Automated Segmentation of Routine Clinical Cardiac Magnetic Resonance Imaging for Assessment of Left Ventricular Diastolic Dysfunction

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Short Title: Automated CMR Assessment of Diastolic Function

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Abbreviations:
CMR = cardiac magnetic resonance
PFR = peak filling rate (absolute)
NPFR = normalized peak filling rate (stroke volume adjusted)
TPFR = time to peak filling rate
DVR = diastolic volume recovery
Abstract

Background: Cardiac magnetic resonance (CMR) is established for assessment of left ventricular (LV) systolic function but has not been widely used to assess diastolic function. This study tested performance of a novel CMR segmentation algorithm (LV-METRIC) for automated assessment of diastolic function.

Methods and Results: 101 patients with normal LV systolic function underwent CMR and echocardiography (echo) within 7 days. LV-METRIC generated LV filling profiles via automated segmentation of contiguous short axis images (204±39 images, 2:04±0:53 minutes). Diastolic function by CMR was assessed via early:atrial filling (E:A) ratios, peak diastolic filling rate (PFR), time to peak filling rate (TPFR), and a novel index – diastolic volume recovery (DVR), calculated as percent diastole required for recovery of 80% stroke volume. Using an echo standard, patients with vs. without diastolic dysfunction had lower E:A ratios, longer TPFR, lower stroke volume adjusted PFR, and greater DVR (all p<0.05). Prevalence of abnormal CMR filling indices increased in relation to clinical symptoms classified by NYHA functional class (p=0.04) or dyspnea (p=0.006). Among all parameters tested, DVR yielded optimal performance vs. echo (AUC: 0.87±0.04, p<0.001); Using a 90% specificity cutoff, DVR yielded 74% sensitivity for diastolic dysfunction. In multivariate analysis, DVR (OR 1.82, CI 1.13-2.57, p=0.02) was independently associated with echo-evidenced diastolic dysfunction after controlling for age, hypertension, and LV mass (χ² = 73.4, p<0.001).

Conclusions: Automated CMR segmentation can provide LV filling profiles that may offer insight into diastolic dysfunction. Patients with diastolic dysfunction have prolonged diastolic filling intervals, which is associated with echo-evidenced diastolic dysfunction independently of clinical and imaging variables.

Key Words: diastolic dysfunction, cardiovascular magnetic resonance, echocardiography
Introduction

Left ventricular (LV) diastolic dysfunction is a common cause of heart failure, occurring in up to 40-50% of heart failure patients.\textsuperscript{1,2} Identification of diastolic dysfunction is important for assessment of prognosis and tailoring of therapy. Altered LV compliance changes the timing profiles of LV filling and leads to diastolic dysfunction. LV filling profiles have been used to assess diastolic function by other imaging modalities, such as radionuclide cineangiography (RNCA).\textsuperscript{3-5} Similar applications for cardiac magnetic resonance (CMR) imaging have been impractical as manual planimetry of all LV images across all temporal phases would typically require tracing of over two hundred images per patient. Thus, whereas CMR is an accepted reference standard for LV systolic function, its use for assessment of diastolic function is limited and additional testing, such as echocardiography (echo) is typically employed to establish this diagnosis.

Automated segmentation of isolated end-diastolic and end-systolic phases is well-established for measurement of LV ejection fraction.\textsuperscript{6-8} By extension, automated segmentation of LV volumes across all temporal phases holds the potential to rapidly assess diastolic filling patterns. An advantage of this approach is its application to standard cine-CMR data without additional dedicated imaging, which can be prohibitive in heart failure patients with limited breath hold capabilities. While automated segmentation holds the potential to markedly increase the yield of standard CMR exams, its utility for distinguishing between normal and abnormal diastolic filling has not been validated.

We have recently developed an automated segmentation algorithm (LV-METRIC) that quantifies LV volume based on per-voxel signal intensity and employs no assumptions regarding LV shape.\textsuperscript{8} In our initial validation study, LV-METRIC closely agreed with phantom volumes and LV ejection fraction as manually measured in clinical patients.\textsuperscript{8} The current study was designed to evaluate whether volumetric filling profiles generated automatically by LV-METRIC
can be useful to distinguish between patients with and without isolated diastolic dysfunction as established by the reference standard of echo.

Methods

Population

This study included consecutive patients with normal LV systolic function (EF ≥ 55% on echo and cine-CMR) who underwent echo assessment of diastolic function within 7 days of CMR. Three patients were excluded whose CMR data prohibited qualitative assessment of LV performance due to atrial fibrillation or ventricular ectopy. No patients were excluded based on clinical characteristics or quantitative processing results. Imaging was performed between September 2005 and April 2009 at Weill Cornell Medical College. The study was conducted in accordance with the Cornell Institutional Review Board (IRB), which approved the research protocol. All prospectively enrolled patients provided written informed consent and the IRB approved use of pre-existing clinical data.

