Evaluation of left ventricular mass on cadmium-zinc-telluride imaging: Validation against cardiac magnetic resonance

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Background. **Single-photon emission computed tomography has shown relevant limitations in the quantification of left ventricular (LV) mass. We sought to compare the estimates of LV mass on Cadmium-Zinc-Telluride (CZT) myocardial perfusion imaging (MPI) as compared to cardiac magnetic resonance (CMR).**

Methods and results. **Twenty-five patients underwent MPI on a CZT camera and CMR on a 1.5 T scanner within 12 ± 3 weeks. LV mass was quantified on CZT images using two softwares: 4D-MSPECT (4DM) and Emory Cardiac Toolbox (ECTb). LV mass by CMR was quantified using MASS software (Medis, Leiden, The Netherlands). LV mass values obtained with 4DM and ECTb were highly reproducible [intraclass correlation coefficients .98 (95% CI .97-.99), and .98 (95% CI 0.97-.99), respectively]. The mean LVM mass values were 151 ± 44 g on CMR, 151 ± 43 g with 4DM (P = NS vs CMR), and 157 ± 42 g with ECTb (P < .001 vs CMR; P = .007 vs 4DM) CZT images. There was an excellent correlation between LV mass values between CMR and both 4DM (R^2 = .95; P < .001) and ECTb (R^2 = .98; P < .001) with narrow limits of agreement (− 13.6% to + 13.4% for 4DM, and − 5.6% to + 14.1% for ECTb).**

Conclusions. **The evaluation of LV mass is feasible on CZT images, showing excellent agreement with CMR. (J Nucl Cardiol 2019;26:899–905.)**

Key Words: Cadmium-Zinc-Telluride • cardiac magnetic resonance • SPECT • left ventricular mass

Abbreviations			
LVH	Left ventricular hypertrophy	CMR	Cardiac magnetic resonance
SPECT	Single-photon emission computed tomography	4DM	Corridor 4D-MSPECT
CZT	Cadmium-Zinc-Telluride	ECTb	Emory cardiac toolbox

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The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

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INTRODUCTION

Left ventricular (LV) hypertrophy (LVH) associates with an increased risk of cardiac events.[1,2] Accordingly, the precise quantification of LV mass has become an important additional parameter for the evaluation of cardiac patients. While cardiac imaging has always played a central role for the evaluation of LVH, it has been only with the introduction of three-dimensional imaging techniques that the absolute quantification of LV mass has become feasible.[3–6] Due to its elevated image quality, cardiac magnetic resonance (CMR) still represents the gold standard for the non-invasive measurement of LV mass and for the diagnosis of LVH.[3,4] On the other hand, while representing a reference technique for the assessment of myocardial perfusion, cardiac single-photon emission computed tomography (SPECT) has generally shown relevant limitations in the quantification of LV mass, predominantly due to its lower spatial resolution.[5,6] The recently introduced cardiac cameras equipped with Cadmium-Zinc-Telluride (CZT) detectors are characterized by significantly higher photon sensitivity and spatial resolution than traditional SPECT devices, allowing a better evaluation of myocardial perfusion and accurate estimation of LV function.[7,8] Whether the favorable technical characteristics of CZT cameras may also lead to a precise assessment of LV mass has not been yet evaluated.

We aimed at assessing the accuracy of different commercially available software packages for myocardial perfusion imaging (MPI) [Corridor 4D-MSPECT (4DM) and Emory Cardiac Toolbox (ECTb)] in the quantification of LV mass on CZT images as compared to CMR.

MATERIALS AND METHODS

Patient Population

Twenty-five subjects underwent MPI with gated ^{99m}Tc-tetrofosmin acquisition on a CZT camera (Discovery NM 530c; GE Healthcare; Haifa, Israel) and CMR within 12 ± 3 weeks were selected retrospectively. Eighteen/25 (72%) patients had a history of acute myocardial infarction and were submitted to multimodality cardiac imaging for the evaluation of myocardial viability. The remaining patients were submitted to MPI and CMR for the characterization of a suspected cardiomyopathy. Exclusion criteria were: hemodynamic instability, severely symptomatic heart failure, active myocardial inflammatory/infective disease, a recent (< 6 months) cardiovascular event, and the presence of an absolute contraindication to CMR.

