

Myocardial Edema on T2-Weighted MRI New Marker of Ischemia Reperfusion Injury and Adverse Myocardial Remodeling

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Importance of Evaluation of Ischemia/ Reperfusion Injury by Magnetic Resonance Imaging

Although the advances in revascularization therapy have drastically decreased the mortality after ST-segment-elevation myocardial infarction (STEMI), the number of patients who develop heart failure after the reperfusion therapy continues to increase. More than 30% of the patients who survive STEMI develop heart failure long-term.¹ Clinical studies have demonstrated that the larger infarct size (IS) and the resultant left ventricular dysfunction at the time of initial treatment significantly correlate with the likelihood of future adverse ventricular remodeling and arrhythmia.² Thus, the efforts to minimize the IS by prompt reperfusion therapy is the primary rationale in the treatment of STEMI in preventing heart failure and catastrophic cardiovascular events. Myocardial salvage determined by the initial perfusion defect, that is, myocardium at risk (MaR) and the final IS, is a surrogate marker of a successful reperfusion therapy to predict clinical outcome.³ Despite significant technological advances in the reperfusion therapy, myocardial reperfusion injury substantially decreases the myocardial salvage and increases the final tissue injury, which may account for $\leq 50\%$ of the final IS.⁴ Even though various pre- or post-conditioning strategies, including stress (reversible ischemia, exercise, and hypothermia) and pharmaceutical intervention, may help to protect the heart from the ischemia/reperfusion (I/R) injury, the efficacy of these treatments has not been sufficiently demonstrated in clinical studies. Thus, a robust imaging modality to assess the I/R injury and predict future cardiovascular events addresses a critical unmet clinical need.

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In ischemic heart disease, myocardial edema detected by magnetic resonance imaging (MRI) as high signal intensity on T2-weighted imaging (T2-WI) is a phenomenon associated with reperfusion. It is known that a permanent occlusion of the coronary artery leads to minimal myocardial edema.⁵ The restoration of coronary blood flow increases the swelling of individual cardiomyocytes and exacerbates the interstitial edema secondary to

reactive hyperemia and leakage from damaged capillaries.⁵ At revascularization, the cellular debris from the ruptured atherosclerotic culprit lesion(s) and the released soluble vasoconstrictive, thrombogenic, and inflammatory substrates contribute to microvascular flow impairment.⁴ In addition, the myocardial I/R impairs microcirculation directly as demonstrated in the experimental occlusion and reperfusion of nonatherosclerotic coronary arteries in the preclinical animal models.² These studies demonstrated that the swelling of the endothelial cells, obstruction of the capillary bed by platelet aggregation, and compression of the vasculature by interstitial edema result in microvascular obstruction (MVO) or no-reflow phenomenon.² Furthermore, advanced capillary destruction leads to intramyocardial hemorrhage (IMH). At the end of this complex post-injury physiology, MVO and IMH emerge in an anatomically dependent location. Using late gadolinium enhancement and T2-WI MRI, these lesions are delineated reliably as contrast void and low signal intensity, respectively, with excellent histological correlation.⁶ Most importantly, these I/R injury-associated MRI findings predict the major adverse cardiac events (MACE).⁷

Although the current standard methods to detect and evaluate the severity of the I/R injury include electrocardiographic evidence of persistent ST-segment elevation, angiographic finding of no-reflow or poor TIMI (thrombolysis in myocardial infarction) blush grade, and poor myocardial salvage on SPECT (single-photon emission computed tomography), the integrative ability of cardiac MRI has also been recognized. This imaging technique combines T1-WI to identify the myocardial edema to delineate the MaR and late gadolinium enhancement to assess the IS, MVO, and IMH. Myocardial edema appearing in the early stages of the reperfusion STEMI corresponds well with the histological IS in an animal model.⁸ Myocardial salvage index evaluated by cardiac MRI is reported to be a useful predictor of MACE.⁹

However, careful attention must be paid in evaluating the MaR and IS by cardiac MRI because they undergo dynamic changes, especially, during the first week of myocardial infarction. The extent of myocardial edema affected by the several clinical or pathological factors, including ischemic duration, concomitant diseases, and reperfusion injury, may confound the evaluation of MaR. In a clinical study, MaR by T2-WI obtained at 5 to 7 days post-intervention corresponded well with the initial perfusion defect on SPECT. However, in an individual case-by-case review, T2-WI showed a significantly different size of MaR compared with SPECT depending on the occlusion time and presence of spontaneous reperfusion.¹⁰ Thus, the measurement of myocardial edema on T2-WI may evaluate the extent of I/R injury more reliably and provide a more accurate prediction of MACE in this highly vulnerable patient population.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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New Insight Into Myocardial Edema Post-I/R Injury