Comprehensive clinical data were collected at the time of CMR including cardiac risk factors, coronary artery disease (CAD) history, NYHA functional class, and medication regimen. Self-reported data were supplemented by review of medical records for casual blood pressure, invasive filling pressures, and clinical indices.

Imaging Protocol

Echocardiography

Transthoracic echoes were performed using commercially available equipment (General Electric Vivid-7 or Siemens Sequoia). Images were acquired in apical and parasternal orientations and linear quantitative measurements were performed on parasternal views in
accordance with American Society of Echocardiography guidelines. Mitral valve inflow parameters were acquired in an apical 4 chamber view via pulsed-wave Doppler sampling performed at the mitral valve leaflet tips perpendicular to the valve annulus. Tissue Doppler profiles were acquired in apical 4 chamber view with sampling performed at the basal septum and, if technically feasible, lateral wall.

The echo diagnosis of diastolic dysfunction was adjudicated in all cases by a single experienced echocardiographer (RBD) who was blinded to patient identity and CMR results. In accordance with established guidelines, diastolic performance was graded as follows:

- **Normal**: E/A ≥0.8, septal e’ ≥8, lateral e’ ≥10, deceleration time 140-240ms
- **Grade 1 (mild)**: E/A <0.8, septal e’ <8, lateral e’ <10, deceleration time >240ms
- **Grade 2 (moderate)**: E/A 0.8-1.5, septal e’ <8, lateral e’ <10, deceleration time 140-240ms
- **Grade 3 (severe)**: E/A ≥2, septal e’ <8, lateral e’ <10, deceleration time <140

In patients with equivocal tissue Doppler indices (i.e. abnormal lateral but normal septal e’ amplitude), e’/a’ reversal (<1) and pulmonary vein flow profiles were used to establish presence of diastolic dysfunction.

**CMR Imaging**

CMR exams were performed using 1.5 Tesla scanners (General Electric). Cine-CMR used a commercially available 2D steady state free precession pulse sequence. Images were acquired in contiguous short axis slices from the level of the mitral valve annulus through the LV apex. Typical parameters were as follows: repetition time (TR) 3.5 msec, echo time (TE) 1.6 msec, flip angle 60°, in-plane spatial resolution 1.9 mm x 1.4 mm, slice thickness 6mm, inter-
slice gap 4mm. Mean reconstructed temporal resolution (RR interval/# cardiac phases) was 36 ± 10 msec and absolute temporal resolution (TR x views per segment) was 75 ± 17 msec.

**Automated CMR Segmentation**

**Systolic Function and Morphology**

LV volumetric and myocardial mass quantification was performed automatically using LV-METRIC. As previously described, the algorithm automatically segments the endocardial border excluding papillary and trabecular structures from the blood volume for assessment of chamber volumes. Epicardial segmentation was also performed for automated volumetric quantification of LV mass. For all segmentations, user input included identification of the slice range to be segmented and definition of the valve annulus. Optional user corrections were provided by manually contouring to restrict region-growth and by adjusting blood sensitivity.

End-diastolic volume (EDV) and end systolic chamber volume (ESV) were calculated using Simpson’s method, and EF calculated as $EF = \frac{[EDV - ESV]}{EDV} \times 100$. Basal and apical image positions were defined in accordance with previously reported criteria, with the basal LV defined by the basal most image encompassing at least 50% circumferential myocardium. LV mass was quantified based on automated border detection of end-diastolic endocardial and epicardial contours, with mass determined as the product of myocardial volume and specific gravity ([EpiEDV - EDV] * 1.05).

**Diastolic Function**

For assessment of diastolic function, LV-METRIC segmentation for each short axis slice was performed across all temporal phases (Figure 1A). Volumetric data were transferred into an automated processing tool developed in MATLAB (MathWorks Inc, Natick, MA) to analyze the LV volume-filling time course. To assess LV filling profiles, basal and apical image positions
were defined as the locations in which ≥50% myocardium was present during systole and diastole. The following CMR diastolic parameters were evaluated:

- **Peak Filling Rate** [PFR] - maximal LV filling rate defined by maximal change in LV volume between sequential temporal phases (Δ volume/Δ phase); This index was also adjusted for stroke volume to generate **Normalized Peak Filling Rate** [NPFR]
- **Time to Peak Filling Rate** [TPFR] - time interval between end-systole and peak filling rate
- **Diastolic Volume Recovery** [DVR] - proportion of diastole required for recovery of a given percentage (i.e. 80%) of stroke volume

The volumetric filling curve was also transformed to the first derivative in order to obtain early (E) and late (A) filling profiles, similar to a typical mitral inflow pattern. **Figures 1B and 1C** provide representative graphic illustrations of each parameter in relation to LV-METRIC generated filling profiles.

