively enrolled patients who underwent pPCI during a 6-year period.	MBG can be used to describe the effectiveness of myocardial reperfusion and is an independent predictor of long-term mortality.	Interobserver and intraobserver variabilities associated with subjective angiographic assessments.
Coronary Flow Reserve (CFR) [43]	89 prospectively enrolled patients who underwent pPCI during a 4-year period and subsequent physiologic study.	A CFR value ≥ 2.0 is considered normal. Complimentary assessment of microcirculation by the	Possible significant variability of tracings between different beats. Does not distinguish between epicardial and

Diagnostic Methods	Study Design	Results	Limitations
		IMR and CFR may be useful to evaluate myocardial viability and predict the long-term prognosis of STEMI patients.	microvascular components of coronary resistances. Requires maximal hyperemia using adenosine.
Microvascular resistance index (IMR) [44]	288 prospectively enrolled patients with STEMI during a 11-year period.	An IMR > 40 is a multivariable associate of left ventricular and clinical outcomes after STEMI, regardless of infarct size. IMR has superior clinical value for risk stratification.	Manual injection of saline may be a source of variability. It requires achievement of maximal hyperemia and the use of adenosine.
Electrocardiogram (ECG) [36]	180 prospectively enrolled patients with a first acute STEMI.	Residual ST-segment elevation and the number of Q waves on the ECG shortly after pPCI have complementary predictive value on myocardial function, infarct size and extent, and MVO.	Discordance between resolution of ST-segment elevation and the angiographic indices of NR.
Myocardial Contrast Echocardiography (MCE) [40]	110 prospectively enrolled patients who underwent pPCI in a multicenter study.	Among patients with TIMI 3 flow, MVO extension, as detected and quantified by MCE, is the most powerful independent predictor of LV remodeling after STEMI compared with persistent ST-segment elevation and degree of MBG.	Operator-dependent and limited by the possible poor acoustic window.

Diagnostic Methods	Study Design	Results	Limitations
Cardiac Magnetic Resonance (CMR) [6]	Pooled analysis using individual patient data from seven randomized primary PCI trials	The presence and extent of MVO measured by CMR after primary PCI in STEMI are strongly associated with mortality and hospitalization for HF within 1 year.	Usually performed 2 to 7 days after pPCI. Not widely available locally. Not performable in all patients.
Positron Emission Tomography (PET) [37]	Seven porcine model with left anterior descending coronary artery occlusion/reperfusion underwent PET-CT within 3 days of infarction.	Increased regional FDG uptake in the area of acute infarction is a frequent occurrence and indicates tissue inflammation that is commonly associated with MVO.	Expensive and difficult to obtain locally.

Elevation Contrast LV, Left Emission

s has only partially translated to humans with benefits on surrogate endpoints but no impact on endpoints such as cardiovascular mortality. To date, the main treatment of NR is based on the use of intracoronary drugs that can result in vasodilation in the coronary arteries. Several studies have shown possible efficacy for vasodilator drugs, such as adenosine, calcium channel blockers, and sodium nitroprusside, used singularly or in combination, and antiplatelet drugs such as glycoprotein IIB/IIIA inhibitors. Alongside these, nonpharmacologic treatment strategies such as coronary post-conditioning, remote ischemic conditioning, or tools to reduce the embolization of thrombotic material and increase coronary flow have also been investigated in several trials, but there is still no therapy, single or in combination, aimed at reducing ischemia/reperfusion injury that is clearly associated with improved clinical outcomes [1][45].

References

1. Ibanez, B.; James, S.; Agewall, S.; Antunes, M.J.; Bucciarelli-Ducci, C.; Bueno, H.; Caforio, A.L.P.; Crea, F.; Goudevenos, J.A.; Halvorsen, S.; et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur. Heart J. 2018, 39, 119–177.
2. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N. Engl. J. Med. 1985, 312, 932–936.
3. Niccoli, G.; Kharbanda, R.K.; Crea, F.; Banning, A.P. No-reflow: Again prevention is better than treatment. Eur. Heart J. 2010, 31, 2449–2455.

