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Geometry-Independent Inclusion of Basal Myocardium Yields Improved Cardiac Magnetic Resonance Agreement with Echocardiography and Necropsy Quantified Left Ventricular Mass

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Abstract

Objectives—LV mass (LVM) is widely used to guide clinical decision-making. Cardiac magnetic resonance (CMR) quantifies LVM by planimetry of contiguous short axis images, an approach dependent on reader-selection of images to be contoured. Established methods have applied different binary cutoffs using circumferential extent of LV myocardium to define the basal LV, omitting images containing lesser fractions of LV myocardium. This study tested impact of basal slice variability on LVM quantification.

Methods—CMR was performed in patients and laboratory animals. LVM was quantified with full inclusion of LV myocardium, and by established methods that use different cutoffs to define the LV basal-most slice: (1) 50% circumferential myocardium at end-diastole alone (ED_{50}), (2) 50% circumferential myocardium throughout both end-diastole and end-systole (EDS_{50}).

Results—150 patients and 10 lab animals were studied. Among patients, fully inclusive LVM (172.6±42.3gm) was higher vs. ED_{50}(167.2±41.8gm) and EDS_{50}(150.6±41.1gm; both $p<0.001$). Methodological differences yielded discrepancies regarding proportion of patients meeting

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Conflicts of Interests: The authors' institution (Weill Cornell) has submitted a patent for the automated left ventricular quantification algorithm (LV-METRIC) used in this study.

established criteria for LV hypertrophy and chamber dilation ($p<0.05$). Fully inclusive LVM yielded smaller differences with echocardiography ($\Delta=11.0\pm28.8$gm) than did ED_{50} ($\Delta=16.4\pm29.1$gm) and EDS_{50} ($\Delta=33.2\pm28.7$gm, both $p<0.001$). Among lab animals, ex-vivo LV weight (69.8±13.2gm) was similar to LVM calculated using fully inclusive (70.1±13.5gm, $p=0.67$) and ED_{50} (69.4±13.9gm, $p=0.70$) methods, whereas EDS_{50} differed significantly (67.9±14.9gm, $p=0.04$).

Conclusions—Established CMR methods that discordantly define the basal-most LV produce significant differences in calculated LVM. Fully inclusive quantification, rather than binary cutoffs that omit basal LV myocardium, yields smallest CMR discrepancy with echocardiography-measured LVM and non-significant differences with necropsy-measured LV weight.

Keywords

left ventricular mass; cardiovascular magnetic resonance; echocardiography

Introduction

Left ventricular mass (LVM) is widely used to assess cardiac remodeling and therapeutic response. Cardiac magnetic resonance (CMR) is well suited to measure LVM as it provides high spatial resolution imaging and excellent endocardial definition. However, echocardiography is the predominant clinical modality used to assess LVM, as it is widely available, well validated, and cost-effective for population-based imaging. Prior comparative studies have demonstrated marked discordance between CMR and echocardiography,[1–4] with systematically lower values by CMR compared to echo LVM quantified using formulae developed and validated based on necropsy-verified LV weight.[5–8] Discordance between imaging modalities holds the potential to affect diagnostic classifications and clinical decision-making.

While one major reason for differences between modalities concerns geometric assumptions inherent in echo formulae, it is also possible that methodological issues may impact CMR. CMR quantifies LVM via planimetry of contiguous short axis images from the LV base through the apex. Irrespective of image quality, this approach is fundamentally predicated on anatomic boundaries included within myocardial contours. For example, prior research has demonstrated that omission of papillary muscles and trabeculae reduces CMR-calculated LVM, altering clinical patient classifications and yielding discordance with necropsy-verified LV weight.[9–11] It is also possible that results can be impacted by methodological differences concerning which actual images are analyzed for calculation of LVM. Prior CMR studies have defined the basal LV using binary cutoffs based on circumferential extent of LV myocardium, [4,12–14] omitting LV short axis slices containing lesser fractions of myocardium. Different binary cutoffs have been used to define the basal LV,[4,12–17] resulting in variable omission of CMR visualized LV myocardium from calculated LVM.

This study compared LVM, quantified by CMR using different established basal LV criteria, to independent references of LVM measured by echocardiography and necropsy. In patients, echocardiography (echo) was performed within 1 day of CMR and used as a clinical comparator for LVM. In laboratory animals, sacrifice was performed after CMR, with

imaging results compared to ex-vivo LV weight. The aim was to examine the impact of methodological variability concerning basal slice assignment on CMR measured LVM.

Methods

Clinical Protocol

The study population comprised patients enrolled in a post-myocardial infarction (MI) registry who underwent CMR and echo within a one-day interval.[18] The sole exclusion criterion was absence of basal short axis images (i.e. superior to the mitral annulus) necessary to compare binary cutoff methods to fully inclusive LV mass quantification. CMR was performed between 9/2006 and 08/2012 at Weill Cornell Medical College. The study was conducted in accordance with the Weill Cornell Institutional Review Board; written informed consent was obtained at study enrollment.