**Statistical Methods**

Comparisons between groups with or without diastolic dysfunction were made using Student’s t test for continuous variables (expressed as mean±standard deviation and/or median, interquartile range [IQR]). Categorical variables were compared using Chi-square or, when fewer than 5 expected outcomes per cell, Fisher’s exact test. Overall diagnostic test performance was evaluated using receiver operator characteristics (ROC) curves, with comparison between ROC curves performed using a univariate z score test of the difference between the partial areas under the two performance curves between specificities of 80% and 100%, a clinically relevant range of specificity for assessment of diastolic dysfunction. Test sensitivity was compared using McNemar’s test for paired proportions. Logistic regression analyses and bivariate correlation coefficients were employed to evaluate associations between CMR and echo 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

Population characteristics

The study population consisted of 101 patients who underwent CMR and echo within 7 days of one another (mean 1.4±2.1 days, median 0.0 [IQR 0.0, 2.0]). 50 patients had echo-evidenced diastolic dysfunction. When classified according to severity, diastolic dysfunction was mild (grade 1) in 38% (n=19), moderate (grade 2) in 60% (n=30), and severe (grade 3) in 2% (n=1) of affected patients.

As shown in Table 1, patients with echo-evidenced diastolic dysfunction were older, were more likely to have clinically-diagnosed hypertension, and had higher clinically-measured systolic blood pressure than those without diastolic dysfunction (p<0.001). Left atrial volume and MR severity did not differ significantly between groups; 96% of patients had MR graded as less than or equal to mild severity by echo. Both echo and cine-CMR demonstrated higher LV mass among patients with diastolic dysfunction (p<0.001), despite smaller measurements by CMR compared to echo (mean Δ 27±20gm/m² p<0.001, median 26 [IQR 16, 36]).

CMR Diastolic Parameters

LV-METRIC successfully generated LV volumetric filling profiles in all patients; Mean processing time was 2:04 ± 0:53 minutes, which included time for automated segmentation (204±39 images), visual review of segmented data, and any manual corrections. In 48% of patients, LV segmentation required only manual delineation of the LV outflow tract and apical borders. Additional manual corrections of LV-METRIC contours were necessary in the remainder of the population (mean 3±4 corrections/exam, median 1 [IQR 0, 4]) (1.4% of all images [288/20,584]).

Table 2 reports CMR diastolic parameters for patients stratified according to diastolic filling classified by echo. As shown, patients with echo-evidenced diastolic dysfunction had longer normalized peak filling rate and absolute time to peak filling (both p<0.001) than those
without diastolic dysfunction. Diastolic dysfunction was also characterized by higher DVR (p<0.001), calculated as the proportion of diastole required for LV recovery of 80% stroke volume. Among all CMR diastolic indices tested, only DVR significantly correlated with echo-evidenced deceleration time (r=0.29, p<0.01)

Derivative transformation of volumetric curves yielded distinct E and A waves in 76% of patients (Figure 1C), with absence of discernable E and A waves in the remainder. CMR-generated E:A filling ratios differed between patients with and without diastolic dysfunction, with lower absolute E:A ratio in the diastolic dysfunction group (p<0.001). When E:A ratios were categorized using a binary threshold of 1, there was moderate agreement between CMR and echo (kappa .50, p<0.001), although the two modalities were discordant in 16% (12/76) of patients.

Performance of CMR Parameters

Figure 2 provides receiver operating characteristics (ROC) curves for CMR-derived diastolic variables. As shown, DVR yielded improved overall performance as compared to both PFR and TPFR based on total area under the ROC curve (p<0.001 for both comparisons). Among all diastolic time intervals, DVR yielded the best diagnostic performance using a threshold of 80% of LV stroke volume (AUC 0.87), with slightly worse performance achieved when thresholds between 50-90% of stroke volume were tested (AUC 0.75–0.86).