4. Tasar, O.; Karabay, A.K.; Oduncu, V.; Kirma, C. Predictors and outcomes of no-reflow phenomenon in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Coron. Artery Dis. 2019, 30, 270–276.
5. Niccoli, G.; Burzotta, F.; Galiuto, L.; Crea, F. Myocardial no-reflow in humans. J. Am. Coll. Cardiol. 2009, 54, 281–292.
6. De Waha, S.; Patel, M.R.; Granger, C.B.; Ohman, E.M.; Maehara, A.; Eitel, I.; Ben-Yehuda, O.; Jenkins, P.; Thiele, H.; Stone, G.W. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: An individual patient data pooled analysis from seven randomized trials. Eur. Heart J. 2017, 38, 3502–3510.
7. Caiazzo, G.; Musci, R.L.; Frediani, L.; Umińska, J.; Wanha, W.; Filipiak, K.J.; Kubica, J.; Navarese, E.P. State of the Art: No-Reflow Phenomenon. Cardiol. Clin. 2020, 38, 563–573.
8. Kaur, G.; Baghdasaryan, P.; Natarajan, B.; Sethi, P.; Mukherjee, A.; Varadarajan, P.; Pai, R.G. Pathophysiology, Diagnosis, and Management of Coronary No-Reflow Phenomenon. Int. J. Angiol. 2021, 30, 15–21.
9. Montone, R.A.; Camilli, M.; Del Buono, M.G.; Meucci, M.C.; Gurgoglione, F.; Russo, M.; Crea, F.; Niccoli, G. “No-reflow”: Update su diagnosi, fisiopatologia e strategie terapeutiche. G. Ital. Cardiol. 2020, 21, 4S–14S.
10. Porto, I.; Biasucci, L.M.; De Maria, G.L.; Leone, A.M.; Niccoli, G.; Burzotta, F.; Trani, C.; Tritarelli, A.; Vergallo, R.; Liuzzo, G.; et al. Intracoronary microparticles and microvascular obstruction in patients with ST elevation myocardial infarction undergoing primary percutaneous intervention. Eur. Heart J. 2012, 33, 2928–2938.
11. Heusch, G.; Kleinbongard, P.; Böse, D.; Levkau, B.; Haude, M.; Schulz, R.; Erbel, R. Coronary microembolization: From bedside to bench and back to bedside. Circulation 2009, 120, 1822–1836.
12. Weis, S.M.; Cheresh, D.A. Pathophysiological consequences of VEGF-induced vascular permeability. Nature 2005, 437, 497–504.
13. Bouleti, C.; Mewton, N.; Germain, S. The no-reflow phenomenon: State of the art. Arch. Cardiovasc. Dis. 2015, 108, 661–674.
14. Ambrosio, G.; Tritto, I. Reperfusion injury: Experimental evidence and clinical implications. Am. Heart J. 1999, 138, S69–S75.
15. Fröhlich, G.M.; Meier, P.; White, S.K.; Yellon, D.M.; Hausenloy, D.J. Myocardial reperfusion injury: Looking beyond primary PCI. Eur. Heart J. 2013, 34, 1714–1722.

