In all subjects, the peak p17 peptide level occurred after PCI and was positively correlated with the peak cTnI ($r = 0.48$, $p = 0.011$) and peak CK-MB ($r = 0.56$, $p = 0.002$, Spearman for all) levels. The correlations were not tight, suggesting that both necrosis and apoptosis play a role in determining infarct size. The use of this novel assay for the first time sets the stage to investigate this critical balance. The rise and fall of p17 peptide and its correlation with peak cTnI and CK-MB suggest that serum p17 likely came from injured myocardium. A calpain (4) and stretch-mediated (5) myocyte apoptosis may have also contributed to the serum p17 level.

Limitations include the lack of concurrent myocyte evidence of apoptosis and unknown p17 release kinetics. Designing therapies to inhibit apoptosis may provide benefit to STEMI patients.

Mariela Agosto, MD
Michael Azrin, MD
Kanwar Singh, MD
Allan S. Jaffe, MD
***Bruce T. Liang, MD**

*Calhoun Cardiovascular Center
University of Connecticut School of Medicine
263 Farmington Avenue
MC3946
Farmington, Connecticut 06032
E-mail: bliang@uchc.edu

doi:10.1016/j.jacc.2010.08.628

Please note: This work was supported by a grant from the Department of Public Health, State of Connecticut (2#010-0083). Dr. Jaffe is a consultant for Beckman, Siemens, Abbott, Roche, Inverness, and Ortho. All other authors have reported that they have no relationships to disclose. The authors thank Jayne Schumacher for assistance in patient enrollment.

REFERENCES

1. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309:331–6.
2. Braunwald E, Kloner RA. Myocardial reperfusion: a double edged sword? J Clin Invest 1985;76:1713–9.
3. Budihardjo I, Oliver H, Lutter M, et al. Biochemical pathways of caspase activation during apoptosis. Annu Rev Cell Dev Biol 1999;15:269–90.
4. Feng J, Schaus BJ, Fallavollita JA, Lee T-C, Canty JM. Preload induces troponin I degradation independently of myocardial ischemia. Circulation 2001;103:2035–7.
5. Anversa P, Olivetti G, Meggs LG, Sonnenblick EH, Capasso JM. Cardiac anatomy and ventricular loading after myocardial infarction. Circulation 1993;87 Suppl VII:22–7.

Letters to the Editor

Myocardial Salvage Index and Infarct Size Represent Related But Distinct Components of Acute ST-Segment Elevation Myocardial Infarction

One of the conclusions of Eitel et al. (1), that the myocardial salvage index (MSI) assessed by cardiac magnetic resonance is the strongest inverse correlate of major adverse cardiac events and mortality at 6-month follow up (compared with infarct size [IS] alone measured in the acute phase by late gadolinium enhancement by cardiovascular magnetic resonance), is not supported by the data presented.

Inspection of the receiver-operating characteristic curves reveals that the predictive value of IS is similar to that indicated by the MSI (area under the curve: 0.791 vs. 0.803), and I suspect that it would be confirmed to be nonsignificant by appropriate statistical analysis comparing the 2 variables, which was not performed. This is also expected from the large body of clinical evidence accumulated thus far that final IS and consequently extent left ventricular dysfunction determine the major adverse cardiac events and mortality resultant from acute ST-segment elevation myocardial infarction (ASTEMI), as demonstrated by Larose et al. (2) in the same issue of the *Journal*, regardless of the extent of the MSI. Thus, if a large infarct was reperfused optimally with a large MSI consequently with a small final IS, the major adverse cardiac events and mortality would be similar to those of a small infarct reperfused suboptimally with a small MSI but still a small final IS. This is important because IS measurement (but not MSI) can be similarly accomplished by delayed contrast enhancement computed tomography myocardial perfusion imaging with similar accuracy (from preliminary studies) (3) and myocardial contrast echocardiography. Hence, this important prognostic variable could become more rapidly and widely available clinically.