Table 3 reports sensitivity, positive, and negative predictive value of all CMR diastolic indices calculated based on a matched specificity cutoff (90%). As shown, sensitivity of DVR (74%) was approximately two-fold greater than TPFR (38%) or NPFR (30%) (both p<0.001). Among the 13 (26%) patients with echo-evidenced diastolic dysfunction that were missed by CMR-evidenced DVR, 4 had mild, 8 moderate, and 1 severe grade diastolic dysfunction. In the one patient with severe (grade 3) diastolic dysfunction, DVR was classified as normal whereas PFR was classified as abnormally low (based on 90% specificity cutoff), suggesting that this latter parameter may be useful for identifying restrictive filling.
Clinical and Hemodynamic Associations

CMR diastolic parameters differed significantly when patients were grouped based on clinical status. Figure 3A reports the prevalence of CMR-evidenced diastolic dysfunction (based on abnormal DVR or PFR) among patients stratified by NYHA functional class; Prevalence of diastolic dysfunction (using cutoffs in Table 3) was increased in relation to severity of functional impairment and was greater among patients with NYHA class III or IV (80%) compared to those with class II (58%) or class I (41%) status (p=0.04). When grouped according to binary presence or absence of clinical dyspnea (Figure 3B), there was nearly a two-fold greater prevalence of CMR-evidenced diastolic dysfunction (PFR or DVR) among symptomatic versus asymptomatic patients (p=0.006). A similar relationship was evident when prevalence of abnormal DVR alone was compared between patients grouped by dyspnea status (63% vs. 39%, p=0.02).

CMR diastolic parameters also stratified groups based on invasive filling pressures. Among the subgroup of the population (n=22) that underwent CMR and invasive angiography within a narrow interval (mean 1.5±1.2 days, median 2 [IQR 0, 2]), patients with abnormal PFR (based on Table 3 cutoffs) had higher LV end-diastolic filling pressures than those with normal PFR (32±14 vs. 18±6 mmHg, p<0.01). A similar trend was demonstrated when LV end-diastolic filling pressures were compared between patients stratified based on DVR (22±10 vs. 15±4 mmHg, p=0.08).

Predictors of Diastolic Function

Clinical and imaging parameters were examined to determine whether CMR diastolic indices yielded incremental value after controlling for standard predictors of diastolic dysfunction. As shown in Table 4, logistic regression demonstrated that DVR was an independent predictor of echo diastolic dysfunction even after controlling for age, clinically diagnosed hypertension, and CMR-quantified left ventricular mass. The relationship between DVR and diastolic dysfunction was continuous, with over a 75% increase in relative risk for
diastolic dysfunction conferred by every 10 percentage point increment in DVR. Table 5 substitutes echo-evidenced LV mass in the multivariate model, demonstrating that the relationship between DVR and diastolic dysfunction was independent of the modality used to measure LV hypertrophy.

Discussion

This study provides several new observations concerning automated CMR assessment of LV diastolic function: First, automated CMR processing was robust, providing LV filling profiles in all patients tested within an average time of approximately 2 minutes; Filling curves were generated using standard cine-CMR images that were not tailored for diastolic assessment. Second, among a diverse population with normal systolic function, CMR-evidenced diastolic filling parameters generally stratified between patients with and those without echo-evidenced diastolic dysfunction. Prevalence of abnormal CMR diastolic filling parameters increased in relation to clinical heart failure status as classified based on NYHA functional class or the binary presence or absence of dyspnea. Third, CMR-evidenced diastolic filling (DVR) was an independent predictor of echo-evidenced diastolic dysfunction even after controlling for clinical and imaging variables such as hypertension and LV mass.

Automated segmentation is important for assessment of LV filling as cavity volumes must be measured on hundreds of short axis cine images, making manual tracing impractical for widespread clinical application. In prior validation studies, LV-METRIC reduced processing time by >90% vs. manual tracing and closely agreed with both phantom volumes and clinical patient data. LV-METRIC relies on two simple assumptions; (1) signal intensity of blood differs from that of myocardium, and (2) LV blood is surrounded by myocardium. This approach
differs from other automated segmentation algorithms, which have typically employed elegant
but restrictive assumptions regarding LV shape or contour deformation.\textsuperscript{6,7} LV-METRIC does not
employ geometric assumptions and can thereby accommodate differences in LV shape and
remodeling patterns among patients with diastolic dysfunction.