The study was approved by the local Ethical Committee and conformed to the Declaration of Helsinki on human research. Written informed consent was obtained from every patient after complete explanation of the protocol.

CZT Protocol

Fifteen patients underwent a standard stress/rest MPI protocol, while the remainders were submitted to a rest-only scan for the evaluation of myocardial viability. The mean injected dose of ^{99m}Tc-tetrofosmin for rest acquisition was 280 ± 20 MBq for the stress/rest protocol, and 148 ± 10 MBq in the case of rest-only scans. After the injection of ^{99m}Tc-tetrofosmin an 8-min-long gated CZT scan was performed.[7,8] In patients with previous MI, tracer injection was anticipated by the administration of sublingual nitrates. Images were reconstructed on a standard workstation (Xeleris II; GE Healthcare) using a dedicated iterative algorithm with 50 iterations. A Butterworth post-processing filter (frequency .37, order 7) was applied to the reconstructed slices. Images were reconstructed without scatter or attenuation correction.

CMR Protocol

Study participants were scanned by a 1.5-T unit (CVi, GE Healthcare, Milwaukee, USA) using an eight-channel phased-array surface receiver coil and vectorcardiogram triggering.[9]

Biventricular volumes, masses, and ejection fractions were quantified by breath-hold steady-state free-precession cine imaging in cardiac short axis. Ventricles were completely encompassed by contiguous 8-mm-thick slices (with no interslice gap). Sequence parameters were: 1 excitation, matrix 224 × 224, field-of-view (FOV) 380 mm (in-plane resolution 1.69 × 1.69 mm), phases 30 per cardiac cycle, repetition time (TR) = 2/echo time (TR range 3.4-4.8 ms), flip angle: 60°, and segments (or views per segment) range 16-24 (set in order to avoid view sharing).

To detect the presence of macroscopic myocardial fibrosis, LGE (late gadolinium enhancement) short-axis images were acquired 10-18 minutes after Gadolinium-based contrast medium intravenously administrated at the standard dose of 0.2 mmol/kg. Also, vertical, horizontal, and oblique long-axis views were acquired. LGE images were not acquired in patients with a glomerular filtration rate < 30 mL/minutes/1.73 m^2. LGE was considered present when visualized in two different views.[10]

Analysis of CZT Images

Rest CZT images were used for LV perfusion and functional analyses. Images were scored semi-quantitatively using the same 17-segment LV model and a five-point scale and the summed rest score (SRS) was calculated.[7] LV function analysis was performed on 16-frame reformatted gated images obtained at rest.

Analysis of Mass by 4DM Software

This technique employs a cylindric-spheric coordinate system to process data on the basis of a two-dimensional gradient image. Weighted spline and thresholding techniques are then used to refine the epi- and endocardial surface estimates. Fitted to Gaussian function, wall position and

thickness are then estimated. The algorithm then applies gradient and segment operators, along with phase analysis, to track the surface contours of the left ventricle through the cardiac cycle. The resulting valve plane was visually verified for accuracy and corrected if necessary. Myocardial mass is computed from the volume defined by the endocardial and epicardial LV surfaces.[11]

Analysis of Mass by ECTb

This approach uses the myocardial location of the maximal count (corrected for scatter) to determine the mid-point of the myocardial wall segment. The assumption is made that at end diastole, the LV myocardial thickness is 1 cm thick. This defines both the 3D endocardial and epicardial surfaces. It then uses the regional change in counts from the end-diastolic frame to determine the change in endocardial/epicardial surface location. From these endocardial surfaces, LV volumes are determined in terms of the total number of voxels (volume elements) inside the surface. The volume between the epicardial and endocardial 3D surfaces yields the LV myocardial volume that, multiplied by the specific gravity of myocardium, estimates the myocardial mass.[12]

