European Heart Journal – Cardiovascular Imaging (2016) **17**, 754–755
doi:10.1093/ehjci/jew074

EDITORIAL

Area at risk in acute myocardial infarction: oedema imaging and species-specific findings

Andrew E. Arai*

Department of Health and Human Services, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room B1D416, MSC 1061, 10 Center Dr., Bethesda, MD 20892-1061, USA

Online publish-ahead-of-print 4 May 2016

Norlund *et al.*[1] from Lund University addressed two distinctly different aims in this edition of the European Heart Journal Cardiovascular Imaging. Their primary aim was to compare the diagnostic accuracy and image quality of T_2-STIR (T_2-weighted Short Tau Inversion Recovery) oedema imaging and CE-SSFP (contrast enhanced steady-state free precession cine MRI) with respect to determining myocardium at risk (MaR). Their second aim was to determine whether there is a bimodal temporal response to oedema or MaR imaging in humans as recently described in swine and possibly also present in dogs.

They used data from three separate studies to have multi-centre and multi-vendor representation of CMR MaR methodologies. They picked two clinical trials that used CMR to determine myocardial salvage: the CHILL-MI trial[2] and the MITOCARE study.[3] These studies provided real world experience in clinical trials aimed at measuring myocardial salvage. To address the second aim of the study, they also included patients from a third study[4] to ensure that they had data on Day 1 after myocardial infarction.

With respect to their first aim on image quality, Norlund *et al.*[1] found that T_2-STIR performs poorly for imaging MaR; only 65% of T_2-STIR datasets were considered of diagnostic quality. No clinical trial can afford to lose 35% of their population due to an imperfect imaging end point. Fortunately, CE-SSFP was of diagnostic quality in 97% of patients. That was even higher than the successful rate of completing myocardial infarction imaging with late gadolinium enhancement images, the critical second part of the CMR measurement of myocardial salvage.

The use of CE-SSFP cine MRI as a measurement of the MaR raised questions about how it works and how it might compare with other methods. Clearly CE-SSFP worked better than qualitative T_2-STIR images. Whether T_2 maps,[5] T_1 maps,[6] extracellular volume fraction maps, or other quantitative approaches might work better for quantifying MaR will require future study. A more fundamental but related question concerns exactly what is seen on CE-SSFP cine MRI. Why does CE-SSFP work for imaging MaR?

The paper does not provide enough details to delve deeply into the methods but do frame the general characteristics of why CE-SSFP cine MRI might highlight the MaR. First, the studies used multi-slice, multi-phase SSFP cine MRI methods available on each vendor's scanner. An SSFP sequence with TE in the range of 1.3–1.7 ms and a TR of 2.9–3.7 ms has intrinsic T_2/T_1 contrast.[7] This means that signal intensity will increase as T_2 get longer, as expected with myocardial oedema in the MaR. Signal intensity also increases on an SSFP image as T_1 decreases since the T_1 is in the denominator of the contrast relationship. Since T_1 is longer in oedematous myocardium compared with normal myocardium, there will be a slight loss in signal intensity from this mechanism. Overall, MaR should be brighter on CE-SSFP 5 min after gadolinium-based contrast is injected due to both oedema and early gadolinium enhancement. Since gadolinium likely plays an important role in the success of CE-SSFP, timing issues become important since gadolinium is used in both the MaR and the myocardial infarction measurements of myocardial salvage.[8]

The second aim of the study highlights an important pathophysiological question concerning the dynamics of oedema after acute myocardial infarction. Fernández-Jiménez *et al.* from Madrid found that T_2 abnormalities and oedema followed a bimodal temporal response in a swine acute myocardial infarction model.[9] T_2 abnormalities and post-mortem measurements of water content were prominent on Day 0, almost resolved by 24 h, were detectable on Day 4, but became prominent again by Day 7. In reperfused MI, neutrophils dominated ischaemic myocardium on Day 1 post-MI, macrophages dominated on Day 4, and collagen became prominent by Day 7.[10] Reperfusion status and steroid treatment also modulated CMR and pathophysiological characteristics of the myocardium. They concluded that the first wave of pathologic changes were due to reperfusion while the second phase represented healing. Dogs may go through a similar bimodal pattern of oedema after acute myocardial infarction as evidenced by decreasing T_2 in the MaR from Day 0 to Day 2[11] and nearly complete resolution on Day 4.[12]

Human data do not support a conclusion that oedema fades in a few days or follows a bimodal pattern after acute myocardial infarction. Collectively, human studies from Lund,[1] Oxford,[13] and the US

The opinions expressed in this article are not necessarily those of the Editors of *EHJCI*, the European Heart Rhythm Association or the European Society of Cardiology.

* Corresponding author. Tel: +1 301 496 3658; Fax: +1 301 402 2389. E-mail: araia@nih.gov

National Institutes of Health[14] do not show evidence of the bimodal temporal pattern of oedema during the first week after acute myocardial infarction. The study by Nordlund *et al.*[1] provides data in over 200 patients and spans Day 1–7 post-MI with data analysis at the level of current clinical trials. Dharmakumar concluded that the bimodal temporal course of oedema in the swine model will '. . . add to the understanding of tissue characteristics of acute MI, but are limited to the specific animal model investigated'.[15] Perhaps this means that there is an overlap in the time period of post-ischaemic oedema and the start of the healing phase in humans.