Our results demonstrate that decreased peak filling rates and prolonged time to peak
filling are associated with presence of echo-evidenced diastolic dysfunction. These findings are
in general agreement with prior studies that have used RNCA\textsuperscript{3,5,16} or SPECT\textsuperscript{17} to evaluate LV
filling profiles. Moreover, although differences between modalities prohibit volumetric
comparisons for absolute peak filling rates, mean normative values for time to peak filling rate
for our CMR results (160 msec) were similar to prior values published for RNCA (172-198
msec)\textsuperscript{5,16} and SPECT (165 msec)\textsuperscript{17} Unlike nuclear imaging, CMR involves no radiation exposure
and is thereby well suited for population-based screening and serial imaging of patients with
diastolic dysfunction to evaluate response to targeted therapies. Additionally, as CMR provides
high spatial-resolution imaging, it enables study of other indices that are associated with
impaired diastolic performance but not typically imaged by nuclear techniques, including
myocardial mass, left atrial size, and pericardial thickness.

In addition to absolute peak filling rate and time required to achieve peak filling, we
report a new index – diastolic volumetric recovery time (DVR) – that can be used to assess
diastolic function. Our findings demonstrate that this parameter, which accounts for variance in
heart rate and stroke volume, had excellent diagnostic performance as evidenced by ROC
analysis (AUC = 0.87), with superior overall performance to either NPFR or TPFR (p<0.001).
As DVR measures the proportion of diastole required for recovery of a given fraction of stroke
volume, it accounts for per-patient differences in heart rate and volume status, which can affect
peak filling rate.\textsuperscript{3,18} Consistent with our finding that DVR provides incremental value compared to PFR, prior studies using radionuclide imaging have reported that peak filling rate is affected by loading conditions whereas proportional filling (i.e. filling fraction completed during the first half of diastole) is load independent.\textsuperscript{19} Our finding that an optimal diagnostic threshold for DVR is 80% suggests that this parameter reflects LV filling prior to atrial contraction; Prior studies using invasive hemodynamic measurements have shown that in normal controls, approximately 80% (79\pm 7\%) of LV stroke volume occurs during active early diastolic LV relaxation and subsequent diastasis.\textsuperscript{20}

Prior CMR studies have used dedicated imaging techniques to assess LV diastolic dysfunction. Phase contrast imaging has been used to assess mitral and pulmonary vein inflow patterns as a means of distinguishing between patients with and without diastolic dysfunction.\textsuperscript{21,22} Other investigations have employed phase contrast to identify regional myocardial tissue profiles in a manner analogous to tissue Doppler imaging.\textsuperscript{23} Myocardial tagging can also be used to evaluate myocardial torsion and diastolic strain rate.\textsuperscript{24} However, these approaches require additional imaging for dedicated assessment of diastolic function, which can be technically challenging, increase exam duration, prolong processing time, and prohibitive for patients with limited breath-hold capabilities.

While our study used a dedicated automated segmentation algorithm to assess diastolic parameters, the data were obtained from a standard, commercially available, steady state free precession cine-CMR sequence that required no additional imaging beyond that which is commonly applied to assess systolic function. To evaluate the broad applicability of this approach, we tested performance among pre-existing exams that were not requested or tailored for assessment of diastolic function. Consistent with our findings, CMR assessment of LV filling
curves has been shown to be feasible in smaller studies,\textsuperscript{25-28} and derived CMR parameters have been correlated with echo indices of diastolic function and invasive filling pressures.\textsuperscript{26,28} Maciera et al. used an automated method to study normal distributions of LV peak filling rates and time to peak filling rates among patients without known risk factors or history of cardiovascular disease.\textsuperscript{27} However, as this study was limited to normal controls, the utility of CMR to assess diastolic dysfunction was not tested. Our study compared automated CMR segmentation to echo, which is widely used to assess LV diastology.\textsuperscript{10}

In addition to assessment of diastolic performance based on cavity volumes, LV-METRIC can also employ an automated algorithm to measure myocardial mass.\textsuperscript{12} This feature is not necessary to generate filling curves. However, it provides adjunctive data regarding myocardial hypertrophy, which can contribute to diastolic dysfunction. In our study, LV mass by CMR was significantly lower than echo-derived mass. While this may be due to limitations of the automated algorithm used to quantify mass, an alternative explanation relates to methodological differences; Mass by CMR was obtained from 3D delineation of endo/epicardial contours whereas echo-derived mass was obtained using a 1D linear formula that incorporates assumptions regarding LV geometry. Prior studies have shown that volumetric mass by CMR yields lower values than does linear-derived mass by echo\textsuperscript{29,30} and that magnitude of difference between modalities is greatest in patients with LV remodeling.\textsuperscript{31}