Analysis of CMR Images

Analysis of CMR images was performed using a commercially available software package (MASS 6.1, Medis, Leiden, Netherland).[9] Endocardial and epicardial contours of LV myocardium were manually traced in the end-diastolic and the end-systolic phases. LV end-diastolic and end-systolic volumes were measured as previously described. The contouring was performed including papillary muscle only on the slices where they were attached to the wall with smooth contouring, avoiding trabeculations. LV mass was measured by the product of myocardial volumes (epicardial volumes minus endocardial volumes) per 1.05 g/ml, which is the estimated density of normal myocardium. In every patient, the presence of significant LVH was defined according to CMR results based on previously reported cut-offs: > 74 g/m^2 in men and > 63 g/m^2 in women.[4]

Statistical Analysis

To assess the interobserver variability, LV mass measurements 4DM, and ECTb were carried out by two independent expert investigators unaware of the results of the other software, and the intraclass correlation coefficients (ICCs) based on the absolute agreement of the single measures of the different raters were calculated. Paired Student's *t* testing was performed to determine if the LVM measurements obtained by cardiac CMR were significantly different from those obtained by either 4DM or ECTb. Pearson correlation and Bland-Altman analysis were used for evaluation of the continuous values. A P value $< .05$ was considered statistically significant. The agreement between the CZT software and CMR in defining the presence of LVH was computed through Cohen's kappa statistic. Statistical analyses were performed using JMP statistical software (SAS Institute Inc, version 4.0.0) and Stata software (Stata Statistical Software: Release 10, StataCorp. 2007, College Station, TX).

RESULTS

Baseline characteristics of the study patients are given in Table 1.

Imaging Results and Interobserver Variability

The major outputs of CZT and CMR imaging are reported in Table 2. The mean LV EF (left ventricular ejection fraction) of the study population was 48% ± 13%. On CZT images, four patients presented a homogeneous LV perfusion, while the remainders had signs of a previous myocardial necrosis, with a mean SRS of 15 ± 11. Similarly, on CMR images, LGE was evident in 21 patients, involving a mean of 4.8 ± 3.1 LV segments. In three of those patients, regional perfusion abnormalities at SPECT coupled with a non-ischemic pattern of LGE on CMR were revealed, consistent with a cardiomyopathy.

The interobserver variability for the quantification of LV mass was excellent for both software with ICCs of .98 (95% CI .97-.99), and .98 (95% CI .97-.99) for 4DM, and ECTb, respectively.

Comparison of CMR and 4DM-SPECT

The mean values of LV mass obtained on CMR and with 4DM software were not statistically different (mean difference 0.16 g; P = NS). Comparison of LV mass

Table 1. Clinical characteristics

Parameter	Global population (25 patients)
Demographics	
Age (years)	75 ± 11
Male gender, *n* (%)	18 (72)
Previous myocardial infarction, *n* (%)	18 (72)
Cardiovascular risk factors	
Family history of CAD, *n* (%)	3 (12)
Diabetes, *n* (%)	6 (24)
Hypercholesterolemia, *n* (%)	12 (48)
Hypertension, *n* (%)	15 (60)
Smoking, *n* (%)	4 (16)

Table 2. Imaging results

Parameter (25 patients)	CMR	4DM	ECTb
LV end-diastolic volume (ml)	143 ± 55	141 ± 66	142 ± 58
LV end-systolic volume (ml)	81 ± 49	78 ± 56	80 ± 53
LV ejection fraction (%)	48 ± 13	48 ± 14	48 ± 11
LV mass (g)	151 ± 44	151 ± 43	157 ± 42
LV mass coefficient of variation	0.29	0.29	0.27
LV hypertrophy, *n* (%)	13 (52)	14 (56)	17 (68)

between CMR and 4DM revealed an excellent correlation ($R^2 = 0.95$; $P < .001$) with narrow limits of agreement (− 13.6% to +13.4%) (Figure 1A). Similar results were confirmed even after limiting the analysis to patients with previous acute myocardial infarction (Figure 2A). The accuracy of 4DM in unmasking the presence of LVH was 88% (sensitivity: 92%; specificity: 83%).

