

## Editorial

## Risk Assessment Following ST-segment Elevation Myocardial Infarction

## Evaluación del riesgo tras infarto de miocardio con elevación del segmento ST

Edwin Wu<sup>a,\*</sup> and Daniel C. Lee<sup>a,b</sup><sup>a</sup> Bluhm Cardiovascular Institute, Division of Cardiology, Departments of Medicine and Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States<sup>b</sup> Feinberg Cardiovascular Research Institute, Division of Cardiology, Departments of Medicine and Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

## Article history:

Available online 3 July 2013

A lot of emphasis on providing prompt recognition and immediate therapy in patients presenting with ST-segment elevation myocardial infarction (STEMI) has been put forth by guidelines from the European and American Cardiology Societies center. These recommendations are in place in order to limit the extent and severity of irreversible myocardial injury. In fact, much of the gains in short-term and long-term reduction in mortality following STEMI, stems from prompt reperfusion to limit the immediate myocardial infarct size and to promote long-term myocardial healing. However, despite recent advances and adherence to guidelines, there remains an elevated morbidity and mortality following acute myocardial infarction.

Predicting the prognosis of patients during the convalescence stage remains tricky, but it has been long recognized and well established that determination of left ventricular (LV) function is an important determinant of survival. Current clinical practice and guidelines recommend obtaining an assessment of the left ventricular ejection fraction (LVEF), frequently performed using transthoracic echocardiography. This remains currently true despite continued modern advances including thrombolytics, primary percutaneous reperfusion, antiplatelets, lipid-lowering, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors. It is this simplicity in obtaining the LVEF—and the indirect measure of the acute infarct burden on the myocardium—that targets therapy to help reduce heart failure readmissions and cardiac death.

Acute LV dysfunction can be potentially reversible by myocardial salvage secondary to reperfusion, although LV dysfunction can continue for days to weeks due to the presence of stunned myocardium. Therefore, the presence of severe LV dysfunction can be a poor surrogate for the amount of irreversibly injured myocardium that is present.<sup>1</sup> Hence, automated implantable defibrillators are not recommended until after a 40-day waiting period even if a patient's LV function is very dysfunctional and below 35% within the first weeks after acute myocardial infarction. In addition, ACE inhibitors are only strongly advised if the LVEF

functioning is below 40%. In a recent meta-analysis of ACE-inhibitor use following STEMI, the readmission rate for heart failure was 20% lower in the ACE inhibitor treated group when compared with the placebo group (13.7% for patients receiving ACE inhibitors vs 18.9% in the placebo group). In fact, in patients following acute myocardial infarction, ACE-inhibitor therapy resulted in the greatest reduction in death, heart failure readmissions, or repeat myocardial infarction only in those with severely reduced LVEF.<sup>2</sup> However, despite these efforts, adverse ventricular remodeling continues to occur and recent estimates note that mortality following STEMI remains elevated.<sup>3</sup>

Cardiovascular magnetic resonance (CMR), over the last decade, has increasingly become a popular method to assess patients following acute myocardial infarction due to its high spatial resolution and comprehensive ability to assess myocardial function, perfusion, or other sequelae following acute myocardial infarction. In particular, because of the high natural contrast between myocardial tissue, blood pool, and surrounding lung tissue, CMR has become increasingly compelling not only as a research tool but also as a clinically important noninvasive tool in the cardiologist's armamentarium. The determination of LV volumes, ejection fraction, and mass, has great reproducibility with limited artifacts and without the limitations of poor echocardiographic windows.

But beyond the simple measurement of LV volumes, CMR possesses the unique ability to assess areas of myocardial infarction both following acute infarct and chronic scar by late gadolinium enhancement (LGE) imaging. Early studies revealed a close correlation between LGE-determined infarct and other less specific markers including LV volumes, wall motion, and ejection fraction. Infarct size directly correlates with LVEF within a few months following reperfused STEMI.<sup>4</sup> In fact, LGE can be a more specific marker for determining the extent of irreversible myocardial damage for an individual patient as LVEF is influenced both by residual stunning in a viable myocardium and the necrotic, nonviable myocardium.

Many studies have investigated a myriad of CMR parameters that can be obtained within a single study, including ventricular volumes and function, infarct size, myocardial edema, myocardial salvage, myocardial perfusion, and microvascular obstruction. These parameters have been evaluated in single center studies and have been shown as independent predictors of prognosis. However, in the article published in *Revista Española de Cardiología*,

## SEE RELATED ARTICLE:

<http://dx.doi.org/10.1016/j.rec.2013.01.016>, Rev Esp Cardiol. 2013;66:613–22.

\* Corresponding author: Bluhm Cardiovascular Institute, Division of Cardiology, Departments of Medicine and Radiology, Northwestern University Feinberg School of Medicine, 676 North St Clair, Suite 600, Chicago, IL 60611, United States.