CMR Image Acquisition—CMR was performed at 1.5 Tesla (General Electric) using a standard 2-dimensional steady state free precession (SSFP) pulse sequence (typical parameters - repetition time 3.5 msec, echo time 1.6 msec, flip angle 60°). SSFP images were acquired with a slice thickness of 6.0 mm and inter-slice gap of 4.0 mm (typical temporal resolution 30–50 msec, in-plane spatial resolution 1.6 mm × 1.3 mm).

Short-axis images were acquired from above the mitral annulus through the LV apex, such that all LV myocardium was encompassed within the acquired range of short axis images.

CMR Image Analysis for LV Mass Quantification—LVM and end-diastolic chamber volumes were measured on consecutive short axis cine-CMR images. Papillary muscles and trabeculae were included within myocardial contours. Quantification was performed using previously validated automated segmentation algorithms,[19,20] with inclusion of myocardial partial voxel content (fractional myocardium admixed with blood in a single voxel) within total LVM. For endocardium, segmentation was performed using a geometry-independent algorithm that quantifies the mixture of blood and myocardium in each LV pixel. Segmentation is accomplished by computing blood and myocardial signal intensity distributions for each image individually and subsequently using that information to determine partial voxel content - defined as per voxel myocardial (or blood) content, for every voxel comprising the LV.[19,20] For epicardium, segmentation was performed using an active contour model that uses location and signal intensity information resulting from the endocardial segmentation, in addition to signal intensity and edges at the epicardial-pericardial interface.[20] High intra- and inter-observer reproducibility for the quantification method has been previously reported.[1] User input included identification of short axis images comprising the basal and apical LV.

To test the impact of binary cutoffs on basal slice assignment, short axis images were quantitatively planimetered to determine (1) chamber circumference, and (2) chamber length bordered by LV myocardium (i.e. myocardial length). Percent myocardial circumference for each short axis image was calculated as: 100 * LV myocardial length/chamber circumference (Figure 1). The basal LV was defined using two established binary cutoff methods predicated on circumferential extent of LV myocardium:

- LV myocardium ≥ 50% LV short axis circumference as measured at end-diastole (ED_{50})[1,10,21–24]
- LV myocardium ≥ 50% LV short axis circumference as measured at both end-diastole and end-systole (EDS_{50})[4,12–14]

Binary cutoff methods were compared to fully inclusive LVM quantification, whereby LVM was calculated with inclusion of all visualized LV myocardium, irrespective of circumferential extent on short axis images (Figure 2).

Validation Protocol

Clinical Validation – Echocardiography—Echocardiography (echo) was performed within 1 day of CMR in all patients. Image analysis was performed by an experienced, ACC/AHA level III certified, reader (RBD) blinded to CMR results. LVM was quantified in accordance with established consensus guidelines:[25] Linear measurements were used to calculate LVM using a standard formula $(0.8 * \{1.04[(\mathrm{LVIDd}+\mathrm{PWTd}+\mathrm{SWTd})^3-(\mathrm{LVIDd})^3]\}+0.6\mathrm{g})$ developed and validated based on necropsy-verified LV weight.[5–8]

Ex-Vivo Validation - Necropsy—Necropsy validation of LVM was obtained in a pre-existing cohort of animals that underwent CMR immediately prior to sacrifice, with confirmation of LVM based on ex-vivo weight.[11,26] For the current study, CMR images were retrieved from image archives, analyzed using all three methods for basal slice selection, and compared to necropsy-verified LV weight.

Statistical Methods

Continuous variables (expressed as mean±standard deviation) were compared using paired Student's t-test for two-group comparisons. Categorical variables were compared using Chi-square and McNemar's test for paired proportions. Bivariate correlation coefficients were used to evaluate associations between continuous parameters. Two-sided $p < 0.05$ was considered indicative of statistical significance. Statistical calculations were performed using SPSS 12.0 (SPSS Inc, Chicago, IL).

Results

Patient Population

Basal slice methods were tested in 150 patients undergoing CMR as part of an ongoing registry examining post-myocardial infarction LV remodeling.[18] 40 otherwise eligible patients (21%; 40/190) were excluded due to absence of sufficient basal short axis images (i.e. superior to the mitral annulus) necessary to compare binary cutoff methods to fully inclusive LVM. No patients were excluded based on clinical characteristics. Table 1 details characteristics of the study population.

Basal Slice Geometry

Circumferential extent of basal slice LV myocardium varied across the study population. 31% of basal slices contained LV myocardium comprising <50% chamber circumference

(Figure 3A). LVM contained within basal LV slices correlated with circumferential extent of LV myocardium (r=0.57, p<0.001) (Figure 3B).

