^{82}Rb PET/CT left ventricular mass computations

Andrew Van Tosh, MD,^{a,c} and Kenneth J. Nichols, MD^b

^a Department of Cardiovascular Research, St. Francis Hospital, Roslyn, NY

^b Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

^c Noninvasive Imaging Laboratory, St. Francis Hospital, Roslyn, NY

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The estimation of left ventricular (LV) mass has become an increasingly important component of standard myocardial perfusion nuclear imaging studies. This progress has been prompted by two developments. First is the growing recognition that ventricular mass and left ventricular hypertrophy (quantified in terms of LV mass and volume) play a critical role in determining cardiac prognosis for mortality, heart failure, stroke, and coronary events.¹ As demonstrated in the MESA (Multi-Ethnic Study of Atherosclerosis) trial, LVH diagnosed on the basis of cardiac MR measurements predict heart failure events with an accuracy of 87%.^{2,3} Second are technological improvements in count rate capability and imaging spatial resolution of PET and CZT imaging systems.

In the current issue of the *Journal of Nuclear Cardiology*, Malahfji et. al. report the correlation of LV mass between ^{82}Rb PET myocardial perfusion studies and cardiac MR imaging in 105 patients who underwent PET and cardiac MR for evaluation of ischemia or cardiac inflammation, 33% of whom had evidence of LVH.⁴ They found good correlation between PET and cardiac MR LV mass measurements. The work of Malahfji et. al. follows two other recent articles in the *Journal*, which further our acceptance of LV mass determinations by nuclear techniques. Using the same software as the current article,⁵ Byrne et. al. established that LV mass determinations by adenosine ^{82}Rb PET were highly reproducible over an average interval of 17

days in healthy volunteers.⁶ Sala et. al. studied 35 patients with CZT cameras and ultra-low dose ^{201}Tl , and established that there was at least a modest correlation with LV mass determined by cardiac MR.⁷ These papers may presage a new area of interest in nuclear cardiology. To further define the potential importance of this avenue of investigation, the importance of LV mass in determining cardiac prognosis, and the steps in the development of non-invasive estimation of LV mass, should be reviewed.

The first validation of non-invasive techniques for calculating myocardial mass was echocardiographic,⁸ which analyzed ante-mortem echocardiograms in 34 patients, and presented M-mode formulae for estimating LV mass. These calculations correlated well with autopsy specimens later obtained from the same patients. More recently, 2D echo techniques for estimating LV mass have been developed. Reproducibility of LV mass measures by echo varies with correlation values of $r = 0.80\text{--}0.87$, which can be improved by harmonic imaging.⁹ 3D echo measurements, which allow for improved determination of the LV long axis, have been shown to be more reproducible than 2D, and yield better correlation with cardiac MR measurements.¹⁰

Cardiac magnetic resonance imaging has been accepted as the “gold standard” for non-invasive calculation of cardiac mass. The technology has high resolution, is free of geometric assumptions, or dependence on acoustic windows.⁹ Mass is calculated from a series of neighboring slices from base to apex, determining the endocardial and epicardial borders, calculating the two volumes and adjusting for density. Trabeculae may or may not be included, depending on the methodology. Inter-study reproducibility has been reported to be as high as $r = 0.99$.¹¹ LV mass determinations by cardiac MR have been also been validated in explanted hearts in the study of Farber.¹² Measurements of LV mass by echo and cardiac MR have shown a good correlation. In general, cardiac MR reproducibility has

Reprint requests: Andrew Van Tosh, MD, Department of Cardiovascular Research, St. Francis Hospital, Roslyn, NY; Andrew.VanTosh@chsli.org

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exceeded that of echocardiography.¹³ Neither technique uses ionizing radiation.

The importance of LV mass measurements is reflected in its significant influence on cardiac prognosis, in patients with and without known heart disease. LVH and increase in LV mass have generally been considered an adaptive reaction to reduce wall stress. But its independent association with an adverse prognosis suggests that progressive LVH has deleterious effects, perhaps related to associated fibrosis, which develops concurrently.¹⁴ One question in studies relating LV mass to prognosis is how to decide among several alternative methods to index LV mass for body size. This is best done through use of an allometric function combining gender and body size.^{2,9} A previous study has shown that patients with abnormal LV mass index on quantitative PET imaging have significantly lower global myocardial blood flow, representing a higher risk for coronary events.¹⁵

In normal subjects with risk factors in the Framingham study, LV mass was a determinant of sudden cardiac death with a hazard ratio of 1.45.¹⁶ In the MESA study, cardiac MR-derived LV mass/volume was a strong predictor of CHD, stroke and heart failure.² In patients being followed for hypertension, or who are post-angiography or post-MI, LV mass determined by echocardiography or cardiac MR is also prognostic of future adverse cardiac events.¹

Nuclear cardiology approaches to estimate LV mass have predominantly utilized myocardial perfusion imaging. Calculations of LV mass by gated SPECT in 38 patients compared to 3D echo found a modest correlation of $r = 0.70$, with a slight tendency of SPECT to over-estimate LV mass at low values, and underestimate it at higher values.¹⁷ Schepesis et. al. compared ^{99m}Tc SPECT values for LV mass with CT imaging. There was a good correlation between the two measurements, but SPECT values systematically over-estimated mass values by CT by a mean of 23 gm. Other studies have also used PET ¹⁸FDG metabolic imaging to evaluate myocardial mass.¹⁸