Comparison of CMR and ECTb

The mean values of LV mass obtained with ECTb software was slightly higher than that obtained on CMR (mean difference 5.5 g; $P < .001$). Comparison of LV mass between CMR and ECTb revealed an excellent correlation ($R^2 = 0.98$; $P < .001$) with narrow limits of agreement (− 5.6% to + 14.1%), but with a significant trend towards the underestimation at higher mass values (Figure 1B). The same trend was further confirmed even after limiting the analysis to only patients with previous acute myocardial infarction (Figure 2B). The accuracy of ECTb in unmasking the presence of LVH was 84% (sensitivity: 100%; specificity: 67%).

The agreement between the two CZT software vs CMR in defining the presence of LVH was still good (Kappa value vs CMR: .76 ± .13 for 4DM and .67 ± .14 for ECTb), though higher for 4DM. On the contrary, 4DM and ECTb agreed only moderately in unmasking the presence of LVH (Kappa value .58 ± .16).

DISCUSSION

The present study shows that estimates of LV mass derived from CZT images compare well with the gold standard represented by CMR. While both MPI software could individuate accurately patients with significant LVH, ECTb-derived measurements tended to slightly underestimate LV mass at higher values.

LV Mass in the Era of CZT Devices

A precise evaluation of LV mass has become a ''sine qua non'' in the management of cardiac patients, helping, for instance, to monitor the effects of targeted therapeutic interventions.[1,2] CMR represents undoubtedly the gold standard for the assessment of cardiac anatomy and function and for the absolute quantification of LV mass.[3,4] Interestingly, while estimates of LV mass may also be obtained on cardiac SPECT imaging, through three-dimensional modeling of LV walls, the limited spatial resolution of traditional devices has greatly affected the accuracy of this evaluation.[5,6] The recent introduction of dedicated cardiac cameras based on CZT detectors has represented a relevant breakthrough in MPI, being those devices characterized by a better photon sensitivity and image resolution than traditional SPECT cameras.[7,8]

Present study shows that values of LV mass that are automatically computed on CZT imaging are comparable to the ones obtained on CMR, being able to individuate the presence of pathologic LV hypertrophy in the great majority of patients. Moreover, the evaluation of LV mass on CZT is only marginally affected by the presence of myocardial perfusion abnormalities, underscoring the validity of the three-dimensional modeling of LV structure on MPI.

Evaluation of LV Mass on CZT: Comparison of Two Software

In modern nuclear cardiology, quantitative software packages are used regularly to support data analysis.[13,14] Those softwares allow both the automatic evaluation of myocardial perfusion and the quantitation of LV structural and functional parameters, such as volumes and EF. While quantitative analysis has been shown to improve accuracy and reduce inter-observed variability, a consistent variability between the outputs obtained with the different softwares has been reported.[13,14] One of the main sources of variability may depend on the specifics of the proprietary three-dimensional modeling algorithm that is used for LV reconstruction. In particular, while 4DM uses a cylindrical-spherical sampling profile to estimate LV shape (enclosing part of the outflow tract to the LV volume),[11] ECTb determines the