Their other conclusion that MSI determined by cardiac magnetic resonance provides the best clinical investigative tool to measure success of therapies to limit IS in ASTEMI is of course entirely valid. More important, comparing the curve depicting the relationship between the time to reperfusion and the MSI (that they have elegantly demonstrated) in control and treatment groups is uniquely able to measure IS reduction in humans by therapeutic measures to reduce reperfusion injury because this methodology controls for the critical time to reperfusion variable in clinical research in ASTEMI, which is the major determinant of MSI and hence final IS. IS measurement alone in this research area would be clearly inadequate. MSI by itself would be an excellent and comprehensive measure of the effectiveness of an ASTEMI reperfusion program superior to door-to-balloon time.

***Nagendra Ramanna, MD**

*3517 Stokesmont Road
Nashville, Tennessee 37215
E-mail: nramanna@comcast.net

doi:10.1016/j.jacc.2010.10.010

REFERENCES

1. Eitel I, Desch S, Fuernau G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. J Am Coll Cardiol 2010;55:2470–9.
2. Larose E, Rodes-Cabau J, Pibarot P, et al. Predicting late myocardial recovery and outcomes in the early hours of ST-segment elevation myocardial infarction: traditional measures compared with microvascular obstruction, salvaged myocardium, and necrosis characteristics by cardiovascular magnetic resonance. J Am Coll Cardiol 2010;55:2459–69.
3. Desai M, Flamm S. End of the road for delayed hyperenhancement cardiac magnetic resonance? J Am Coll Cardiol Img 2009;2:412–20.

Reply

We thank Dr. Ramanna for his interest in our work. Our large prospective study for the first time demonstrated that myocardial salvage assessed by cardiac magnetic resonance predicts clinical outcome in acute reperfused myocardial infarction patients (1). Indeed, the myocardial salvage index (MSI) was the strongest predictor of mortality and major adverse cardiac events (MACE) according to our statistical analysis.

We performed a conditional stepwise Cox regression analysis with the candidate variables infarct size, microvascular obstruction, MSI, Thrombolysis In Myocardial Infarction flow grade after percutaneous coronary intervention, Killip class, left ventricular ejection fraction, and ST-segment resolution. After 3 steps, MSI remained the only significant prediction factor for the combined end point. Furthermore, MSI had a better predictive value for mortality than infarct size in our (unadjusted) receiver-operating characteristic curve analysis (0.818 vs. 0.701). The p value for the comparison (not shown in the paper) is 0.02. For MACE, however, the difference was not statistically significant (0.803 vs. 0.791, $p = 0.65$). However, it should be kept in mind that the *c* statistic is relatively insensitive compared with more global models adjusting for other variables (such as the regression model used in the paper) (2). Thus, we feel confident to conclude that in our study of 208 infarction patients, MSI was the strongest correlate of mortality and MACE.

Nevertheless, we agree with Dr. Ramanna that in myocardial salvage assessment, it is indeed the final infarct size that can be considered the true biological target of interest. We also believe that further studies are required to clarify the relationship between the salvaged area at risk and clinical outcome.

We agree with Dr. Ramanna that myocardial salvage is a very promising clinical investigative tool to test the efficacy of different reperfusion therapies among patients with acute myocardial infarction. Infarct size reduction is suboptimal to assess the efficacy of reperfusion therapy because the final infarct size depends on multiple factors such as the extent of the area at risk, collateral blood flow, duration of myocardial ischemia, and metabolic demand (3). Therefore, measuring only infarct size might impose a potential bias, and myocardial salvage with an adjustment for the area at risk may be a better surrogate end point in clinical trials.

***Ingo Eitel, MD**
Steffen Desch, MD
Gerhard Schuler, MD
Holger Thiele, MD

*Department of Internal Medicine/Cardiology
University of Leipzig Heart Center
Strümpellstrasse 39
04289 Leipzig
Germany
E-mail: ingoeitel@gmx.de

doi:10.1016/j.jacc.2010.09.025

REFERENCES

1. Eitel I, Desch S, Fuernau G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. J Am Coll Cardiol 2010;55:2470–9.
2. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115:928–35.
3. Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. Circulation 1992;86:81–90.