16. Riksen, N.P.; Franke, B.; van den Broek, P.; Smits, P.; Rongen, G.A. The 1976C>T polymorphism in the adenosine A2A receptor gene does not affect the vasodilator response to adenosine in humans in vivo. Pharmacogenet. Genom. 2007, 17, 551–554.
17. Kloner, R.A.; King, K.S.; Harrington, M.G. No-reflow phenomenon in the heart and brain. Am. J. Physiol. Heart Circ. Physiol. 2018, 315, H550–H562.
18. Gibson, C.M.; Cannon, C.P.; Daley, W.L.; Dodge, J.T.; Alexander, B.; Marble, S.J.; McCabe, C.H.; Raymond, L.; Fortin, T.; Poole, W.K.; et al. TIMI frame count: A quantitative method of assessing coronary artery flow. Circulation 1996, 93, 879–888.
19. Van ’t Hof, A.W.; Liem, A.; Suryapranata, H.; Hoorntje, J.C.; de Boer, M.J.; Zijlstra, F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: Myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998, 97, 2302–2306.
20. Bulluck, H.; Foin, N.; Tan, J.W.; Low, A.F.; Sezer, M.; Hausenloy, D.J. Invasive Assessment of the Coronary Microcirculation in Reperfused ST-Segment-Elevation Myocardial Infarction Patients: Where Do We Stand? Circ. Cardiovasc. Interv. 2017, 10, e004373.
21. Knaapen, P.; Camici, P.G.; Marques, K.M.; Nijveldt, R.; Bax, J.J.; Westerhof, N.; Götte, M.J.W.; Jerosch-Herold, M.; Schelbert, H.R.; Lammertsma, A.A.; et al. Coronary microvascular resistance: Methods for its quantification in humans. Basic Res. Cardiol. 2009, 104, 485–498.
22. Fearon, W.F.; Low, A.F.; Yong, A.S.; McGeoch, R.; Berry, C.; Shah, M.G.; Ho, M.Y.; Kim, H.-S.; Loh, J.P.; Oldroyd, K.G. Prognostic value of the Index of Microcirculatory Resistance measured after primary percutaneous coronary intervention. Circulation 2013, 127, 2436–2441.
23. Fahrni, G.; Wolfrum, M.; De Maria, G.L.; Cuculi, F.; Dawkins, S.; Alkhalil, M.; Patel, N.; Forfar, J.C.; Prendergast, B.D.; Choudhury, R.P.; et al. Index of Microcirculatory Resistance at the Time of Primary Percutaneous Coronary Intervention Predicts Early Cardiac Complications: Insights From the OxAMI (Oxford Study in Acute Myocardial Infarction) Cohort. J. Am. Heart Assoc. 2017, 6, e005409.
24. Fearon, W.F.; Balsam, L.B.; Farouque, H.M.O.; Caffarelli, A.D.; Robbins, R.C.; Fitzgerald, P.J.; Yock, P.G.; Yeung, A.C. Novel index for invasively assessing the coronary microcirculation. Circulation 2003, 107, 3129–3132.
25. De Maria, G.L.; Scarsini, R.; Shanmuganathan, M.; Kotronias, R.A.; Terentes-Printzios, D.; Borlotti, A.; Langrish, J.P.; Lucking, A.J.; Choudhury, R.P.; Kharbanda, R.; et al. Angiography-derived index of microcirculatory resistance as a novel, pressure-wire-free tool to assess coronary microcirculation in ST elevation myocardial infarction. Int. J. Cardiovasc. Imaging 2020, 36, 1395–1406.

26. Ciofani, J.L.; Allahwala, U.K.; Scarsini, R.; Ekmejian, A.; Banning, A.P.; Bhindi, R.; De Maria, G.L. No-reflow phenomenon in ST-segment elevation myocardial infarction: Still the Achilles' heel of the interventionalist. Future Cardiol. 2021, 17, 383–397.
27. Gragnano, F. Microvascular Obstruction Treatment Efficacy Measured Using Dynamic Microvascular Resistance (dMVR): First-in-Man Study Diagnosis Sequence Patient Cohort, EuroPCR e-Course, Paris 2020. Available online: https://media.pcronline.com/diapos/PCReCourse2020/226-20200627_0900_Hotline_and_Innovation_Channel_Gragnano_Felice_0000_ (accessed on 25 June 2020).
28. Lima, J.A.; Judd, R.M.; Bazille, A.; Schulman, S.P.; Atalar, E.; Zerhouni, E.A. Regional heterogeneity of human myocardial infarcts demonstrated by contrast-enhanced MRI. Potential mechanisms. Circulation 1995, 92, 1117–1125.
29. Wu, K.C.; Kim, R.J.; Bluemke, D.A.; Rochitte, C.E.; Zerhouni, E.A.; Becker, L.C.; Lima, J.A. Quantification and time course of microvascular obstruction by contrast-enhanced echocardiography and magnetic resonance imaging following acute myocardial infarction and reperfusion. J. Am. Coll. Cardiol. 1998, 32, 1756–1764.
30. Ganame, J.; Messalli, G.; Dymarkowski, S.; Rademakers, F.E.; Desmet, W.; Van de Werf, F.; Bogaert, J. Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. Eur. Heart J. 2009, 30, 1440–1449.
31. Zia, M.I.; Ghugre, N.R.; Connelly, K.A.; Strauss, B.H.; Sparkes, J.D.; Dick, A.J.; Wright, G.A. Characterizing myocardial edema and hemorrhage using quantitative T2 and T2* mapping at multiple time intervals post ST-segment elevation myocardial infarction. Circ. Cardiovasc. Imaging 2012, 5, 566–572.
32. García-Dorado, D.; Oliveras, J.; Gili, J.; Sanz, E.; Pérez-Villa, F.; Barrabés, J.; Carreras, M.J.; Solares, J.; Soler-Soler, J. Analysis of myocardial oedema by magnetic resonance imaging early after coronary artery occlusion with or without reperfusion. Cardiovasc. Res. 1993, 27, 1462–1469.
33. Croisille, P.; Revel, D.; Saeed, M. Contrast agents and cardiac MR imaging of myocardial ischemia: From bench to bedside. Eur. Radiol. 2006, 16, 1951–1963.
34. Bulluck, H.; Dharmakumar, R.; Arai, A.E.; Berry, C.; Hausenloy, D.J. Cardiovascular Magnetic Resonance in Acute ST-Segment-Elevation Myocardial Infarction: Recent Advances, Controversies, and Future Directions. Circulation 2018, 137, 1949–1964.
35. Tjandrawidjaja, M.C.; Fu, Y.; Westerhout, C.M.; White, H.D.; Todaro, T.G.; Van de Werf, F.; Mahaffey, K.W.; Wagner, G.S.; Granger, C.B.; Armstrong, P.W.; et al. Resolution of ST-segment depression: A new prognostic marker in ST-segment elevation myocardial infarction. Eur. Heart J. 2010, 31, 573–581.