Methodological Discordance

Established methods discordantly assigned basal LV image position in nearly all (96%) exams.ED_{50} and EDS_{50} differed from each other in 85% of cases, and from fully inclusive LVM quantification in 46% and 96% of cases respectively. Variance with fully inclusive LVM differed between binary cutoff methods: In cases of methodological discordance, ED_{50} differed from fully inclusive LVM by ≥1 LV short axis image position in 48%, and EDS_{50} differed from fully inclusive LVM by ≥2 short axis images in 52% of cases. Intra-observer reproducibility was high for all CMR methods (ED_{50} κ = 1.00, EDS_{50} = 0.90, fully inclusive = 1.00), as was inter-observer reproducibility (ED_{50} κ = 0.78, EDS_{50} = 0.80, fully inclusive = 1.00).

Table 2 reports LVM by each method, demonstrating lower LVM by both binary methods compared to full myocardial inclusion (both p<0.001). LVM excluded using binary cutoffs constituted 5.4±6.5gm (2.7±3.2 gm/m^2) for ED_{50} and 22.0±10.0gm (11.2±5.0 gm/m^2) for EDS_{50}, respectively constituting 3.2% and 13.0% of total LVM. Whereas overall mean differences between methods were small, over a third (39%) of patients manifested ≥5% difference between ED_{50} and fully inclusive LVM. In comparison, nearly all patients (95%) manifested ≥5% difference between EDS_{50} and fully inclusive LVM, and two thirds (65%) demonstrated ≥10% difference between these methods.

Table 2 also reports end-diastolic chamber volumes for three CMR methods, demonstrating larger volumes for the full myocardial inclusive method (i.e. accounting for fractional components of basal slice chamber volume subtended by LV myocardium), as compared to both ED_{50} and EDS_{50} (both p<0.001). Consistent with LVM results, EDS_{50} yielded greater volumetric differences with the fully inclusive method than did ED_{50} (p<0.001): nearly three-fourths (72%) of patients demonstrated ≥10% difference in chamber volumes between EDS_{50} and the fully inclusive method.

Methodological differences impacted diagnostic classifications regarding LV chamber dilation. As shown in Table 2B, both binary cutoff methods yielded a smaller proportions of patients meeting an established CMR cutoff[27] for LV chamber dilation than did full myocardial inclusion (both p<0.05). Additionally, EDS_{50} yielded a smaller proportion of patients categorized with LV hypertrophy (p=0.004).[28]

Validation

Each CMR method was independently compared to two standards; (1) a clinical standard of LVM measured on echo, and (2) an ex-vivo standard of LVM as weighed at time of necropsy.

LV Mass by Echocardiography—Echo was performed within 1 day of CMR in all patients (99% same day). 96% of echos (n=144) were technically sufficient to quantify LVM. Figure 4A compares LVM by echo and CMR, demonstrating that all CMR methods yielded lower LVM than did echo (p<0.001). However, as shown in 4B, fully inclusive

LVM yielded smaller differences with echo (Δ=11.0±28.8gm) than did ED_{50} (Δ=16.4±29.1gm) and EDS_{50} (Δ=33.2±28.7gm, both p<0.001).

Differences between fully inclusive LVM and echo were similar among patient sub-groups stratified based on male/female gender (Δ=9.8±29.4gm vs. 17.1±25.3gm, p=0.26), or by presence or absence of clinically documented hypertension (Δ=8.6±29.9gm vs. 12.9±28.0gm, p=0.38), with fully inclusive LVM yielding smaller differences with echo than either binary cutoff methods in each sub-group (all p<0.001).

LV Weight at Necropsy—LVM quantification methods were also tested in a pre-existing cohort of 10 animals (8 dogs, 2 pigs) that underwent CMR prior to sacrifice. Figure 5 shows results of each CMR method compared to the reference standard of ex-vivo LV weight. In lab animals, ex-vivo LV weight (69.8±13.2gm) was similar to LVM calculated using fully inclusive (70.1±13.5gm, p=0.67) and ED_{50} (69.4±13.9gm, p=0.70), whereas EDS_{50} (67.9±14.9gm, p=0.04) yielded small but significant differences with LV weight at necropsy.

Discussion

This is the first study to identify methodological differences in LV basal slice definitions as a cause of variability in CMR-quantified LVM. There are several key findings: (1) LV myocardium actually imaged by CMR is frequently omitted from LVM as calculated using established CMR methods. Nearly half (46%) of exams included short axis images with LV myocardium insufficient to satisfy established CMR criteria that define the basal-most LV using a binary cutoff (i.e. 50% myocardial circumference). (2) Established methods yield significant differences (p<0.001) with fully inclusive LVM, with magnitude of difference proportional to stringency of binary cutoff. Methodological variability can affect clinical patient classifications, as evidenced by significant differences in proportion of patients classified with LVH or chamber dilation (both p<0.05). (3) Fully inclusive LVM quantification yields smaller differences with the clinical standard of echo-quantified LVM than do binary methods, and non-significant differences with the ex-vivo standard of necropsy-evidenced LV weight.