It is important to recognize that while LV filling profiles add to the information obtained from routine CMR exams, approximately one fourth of patients with echo-evidenced diastolic dysfunction were not identified by CMR indices. There are several potential explanations for discordance between CMR and echo. First, while the interval between tests was short (1.4±2.1 days), diastolic performance can rapidly change due to alterations in LV loading conditions and
it is possible that performance varied during the narrow interval between tests. Second, due to its high temporal resolution, echo may detect subtle manifestations of diastolic dysfunction that are not evidenced by lower temporal resolution imaging by routine cine-CMR. Third, while tissue Doppler is a common criterion for diastolic dysfunction, it can be influenced by regional abnormalities that may not alter global diastolic filling as measured by cine-CMR. Indeed, while our study compared CMR filling parameters to echo-Doppler, use of echo as an absolute reference standard is a limitation given debate regarding how echo patterns of diastolic dysfunction should be interpreted with respect to their clinical context.\textsuperscript{10,11} However, echo is widely used to assess diastolic performance and consensus guidelines,\textsuperscript{10} which were employed in this study, offer one means to standardize interpretation of echo-evidenced diastolic filling patterns.

Several additional limitations should be acknowledged. While results demonstrate that LV filling profiles generated by automated processing of routine cine-CMR can be useful to assess the binary presence or absence of echo-evidenced diastolic dysfunction, the utility of CMR for assessing graded severity of diastolic dysfunction was not tested. Additionally, while CMR diastolic parameters were associated with higher LV filling pressures in a sub-group that underwent angiography, CMR was not compared to invasive hemodynamics in the majority of subjects. Finally, data is lacking concerning the prognostic implications of CMR-evidenced diastolic dysfunction and the correlation between CMR diastolic parameters and serologic indices such as brain natriuretic peptide.

In summary, this study demonstrates that automated CMR segmentation can generate LV filling profiles that may offer insight into diastolic dysfunction. Prolongation of diastolic filling on cine-CMR is associated with echo-evidenced diastolic dysfunction independently of other
clinical and imaging variables. Future research is warranted to assess whether automated CMR assessment of diastolic filling can be used to grade severity of diastolic dysfunction, assess invasive filling pressures, or predict clinical outcomes.

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**Conflicts of Interests:** The authors’ institution has submitted a patent for the automated segmentation algorithm (LV-METRIC) described in this study.
References


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comparison with tissue Doppler imaging and invasive measurement. J Am Coll Cardiol 2005;45:1109-16.