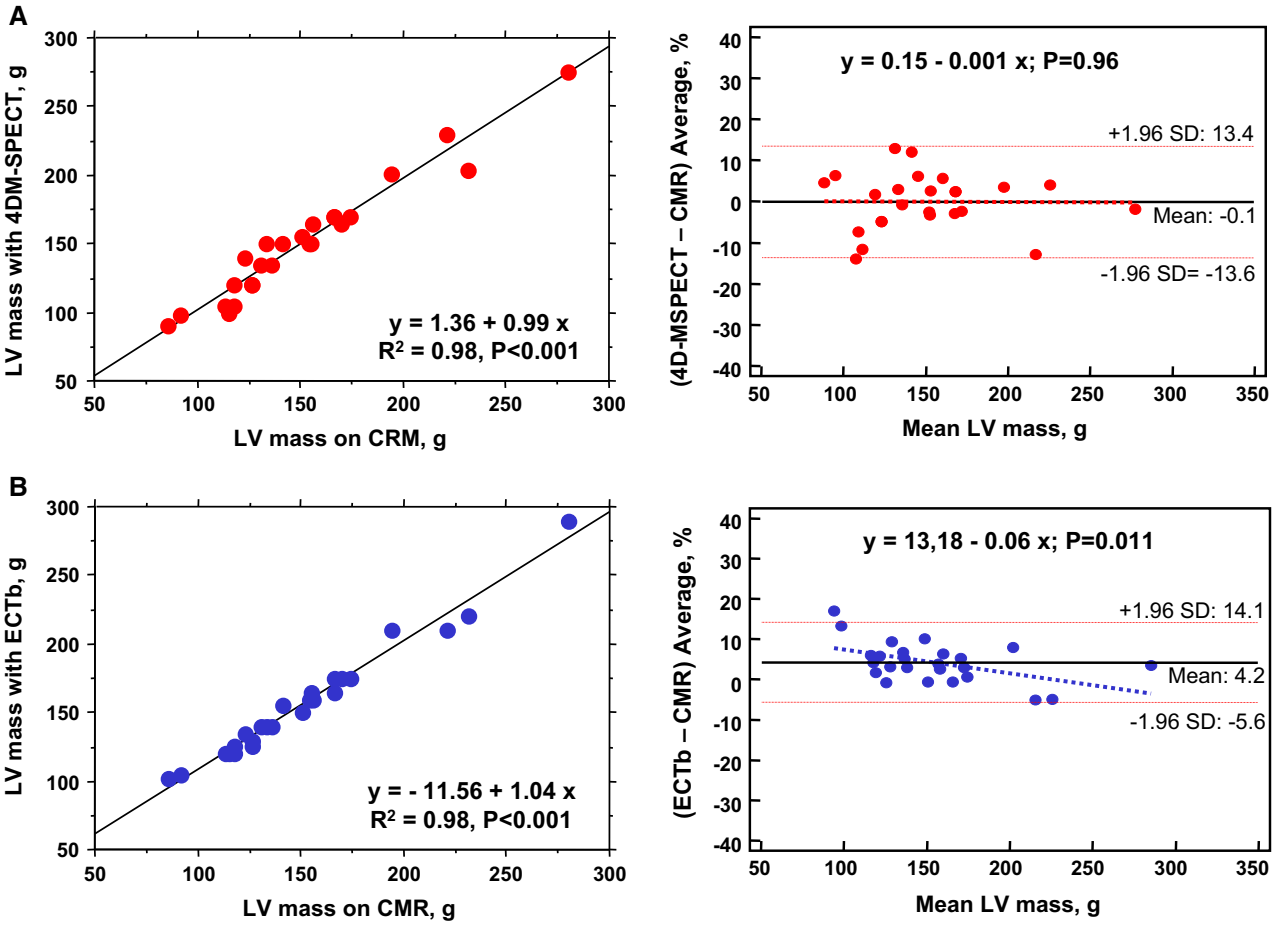

Figure 1. Linear regression analysis and Bland-Altman plots for comparison of LV mass values obtained on CMR and on CZT images with either 4DM (Panel **A**) or ECTb (Panel **B**) software in the entire study population.