This study by Fernández-Jiménez et al¹¹ showed that the detection of myocardial edema with longer T2 relaxation times represents the complex pathophysiology post-I/R injury. The investigation systematically demonstrated that the myocardial edema does not correspond with the MaR detected by the initial perfusion defect. The authors confirmed the dynamic bimodal pattern of myocardial edema during the first week post-I/R injury. IS also changed dynamically during this period, suggesting the inaccuracy of myocardial salvage evaluated by T2 and late gadolinium enhancement. The authors compared the areas with T2 edema to the true MaR area with initial perfusion defect detected by arterial MDCT (multidetector computed tomography). The cardioprotective procedures and the duration of ischemia significantly affected the myocardial edematous waves. Although myocardial edema on T2-WI overestimated the MaR because of myocardial swelling in the hyperacute phase of 120 minutes post-I/R, it corresponded well with MaR at days 4 and 7. Interestingly, cardioprotection (preconditioning or short ischemic duration) diminished both hyperacute and deferred edematous waves, resolving edema at an earlier phase and leading to the underestimation of the area at risk. T2-WI severely underestimated the MaR at day 1 because of the resolution of edema in all I/R groups with or without cardioprotection. Furthermore, severe edema was associated with the higher degree of I/R injury represented by MVO/IMH, larger IS, and poor ejection fraction. The study characterized the dynamic myocardial tissue changes represented by myocardial edema, IMH/MVO, and IS taking place in the acute phase of I/R injury. The preconditioning and the duration of ischemia significantly affected the homeostatic balance between myocardial tissue injury and repair in a complex temporal pattern during the week after I/R injury. This study reminds us that we need to consider the timing, imaging modality, and cardioprotective conditions to evaluate the MaR, IS, and myocardial salvage. Although the feasibility to evaluate myocardial salvage evaluation needs further examination, detection of myocardial edema correlates well with I/R injury and may test the efficacy of novel cardioprotective strategies.

Future Perspectives

The temporal and spatial changes of edema formation post-I/R injury should be confirmed in clinical studies and correlated with clinical events. Evaluation of prolongation of T2 relaxation times, representing myocardial edema, could be a promising method to reveal the complex mechanisms of I/R injury and understand the potential cardioprotective strategies. An optimized analysis of T2-WI, preconditioning pattern, coronary anatomy, imaging protocol, culprit lesion, and TIMI flow grade may enable precise insight into the extent of myocardial I/R injury and salvage to provide better tissue characterization. Reliable evaluation of myocardial edema may provide a precise prognosis of STEMI patients by establishing a predictive algorithm, combining index ischemia and tissue composition, to determine the likelihood of the occurrence of MACE.

Second, the pathological significance of myocardial edema should be clarified in future studies. Edema itself may have

adverse effects on cardiac remodeling as it is known to exacerbate myocardial cell stunning.¹² The pathological significance of the 2 waves of edema peaks has not yet been clarified. T2 does not merely represent myocardial edema but is also influenced by IMH/MVO to diminish the T2 values, leading to an apparent second peak.¹³ Previous study by the authors also demonstrated that the myocardial water content does not normalize while the T2 signal does between the first and second peaks of myocardial edema.⁵ Although the authors claimed in their previous article that the deferred edematous wave is associated with the healing inflammation, the specific roles of the inflammatory process in myocardial repair, remodeling, and dysfunction after I/R and the effects of cardioprotection have yet to be clarified.⁵

Finally, the importance of heterogeneous tissue characteristics of the infarcted myocardium has been noted recently. Heterogeneous characteristics of the peri-infarct zones characterized by uneven distribution of the gadolinium- and manganese-based contrast studies have important prognostic importance with regard to cardiac dysfunction, arrhythmogenesis, and mortality.¹⁴ Peri-infarct ischemia is a critical prognostic factor in post-infarct MACE.¹⁵ The infarct and peri-infarct zones most likely display different T2 relaxation times, which are expected to vary temporally. The role of I/R injury and myocardial edema in the formation of heterogeneous infarct tissues and eventual MACE needs to be elucidated. Post-infarct ischemia, arrhythmogenesis, and left ventricular remodeling, which all represent significant clinical events, must be addressed by accurate characterization of the myocardium.

Disclosures

None.