Table 1. Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Normal Diastolic Filling† (n=51)</th>
<th>Diastolic Dysfunction† (n=50)</th>
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<td><strong>CLINICAL</strong></td>
<td></td>
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<tr>
<td>Age (year)</td>
<td>51±18</td>
<td>41±14</td>
<td>62±14</td>
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<td>Male gender</td>
<td>59%</td>
<td>55% (28)</td>
<td>64% (32)</td>
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<tr>
<td><strong>Blood Pressure</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124±18</td>
<td>116±12</td>
<td>132±19</td>
<td>&lt;0.001</td>
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<td>Diastolic blood pressure (mm Hg)</td>
<td>70±11</td>
<td>70±10</td>
<td>71±11</td>
<td>0.59</td>
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<tr>
<td><strong>Heart Rate</strong></td>
<td></td>
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<td></td>
<td>69±11</td>
<td>70±11</td>
<td>69±11</td>
<td>0.80</td>
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<td><strong>Atherosclerosis Risk Factors</strong></td>
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<tr>
<td>Hypertension</td>
<td>45%</td>
<td>16% (8)</td>
<td>74% (37)</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes Mellitus</td>
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<td>10% (5)</td>
<td>30% (15)</td>
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<td>Hypercholesterolemia</td>
<td>39%</td>
<td>29% (15)</td>
<td>48% (24)</td>
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<td>4% (2)</td>
<td>10% (5)</td>
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<td>Family History</td>
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<td>35% (18)</td>
<td>44% (22)</td>
<td>0.37</td>
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<tr>
<td><strong>Coronary Artery Disease</strong></td>
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<tr>
<td>Prior Myocardial Infarction</td>
<td>35%</td>
<td>28% (14)</td>
<td>42% (21)</td>
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<tr>
<td>Prior Coronary Revascularization</td>
<td>27%</td>
<td>24% (12)</td>
<td>30% (15)</td>
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<tr>
<td><strong>NYHA Functional Class (I/II/III/IV)</strong></td>
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<td>44/6/1/-</td>
<td>55/6/8/1</td>
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<td>Dyspnea</td>
<td>24%</td>
<td>75% (18)</td>
<td>25% (6)</td>
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<td><strong>Medications</strong></td>
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<tr>
<td>Beta-blocker</td>
<td>51%</td>
<td>35% (18)</td>
<td>66% (33)</td>
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<td>ACE-Inhibitor/Angiotensin Receptor</td>
<td>38%</td>
<td>26% (13)</td>
<td>50% (25)</td>
<td>0.01</td>
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<td>Blocker</td>
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<tr>
<td>Thiazide diuretic</td>
<td>11%</td>
<td>2% (1)</td>
<td>20% (10)</td>
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<td>Loop diuretic</td>
<td>99%</td>
<td>4% (2)</td>
<td>14% (7)</td>
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<td>Calcium channel blocker</td>
<td>4%</td>
<td>2% (1)</td>
<td>6% (3)</td>
<td>0.36</td>
</tr>
<tr>
<td>HMG CoA-Reductase Inhibitor</td>
<td>45%</td>
<td>35% (18)</td>
<td>54% (27)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Aspirin</td>
<td>50%</td>
<td>31% (16)</td>
<td>68% (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ECHOCARDIOGRAPHY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LV Morphology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic diameter (cm)</td>
<td>5.2±0.6</td>
<td>5.2±0.6</td>
<td>5.3±0.6</td>
<td>0.41</td>
</tr>
<tr>
<td>End-systolic diameter (cm)</td>
<td>3.4±0.5</td>
<td>3.4±0.5</td>
<td>3.4±0.5</td>
<td>0.83</td>
</tr>
<tr>
<td>Anteroseptal wall thickness (cm)</td>
<td>1.0±0.2</td>
<td>0.9±0.1</td>
<td>1.0±0.3</td>
<td>0.006</td>
</tr>
<tr>
<td>Posterolateral wall thickness (cm)</td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
<td>1.0±0.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.30±.13</td>
<td>0.27±.13</td>
<td>0.33±.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Myocardial mass (gm/m²)</td>
<td>92±22</td>
<td>85±15</td>
<td>101±25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LV Systolic Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>63±6</td>
<td>63±6</td>
<td>64±6</td>
<td>0.42</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>35±5</td>
<td>34±5</td>
<td>35±5</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>LV Diastolic Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceleration Time (msec)</td>
<td>211±61</td>
<td>192±41</td>
<td>235±74</td>
<td>0.002</td>
</tr>
<tr>
<td>Mitral Inflow E/A Ratio</td>
<td>1.3±0.5</td>
<td>1.5±0.4</td>
<td>1.1±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler e’ (septal)</td>
<td>8±4</td>
<td>11±3</td>
<td>6±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler e’ (lateral)</td>
<td>11±5</td>
<td>15±3</td>
<td>8±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler E/e’ †</td>
<td>11±8</td>
<td>7±3</td>
<td>15±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler e’/a’ †</td>
<td>1.1±0.6</td>
<td>1.5±0.5</td>
<td>0.7±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Mitral Regurgitation (0-4 severity scale)</strong></td>
<td>0.7±0.3</td>
<td>0.6±0.2</td>
<td>0.7±0.4</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>CARDIAC MAGNETIC RESONANCE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LV Systolic Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>66±7</td>
<td>63±6</td>
<td>68±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke Volume (ml)</td>
<td>84±23</td>
<td>84±21</td>
<td>84±24</td>
<td>0.95</td>
</tr>
<tr>
<td>LV Morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>127±33</td>
<td>132±31</td>
<td>123±36</td>
<td>0.20</td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td>44±15</td>
<td>48±14</td>
<td>39±15</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Myocardial mass (gm/m²)</td>
<td>67±18</td>
<td>60±13</td>
<td>74±20</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Left Atrial Volume (ml/m²)</td>
<td>47±17</td>
<td>45±11</td>
<td>48±20</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Boldface type = p < 0.05  * p < 0.1  † calculated using average of septal and lateral e'
Table 2. CMR Diastolic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Normal Diastolic Filling*</th>
<th>Diastolic Dysfunction*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>E:A wave (peak amplitudes)</td>
<td>2.2±1.5</td>
<td>3.1±1.6</td>
<td>1.6±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak Filling Rate (ml/sec)</td>
<td>286±90</td>
<td>301±79</td>
<td>272±99</td>
<td>0.11</td>
</tr>
<tr>
<td>Normalized Peak Filling Rate (stroke volume adjusted)</td>
<td>3.5±0.9</td>
<td>3.6±0.8</td>
<td>3.3±0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Time to Peak Filling Rate (msec)</td>
<td>194±122</td>
<td>160±77</td>
<td>229±149</td>
<td>0.005</td>
</tr>
<tr>
<td>Diastolic Volume Recovery (80% stroke volume)</td>
<td>70±15</td>
<td>60±14</td>
<td>79±9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Boldface type indicates p value < 0.05
* Diastolic categories assigned using an echo standard
Table 3. Performance of CMR Diastolic Indices*