midpoint of LV wall through the location of the maximal count, assuming a LV wall thickness at end diastole of 1 cm.[12] Accordingly, if 4DM may slightly overestimate LV volumes if compared to CMR,[12] ECTb is theoretically more prone to underestimate LV mass values,[6] particularly in case of significant LVH. Our data show that both software have an elevated accuracy in quantifying LV mass with respect to CMR. However, while 4DM provides accurate estimates of LV mass over the entire range of values, ECTb measures tend to overestimate the effective LV mass at lower values and underestimate at higher values. The latter finding might have some relevance in daily clinical practice, suggesting that the accuracy of SPECT imaging in defining the presence of LVH could be influenced by the specific software that is used, somehow diminishing the reliability of the methodology. However, despite some differences in the performance of the various softwares, the overall diagnostic power of SPECT imaging in the definition of the presence and severity of LVH remained high, comparing well to the reference standard represented by CMR.

LIMITATIONS

The retrospective nature of the study prevents the evaluation of a homogeneous population of patients. In particular, the relative majority of the patients had suffered a previous MI, possibly impacting the accuracy of LV mass assessment on SPECT. However, the accuracy of CZT imaging in quantifying LV mass was preserved also in patients with a history of MI, further highlighting the general validity of this approach. The selection of patients with a higher degree of LVH would have probably allowed a better comparison of the different methodologies. However, our data showed that the accuracy of CZT in quantifying LV mass was maintained also in the lower ranges of mass values, discriminating well patients with normal cardiac structure from the pathologic ones. However, the results of