A review of prior CMR literature provides context to our current findings, demonstrating substantial methodological variability in published criteria for the basal LV: Figure 6 illustrates results of a systematic Pubmed query performed using the search terms “left ventricular mass”, “left ventricular hypertrophy”, “myocardial mass”, “hypertrophy and cardiac MRI”, “CMR or magnetic resonance imaging”. Of a total 129 original research papers (between 2000–12) that measured LVM, basal slice criteria were unspecified in 35%, included all LV myocardium in a small minority (5%), with the remainder evenly divided in use of anatomic landmarks (30%) or quantitative cutoffs (30%). Marked variability was present concerning published anatomic and quantitative criteria used to define the basal LV short axis slice. Regarding quantitative cutoffs, 20% of studies used a binary threshold of ≥50% myocardial circumference during end diastole alone (ED_{50}) whereas 8% required that this 50% threshold be satisfied during both end-diastole and end-systole (EDS_{50}). More stringent cutoffs have also been applied, including calculation of LVM with omission of

short axis images containing LV myocardium spanning <75% or 100% of chamber circumference.[15–17] Taken together, our results and review of prior literature indicate that methodological differences concerning basal slice criteria may contribute to discrepancies regarding calculated LVM.

Among our population, significant heterogeneity existed in circumferential extent of basal LV myocardium. Myocardial circumference, as measured on end-diastolic short axis images, ranged from 20–100%. Nearly half (43%) of all exams included basal images in which circumference was within ±10 points of the 50% threshold widely used in established literature. Importantly, for our study, myocardial circumference was uniformly measured using a dedicated quantitative protocol. However, in clinical practice, this parameter is typically assessed visually, an approach that may be especially challenging when myocardial circumference is slightly above or below a given cutoff as applied to define the basal-most LV short axis image. Taken together, these factors highlight the potential challenges of including or excluding LV myocardium from LVM based on a binary threshold.

Our findings are of broad relevance to prior studies that have compared CMR to echo. Of course, it is important to recognize that differences between modalities are partially due to echo-specific factors. Echo employs geometric assumptions that may not be valid for individual patients, especially those with advanced LV remodeling. Image quality can also affect echo, whereas CMR provides excellent endocardial definition that enables highly reproducible LVM quantification.[29,30] However, prior papers have demonstrated systematically lower LVM by CMR vs. echo,[1–4] suggesting biases not fully explained by echo limitations in context of several studies showing unbiased estimation of echo-derived LVM vs. necropsy-verified LV weight.[5,6,8] From a clinical perspective, echo is widely available, prognostically validated, and inexpensive, supporting its use as a primary screening modality to measure LV mass, with more costly testing such as CMR reserved for cases with non-diagnostic or technically challenging echoes. Prior work by our group has demonstrated CMR factors can contribute to discrepancy with echo. For example, failure to account for partial voxels (i.e. LV myocardium admixed with blood pool within individual voxels) is one reason for CMR discordance with both echo-quantified LVM and necropsy-verified LV weight.[1] Current findings, obtained using a highly reproducible quantification algorithm that accounts for myocardial partial voxels, demonstrate that use of binary criteria to define the basal-most LV is another CMR reason for discordance, yielding differences with both necropsy and echo measurements proportional to magnitude of myocardium omitted from CMR measured LVM. These results are consistent with the fact that echo formulae were extrapolated from autopsy measured total LV weight, and would thus be expected to best agree with CMR measurements of LVM that account for all LV myocardium actually imaged.

There are several limitations to this study. First, CMR criteria for basal slice selection were compared to echo-quantified LVM among post-MI patients, rather than an unselected population. While this enabled us to compare CMR to echo among a cohort in which both modalities were acquired within a narrow (1 day) interval, further study is needed to examine the impact of basal slice variability among normative cohorts and patients with advanced LV remodeling. Second, cine-CMR was performed using conventional breath-held

two-dimensional imaging, rather than three-dimensional approaches. However, the purpose of our study was to evaluate the impact of basal slice variability in routine clinical practice, a setting in which 2D cine-CMR is a component of nearly all exams. Third, our study used an automated CMR algorithm to quantify LVM, whereas many CMR centers do so using manual planimetry. However, it is important to note that the automated algorithm employed in the current study has been previously shown to yield improved reproducibility compared to manual planimetry and excellent agreement with both ex-vivo LV weight as well as phantom-verified chamber volumes,[1,19] thereby supporting its use as a reliable means of quantifying methodology-associated differences in LVM.

In summary, results of this study show that established CMR methods which exclude fractional components of basal LV myocardium yield discordant results concerning LVH and/or chamber dilation, as well as increased magnitude of difference with echocardiography. Findings add to a growing body of literature demonstrating the importance of methodological standardization when comparing population-based LVM measured using a single imaging modality, or comparing quantitative indices measured by different tests such as CMR and echocardiography.