E-mail address: ed-wu@northwestern.edu (E. Wu).

Merlos et al.<sup>5</sup> sought to assess the independent contribution of each of these CMR indices, adjusted for clinical risk factors, in long-term prognosis following STEMI. Over a 2-year period, 206 consecutive patients presented for a comprehensive CMR evaluation following prompt, contemporary primary reperfusion with either primary angioplasty or a pharmaco-invasive strategy for a STEMI. This prospective cohort of patients was followed for a median of 51 months for a composite endpoint of cardiac death, nonfatal myocardial infarction and readmission for heart failure. Thirty-nine major adverse cardiac events (MACE) were detected in 29 patients. This cohort was one of the larger single center studies to investigate long-term prognosis in a group of patients following STEMI, and included a comprehensive CMR evaluation that included several quantitative indices: a) LV end-diastolic volume index; b) LV end-systolic volume index; c) LVEF; d) LV mass; e) LVEF with low-dose dobutamine; f) LV infarct size; g) LV edema; h) LV salvage index, and i) LV microvascular obstruction. Additionally, these indices were compared with semiquantitative equivalents scored on a 17-segment model including: a) resting wall motion abnormality; b) wall motion abnormality with low-dose dobutamine; c) transmural necrosis >50% of the wall; d) presence of edema; e) resting first-pass perfusion defect, and f) presence of persistent hypoperfusion on LGE. In a multivariate analysis which included 11 clinical variables and 15 CMR variables, the authors concluded that in addition to age and elevated heart rates, the transmural extent of infarct was the only CMR index that independently predicted MACE outcome. Moreover, the C-statistics increased from 0.75 to 0.83, demonstrating the improved predictive value of obtaining the transmural extent of infarct beyond traditional clinical risk predictors.

The fact that a simple index, available by visual analysis, can provide powerful prognostic information and might outperform more time-consuming indices based on tedious manual segmentation, is certainly an intriguing finding. However, these results must be interpreted within the context of the study limitations.

The optimal infarct sizing technique by LGE remains somewhat controversial. Current quantitation methods of the LGE include manual planimetry of “bright” pixels or setting a signal intensity threshold cutoff as compared to a normal myocardium. This is defined either as multiple standard deviations above the mean signal of normal myocardium or 50% of the maximum intensity within the infarct tissue, ie, full-width at half maximum intensity. Several studies have demonstrated that a threshold of 2 standard deviations above normal overestimates infarct size,<sup>6</sup> and that a higher threshold or use of full-width at half maximum intensity is more appropriate. It is possible that the inclusion of noninfarcted myocardium with pixel intensities 2 standard deviations above the mean may have negatively influenced the performance of the quantitative technique.

Many investigators divide the myocardium into 17 segments to grade the extent and severity of LGE, and advocate for this approach. Segments are then graded on a scale describing the transmural extent of LGE through each segment, and the scored segments can be summed to estimate the infarct size. A major advantage of this semiquantitative approach is that it saves time as compared with fully quantitative techniques. Although the segmentation can be increased to 72 segments, as originally described by Kim et al.,<sup>7</sup> this requires a longer analysis time while theoretically providing a more accurate infarct-size estimation. As segmentation is likely an estimation of a quantitative analysis, another potential explanation for why the qualitative analysis would trump the quantitative analysis, in the current study by Merlos et al.,<sup>5</sup> may be that the 2 variables are collinear, which may bias the results of multivariable modeling.

Beyond evaluating the size of infarction, the integrity and maintenance of microvascular perfusion during acute infarction

can be important. Microvascular obstruction can be assessed using different CMR methods, such as a delayed wash-in of gadolinium contrast during first-pass perfusion or the persistent absence of gadolinium enhancement within the infarct core on LGE.<sup>8</sup> As with the other CMR predictors, Merlos et al.<sup>5</sup> also demonstrated that first-pass hypoperfusion and LGE microvascular obstruction were both independent predictors of MACE. Additionally, the presence of microvascular obstruction has been associated with larger infarct sizes, lower LVEF, worse functional recovery, and greater myocardial thinning. Previous publications by Wu et al.<sup>9</sup> and Hombach et al.<sup>10</sup> found that microvascular obstruction was a stronger predictor of prognosis than infarct size, which contrasts the current findings by Merlos et al.<sup>5</sup> These differences are important and deserve further investigation.