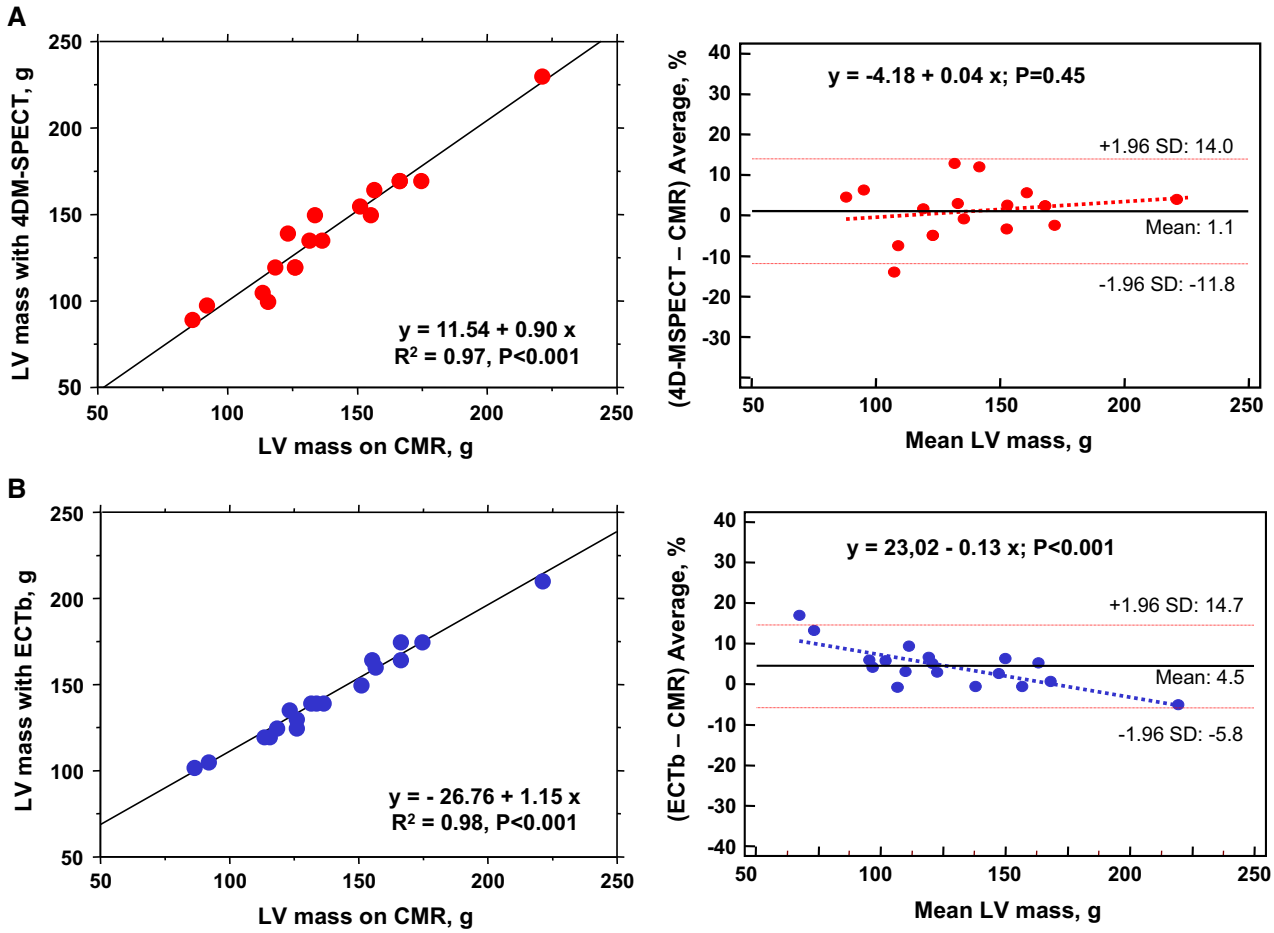

Figure 2. Linear regression analysis and Bland-Altman plots for comparison of LV mass values obtained on CMR and on CZT images with either 4DM (Panel **A**) or ECTb (Panel **B**) software in patients with previous MI.

the analyses were confirmed even after considering only patients with a previous MI, demonstrating that the accuracy of the three-dimensional LV modeling is maintained even in the presence of myocardial perfusion defects. While CMR is generally considered the reference technique for the evaluation of cardiac structure, it is also subject to a series of possible methodological drawbacks and possible artifacts that may limit the accuracy of the its outputs. Above all, the inclusion or myocardial trabeculations in the computation of LV mass is still a matter of debate.[15] Nevertheless, given the significance of the results obtained, it is rather unrealistic that this possible inconvenience might have impacted the validity of our findings. The small sample size represents a limitation that somehow raises the chance for type II error. However, while the complexity of the imaging protocol prevented the inclusion of a larger population of patients, it appears unlikely that the strength of the correlations would have been modified significantly. The accuracy of the two SPECT software in defining the presence of LVH could have improved if specific cut-off values for both 4DM and ECTb obtained in normal patient populations were chosen. However, while the limited patient population of the present study prevented such analysis, the use of a gold standard technique such as CMR as a common benchmark for the evaluation of both SPECT softwares helped to homogenize the results. Only global LV mass was measured using cut-offs derived from CMR for the definition of LVH.[4] In this respect, while SPECT-specific cut-offs for LV mass values should be better implemented for the definition of LVH, this was beyond the scope of our proof-of-concept study.

CONCLUSIONS

LV mass can be quantified accurately on MPI with a CZT camera using various commercially available software, discriminating most of the patients with LVH. These preliminary data seem to indicate the

possibility to consider LV mass as a valuable additional functional measure that can be obtained on a routinary MPI assessment.

NEW KNOWLEDGE GAINED

Our study shows that the quantification of LV mass is feasible with modern SPECT cameras equipped with CZT detectors, offering comparable results to those obtained with the reference standard of CMR.

In particular, while a slight overestimation of the real LV mass values can be observed depending on the software that is used, CZT allows to unmask correctly the presence of LVH in the majority of patients.

Disclosure

Drs. Alessia Gimelli, Riccardo Liga, Serena Magro, Salvatore Novo, Roberto Pedrinelli, Anna Sonia Petronio, Paolo Marzullo, and Alessia Pepe have no conflict of interest to disclose.

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