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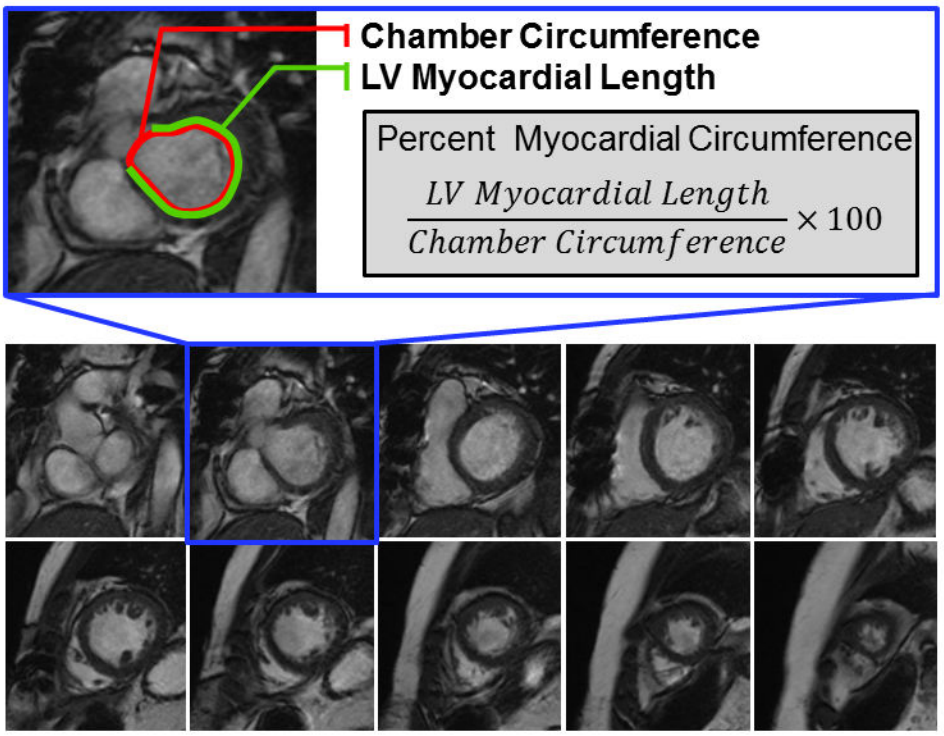

Figure 1. Basal Circumference Quantification

Representative illustration of quantitative method used to measure circumferential extent of LV myocardium within basal short axis images: LV myocardial length (green) and total chamber circumference (red) were each planimetered, with percent myocardial circumference calculated as the proportion of the two (green/red).

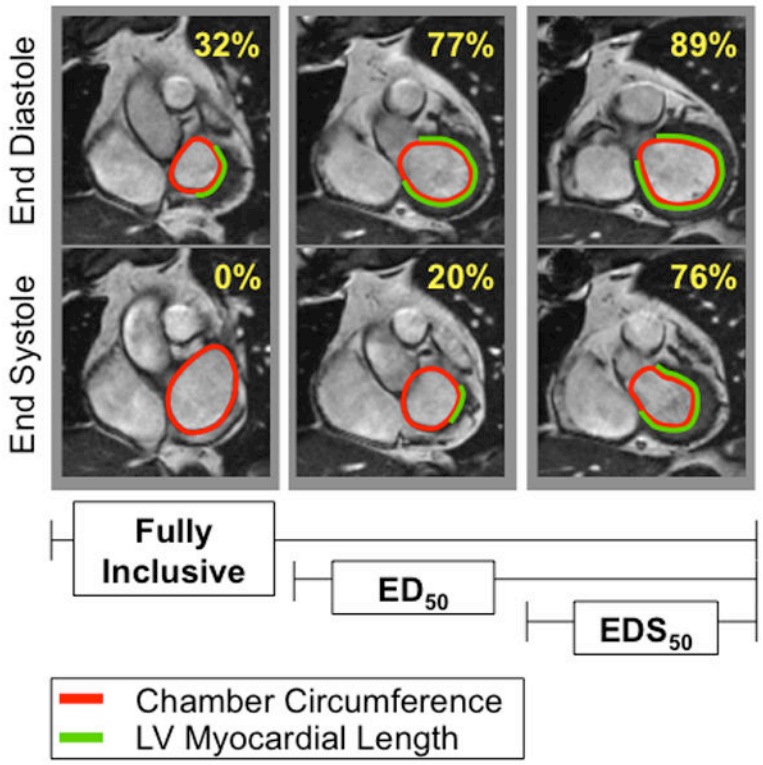

Figure 2. Typical Example

Typical patient example demonstrating discordance between established CMR methods (% myocardial circumference denoted in yellow font): Whereas ED_{50} localized the basal LV to a short axis image with end-diastolic circumference 77% LV myocardium (yellow font), EDS_{50} excluded this image based on end-systolic circumference (20% LV myocardium), and instead localized the basal LV to a subsequent image (89% end-diastole, 76% end-systole). Both binary cutoff methods excluded LV myocardium (32% end-diastole, 0% end-systole) contained within a more basal short axis image. Accordingly, LV mass was lower by both binary methods (EDS_{50}: 157gm, ED_{50}: 172gm) compared to fully inclusive quantification (185gm).