References

- Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*. 2011;8:30–41. doi: 10.1038/nrcardio.2010.165.
- Heusch G, Libby P, Gersh B, Yellon D, Böhm M, Lopaschuk G, Opie L. Cardiovascular remodelling in coronary artery disease and heart failure. *Lancet*. 2014;383:1933–1943. doi: 10.1016/S0140-6736(14)60107-0.
- Ndrepepa G, Mehilli J, Schwaiger M, Schühlen H, Nekolla S, Martinoff S, Schmitt C, Dirschinger J, Schömig A, Kastrati A. Prognostic value of myocardial salvage achieved by reperfusion therapy in patients with acute myocardial infarction. *J Nucl Med*. 2004;45:725–729.
- Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med*. 2007;357:1121–1135. doi: 10.1056/NEJMra071667.
- Fernández-Jiménez R, García-Prieto J, Sánchez-González J, Agüero J, López-Martín GJ, Galán-Arriola C, Molina-Iracheta A, Doohan R, Fuster V, Ibáñez B. Pathophysiology underlying the bimodal edema phenomenon after myocardial ischemia/reperfusion. *J Am Coll Cardiol*. 2015;66:816–828. doi: 10.1016/j.jacc.2015.06.023.
- Robbers LF, Eerenberg ES, Teunissen PF, Jansen MF, Hollander MR, Horrevoets AJ, Knaapen P, Nijveldt R, Heymans MW, Levi MM, van Rossum AC, Niessen HW, Marcu CB, Beek AM, van Royen N. Magnetic resonance imaging-defined areas of microvascular obstruction after acute myocardial infarction represent microvascular destruction and haemorrhage. *Eur Heart J*. 2013;34:2346–2353. doi: 10.1093/eurheartj/eh100.
- Reichek N. Meta-analysis of MACE in MI: what's the MO? *JACC Cardiovasc Imaging*. 2014;7:953–955. doi: 10.1016/j.jcmg.2014.07.005.
- Ruder TD, Ebert LC, Khattab AA, Rieben R, Thali MJ, Kamat P. Edema is a sign of early acute myocardial infarction on post-mortem magnetic resonance imaging. *Forensic Sci Med Pathol*. 2013;9:501–505. doi: 10.1007/s12024-013-9459-x.

9. Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G, Thiele H. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol*. 2010;55:2470–2479. doi: 10.1016/j.jacc.2010.01.049.
10. Hadamitzky M, Langhans B, Hausleiter J, Sonne C, Kastrati A, Martinoff S, Schömig A, Ibrahim T. The assessment of area at risk and myocardial salvage after coronary revascularization in acute myocardial infarction: comparison between CMR and SPECT. *JACC Cardiovasc Imaging*. 2013;6:358–369. doi: 10.1016/j.jcmg.2012.10.018.
11. Fernández-Jiménez R, Galán-Arriola C, Sánchez-González J, et al. Effect of ischemia duration and protective interventions on the temporal dynamics of tissue composition after myocardial infarction. *Circ Res*. 2017;121:439–450. doi: 10.1161/CIRCRESAHA.117.310901.
12. Bragadeesh T, Jayaweera AR, Pascotto M, Micari A, Le DE, Kramer CM, Epstein FH, Kaul S. Post-ischaemic myocardial dysfunction (stunning) results from myofibrillar oedema. *Heart*. 2008;94:166–171. doi: 10.1136/hrt.2006.102434.
13. Afanasyeva M, Georgakopoulos D, Rose NR. Autoimmune myocarditis: cellular mediators of cardiac dysfunction. *Autoimmun Rev*. 2004;3:476–486. doi: 10.1016/j.autrev.2004.08.009.
14. Heidary S, Patel H, Chung J, Yokota H, Gupta SN, Bennett MV, Katikireddy C, Nguyen P, Pauly JM, Terashima M, McConnell MV, Yang PC. Quantitative tissue characterization of infarct core and border zone in patients with ischemic cardiomyopathy by magnetic resonance is associated with future cardiovascular events. *J Am Coll Cardiol*. 2010;55:2762–2768. doi: 10.1016/j.jacc.2010.01.052.
15. Tsukiji M, Nguyen P, Narayan G, Hellinger J, Chan F, Herfkens R, Pauly JM, McConnell MV, Yang PC. Peri-infarct ischemia determined by cardiovascular magnetic resonance evaluation of myocardial viability and stress perfusion predicts future cardiovascular events in patients with severe ischemic cardiomyopathy. *J Cardiovasc Magn Reson*. 2006;8:773–779. doi: 10.1080/10976640600737615.

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