One hypothesis for the relatively moderate correlation between SPECT mass calculations and other modalities is the limited resolution of SPECT, which is not sufficient to allow accurate quantification of LV wall thickness at rest. Despite considerable improvements in PET systems and reconstruction algorithms, ⁸²Rb PET scans rarely have sufficient spatial resolution to enable accurate measurement of myocardial wall thickness, due to their high positron range.¹⁹⁻²¹ With F-18, mean positron range in soft tissue is less than 1 mm and PET system spatial resolution of 4 mm can be achieved, but with ⁸²Rb mean positron range in soft tissue is 5 mm and PET system spatial resolution is closer to 7-8 mm. LV

wall thickness for most patients typically is 10 mm at end diastole. Partial volume effects limit measurement of myocardial wall thickness to greater than twice the FWHM of imaging systems.²² Consequently, PET mass computations are expected to be more representative of differences among patients as to the number of apex-to-base slices and abnormally increased LV radii than they are to abnormal myocardial wall thickness. Attempts have been made to use higher resolution PET imaging with ¹⁸FDG to evaluate LV mass versus a cardiac MR standard.^{18,23} However, only small numbers of patients being evaluated for viability or cardiac inflammation were tested, though correlations of up to $r = 0.87$ were reported.

The current study, of Malahfji et. al.,⁴ is the largest series evaluating the use of PET imaging to determine LV mass versus a cardiac MR reference standard, with 105 patients. Indications for the studies were evaluation of ischemia (rest/stress studies), viability, or cardiac inflammation. The patients underwent standard PET perfusion imaging, with 4DM algorithms used to calculate LV mass. Cardiac MR evaluations were performed using the FFSP approach and standard methodology for calculating mass. Trabeculae were included in cardiac MR mass determinations, while other studies (MESA) have chosen to exclude them. The salient findings were that there was a good correlation ($r = 0.81$) between LV mass by PET and cardiac MR. Median LV mass was 168 gm by cardiac MR and 174 by PET, with a mean difference of 29 gm. The same positive bias at lower mass values seen in prior studies was also noted here. PET LV mass determinations had a high inter-observer reproducibility, and high reproducibility from rest to stress, a finding duplicated by others.²⁴

A major strength of the current study is that their sample size of 105 patients is larger than many related mass validation studies. Their patient group was diverse, and the relationship between PET and cardiac MR LV mass remained good in all subgroups tested, including those with and without LVH, normal or reduced LV function, and despite the presence or absence of chronic myocardial infarction or scarring. Their PET mass determinations would, thus, be applicable to the wide population of patients presenting for PET imaging. The equipment used for the evaluations was excellent. Among currently available systems, the most recent generation of digital PET/CT scanners provides excellent count rate capability, and improved temporal and spatial resolution over previous technology. The MRI equipment used also was state of the art and was able to image at pixel sizes on the order of 2 mm. The MRI studies were performed with a time resolution of 35-40 msec, so that the framing rate was equivalent to 25-28 cine frames/R-R interval. Consequently, blurring due to

cardiac contraction would not have affected MRI mass computations appreciably, although periodic motion and non-periodic motion may reduce accuracy of both cardiac MR and ⁸²Rb PET myocardial perfusion imaging mass measurements if not accounted for.²⁵ The ⁸²Rb - PET acquisitions were performed at a somewhat coarser framing rate of 16 frames/R-R, which is still an improvement over the use of 8 frames/R-R interval that has more often been reported in cardiac PET/CT studies.

There are some technical challenges in performing these types of validations. Cardiac MR spatial resolution can be high, but at too high a temporal resolution, the noise-to-signal ratio of the MR image can become excessive and exacerbate automated algorithms or expert's identification of LV edges. Manual drawings of all apex-to-base levels of all 25–28 parts of the cardiac cycle become excessively time consuming, which is the likely reason that a somewhat larger than usual interslice spacing was used, and why cardiac MR volume inter-observer variability was assessed for only a subgroup of 15 of all 105 patients. Delineating the epicardial and endocardial MRI edges is not trivial, requiring expertise, and is complicated by the decision to include or exclude trabeculations and papillary muscles. In this investigation, these were included, but the literature reports more reproducible results are obtained when these are excluded.²⁶ The spatial resolution of ⁸²Rb PET studies precludes the inclusion of these structures. This disparity may account for some of the variation in mass values between the two modalities.

The correlation between LV mass by PET and cardiac MR in Malahfji, et. al. is similar to those found in previous SPECT studies, despite the improved resolution of PET. However, the difference in LV mass between the two modalities is relatively small – in this study a mean of 29 gm. Although cardiac MR is the “gold standard” for determining LV mass,¹² technical choices in cardiac MR methodology, such as inter-slice distance, inclusion/exclusion of papillary muscles, manual versus automated edge detection, also may lead to variation in the absolute values obtained. Malahfji et. al. point out that investigations of the treatment of hypertension and renal failure require accurate and reproducible serial determinations of LV mass. The study of Byrne et. al.,⁶ documents the reproducibility of LV mass determinations on PET MPI performed within a 3 week interval. These two studies, taken together, suggest that LV mass can be followed by PET MPI. In those patients who do undergo serial PET or nuclear studies for clinical purposes, who have CAD, hypertension, or valvular heart disease, the nuclear cardiologist can now take the opportunity to evaluate and report on their patient's LV mass progression with some degree of reliability.

Compliance with ethical standards

Disclosures

Andrew Van Tosh serves as a consultant to Astellas Pharmaceuticals, Inc. Kenneth Nichols participates in royalties from Syntermid, Inc.

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