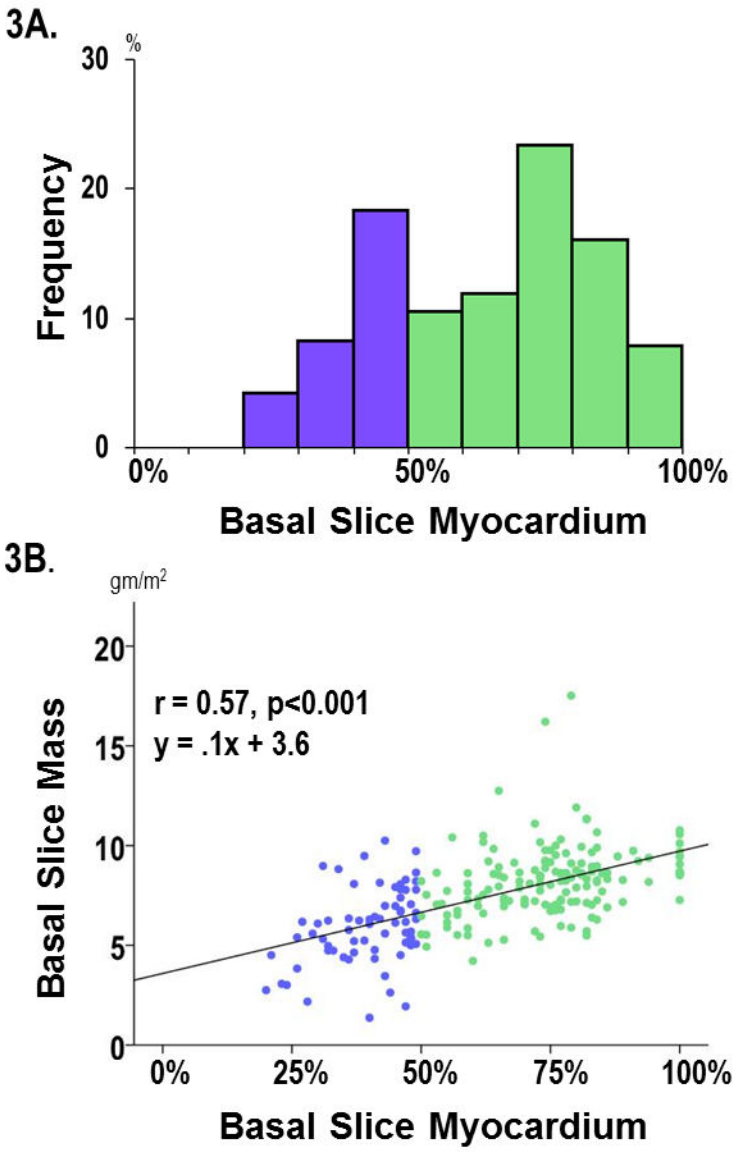

Figure 3. Distribution and Geometry of Basal LV Myocardium

3A. Distribution of circumferential extent of LV myocardium among patient cohort (blue <50%, green ≥50%).

3B. Scatter-plot demonstrating correlation between circumferential extent of LV myocardium and LV mass comprised within each basal short axis slice.