Preclinical experiments clearly play a critical role in understanding pathophysiology, and the studies highlighted in this section have advanced our understanding of T_2 after acute MI. T_2 is not a simple and stable binary marker of the area at risk in pigs over the course of a week[9,10] and in dogs over the course of 4 days.[11,12] These studies highlight the need for caution in over-interpreting imaging results during a dynamic and complicated post-infarct phase of healing. By analogy, different mammalian species, including humans, develop myocardial necrosis during acute MI at markedly different rates.[16] If the timing of intervention for acute MI was based solely on swine data, there would be no point to human acute percutaneous coronary interventions beyond ~90 min after the onset of coronary occlusion let alone door-to-balloon time. Pigs and rats develop transmural MI much faster than dogs and humans. We are fortunate to have a little more time than predicted by swine models of acute myocardial infarction.

In conclusion, there is still much to learn about acute myocardial infarction. Imaging can play an important role in this learning process. It is important to keep an open mind to new findings. It is also important to recognize the limitations of both preclinical and human-level studies. Neither the level of research can answer all of the important questions. At some point, we need to synthesize the information gained and use what we have learned to guide patient care and to help develop new treatments and better diagnostic methods.

Conflict of interest: A.E.A. has research agreements with Siemens and Bayer Healthcare. These are institutional level research agreements.

Funding

This study was funded by the National Heart, Lung, and Blood Institute Intramural Research Program (HL006136-06).

References

1. Nordlund D, Klug G, Heiberg E, Koul S, Larsen TH, Hoffmann P *et al.* Multi-vendor, multicentre comparison of contrast-enhanced SSFP and T2-STIR CMR for determining myocardium at risk in ST-elevation myocardial infarction. *Eur Heart J Cardiovasc Imaging* 2016;**17**:744–53.
2. Erlinge D, Gotberg M, Lang I, Holzer M, Noc M, Clemmensen P *et al.* Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The chill-mi trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. *J Am Coll Cardiol* 2014;**63**:1857–65.
3. Atar D, Arheden H, Berdeaux A, Bonnet JL, Carlsson M, Clemmensen P *et al.* Effect of intravenous tro40303 as an adjunct to primary percutaneous coronary intervention for acute st-elevation myocardial infarction: Mitocare study results. *Eur Heart J* 2015;**36**:112–9.
4. Carlsson M, Ubachs JF, Hedstrom E, Heiberg E, Jovinge S, Arheden H. Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography. *JACC Cardiovasc Imaging* 2009;**2**:569–76.
5. Giri S, Chung YC, Merchant A, Mihai G, Rajagopalan S, Raman SV *et al.* T2 quantification for improved detection of myocardial edema. *J Cardiovasc Magn Reson* 2009;**11**:56.
6. Ugander M, Bagi PS, Oki AJ, Chen B, Hsu LY, Aletras AH *et al.* Myocardial edema as detected by pre-contrast t1 and t2 cmr delineates area at risk associated with acute myocardial infarction. *JACC Cardiovasc Imaging* 2012;**5**:596–603.
7. Bieri O, Scheffler K. Fundamentals of balanced steady state free precession mri. *J Magn Reson Imaging* 2013;**38**:2–11.
8. Arai AE. Gadolinium can depict area at risk and myocardial infarction: a double-edged sword? *JACC Cardiovasc Imaging* 2011;**4**:619–21.
9. Fernandez-Jimenez R, Sanchez-Gonzalez J, Aguero J, Garcia-Prieto J, Lopez-Martin GJ, Garcia-Ruiz JM *et al.* Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: Imaging and histological tissue characterization. *J Am Coll Cardiol* 2015;**65**:315–23.
10. Fernandez-Jimenez R, Garcia-Prieto J, Sanchez-Gonzalez J, Aguero J, Lopez-Martin GJ, Galan-Arriola C *et al.* Pathophysiology underlying the bimodal edema phenomenon after myocardial ischemia/reperfusion. *J Am Coll Cardiol* 2015;**66**:816–28.
11. Hammer-Hansen S, Ugander M, Hsu LY, Taylor J, Thune JJ, Kober L *et al.* Distinction of salvaged and infarcted myocardium within the ischaemic area-at-risk with t2 mapping. *Eur Heart J Cardiovasc Imaging* 2014;**15**:1048–53.
12. Kim HW, Van Assche L, Jennings RB, Wince WB, Jensen CJ, Rehwald WG *et al.* Relationship of t2-weighted mri myocardial hyperintensity and the ischemic area-at-risk. *Circ Res* 2015;**117**:254–65.
13. Dall'Armellina E, Karia N, Lindsay AC, Karamitsos TD, Ferreira V, Robson MD *et al.* Dynamic changes of edema and late gadolinium enhancement after acute myocardial infarction and their relationship to functional recovery and salvage index. *Circ Cardiovasc Imaging* 2011;**4**:228–36.
14. Berry C, Kellman P, Mancini C, Chen MY, Bandettini WP, Lowrey T *et al.* Magnetic resonance imaging delineates the ischemic area at risk and myocardial salvage in patients with acute myocardial infarction. *Circ Cardiovasc Imaging* 2010;**3**:527–35.
15. Dharmakumar R. Building a unified mechanistic insight into the bimodal pattern of edema in reperfused acute myocardial infarctions: observations, interpretations, and outlook. *J Am Coll Cardiol* 2015;**66**:829–31.
16. Hedstrom E, Engblom H, Frogner F, Astrom-Olsson K, Ohlin H, Jovinge S *et al.* Infarct evolution in man studied in patients with first-time coronary occlusion in comparison to different species - implications for assessment of myocardial salvage. *J Cardiovasc Magn Reson* 2009;**11**:38.