<table>
<thead>
<tr>
<th></th>
<th>Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized Peak Filling Rate</td>
<td>2.81</td>
<td>30% (15/50) †</td>
<td>90% (46/51)</td>
<td>75% (15/20)</td>
<td>57% (46/81)</td>
</tr>
<tr>
<td>Time to Peak Filling Rate</td>
<td>192 msec</td>
<td>38% (19/50) †</td>
<td>90% (46/51)</td>
<td>79% (19/24)</td>
<td>60% (46/77)</td>
</tr>
<tr>
<td>Diastolic Volume Recovery</td>
<td>77% of diastole</td>
<td>74% (37/50)</td>
<td>90% (46/51)</td>
<td>88% (37/42)</td>
<td>78% (46/59)</td>
</tr>
</tbody>
</table>

* Diagnostic performance calculated using a threshold to achieve 90% specificity.
† p <0.001 vs. DVR
Table 4. Multivariate Predictors of Echo-Evidenced Diastolic Dysfunction

**CMR Derived LV Mass**

*Model $\chi^2 = 73.4, p<0.001$*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>0.99 – 1.11</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.42</td>
<td>1.24 – 15.71</td>
<td>0.02</td>
</tr>
<tr>
<td>LV Mass (gm/m²)*</td>
<td>1.71</td>
<td>1.21 – 2.23</td>
<td>0.005</td>
</tr>
<tr>
<td>Diastolic Volume Recovery †</td>
<td>1.82</td>
<td>1.13 – 2.57</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Per 10 gm/m² increment
† Per 10 percent increment
Table 5. Multivariate Predictors of Echo-Evidenced Diastolic Dysfunction

*Echo Derived LV Mass*

Model $\chi^2 = 53.0, p<0.001$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>0.98 – 1.10</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.70</td>
<td>1.10 – 12.44</td>
<td>0.04</td>
</tr>
<tr>
<td>LV Mass (gm/m2)*</td>
<td>1.26</td>
<td>0.87 - 1.65</td>
<td>0.18</td>
</tr>
<tr>
<td>Diastolic Volume Recovery †</td>
<td>1.71</td>
<td>1.07 – 2.39</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Per 10 gm/m2 increment
† Per 10 percent increment
Legends

Figure 1. Typical Example

(1A) Automated LV-METRIC segmentation of representative time points within basal, mid, and apical slice locations (note that all slice locations and temporal phases segmented for diagnostic purposes). Segmentation was performed across spatial (vertical) and temporal (horizontal) domains for volumetric assessment of LV diastology.

(1B) Representative LV filling curves (x-axis = temporal phase, y-axis=volumetric change). Peak filling rate (PFR), defined as maximal slope of Δvolume/Δ temporal phase, and time to peak filling rate (TPFR) are shown on the left-sided graph. Diastolic volume recovery (DVR), calculated as proportion of diastole necessary to recover a threshold of 80% LV stroke volume, is shown on the right-sided graph.

(1C) Typical examples of normal (left) and abnormal (right) inflow patterns generated by first derivative transformation of the volumetric filling curve. Note E:A reversal in association with diastolic dysfunction.

Figure 2. Receiver Operating Characteristics Curves

Among all CMR indices tested, DVR yielded optimal diagnostic performance as evidenced by highest area under the curve (p<0.001 vs. NPFR and TPFR respectively).

Figure 3. Prevalence of Abnormal Diastolic Filling in Relation to Clinical Status

Prevalence of CMR-evidenced diastolic dysfunction was increased among patients with clinically-evidenced heart failure stratified by either NYHA functional class (3A) or binary presence/absence of dyspnea (3B).
Figure 2

The graph shows the Receiver Operating Characteristic (ROC) curves for different parameters:

- **Diastolic Volume Recovery (DVR)**: AUC = 0.87 ± 0.04
- **Time to Peak Filling Rate (TPFR)**: AUC = 0.68 ± 0.05
- **Normalized Peak Filling Rate (NPFR)**: AUC = 0.63 ± 0.06

The p-value for the comparison is less than 0.001.
Figure 3

3A

Prevalence of CMR-evidenced diastolic dysfunction

p = 0.04

NYHA class I  41%
NYHA class II  58%
NYHA class III or IV  80%

3B

Prevalence of CMR-evidenced diastolic dysfunction

p = 0.006

Dyspnea Absent  39%
Dyspnea Present  71%
Automated Segmentation of Routine Clinical Cardiac Magnetic Resonance Imaging for Assessment of Left Ventricular Diastolic Dysfunction

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