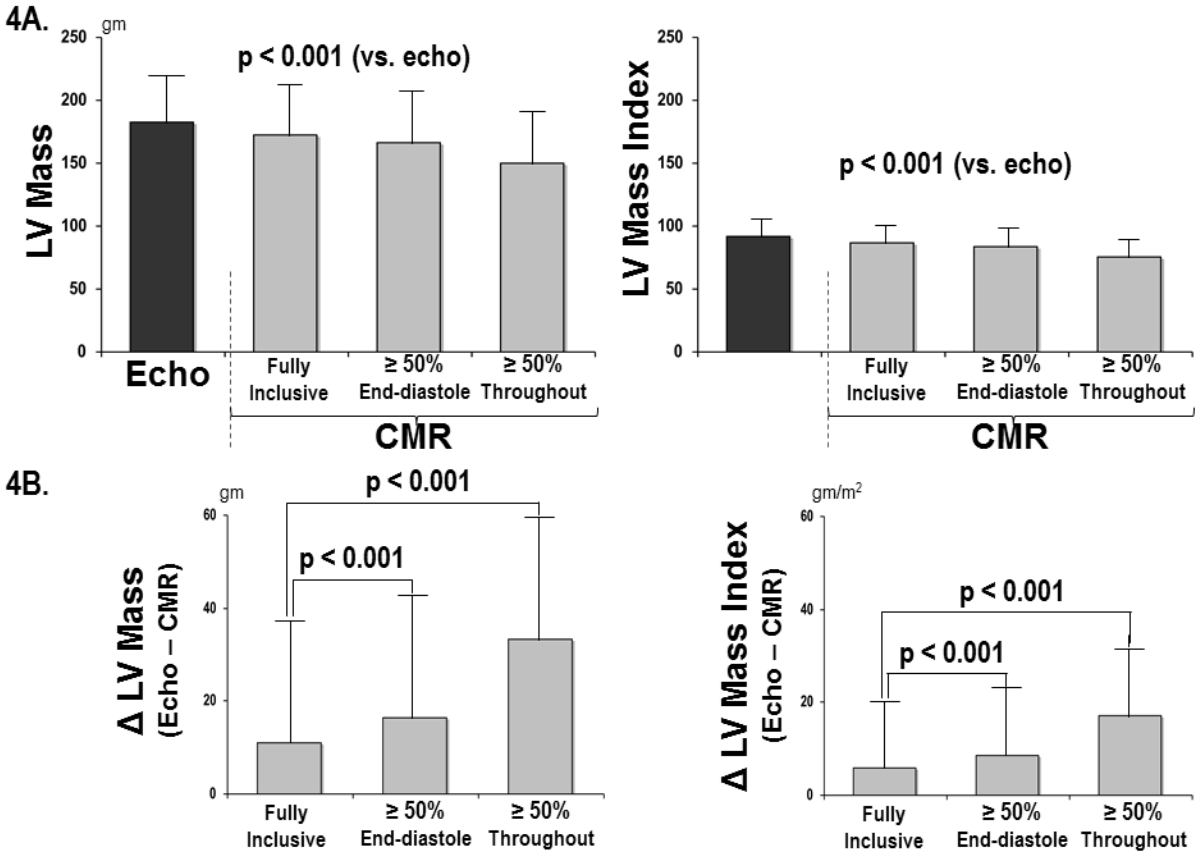

Figure 4. Comparison to Echocardiography

LV mass (mean±SD) by each CMR basal slice selection method (gray bars) compared to echo (black bar). Whereas all CMR methods yielded lower LV mass than did echo (**4A**), differences between modalities (ΔLV mass) were smallest with fully inclusive quantification compared to each binary cutoff method ($p<0.001$).

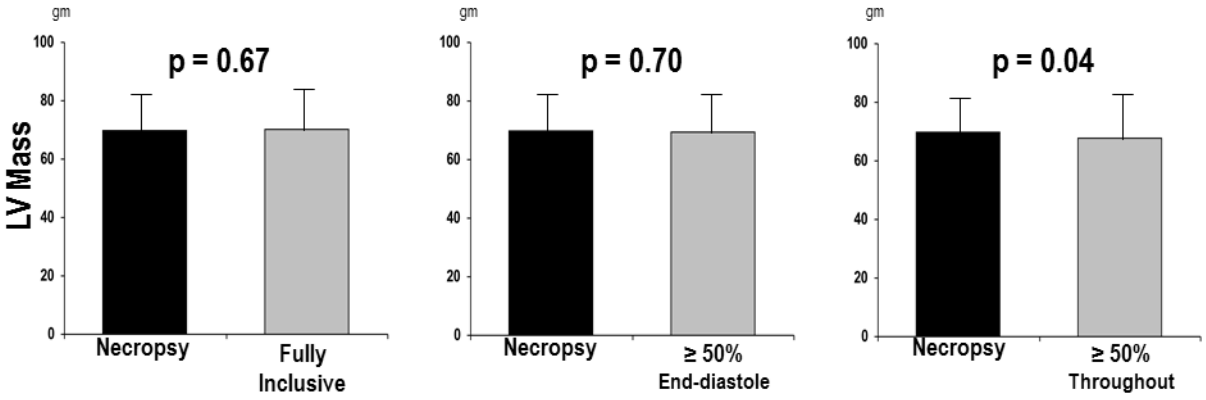

Figure 5. Comparison to Necropsy

LV mass (mean±SD) by each CMR basal slice selection method (gray bars) compared to necropsy-evidenced LV weight (black bar). While both fully inclusive and ED_{50} were similar to necropsy (p=NS), results were lower with EDS_{50} (p=0.04), consistent with more stringent exclusion of basal LV myocardium by the latter CMR method.