As acknowledged by the authors, despite the relatively large number of patients recruited into this single center study, the total number of events used for statistical modeling was only 29: 8 cardiac deaths, 11 nonfatal myocardial infarctions, and 10 readmissions for heart failure. As a general rule of thumb, a minimum of 10 events is recommended per variable included in the model. Even with the extended follow-up period, the small total number of events limits the number of variables that can be confidently investigated without increasing bias and variability.<sup>11</sup> The MACE rate of 14% in the current study is on par with previous studies investigating CMR in STEMI populations: Hombach et al. (110 subjects, 15% MACE, 16 events, 7 deaths)<sup>10</sup>; Wu et al. (122 subjects, 13% MACE, 16 events, 1 death)<sup>4</sup>; Cochet et al. (184 patients, 24%, 44 events, 5 deaths)<sup>12</sup>; de Waha et al. (438 patients, 16% MACE, 69 events, 25 deaths)<sup>13</sup>; and Klug et al. (107 patients, 25% MACE, 27 events, 7 deaths).<sup>14</sup>

The ultimate goal is to understand the additive prognostic value of CMR indices over established clinical variables, but a low number of events have limited the number of important clinical and CMR variables that could be confidently evaluated to date in CMR studies of patients following STEMI. Merlos et al.<sup>5</sup> provide a longer-term follow-up than previous studies and utilize a truly comprehensive CMR protocol which adds low-dose dobutamine wall motion assessment, resting first-pass perfusion, and edema assessment to the standard LGE CMR protocol. Univariable analysis provides further evidence of the prognostic importance of LVEF, infarct size, wall motion abnormalities, edema size, and the extent of transmural infarction on subsequent cardiac events. To fully realize the potential prognostic value of CMR indices, a larger number of STEMI patients will need to be evaluated to achieve the requisite number of MACE endpoints. This could be achieved by pooling together data from multiple sources including data from single center studies<sup>15</sup> or from multicenter registries (Euro CMR registry.) This could provide the adequate statistical power to assess important CMR parameters and deliver more concrete evidence for the added prognostic value of CMR indices in patients following an acute myocardial infarction. Although the measurement of LVEF currently remains vital in the patient's post-infarction care, the cornerstone goal of STEMI therapy primarily aims to reduce the amount of infarcted tissue. CMR should play an increasingly central role in determining the true infarct size and extent with an eye towards reducing heart failure readmissions and cardiac death.

## CONFLICTS OF INTEREST

None declared.

## REFERENCES

1. Rubenstein JC, Ortiz JT, Wu E, Kadish A, Passman R, Bonow RO, et al. The use of periinfarct contrast-enhanced cardiac magnetic resonance imaging for the

- prediction of late postmyocardial infarction ventricular dysfunction. *Am Heart J*. 2008;156:498-505.
2. Flather MD, Yusuf S, Kober L, Pfeffer MA, Hall A, Murray GD, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet*. 2000;355:1575-81.
  3. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333:1091.
  4. Wu E, Ortiz JT, Tejedor P, Lee DC, Bucciarelli-Ducci C, Kansal P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart*. 2008;94:730-6.
  5. Merlos P, López-Lereu MP, Monmeneu JV, Sanchis J, Núñez J, Bonanad C, et al. Valor pronóstico a largo plazo del análisis completo de los índices de resonancia magnética cardiaca tras un infarto de miocardio con elevación del segmento ST. *Rev Esp Cardiol*. 2013;66:613-22.
  6. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *J Am Coll Cardiol Img*. 2011;4:150-6.
  7. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445-53.
  8. Wu E, Izquierdo Gómez MM. Resonancia magnética cardiaca y endotelina-1: un nuevo paso en la detección de la obstrucción microvascular. *Rev Esp Cardiol*. 2011;64:89-91.
  9. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation*. 1998;97:765-72.
  10. Hombach V, Grebe O, Merkle N, Waldenmaier S, Höher M, Kochs M, et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. *Eur Heart J*. 2005;26:549-57.
  11. Hachamovitch R, Di Carli MF. Methods and limitations of assessing new noninvasive tests: Part II: Outcomes-based validation and reliability assessment of noninvasive testing. *Circulation*. 2008;117:2793-801.
  12. Cochet AA, Lorgis L, Lalande A, Zeller M, Beer JC, Walker PM, et al. Major prognostic impact of persistent microvascular obstruction as assessed by contrast-enhanced cardiac magnetic resonance in reperfused acute myocardial infarction. *Eur Radiol*. 2009;19:2117-26.
  13. De Waha S, Desch S, Eitel I, Fuernau G, Zachrau J, Leuschner A, et al. Impact of early vs. late microvascular obstruction assessed by magnetic resonance imaging on long-term outcome after ST-elevation myocardial infarction: a comparison with traditional prognostic markers. *Eur Heart J*. 2010;31:2660-8.
  14. Klug G, Mayr A, Schenk S, Esterhammer R, Schocke M, Nocker M, et al. Prognostic value at 5 years of microvascular obstruction after acute myocardial infarction assessed by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2012;14:46.
  15. Van Kranenburg M, Magro M, De Waha S, Thiele H, Peris VB, Cochet A, et al. Prognostic value of microvascular obstruction and infarct size measured by cardiac magnetic resonance in patients with ST-segment elevation myocardial infarction: a meta-analysis of individual patient data. *J Am Coll Cardiol*. 2013;61:E807.