36. Nijveldt, R.; van der Vleuten, P.A.; Hirsch, A.; Beek, A.M.; Tio, R.A.; Tijssen, J.G.P.; Piek, J.J.; van Rossum, A.C.; Zijlstra, F. Early electrocardiographic findings and MR imaging-verified microvascular injury and myocardial infarct size. JACC Cardiovasc. Imaging 2009, 2, 1187–1194.
37. Lautamäki, R.; Schuleri, K.H.; Sasano, T.; Javadi, M.S.; Youssef, A.; Merrill, J.; Nekolla, S.G.; Abraham, M.R.; Lardo, A.C.; Bengel, F.M. Integration of infarct size, tissue perfusion, and metabolism by hybrid cardiac positron emission tomography/computed tomography: Evaluation in a porcine model of myocardial infarction. Circ. Cardiovasc. Imaging 2009, 2, 299–305.
38. Porter, T.R.; Li, S.; Oster, R.; Deligonul, U. The clinical implications of no reflow demonstrated with intravenous perfluorocarbon containing microbubbles following restoration of Thrombolysis in Myocardial Infarction (TIMI) 3 flow in patients with acute myocardial infarction. Am. J. Cardiol. 1998, 82, 1173–1177.
39. Kaul, S. Myocardial contrast echocardiography: A 25-year retrospective. Circulation 2008, 118, 291–308.
40. Galiuto, L.; Garramone, B.; Scarà, A.; Rebuzzi, A.G.; Crea, F.; La Torre, G.; Funaro, S.; Madonna, M.; Fedele, F.; Agati, L.; et al. The extent of microvascular damage during myocardial contrast echocardiography is superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodeling: Results of the multicenter AMICI study. J. Am. Coll. Cardiol. 2008, 51, 552–559.
41. Niccoli, G.; Scalone, G.; Lerman, A.; Crea, F. Coronary microvascular obstruction in acute myocardial infarction. Eur. Heart J. 2016, 37, 1024–1033.
42. Van't Hof, A.W.J.; Ten Berg, J.; Heestermans, T.; Dill, T.; Funck, R.C.; van Werkum, W.; Dambrink, J.-H.E.; Suryapranata, H.; van Houwelingen, G.; Ottervanger, J.P.; et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): A multicentre, double-blind, randomised controlled trial. Lancet Lond. Engl. 2008, 372, 537–546.
43. Park, S.-D.; Baek, Y.-S.; Lee, M.-J.; Kwon, S.W.; Shin, S.-H.; Woo, S.-I.; Kim, D.-H.; Kwan, J.; Park, K.-S. Comprehensive assessment of microcirculation after primary percutaneous intervention in ST-segment elevation myocardial infarction: Insight from thermodilution-derived index of microcirculatory resistance and coronary flow reserve. Coron. Artery Dis. 2016, 27, 34–39.
44. Carrick, D.; Haig, C.; Ahmed, N.; Carberry, J.; Yue May, V.T.; McEntegart, M.; Petrie, M.C.; Eteiba, H.; Lindsay, M.; Hood, S.; et al. Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment-Elevation Myocardial Infarction. Circulation 2016, 134, 1833–1847.
45. Faruk Akturk, I.; Arif Yalcin, A.; Biyik, I.; Sarikamis, C.; Turhan Caglar, N.; Erturk, M.; Celik, O.; Uzun, F.; Murat Caglar, I.; Oner, E. Effects of verapamil and adenosine in an adjunct to tirofiban

on resolution and prognosis of noreflow phenomenon in patients with acute myocardial infarction. Minerva Cardioangiol. 2014, 62, 389–397.