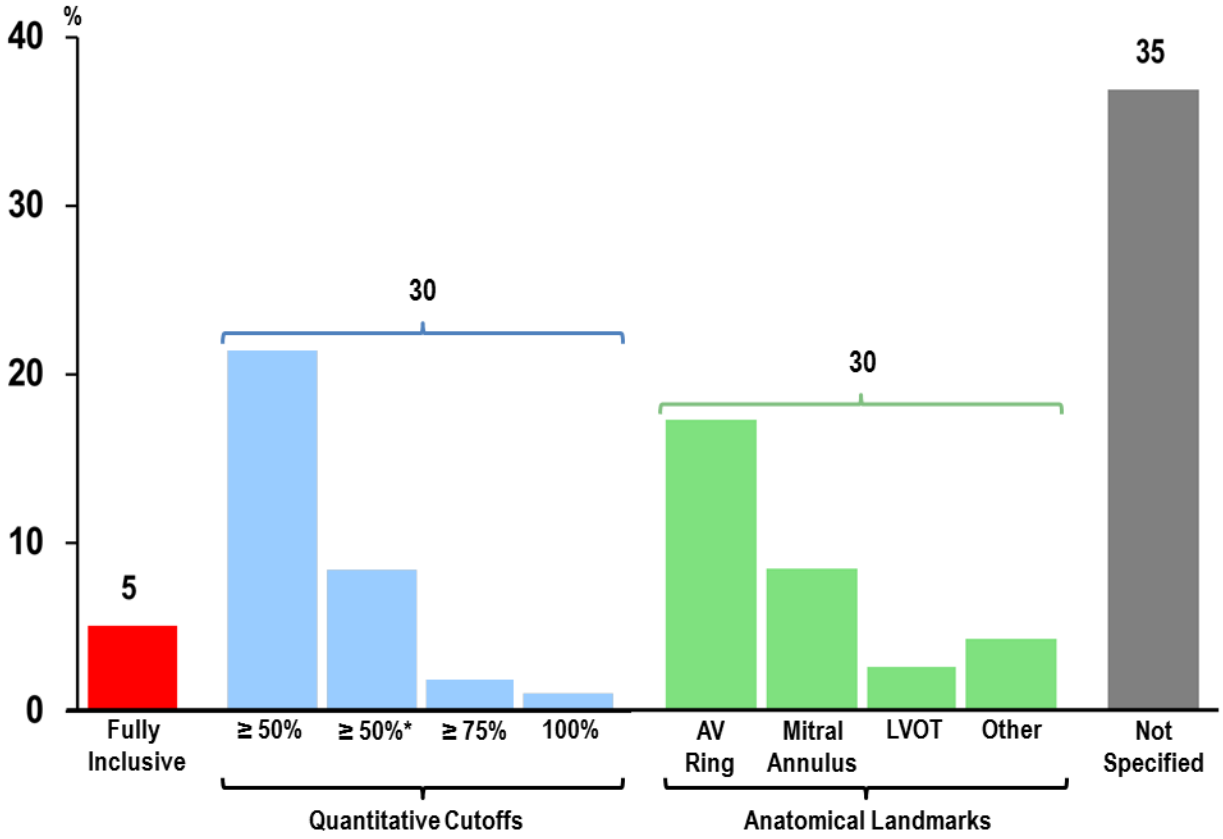

Figure 6. Basal LV Criteria in Established CMR Literature

Frequency of different quantitative (blue bars) and anatomic (green) criteria for LV basal slice selection in published CMR literature. Note that, when specified, quantitative basal slice criteria most frequently used a 50% threshold to identify the basal LV, with exclusion of short axis images containing lesser amounts of LV myocardium.

Table 1

Patient Characteristics

Age (year)	57 ± 12
Male gender	83% (124)
Atherosclerosis Risk Factors	
Hypertension	43% (64)
Hyperlipidemia	47% (71)
Diabetes Mellitus	21% (32)
Tobacco Use	31% (46)
Family History	26% (39)
Coronary Artery Disease History	
Prior Myocardial Infarction	6% (9)
Prior Coronary Revascularization	11% (16)
Cardiovascular Medications	
Beta-blocker	95% (143)
ACE Inhibitor/ARB	64% (96)
HMG-CoA Reductase Inhibitor	94% (141)
Aspirin	100% (150)
Thienopyridines	93% (139)
Myocardial Infarct Parameters	
Infarct Related Artery	
Left Anterior Descending	58% (87)
Right Coronary	35% (52)
Left Circumflex	7% (11)
Infarct Size (% myocardium)	15 ± 9
Post Myocardial Infarction Interval (days)	27 ± 7

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Table 2A

LV Mass and Chamber Size

	Full Myocardial Inclusion	ED_{50}	P	EDS_{50}	P
LV Mass					
gm	172.6 ± 42.3	167.2 ± 41.8	**<0.001**	150.6 ± 41.1	**<0.001**
gm/m^2	87.2 ± 17.7	84.4 ± 17.6		76.0 ± 17.7	
LV End-Diastolic Volume					
ml	136.9 ± 39.7	133.2 ± 39.2	**<0.001**	116.7 ± 38.4	**<0.001**
ml/m^2	69.2 ± 17.6	67.3 ± 17.4		58.9 ± 17.5	

Bold face type indicates p value < 0.05 (data presented as mean±SD). P values calculated for each binary method compared to full myocardial inclusion.

Table 2B

LV Remodeling*

	Full Myocardial Inclusion	ED_{50}	P	EDS_{50}	P
LV Hypertrophy	11% (n=16)	9% (n=13)	0.25	5% (n=7)	**0.004**
LV Concentricity	5% (n=7)	4% (n=6)	1.00	4% (n=6)	1.00
LV Chamber dilation	33% (n=49)	28% (n=42)	**0.016**	18% (n=27)	**<0.001**

*Cutoffs based on established gender-specific normative CMR cutoffs.[27,28]